THE TERTIARY AMIDE AND CARBAMOYL OXY GROUPS IN AROMATIC
DIRECTED METALATION. SYNTHESIS OF POLYSUBSTITUTED BENZENE
AND PYRIDINE DERIVATIVES

by

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Doctor of Philosophy
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TO

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ABSTRACT

Chapter I

Ortho-lithiated tertiary benzamides were produced from the reactions of tertiary benzamides and 1:1 s-BuLi-TMEDA complex in THF at -78°C and subjected to transmetalation with MgBr₂.2Et₂O to give Grignard species which (unlike their lithiated precursors) react with aliphatic aldehydes and allyl bromide to give hydroxyalkyl and 2-allylbenzamides derivatives, respectively. 2-hydroxyalkyl derivatives on treatment with p-toluenesulfonic acid monohydrate gave phthalides. 2-allylbenzamides were converted to 3,4-dihydroisocoumarins, including the natural products mellein and kigelin, by treatment with 6M hydrochloric acid. The transmetalation procedure was also briefly explored with lithiated oxazoline and methoxymethoxybenzene.

Chapter II

Ortho-lithiation of N,N-diethyl O-phenyl carbamates, N,N-dimethyl O-phenyl carbamate and N,N-diethyl O-naphthyl-1 and 2-carbamates with 1:1 s-BuLi-TMEDA complex followed by quenching with various electrophiles lead to a variety of polysubstituted aromatic carbamate derivatives. When allowed to warm to room temperature the ortho lithiated species derived from different types of carbamate derivatives underwent 1,3 O --> C carbamoyl migration to give ortho hydroxyamide derivatives. Metalation of isomeric N,N-diethyl O-tolyl carbamates with LDA was also explored. An 1,4 O --> C carbamoyl migration was achieved from the
lithiation of 0-2-tolyl carbamate with LDA. A study on the mechanism of the 1,3 0 ---> C carbamoyl migration was described. A study on the relative ortho directing capability of N,N-diethyl carbamoyloxy group with tertiary amide and methoxymethoxy directing groups in both inter- and intramolecular competition reactions was undertaken. The iterative metation possibilities on unsubstituted 0-phenyl carbamates derivatives were described. A relatively simple and convenient method for the synthesis of 2(3H)-benzofuranone was also described.

Chapter III

N,N-diethyl 0-pyridyl-2-carbamate, N,N-diethyl 0-pyridyl-3-carbamate and N,N-diethyl 0-pyridyl-4-carbamate were subjected to lithiation using 1:1 s-BuLi TMEDA complex in THF at -78°C and the resulting ortho-lithiated species on treatment with different electrophiles afforded a variety of polysubstituted pyridine derivatives. 0-pyridyl-2-carbamate gave 2,3-disubstituted products while 0-pyridyl-3- and 4-carbamates afforded 3,4-disubstituted products. The metalated species of 0-pyridyl-3-carbamate and 0-pyridyl-4-carbamates when allowed to warm to room temperature afforded isonicotinamide and nicotinamides derivatives respectively. The iterative metation possibilities on some contiguously substituted 0-pyridyl-3- and 4-carbamates, electrophile-induced ipso destannylation to give iodo and acetyl 0-pyridyl carbamates as well as reductive elimination of the carbamate group to afford nicotinamide derivative were also described.
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and/or N,N-Diethyl O-(3-deuterio-4-methoxymethoxy)phenylcarbamate (123c)

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<td>Acetyl</td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>-----------------------</td>
<td></td>
</tr>
<tr>
<td>n-BuLi</td>
<td>n-Butyllithium</td>
<td></td>
</tr>
<tr>
<td>s-BuLi</td>
<td>s-Butyllithium</td>
<td></td>
</tr>
<tr>
<td>t-BuLi</td>
<td>t-Butyllithium</td>
<td></td>
</tr>
<tr>
<td>CsF</td>
<td>Cesium Fluoride</td>
<td></td>
</tr>
<tr>
<td>CH₂Cl₂</td>
<td>Methylene chloride</td>
<td></td>
</tr>
<tr>
<td>DIA</td>
<td>Diisopropylamine</td>
<td></td>
</tr>
<tr>
<td>DMF</td>
<td>Dimethylformamide</td>
<td></td>
</tr>
<tr>
<td>EtOAc</td>
<td>Ethyl acetate</td>
<td></td>
</tr>
<tr>
<td>Et₂O</td>
<td>Diethyl ether</td>
<td></td>
</tr>
<tr>
<td>HRMS</td>
<td>High resolution mass spectrum</td>
<td></td>
</tr>
<tr>
<td>IR</td>
<td>Infra red</td>
<td></td>
</tr>
<tr>
<td>LDA</td>
<td>Lithium diisopropylamide</td>
<td></td>
</tr>
<tr>
<td>LiTMP</td>
<td>Lithium tetramethylenepiperidide</td>
<td></td>
</tr>
<tr>
<td>MeI</td>
<td>Methyl iodide</td>
<td></td>
</tr>
<tr>
<td>MeOD</td>
<td>Deutero methanol</td>
<td></td>
</tr>
<tr>
<td>(MeS)₂</td>
<td>Methyl disulphide</td>
<td></td>
</tr>
<tr>
<td>MS</td>
<td>Mass spectrum</td>
<td></td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
<td></td>
</tr>
<tr>
<td>Py</td>
<td>Pyridine</td>
<td></td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
<td></td>
</tr>
<tr>
<td>TMEDA</td>
<td>Tetramethylethylenediamine</td>
<td></td>
</tr>
<tr>
<td>TMSCl</td>
<td>Chlorotrimethylsilane</td>
<td></td>
</tr>
<tr>
<td>TLC</td>
<td>Thin layer chromatography</td>
<td></td>
</tr>
</tbody>
</table>

( xxii)
CHAPTER I

1.0 INTRODUCTION

1.1 THE AROMATIC DIRECTED ORTHO METALATION REACTION

The aromatic directed ortho metalation reaction (Scheme 1) refers to a class of reactions in which a heteroatom group Z directs the metalating agent, commonly an organolithium base, to deprotonate specifically at the ortho site. The resulting ortho-lithiated species 2 then undergoes

Scheme 1

\[
\begin{align*}
\text{I} & \quad \text{RLi} \quad \rightarrow \quad \text{2} \\
\text{Z} & \quad \text{Li} \\
\text{E} & \quad \text{E} \\
\end{align*}
\]

\[Z = \text{Directing group}\]

reaction with a variety of electrophiles (E+) to afford ortho-substituted products 3.

Since the discovery of the prototype of this reaction by Gilman\(^1\) and by Wittig\(^2\), the methodology has been developed further by Gilman\(^3\) and by many other researchers, notably Hauser\(^4\) and Slocum\(^5\) and their respective co-workers. From their work, a number of heteroatom based substituents have been shown to act as effective ortho directors. As a result, the aromatic directed lithiation is becoming recognized for its increasing utility towards the regiospecific synthesis of polysubstituted
aromatics and heteroaromatics.\textsuperscript{6}

1.1.1 ORTHO METALATION DIRECTORS

The basic characteristic of an ortho metalation director is that it is a heteroatom or heteroatom-carrying functional group. The extensive list of directing groups\textsuperscript{6} is shown in Table 1 classified according to a qualitative order of relative directing abilities\textsuperscript{5, 7, 8, 9, 10}.

**Table 1:** Ortho Metalation Directing Groups

<table>
<thead>
<tr>
<th>STRONG</th>
<th>MODERATE</th>
<th>WEAK</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONHR</td>
<td>CH₃</td>
<td>CH(OH)\textsubscript{2}</td>
</tr>
<tr>
<td>CSNHR</td>
<td>N\textsubscript{EC}</td>
<td>CH\textsubscript{2}OH</td>
</tr>
<tr>
<td>CONR\textsubscript{2}</td>
<td>N\textsubscript{R}\textsubscript{2}</td>
<td></td>
</tr>
<tr>
<td>NHCOR</td>
<td>OMe</td>
<td></td>
</tr>
<tr>
<td>NHCO\textsubscript{2}R</td>
<td>OPO(OR)\textsubscript{2}</td>
<td></td>
</tr>
<tr>
<td>OCONR\textsubscript{2}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH=NR</td>
<td>SM\textsubscript{e}</td>
<td></td>
</tr>
<tr>
<td>OCH(Me)OEt</td>
<td>F, Cl</td>
<td></td>
</tr>
<tr>
<td>CH\textsubscript{2}NHR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OTHP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(CH\textsubscript{2})\textsubscript{n}NR\textsubscript{2}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 1, 2</td>
<td>CN</td>
<td></td>
</tr>
<tr>
<td>SO\textsubscript{2}NHR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SO\textsubscript{2}NR\textsubscript{2}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SO\textsubscript{3}H</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
1.1.2 MECHANISTIC CONSIDERATIONS

A. STRUCTURES OF LITHIATED SPECIES

To understand the detailed mechanism of ortho lithiation, one should at first establish the structures of the reactive intermediates as well as of the reagents. However, with the exception of a few data provided by X-ray determinations\textsuperscript{11} and \textsuperscript{13}C NMR spectroscopy,\textsuperscript{12,13,14,15} little is known about the structures of the ortho lithiated species.

Phenyllithium, 4, complexed with TMEDA, has been reported to be dimeric by X-ray determination.\textsuperscript{15} It is also dimeric in Et\textsubscript{2}O or in THF solution.\textsuperscript{15} The \textsuperscript{13}C NMR spectrum of phenyllithium was reported by Levy.\textsuperscript{12} The X-ray and \textsuperscript{13}C NMR spectroscopic studies on ortho lithiated \textit{N},\textit{N}-dimethylbenzylamine 5 reveals that it is tetrameric in hydrocarbon solvent and dimeric in THF.\textsuperscript{13} Recently, a \textsuperscript{13}C NMR study on \textit{N},\textit{N}-diethylbenzamide 6 and ortho-lithiated \textit{N},\textit{N}-diethylbenzamide, 7 was carried out by Mills.\textsuperscript{14} Figure 1 shows comparison of selected \textsuperscript{13}C NMR spectral parameters of 7 with \textit{N},\textit{N}-diethyl benzamide, 6, phenyllithium, 4 and ortho-lithiated benzylamine 5.

\textbf{Figure 1:} \textsuperscript{13}C NMR Spectral Data for Aromatic Organolithiums
As expected C-2 in 7 is shifted significantly downfield in comparison to that in 6. Furthermore, the C-2 shift in 7 is of similar magnitude to those observed in compounds 4 \textsuperscript{12} and 5. \textsuperscript{13} In phenyllithium the excess electron density is in a nonbonding type orbital orthogonal to the -system.\textsuperscript{12} It can be tentatively concluded that, in the absence of X-ray data, the negative charge on C-2 in 7 is orthogonal to the -system.

B. ORGANOLITHIUM BASES AND SOLVENTS

Considerable evidence demonstrates that organolithium species are oligomers of varying complexity in different solvents.\textsuperscript{6} The degree of aggregation and association of the organolithium bases will in part determine the regioselectivity and the extent of deprotonation.\textsuperscript{16} Organolithiums become kinetically more basic as the aggregate size diminishes.\textsuperscript{6} Therefore in the case of donor solvent association with solvent molecules or TMEDA increases the carbanionic nature of these species and hence their reactivity. Information on three commonly used alkyllithiums will be summarized.

\textit{n-Butyllithium.} \textit{n-BuLi} is known to be hexameric in hydrocarbon
solvent\textsuperscript{17} but becomes a monomeric 1:1 complex with TMEDA in the same solvent.\textsuperscript{18} However, \textit{n}-BuLi has been established to be tetrameric in Et\textsubscript{2}O, THF and THF containing TMEDA. At low temperatures, these tetramers exist in equilibrium with dimers as shown by \textsuperscript{13}C NMR.\textsuperscript{19}

\textit{s-Benzyl lithium}. \textit{s}-BuLi has been reported recently to exist as a mixture of dimer, tetramer and hexamer in hydrocarbon solvent with increasing concentration of hexamer at lower temperature.\textsuperscript{20} At -50°C it forms a 1:1 complex with TMEDA which when warmed to -20°C, equilibrates to a 1:2 complex with TMEDA.\textsuperscript{21}

\textit{t-Benzyl lithium}. \textit{t}-BuLi is tetrameric in hydrocarbon solvent,\textsuperscript{17} but in THF, it forms a 2:1 complex with an associated THF molecule.\textsuperscript{22}

C. THE DIRECTED ORTHO METALATION GROUP

The directing group which usually contains one or more heteroatoms is assumed\textsuperscript{6} to play three major roles in the metatation reaction sequence: a) anchoring the base through the coordination of the non-bonding electrons of one of its heteroatoms.\textsuperscript{23} This primary anchoring is an important consideration in predicting regioselectivity of deprotonation according to the strength of the complex formation when more than one directing group is present; b) provides an inductive electron withdrawing effect which enhances the acidity of the ortho proton to be abstracted thereby facilitating the subsequent deprotonation step; c) stabilizes the ortho metalated intermediate through chelation.
1.1.3. REACTIONS OF ORTHO LITHIATED SPECIES WITH ELECTROPHILES

The broad utility of the directed ortho lithiation reaction is dependent largely on the range of electrophiles which can be introduced. Table 2 lists some of the most commonly used electrophiles and the corresponding substituted products they provide. This list is based on the review by Gschwend and Rodriguez.°

Table 2: Electrophiles Which Undergo Reaction with Ortho Lithiated Species.

<table>
<thead>
<tr>
<th>E⁺</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF₃COCF₃</td>
<td>C(CF₃)₂OH</td>
</tr>
<tr>
<td>R₁COR₂</td>
<td>C(OH)R₁R₂</td>
</tr>
<tr>
<td>Epoxides</td>
<td>CH(R₁)CH(R₂)OH</td>
</tr>
<tr>
<td>ArCOR</td>
<td>C(OH)(R)(Ar)</td>
</tr>
<tr>
<td>ArCOAr</td>
<td>C(Ar)₂OH</td>
</tr>
<tr>
<td>CO₂(H₃O⁺)</td>
<td>CO₂H</td>
</tr>
<tr>
<td>nRX, X=I,Br</td>
<td>R</td>
</tr>
<tr>
<td>ArCN(H₃O⁺)</td>
<td>COAr</td>
</tr>
<tr>
<td>ArCON(CH₃)₂</td>
<td>COAr</td>
</tr>
<tr>
<td>ArCO₂Li</td>
<td>COAr</td>
</tr>
<tr>
<td>RCON(CH₃)₂</td>
<td>COR</td>
</tr>
<tr>
<td>Chemical Symbol</td>
<td>Alternative Representation</td>
</tr>
<tr>
<td>-----------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>RCN</td>
<td>COR</td>
</tr>
<tr>
<td>RCO$_2$Li</td>
<td>COR</td>
</tr>
<tr>
<td>DMF</td>
<td>CHO</td>
</tr>
<tr>
<td>ArCHO</td>
<td>CH(Ar)OH</td>
</tr>
<tr>
<td>ClCONR$_2$</td>
<td>CONR$_2$</td>
</tr>
<tr>
<td>PhNCO</td>
<td>CONHPh</td>
</tr>
<tr>
<td>RNCO</td>
<td>CONHR</td>
</tr>
<tr>
<td>FSO$_2$OMe</td>
<td>Me</td>
</tr>
<tr>
<td>CF$_2$CCl$_2$</td>
<td>CFCCl$_2$</td>
</tr>
<tr>
<td>(SCN)$_2$</td>
<td>CN, SCN</td>
</tr>
<tr>
<td>AcCl</td>
<td>Ac</td>
</tr>
<tr>
<td>Ac$_2$O (MgBr$_2$)</td>
<td>Ac</td>
</tr>
<tr>
<td>ClCH$_2$OCH$_3$</td>
<td>CH$_2$OCH$_3$</td>
</tr>
<tr>
<td>(CH$_3$O)$_2$SO$_2$</td>
<td>CH$_3$</td>
</tr>
<tr>
<td>ClCH$_2$NR$_2$</td>
<td>CH$_2$NR$_2$</td>
</tr>
<tr>
<td>PhCOCl</td>
<td>COPh</td>
</tr>
<tr>
<td>CH$_2$O</td>
<td>CH$_2$OH</td>
</tr>
<tr>
<td>RNCs</td>
<td>CSNHR</td>
</tr>
<tr>
<td>ClCO$_2$R</td>
<td>CO$_2$R</td>
</tr>
<tr>
<td>CH$_2$=CHCHO</td>
<td>CH(OH)=CH$_2$</td>
</tr>
</tbody>
</table>

**Heteroatom Based:**

<table>
<thead>
<tr>
<th>Chemical Symbol</th>
<th>Alternative Representation</th>
</tr>
</thead>
<tbody>
<tr>
<td>D$_2$O</td>
<td>D</td>
</tr>
<tr>
<td>ROD</td>
<td>D</td>
</tr>
<tr>
<td>S</td>
<td>SH</td>
</tr>
</tbody>
</table>
\[(R_2S)_2 \quad R=Me, Ph\]

<table>
<thead>
<tr>
<th>SR</th>
<th>(SO_2Ph)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Br</td>
<td>Br</td>
</tr>
<tr>
<td>Br</td>
<td>Br</td>
</tr>
<tr>
<td>Br</td>
<td>Br</td>
</tr>
<tr>
<td>Br</td>
<td>Br</td>
</tr>
<tr>
<td>Cl</td>
<td>Cl</td>
</tr>
<tr>
<td>Cl</td>
<td>Cl</td>
</tr>
<tr>
<td>I</td>
<td>(\beta(OME)_2)</td>
</tr>
<tr>
<td>I</td>
<td>OH</td>
</tr>
<tr>
<td>I</td>
<td>OH</td>
</tr>
<tr>
<td>SiR_3</td>
<td>(product)</td>
</tr>
</tbody>
</table>

\(R_2SiCl_2, R = Me, Ph\)

\[\text{product}\]
1.1.4. RECENT APPLICATIONS OF DIRECTED METALATION REACTION

The directed metalation methodology has become a routine tool for the regiospecific preparations of polysubstituted aromatic derivatives. A few examples are given below to demonstrate the utility of the methodology (Table 3).

**Table 3: Synthetic Applications of Aromatic Directed Lithiation Reaction**

<table>
<thead>
<tr>
<th>Starting Material</th>
<th>Lithiation Condition</th>
<th>Electrophiles</th>
<th>Product/Intermediate</th>
<th>Yield, %</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Naphthalene" /></td>
<td>n-BuLi</td>
<td>HO⁻</td>
<td><img src="image2" alt="Naphthalene" /></td>
<td>78-82</td>
<td>24</td>
</tr>
<tr>
<td><img src="image3" alt="Indole" /></td>
<td>LDA</td>
<td>(C₆H₅)₂CO</td>
<td><img src="image4" alt="Indole" /></td>
<td>43</td>
<td>26</td>
</tr>
</tbody>
</table>
1.1.5. THE SIGNIFICANCE OF THE ORTHO METALATION REACTION

The importance of the directed ortho metalation process lies in its excellent capability for the regioselective synthesis of carbon and hetero-atom based 1,2-disubstituted aromatic derivatives which are invariably difficult to prepare by classical electrophilic aromatic substitution chemistry. The latter class of reactions are usually non-regioselective, require harsh conditions and lack flexibility in terms of potential electrophiles which can be introduced. Ortho, para-directing groups lead predominantly to p-substituted products. This problem of regioselectivity is of course enhanced by the presence of more than one substituent on the aromatic ring.
In contrast, in the directed lithiation reaction, metalation can be achieved regioselectively ortho to a directing group (EWG or EDG) in the presence of a number of other groups with the provision that these must be unreactive to the strong alkyllithium bases.

There are some other methods of interest, namely sigmatropic rearrangements, ipso electrophilic substitution, nucleophilic aromatic substitution, cycloaddition reactions of suitably substituted non aromatics followed by aromatization, carbanionic cyclization, which are also used for the preparation of ortho-disubstituted aromatic derivatives. However, these methods lack the same scope and general utility as the directed ortho metalation reaction.

The directed metalation methodology may be highly commended for its efficiency and wide applicability in the regiospecific synthesis of 1,2-disubstituted aromatics. This may be demonstrated by the following examples:

(a) Compound 11, an intermediate for zealeranone (zearalenone), 12, synthesis, was prepared from compound 8 by a three-step sequence in 86% overall yield (Scheme 2). This compares very favorably with the earlier classical six-step preparation of 9% overall yield.
(b) Compound 14 is a potential intermediate for the synthesis of 
(+)-averufin,\textsuperscript{31} which in turn is a central intermediate in aflatoxin 
biosynthesis. Using directed metalation, 14 was prepared from 13 in 
95% yield. All attempts to prepare 14 by classical methods were 
unsuccessful (Scheme 3).\textsuperscript{31}
1.1.6. TRANSMETALATION

Transmetalation (interconversion of one organometallic to another) is probably the most general method for preparing those organometallics that are either impossible or difficult to obtain directly from organic compounds (eqn. 1).

\[ RM + M'X \rightarrow RM' + MX \]  \hspace{1cm} (1)

For a reaction to proceed in a forward direction, \( M \) should be more electropositive than \( M' \). However, in cases where \( M' \) is more electropositive than \( M \), it is still possible to produce an equilibrium concentrations of \( RM' \) and use it in a desired reaction.32

Organolithiums and Grignard reagents are highly electropositive and, therefore, have been used most extensively as parent organometallics (RM). Organometallics of all metals that are more electronegative than lithium and magnesium are commonly prepared by transmetalation.32
Selective reactivity of many common electrophilic functional groups may be mediated by choice of metal of the organometallic reagent. Some examples of preparation and utility of RM reagents (R = aryl) obtained via transmetalation are presented below.

A. ORGANOZINC COMPOUNDS

Negishi\(^{33}\) reported the preparation of arylzinc compounds, 15, by the transmetalation of the corresponding aryllithiums with zinc halides and used these for the synthesis of biaryls and diaryl methanes 16, by the nickel or palladium catalyzed coupling reaction with aryl halides (eqn 2).

\[
\begin{align*}
\text{ZnX}_2 \quad \text{RLi} \quad \text{ZnX + Ar'} \quad \frac{\text{Ni(PPh}_3)_4}{15} \quad \frac{\text{Cl}_2\text{Pd(PPh}_3)_2}{16} \quad \frac{\text{R - Ar}}{\text{or}} \quad 85-95% \\
\end{align*}
\]

R = Ar, ArCH\(_2\); X = Cl, Br; X' = Br, I

Raphael\(^{34}\) prepared compound 20 by the coupling of arylzinc chloride, 18 with 19. Compound 18 was prepared by ZnCl transmetalation of organolithium 17 which in turn, is available by metal-halogen exchange (n-BuLi/THF/-78°C) of 3,4-methylenedioxy bromobenzene (Scheme 4).
Arylacetic ethyl esters, 21, were prepared by the reaction of arylzinc chlorides (prepared by ArLi + ZnCl₂) with ethyl bromoacetate in presence of a nickel (II) catalyst\textsuperscript{35} (eqn. 3).

\[
\text{ArZnCl} + \text{BrCH}_2\text{CO}_2\text{Et} \xrightarrow{\text{Ni(II)}} \text{ArCH}_2\text{CO}_2\text{Et} \quad 38-60\% \quad \text{(3)}
\]

\[
\text{Ar} = \begin{array}{c}
\begin{array}{c}
\text{R} \\
\end{array}
\end{array}
\quad \begin{array}{c}
\begin{array}{c}
\text{X} \\
\text{R}
\end{array}
\end{array}
\]

R = H, o-OCH₃, o-CH₃ \quad X = O, S, Se
Other methods\textsuperscript{36} are less attractive due to high reaction temperatures and long reaction times.

Greene\textsuperscript{37} prepared $\beta$-cuparenone, 24, by the nickel acetylacetonate catalyzed conjugate addition of di-p-tolylzinc, 22, to trimethylcyclopent- enone, 23, (Scheme 5), compound 22 may be prepared easily (Li, p-CH$_3$C$_6$H$_4$Br, ZnBr$_2$, ether, ultrasonic irradiation),

Scheme 5

B. GRIGNARD REAGENTS

Conversion of organolithium compounds to Grignard reagents is perhaps the most widely used transmetalation process. The first example of conversion of an organolithium compound to a Grignard reagent is due to Gilman\textsuperscript{38} (Scheme 6).
Recent applications of this transmetalation include:

Mg for Li transmetalation was used for the preparation of benzocyclobutanol, 30, from \( \alpha \)-halostyrene oxide, 28 by Durst and coworkers (Scheme 7).

Trost used Mg for Li transmetalation reaction for the amination of aromatics where the corresponding organolithium species failed to react with the amination reagent, azidomethyl phenyl sulfide (eqn. 4).
Kumada reported a dramatic increase in yields of the arylated and heteroarylated products, 36, by the transmetalation of the lithiated heterocycles, 34, to either Grignard or to organozinc intermediates, 35 (Scheme 8).
Also \( \text{Ar} = \text{C}_6\text{H}_5\text{Br}, 3\)-Bromothiophene, 2- and 3-Bromopyridine; Yields: 66-87%.

C. ORGANOTIN COMPOUNDS

Stille\textsuperscript{42} recently reported the preparation of the tin naphthalene derivative 38 from bromonaphthalene, 37 via an intermediate aryl lithium species (Scheme 9). Compound 38 was used for the synthesis of vitamin K (39) as shown.

\[ \begin{align*}
\text{Br} & \quad \text{OH} \\
& \quad \text{37} \\
& \quad \text{1) 2} \times \text{BuMe}_2\text{SiCl} \\
& \quad \text{2) 2} \times \text{BuLi} \\
& \quad \text{3) Me}_3\text{SnCl} \\
& \quad \text{65% (overall)} \\
\end{align*} \]

\[ \begin{align*}
\text{Br} & \quad \text{OH} \\
& \quad \text{37} \\
& \quad \text{1) 10\% ZnCl}_2 \cdot \text{Et}_2\text{O} \\
& \quad \text{2) } \text{Br} \quad \text{3) py • chlorochromate} \\
\end{align*} \]

An example of carbon-carbon bond formation via PdCl\(_2\) catalyzed acylation of tin heteroaromatics 40 has been reported\textsuperscript{43} (Scheme 10).

\[ \begin{align*}
& \text{40} \\
& \text{Me}_3\text{SnNa or RLi/Me}_3\text{SnCl} \\
\end{align*} \]

\[ \begin{align*}
& \text{SO}_3\text{H} \\
& \text{41} \\
& \text{RCOCl} \\
\end{align*} \]
D. **ORGANOCERIUM COMPOUNDS**

Organocerium reagents 42, available by transmetalation of an organolithium reagent with cerium iodide, undergo nucleophilic addition even to the easily enolizable ketone 43 (eqn. 5).\textsuperscript{44}

\[
\begin{align*}
\text{PhCeI}_2 + \text{Ph} & \quad \text{CO} \quad \text{Me} \quad \rightarrow \quad \text{Ph} \quad - \quad \text{C} \quad - \quad \text{Ph} \\
42 & \quad 43
\end{align*}
\]
1.2 RESULTS AND DISCUSSION

1.2.1 TRANSMETALATION OF ORTHO LITHIATED TERTIARY BENZAMIDES TO
ORTHOMgBr SPECIES

Studies in our laboratory\textsuperscript{8,45} and by other
researchers\textsuperscript{5,7,9,10,45,47} demonstrated that the N,N-diethyl carboxamide
group on an aromatic ring is a powerful ortho director. Since the initial
report by Beak\textsuperscript{48} that N,N-diethylbenzamide could be smoothly and
effectively ortho lithiated, our laboratory has been engaged in systematic
exploration of ortho-lithiated benzamides for the efficient preparation of
contiguously polysubstituted aromatics and for the application of the
derived methodology towards the synthesis of condensed aromatic and
heteroaromatic systems, including anthraquinones, anthracyclines,
benzylisoquinoline, phthalide isoquinoline and phenanthroquinolizidine and
phenanthroindolizidine alkaloids and other natural and unnatural
products.\textsuperscript{8,49}

Although a diverse variety of electrophiles (Table 2) could be
introduced by reaction with ortho-lithiated benzamides, it was found that
allyl bromides, aliphatic aldehydes, pyridine-2-aldehyde, ethyl acetate,
ethylene oxide and benzonitrile failed to give ortho-substituted
products.\textsuperscript{47,50}

The o-lithiated N,N-diisopropylbenzamide when treated with allyl
bromide was found to undergo a metal-halogen exchange reaction yielding
N,N-diisopropyl o-bromobenzamide rather than the o-allylated product.\textsuperscript{47} In
the case of aliphatic aldehydes\textsuperscript{47} and pyridine-2-aldehyde\textsuperscript{50}, no products
were identified.
Encouraged by the transmetalation methodology literature (Section 1.1.6), we explored lithium to magnesium transmetalation and achieved successful coupling with allyl bromide, aliphatic aldehydes, and pyridine-2-aldehyde using this procedure. The failure of the lithioamide and the success of the Grignard species may be rationalized in terms of hard and soft acid-base theory. The lithiated amide is a relatively hard base and hence cannot react with moderately softer electrophilic reagents such as allyl bromide. Ultimately, a metal-halogen exchange occurs. On the other hand, the Grignard species is a relatively softer base than the lithio counterpart and reacts satisfactorily with allyl bromide. For Grignard reagents, Halogen-metal exchange is not a facile reaction. Similarly, aliphatic aldehydes having an acidic α-hydrogen react with the hard lithioamide thereby producing an enolate which in turn may undergo aldol condensations to give polymeric product. However, the magnesium species is a softer base thereby reacting successfully at the carbonyl group producing hydroxyalkylamide derivatives. This explanation parallels the report that phenyllithium abstracts α-hydrogen from acetophenone giving a mixture of enolate and carbinolate in a ratio of 1:23 whereas the corresponding Grignard reagent affords the same mixture in a ratio of 1:∞.

Since the ortho lithiated N,N-diethyl O-arylcarbamate has been shown to couple satisfactorily with both aliphatic aldehydes and allyl bromide (see Section 2.2.1), it appears that the low-reactivity of a lithiated benzamide towards these electrophiles may be inherent to this system.
The advantage of the transmetalation strategy for ortho alkylation and ortho hydroxyalkylation of tertiary-benzamides will be described in this thesis. Comparison of ortho lithium versus ortho magnesium species in reactions of 2-oxazolino 61 and methoxymethoxy 63 directing groups with aliphatic aldehydes will also be discussed.\textsuperscript{51}

1.2.2. PREPARATION OF ORTHO MgBr-BENZAMIDE THROUGH TRANSMETALATION AND ITS REACTION

In general, the preparation of ortho MgBr-benzamide involved the lithiation of N,N-diethyl benzamide with s-BuLi/TMEDA in THF at -78°C (-90°C for N,N-dimethylbenzamide\textsuperscript{55}) under nitrogen followed by addition of MgBr\textsubscript{2}·2Et\textsubscript{2}O and treating the resulting mixture with electrophiles (Scheme 11).

Scheme 11

* These conditions will be referred to as standard conditions and will be represented by RLi unless otherwise indicated.
1.2.3. REACTION OF ORTHO MgBr-BENZAMIDES WITH ALIPHATIC ALDEHYDES. SYNTHESIS OF SUBSTITUTED PHTHALIDES.

The Grignard species 47 were treated with acetaldehyde and n-butyraldehyde to give o-hydroxyalkylamides 49; for convenience, these were not isolated but transformed to phthalides 50 by a p-toluenesulfonic acid catalyzed lactonization reaction (Scheme 12). The results are shown in Table 4.

Scheme 12

\[
\begin{align*}
45 \text{ a-e} & \quad \text{1) } R\text{Li} \\
& \quad \text{2) } \text{MgBr}_2, 2\text{Et}_2\text{O} \\
\end{align*}
\]

R
\[
\begin{align*}
a: & \quad R \text{H} \\
b: & \quad 2\text{-OMe} \\
c: & \quad 3\text{-OMe} \\
d: & \quad 2,5\text{-} (\text{OMe})_2 \\
e: & \quad 2,3,4\text{-} (\text{OMe})_3
\end{align*}
\]
Table 4: Synthesis of Phthalides 50 by Li $\rightarrow$ MgBr Transmetalation.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Electrophile</th>
<th>Product</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>45a</td>
<td>CH$_3$(CH$_2$)$_2$CHO</td>
<td>50a</td>
<td>64</td>
</tr>
<tr>
<td>45a</td>
<td>CH$_3$CHO</td>
<td>50b</td>
<td>61</td>
</tr>
<tr>
<td>45b</td>
<td>CH$_3$(CH$_2$)$_2$CHO</td>
<td>50c</td>
<td>60</td>
</tr>
<tr>
<td>45c</td>
<td>CH$_3$(CH$_2$)$_2$CHO</td>
<td>50d</td>
<td>59</td>
</tr>
<tr>
<td>45d</td>
<td>CH$_3$(CH$_2$)$_2$CHO</td>
<td>50e</td>
<td>75</td>
</tr>
<tr>
<td>45a</td>
<td>Py-2-CHO</td>
<td>50f</td>
<td>88</td>
</tr>
</tbody>
</table>

The characteristic $^1$H NMR signal for the methine proton ($\delta$H 3.39-5.5) and IR absorption frequencies at 1750 cm$^{-1}$ characteristic of 5-membered lactones along with other evidence (see Experimental Section), as well as comparison of the spectral data of 50a 56 and 50b 57 with data for authentic materials, confirmed the structures of the phthalide products.
1.2.4. REACTION OF ORTHO MgBr-BENZAMIDES WITH ALYL BROMIDE

The coupling of Grignard species 47 and 53 with allyl bromide provided o-allylbenzamides 51 and 54 in good to excellent yields (Scheme 13). The results are collected in Table 5.

Scheme 13

\[ \text{CH}_2=\text{CHCH}_2\text{Br} \]

47 a-e \[ \rightarrow \]

51 a-e

\[ R = \text{H} \quad 6-\text{OMe} \quad 3-\text{OMe} \quad (3,6-\text{OMe})_2 \quad 4,5,6-(\text{OMe})_3 \]

52 \[ \xrightarrow{1) \text{RLi}} \]

53

54
Table 5. Synthesis of o-Allylbenzamides 51 and 54.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Electrophile</th>
<th>Product</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>45a</td>
<td>CH₂=CHCH₂Br</td>
<td>51a</td>
<td>71</td>
</tr>
<tr>
<td>45b</td>
<td>CH₂=CHCH₂Br</td>
<td>51b</td>
<td>55</td>
</tr>
<tr>
<td>45c</td>
<td>CH₂=CHCH₂Br</td>
<td>51c</td>
<td>80</td>
</tr>
<tr>
<td>45d</td>
<td>CH₂=CHCH₂Br</td>
<td>51d</td>
<td>63</td>
</tr>
<tr>
<td>45e</td>
<td>CH₂=CHCH₂Br</td>
<td>51e</td>
<td>66</td>
</tr>
<tr>
<td>53</td>
<td>CH₂=CHCH₂Br</td>
<td>54</td>
<td>77</td>
</tr>
</tbody>
</table>

Allylation was confirmed by the presence of signals for the olefinic protons in $^1H$ NMR spectra of the products (δ 5.85-6.20) together with other spectral data (see Experimental). Conversions to dihydro isocoumarins provided chemical corroboration of the ortho-allylation result. Two equivalents of allyl bromide was used to obtain optimum yields as a decrease in yield of the allylated product 50a was observed when 1.0 equivalent of allyl bromide was used. Invariably, 3.0 equivalents of MgBr₂.2Et₂O was also used. It was observed, however, that at least 2.0 equivalents should be used for satisfactory results as 50% of allylated product 50a was obtained when 1.0 equivalent of MgBr₂.2Et₂O was used.

The allylation of 45a was also performed under a variety of conditions to establish optimum yields. The Grignard species 47a was prepared as before and then cooled to different temperatures. In addition, one
experiment was carried out by allowing 47a to undergo reaction with allyl bromide at -78°C without warming to room temperature. The results are shown in Table 6.

**Table 6** Reaction of Allyl bromide with ortho-MgBr Benzamide 47a as a Function of Temperature

<table>
<thead>
<tr>
<th>Temp, °C</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>-78</td>
<td>71</td>
</tr>
<tr>
<td>-78 (without warming to RT)</td>
<td>66</td>
</tr>
<tr>
<td>-40</td>
<td>67</td>
</tr>
<tr>
<td>0</td>
<td>66</td>
</tr>
<tr>
<td>RT</td>
<td>63</td>
</tr>
</tbody>
</table>

As Table 6 indicates no appreciable change in yields as a function of the temperature of quenching with allyl bromide was observed. However, optimum yields were achieved at -78°C and therefore these were chosen for reactions with other benzamide substrates.

_α_-Allylation of 53 required a slight modification of the general transmetalation in that the lithiation was carried out at -90°C. This was found necessary in order to suppress the nucleophilic attack at the N,N-dimethyl amide group by s-BuLi.47

1.2.5. **REACTION OF α-MgBr BENZAMIDE 47a WITH OTHER ELECTROPHILES**

In an attempt to expand our transmetalation methodology, we examined the possibility of coupling a Grignard species 47a with various electrophiles.
The reaction of 47a with ethyl acetate which was originally expected to yield \( \alpha \)-acetyl benzamide 55, resulted in the formation of a 2:1 condensation product 56, isolated as the phthalide 57, in 35% yield (Scheme 14). Attempts to stop the reaction at the expected \( \alpha \)-acetyl benzamide (55) stage by variation of conditions (which included inverse addition and using a large excess of ethyl acetate) failed.

The isolation of 57, however, was not unexpected, since it is the normal end product of a reaction between a Grignard reagent and an ester.

Scheme 14

Reactions of electrophiles such as acetonitrile, ethyl bromoacetate, 1-bromoacetaldehyde diethyl acetal, epibromohydrin, methyl vinyl ketone,
benzyl chloride, benzyl bromide, cyclohexene oxide and styrene oxide which were shown not to couple with the ortho-lithiated N,N-diethylbenzamide\textsuperscript{58} also failed to give condensation products with the Grignard species 47a. In each case, in addition to recovering starting benzamide (60-65%), a self condensation product, the benzophenone 58,\textsuperscript{59} was obtained as a minor product (6-13%). This compound has been previously obtained as a side product from ortho-lithiated benzamides.\textsuperscript{47,60} On the basis of the following observations, it is assumed that compound 58 is formed from either the \(o\)-Li or the \(o\)-MgBr species. When 47a was allowed to warm to room temperature and

\begin{center}
\textbf{Scheme 15}
\end{center}

![Scheme 15](image)

quenched with water, compound 58 was isolated in 17% yield together with starting material (65%). On the other hand, when 47a was generated from \(o\)-bromobenzamide and triply sublimed magnesium followed by the same quenching procedure, benzophenone 58 was obtained in 10\% yield together with N,N-diethyl benzamide (60%).

\subsection*{1.2.6 SYNTHESIS OF DIHYDROISOCOUMARINS FROM \(o\)-ALLYLBENZAMIDES}

The efficient synthesis of \(o\)-allylbenzamides 51 prompted us to
undertake a study of their acid-catalysed transformation into isocoumarin derivatives\textsuperscript{59,60} which included the natural products melein\textsuperscript{62} and kigelin\textsuperscript{63} (Scheme 16).

\textbf{Scheme 16}

\begin{align*}
51\text{a-e} & \xrightarrow{6\text{N} \text{HCl}} 59\text{a-e} \\
\text{a: H} & \\
\text{b: 6-OMe} & \\
\text{c: 3-OMe} & \\
\text{e: 4,5,6-(OMe)}_3 & \\
\text{60} & \\
\end{align*}

Treatment of 51\text{a} with 6N aqueous HCl under reflux afforded 59\text{a} in almost quantitative yield. Treatment of 51\text{b} resulted in cyclization as well as demethylation to give melein, 59\text{b}, a naturally occurring isocoumarin\textsuperscript{62} The 2-allyl-3-methoxybenzamide 51\text{c} yielded a mixture of isocoumarin 59\text{c}, the corresponding phenol 59\text{d}, and the benzofuran 60. The desired kigelin 59\text{e}\textsuperscript{63} was not, however, obtained from 51\text{e} which underwent cyclization only under vigorous condition (6N HCl/reflux/72h) to
give a mixture of products containing didemethylated isocoumarin (by $^1$H NMR analysis) but not kigelin. Therefore, other conditions such as mercuric acetate-catalyzed$^{63a}$ or palladium chloride-catalyzed$^{64}$ cyclization methods, previously used to cyclize o-allylbenzoic acids and their corresponding primary and secondary amides into isocoumarins and isoquinolines,$^{64}$ were explored but proved to be unsuccessful. Finally, kigelin was obtained by the 6N HCl catalyzed cyclization of the N,N-dimethylbenzamide $^{54}$. The success may be due to the less steric congestion of dimethylamide group in $^{54}$ which facilitated its cyclization and aided monodemethylation of the 8-OMe group to kigelin. The results of cyclization of $^{51a}$-e to $^{59}$a-d and of $^{54}$ to $^{59}$e are summarized in Table 7.

Table 7: Synthesis of Dihydroisocoumarins (59) from o-allylbenzamides $^{51}$a-e, $^{54}$.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Conditions</th>
<th>Product</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{51}$a</td>
<td>6N HCl/reflux/20 h</td>
<td>$^{59}$a</td>
<td>93</td>
</tr>
<tr>
<td>$^{51}$b</td>
<td>6N HCl/reflux/4 d</td>
<td>$^{59}$b</td>
<td>75</td>
</tr>
<tr>
<td>$^{51}$c</td>
<td>6N HCl/reflux/18 h</td>
<td>$^{59}$c</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$^{59}$d</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60</td>
<td>12</td>
</tr>
<tr>
<td>$^{54}$</td>
<td>6N HCl/reflux/24 h</td>
<td>$^{59}$e</td>
<td>27</td>
</tr>
</tbody>
</table>
1.2.7. THE REACTIONS OF ORTHO LITHIUM AND BROMOMAGNESIUM PHENYLOXAZOLINE 61 AND METHOXYMETHOXYARENE 63 WITH n-BUTYRALDEHYDE.

The reaction of ortho lithium and bromomagnesium phenyloxazoline 61 \(^{65,66}\) and methoxymethoxyarene 63 \(^{9,67}\) with n-butyraldehyde were compared to determine whether the yields of the products could be improved through the transmetalation procedure (Scheme 17). Results are shown in Table 8.

**Scheme 17**

- \(\text{CH}_3(\text{CH}_2)_2\text{CHO}\)

![Diagram of chemical reactions](image-url)
Table 8: Comparison of o-Li vs. o-MgBr in reactions with n-butyraldehyde for Compounds 61, 63

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Electrophile</th>
<th>Product</th>
<th>Yield, %, via o-Li</th>
<th>o-MgBr</th>
</tr>
</thead>
<tbody>
<tr>
<td>61</td>
<td>CH₃(CH₂)₂CHO</td>
<td>62</td>
<td>65</td>
<td>68</td>
</tr>
<tr>
<td>63</td>
<td>CH₃(CH₂)₂CHO</td>
<td>64</td>
<td>38</td>
<td>66</td>
</tr>
</tbody>
</table>

As seen from Table 8, the reactivity of 61 as either metalated species was similar to give 62, a result which is comparable with the observations of Meyers. However, comparison of the results for compound 63 showed that a higher yield of product 64 could be obtained via the transmetalation method.

1.2.8. CONCLUSION

The transmetalation of ortho-lithiated benzenamides into o-bromomagnesio species and their successful coupling with allyl bromide and aliphatic aldehydes supplements the utility of the benzamide-directed metatallation methodology and emphasizes the additional utility of this transmetalation procedure.
CHAPTER II

2.1. INTRODUCTION

With the increasing importance of aromatic directed metalation methodology for the regioselective synthesis of polysubstituted aromatics,⁸ efforts have been undertaken by various researchers to uncover new and effective aromatic ortho directing groups. To this end, the N,N-diethylcarbamoyloxy group, -OCONEt₂, a new and efficient ortho directing group has been discovered in our laboratory very recently.⁶⁹

![Chemical Structure](image)

The O-arylcarbamates 65 constitute a known class of organic compounds which are used extensively as insecticides⁷⁰ and pharmacological agents⁷¹ and therefore their preparation has been extensively documented.⁷⁰

Although the ortho metalation of secondary N-aryl carbamates²⁸ and -metalation of N,N-diethyl O-benzyl carbamates and N,N-dialkyl O-allyl carbamates⁷² (Scheme 18), have been reported, no report on the metalation of O-aryl carbamates had appeared until our work.⁶⁹
2.1.1 ORTHO LITHIATION OF MASKED PHENOLS

The carbamate system 65 represents a masked phenol derivative and the ortho lithiation reaction of certain masked phenols constituted the earliest known cases of the aromatic directed metalation reaction\(^6\) (Scheme 19).
The ortho metalation of masked phenols began with the pioneering work by Gilman and by Wittig who were the first to show that anisole 72a underwent ortho lithiation when treated with n-butyllithium. This constituted the first example of the aromatic directed metalation reaction. The methoxy group has been used considerably as a protecting and ortho directing group in the metalation of phenols. However, due to the difficulties of deprotection of anisoles to release free phenols, investigations to devise ortho directing groups which are easily removable have ensued. Two such groups are methoxymethoxy group (72b) and tetrahydropyranyl (72c) which were found to enhance the reactivity and regioselectivity of the aromatic ortho lithiation in comparison to the methoxy group. These groups are easily removed by mild acid-catalyzed hydrolysis.
2.1.2. ORTHO LITHIATION OF N,N-DIETHYL 0-ARYL CARBAMATES

Ortho lithiation of N,N-diethyl O-aryl carbamates was achieved by the standard lithiation conditions which was used for ortho deprotonation of N,N-diethyl benzamides (s-BuLi/THEDA/THF/-78°C). The ortho lithiated carbamate 74 was shown to undergo reaction with a variety of electrophiles to give 75. Furthermore, in the absence of any external electrophile, the lithiated species 74 were found to rearrange to give salicylamide derivatives 76 (Scheme 20) a process which may be formally considered to be an anionic equivalent of the ortho Fries rearrangement. Therefore, the carbamate group possesses an added advantage in that it is not only an efficient ortho director but also a carrier of powerful tertiary amide ortho metatation director which, once migrated, can serve for further lithiation. The products 75 can be deprotected to give o-substituted phenols 77 either by base-catalyzed hydrolysis or lithium aluminum hydride reduction, depending on the nature of E.

Scheme 20
\[
\begin{align*}
\text{E}^+ &= \text{MeI, TMSI, Et}_2\text{NCOCl, DMF, CO}_2 \\
R &= \text{H, OMe (o,m,p), Cl (p)} \\
76 & \rightarrow 77
\end{align*}
\]

In the initial study\textsuperscript{60} to establish the effects of substituents in the regioselectivity of metalation, the \_\textsuperscript{3}-methoxy carbamate 78 was tested and led to a mixture of 1,2,3-isomer 79 and 1,2,4-isomer 80 in a ratio of 3:1 (Scheme 21).

![Scheme 21](image)

To establish the regioselectivity in \(\text{o-CH}_3\) vs. \(\text{o-aromatic C-H}\) deprotonation, 81 was subjected to standard metalation conditions to give products 82 and 83 in a ratio of 3:1 (Scheme 22).
In order to explore the full scope and limitations of the carbamate as an ortho metalation director, detailed investigations have been undertaken which constitute part of this thesis. These studies concern: i) the ortho lithiation of N,N-diethyl O-phenyl and O-naphthyl carbamates; ii) ortho lithiation of N,N-dimethyl O-phenyl carbamate, iii) the relative stabilities of lithiated N,N-diethyl and N,N-dimethyl O-phenyl carbamates; iv) the synthesis of salicyamide derivatives and the mechanism of O to C 1,3 carbamoyl migration; v) relative ortho directing capability of carbamoyloxy group to other ortho directing groups, particularly the tertiary amide and the methoxymethoxy group; vi) iterative metalation and vii) the development of a general method for the synthesis of 2(3H)-benzofuranones. The results of these studies will be presented in this section of the thesis.
2.2 RESULTS AND DISCUSSION

2.2.1 SYNTHESIS OF POLYSUBSTITUTED O-ARYL CARBAMATES

In order to establish the scope and limitations of the ortho lithiation of O-aryl carbamates, N,N-diethyl O-aryl carbamates 84 were lithiated under standard conditions (s-BuLi/TMEDA/THF/-78°C) and treated with a variety of electrophiles (Scheme 23). The results are summarized in Table 9.

\[
\begin{align*}
84a-f & \quad \text{Scheme 23} \\
\begin{array}{lll}
R & \quad & E \\
- & \quad & \text{D} \\
a: & H & \text{CH}_2-\text{CH}=\text{CH}_2 \\
b: & 2-\text{OMe} & \text{TMS} \\
c: & 2-\text{Cl} & \text{CONEt}_2 \\
d: & 3-\text{Me} & \text{TMS} \\
e: & 4-\text{Me} & \text{I} \\
f: & 3-\text{OMe} & \text{CONEt}_2 \\
g: & 6-\text{Cl} & 6-\text{TMS} \\
h: & 3-\text{Me} & 6-\text{TMS} \\
i: & 4-\text{Me} & 2-\text{Me} \\
j: & 3-\text{OMe} & 6-\text{Me} \\
k: & 3-\text{OMe} & \text{NMe} \\
\end{array}
\end{align*}
\]
Table 9: Synthesis of Polysubstituted O-Aryl carbamates 85.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Electrophile</th>
<th>Product</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>84a</td>
<td>EtOEt</td>
<td>85a</td>
<td>95 (96%&lt;sub&gt;d1&lt;/sub&gt;)</td>
</tr>
<tr>
<td>84a</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;=CHCH&lt;sub&gt;2&lt;/sub&gt;Br</td>
<td>85b</td>
<td>75</td>
</tr>
<tr>
<td>84b</td>
<td>TMSCl</td>
<td>85c</td>
<td>67</td>
</tr>
<tr>
<td>84b</td>
<td>Et&lt;sub&gt;2&lt;/sub&gt;NCOCl</td>
<td>85d</td>
<td>90</td>
</tr>
<tr>
<td>84c</td>
<td>TMSCl</td>
<td>85e</td>
<td>79</td>
</tr>
<tr>
<td>84c</td>
<td>I&lt;sub&gt;2&lt;/sub&gt;</td>
<td>85f</td>
<td>93</td>
</tr>
<tr>
<td>84c</td>
<td>Et&lt;sub&gt;2&lt;/sub&gt;NCOCl</td>
<td>85g</td>
<td>78</td>
</tr>
<tr>
<td>84d</td>
<td>TMSCl</td>
<td>85h</td>
<td>81 (39)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>84e</td>
<td>TMSCl</td>
<td>85i</td>
<td>83 (17)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>84f</td>
<td>MeI</td>
<td>85j )</td>
<td>(63)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>85k )</td>
<td>(27)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Yield obtained using LDA as base.

Both the excellent chemical yield and high deuterium content of 85a as well as good to excellent yields of 85b-k demonstrate the efficiency of OCON<sub>Et</sub><sub>2</sub> functionality as a powerful ortho directing group. Metallation of 84b occurs ortho to the carbamoyloxy group with high regioselectivity as established by <sup>13</sup>C NMR spectral data of 85d (Table 10) as well as from the product 86 obtained when lithiated 84b is allowed to undergo the anionic equivalent of the ortho Fries rearrangement.<sup>69</sup>
Table 10: Calculated and Experimental Aromatic $^{13}$C NMR Shifts for 85d.

\[
\begin{array}{cccc}
\text{Carbon} & \text{Calcd}\delta & \text{Exptl (rel.int)} \\
\hline
1 & 134.8 & 136.9 (15) \\
2 & 131.3 & 132.5 (30) \\
3 & 119.0 & 118.1 (86) \\
4 & 125.7 & 126.8 (100) \\
5 & 115.1 & 112.8 (80) \\
6 & 152.8 & 152.4 (26) \\
\end{array}
\]

\text{a} The calculated chemical shifts were obtained by adding the substituent shifts\textsuperscript{76} for CH$_3$O and CONEt\textsubscript{2}\textsuperscript{47} to the carbon chemical shifts of N,N-diethyl O-aryl carbamate 84a.
The location of the lithiation was indicated by the reduction in intensity of the newly substituted carbon. The experimental chemical shifts are found to compare very favorably with the calculated shifts of 85d as opposed to the alternate structure in which amide functionality is located ortho to the methoxy group. Thus no metalation ortho to the methoxy group was indicated although the OMe group itself is a moderate ortho directing group. Similar findings were also observed for compound 84c (R = 2-Cl). Although the carbamate was expected to be the dominant ortho directing group, chlorine is known to have a weak inductive acidifying effect on its ortho site as evidenced from the exclusive metalation of N,N-diethyl 0-3-chlorophenyl carbamate at the position between the two functions and precedent for metal-halogen exchange (Scheme 24). 6

![Scheme 24](image)

By changing the base, either ortho lithiation or chloride-metal exchange could be effected.

The $^{13}$C NMR data (Table 11) confirmed the structure of 85g and hence
the position of lithiation.

**Table 11: Aromatic $^{13}$C NMR chemical shifts for 85g.**

![Chemical structure of 85g](image)

<table>
<thead>
<tr>
<th>Carbon</th>
<th>$\delta$ppm</th>
<th>Exptl.(rel.int.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>149.6</td>
<td>145 (7)</td>
</tr>
<tr>
<td>2</td>
<td>131.6</td>
<td>133.6 (13)</td>
</tr>
<tr>
<td>3</td>
<td>124.8</td>
<td>124.9 (86)</td>
</tr>
<tr>
<td>4</td>
<td>126.0</td>
<td>126.3 (93)</td>
</tr>
<tr>
<td>5</td>
<td>129.9</td>
<td>130.4 (100)</td>
</tr>
<tr>
<td>6</td>
<td>127.6</td>
<td>129.0 (15)</td>
</tr>
</tbody>
</table>

$^a$ see Table 10.
These results indicate the superior coordinating power of the carbamoyloxy group with alkyllithium bases over the methoxy or chloro function. Compound 84d afforded the 1,2,4-isomer 85h and not the 1,2,3-isomer in accord with the reported result of an ortho metation reaction when an alkyl group is at meta-position to the methoxymethoxy directing group (Scheme 25). 9 Compound 90, however, afforded the 1,2,3-isomer, 92, as a very minor product depending on the metation conditions. 9

Scheme 25

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Ratio 91:92</th>
</tr>
</thead>
<tbody>
<tr>
<td>t-BuLi/Et₂O/0°</td>
<td>&gt;200:1</td>
</tr>
<tr>
<td>t-BuLi/hexane/0°</td>
<td>&gt;200:1</td>
</tr>
<tr>
<td>n-BuLi/hexane/25°</td>
<td>4:1</td>
</tr>
<tr>
<td>n-BuLi/hexane/25° /THEDA</td>
<td>4:1</td>
</tr>
</tbody>
</table>

Compounds 84d and 84e were also subjected to metation with LDA to compare with the results obtained from the metation of 81 (Scheme 26). 69 In contrast, 84d and 84e led solely to products 85h and 85i in low yields.
These results again strongly point to the need for coordination in ortho metation reactions. Benzyllic metalation of 4-methyl-N,N diethyl benzamide with LDA is not surprising in view of fact that the resultant benzylic anion is stabilized by the electron withdrawing effect of amide functionality (Scheme 27). Of course, no such stabilization is possible for the three isomeric-methyl phenyl carbamate systems.

The result on the metalation of 84f confirmed the preliminary observation. The ratio of the 1,2,3-isomer to the 1,2,4-isomer varied
from 3:1 to 9:1\textsuperscript{54} depending on the nature of electrophiles used in (Table 12).

**Table 12:** Regioselectivity in Metalation of 3-Methoxy O-Phenyl Carbamate 84f

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Electrophile</th>
<th>Yield,%</th>
<th>Ratio 1,2,3: 1,2,4-isomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>s-BuLi/TMEDA THF/-78°C</td>
<td>MeI</td>
<td>93</td>
<td>3 : 1</td>
</tr>
<tr>
<td>s-BuLi/TMEDA THF/-78°C</td>
<td>I\textsubscript{2}</td>
<td>76</td>
<td>9 : 1</td>
</tr>
</tbody>
</table>

These results indicate a much lower regioselectivity of carbamate in comparison to tertiary amide group in metalation at sites common to two directing groups.\textsuperscript{8}
2.2.2 SYNTHESIS OF ORTHO SUBSTITUTED O-NAPHTHYL CARBAMATES

The directed ortho metalation reaction was extended to O-naphthyl carbamates. N,N-diethyl O-1-naphthyl carbamate 95 was found to lithiate cleanly at the 2-position under the standard lithiation condition (s-BuLi/TMEDA/THF/-78°C) to give 2-substituted products 96 (Scheme 28). On the other hand, N,N-Diethyl O-2-naphthyl carbamate 97, was found to afford isomeric 1- and 3-substituted naphthyl carbamates 98, 99 (Scheme 28). The results are shown in Table 13.

Scheme 28

\[
\begin{align*}
95 & \xrightarrow{1)RLI} 96 \\
97 & \xrightarrow{1)RLI} 98a-b \\
99a-b & + \text{E} \rightarrow 100
\end{align*}
\]

\[E = \text{TMS} \quad \text{or} \quad \text{CONEt}_2\]

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Electrophile</th>
<th>Product</th>
<th>Yield$^a$, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>95</td>
<td>Et$_2$NCOCl</td>
<td>96</td>
<td>78</td>
</tr>
<tr>
<td>97</td>
<td>THSCl</td>
<td>98a</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td></td>
<td>99a</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100</td>
<td>20</td>
</tr>
<tr>
<td>97</td>
<td>Et$_2$NCOCl</td>
<td>98b</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100</td>
<td>26</td>
</tr>
</tbody>
</table>

$^a$ Isolated Yields.

The regiospecific metalation at the 2-position of compound 95 has already been chemically confirmed by the conversion of the 2-methylated 1-naphthyl carbamate into the known 2-methyl-1-naphthol.$^6$ Products arising from metalation at the 8-position were not observed. In comparison, 1-methoxynaphthalene has been reported to undergo metalation either at the 2-position (i) n-BuLi/TMEDA/hexane; ii) CO$_2$/CH$_2$N$_2$ (Yield: 60%) or the 8-position (i) t-BuLi/cyclohexane, ii) CO$_2$/CH$_2$N$_2$ (Yield: 35%) depending on the conditions used.$^6$

The lithiation of O-2-naphthyl carbamate 97, is complicated by the availability of two ortho sites. Two isomeric products 98 and 99 were indeed isolated together with the known hydroxy 2-naphthamide derivative 100 showing that predominant products are derived from metalation at the 3-position. These observations parallel the results of metalation of 2-methoxynaphthalene$^6$ and may be rationalized by the enhanced
kinetic acidity at the 3-position over 1-position. The structures of compounds 99a-b were assigned by comparison of their \(^1\)H NMR and IR spectra and physical properties with authentic materials prepared from 1-bromo-2-naphthyl carbamate 101 via metal-halogen exchange and quenching with the appropriate electrophiles (Scheme 29).

![Scheme 29](image)

These results also allow the conclusion that the 1-lithiated 2-carbamoyloxy system is stable with respect to equilibration to the corresponding 3-lithiated species. In further support of this, compound 101 was subjected to metal-halogen exchange (t-BuLi/THF/-78°C) and kept at -78°C for 6 h before treatment with TMSCl. The usual workup afforded only 99a in 85% yield and no other products were identified.

2.2.3 METALATION OF N,N-DIMETHYL O-ARYL CARBAMATES

Next we turned our attention to examine the effect, if any, of replacing the OCONEt\(_2\) group by the N,N-dimethyl carbamoyloxy (OC\(\text{N}Me_2\)) group in
the directed ortho metalation reaction.

When N,N-dimethyl O-phenyl carbamate 102 was subjected to lithiation under the standard conditions (s-BuLi/TMEDA/THF/-78°C) for 45 min, quenched with various electrophiles, and the reaction mixture was allowed to warm to room temperature, the salicylamide derivative 104 was obtained exclusively rather than the expected ortho substituted carbamate derivative 103 (Scheme 30). This result suggested that the rate of the anionic ortho-Fries rearrangement is very fast for 102 compared with the corresponding reaction on the diethyl analogue 84.

![Scheme 30]

Therefore, a more thorough study was undertaken in order to find conditions for the efficient preparation of 1,2-disubstituted products 103 as well as to improve the yield of 104. The results of
these exploratory reactions are summarized in Table 14.

**Table 14: Electrophilic Trapping vs 1,3-Carbamoyl Migration of Ortho Lithiated N,N-Dimethyl O-Phenyl Carbamate.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp°C</th>
<th>Lithiation time (min)</th>
<th>Electrophile</th>
<th>Products, Yield%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>103</td>
</tr>
<tr>
<td>1</td>
<td>-78 -&gt; RT</td>
<td>8h</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>-78</td>
<td>45</td>
<td>MeI</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>-78</td>
<td>10</td>
<td>MeI</td>
<td>a: 60</td>
</tr>
<tr>
<td>4</td>
<td>-95</td>
<td>10</td>
<td>MeI</td>
<td>a: 90</td>
</tr>
<tr>
<td>5</td>
<td>-95</td>
<td>10</td>
<td>Et₂NCOCl</td>
<td>b: 78</td>
</tr>
<tr>
<td>6</td>
<td>-95</td>
<td>10</td>
<td>EtO₂</td>
<td>c: 83(54%d₁)</td>
</tr>
<tr>
<td>7</td>
<td>-95</td>
<td>10</td>
<td>TMSCl</td>
<td>d: 88</td>
</tr>
</tbody>
</table>

As seen from entries 1-3, at temperatures greater than -78°C and long lithiation times, the anionic ortho-Fries rearrangement of 102 was found to be very facile. This may be due to a smaller steric bulk of the N,N-dimethyl carbamoyloxy group relative to OCONEt₂ which allows the rate of formation of the tetrahedral intermediate 105 (See section 2.3.5.) to be faster.
However, at lower temperatures (-95°C, entry 4-7) and short lithiation time (10 min), the problem of rearrangement was overcome and 1,2-disubstituted carbamate derivatives 103 were obtained in excellent yields.

To gain further insight into this problem and to maximize the yields of the anionic ortho-Fries reaction, a comparative study regarding relative stabilities of ortho lithiated N,N-dimethyl and N,N-diethyl O-phenyl carbamates was performed (Scheme 31).

Scheme 31

As seen from these results, the ortho lithiated N,N-dimethyl O-phenyl carbamate underwent the anionic ortho-Fries rearrangement in high yield even at -95°C over a 5.5 h period while the rearrangement of the ortho lithiated N,N-diethyl O-phenyl carbamate (84a) took place only to the extent of 7.5% at -78°C over the same time period.
2.2.4. SYNTHESIS OF SALICYLAMIDES AND HYDROXYNAPHTHAMIDES VIA THE ANIONIC ORTHO FRIES REARRANGEMENT

When the carbamates $84_{c,d,e}$, $95$, $97$ and $103_a$ were subjected to lithiation under certain specified conditions and allowed to warm to room temperature over an 8 h period, the hydroxy amide derivatives $107, 108, 100, 109$; and $110, 111$ respectively were isolated (Scheme 32). The results of these 1,3 O to C carbamoyl migration reactions (anionic ortho-Fries rearrangements) are collected in Table 15.

**Scheme 32**

![Image of Scheme 32 with chemical structures and reactions]

- $R$:
  - $c$: 2-Cl
  - $d$: 3-Me
  - $e$: 4-Me

- $R$:
  - $a$: 3-Cl
  - $b$: 4-Me
  - $c$: 5-Me

- $R$:
  - $d$: 6-Me

- $R$:
  - $e$: 7-Me
Table 15: Synthesis of Salicylamides 107, 110 and Hydroxy naphthamides 108, 100, 109 by 1,3-carbamoyl Migration.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Products</th>
<th>yield, %a</th>
</tr>
</thead>
<tbody>
<tr>
<td>84c</td>
<td>107a</td>
<td>73</td>
</tr>
<tr>
<td>84d</td>
<td>107b</td>
<td>50</td>
</tr>
<tr>
<td>84e</td>
<td>107c</td>
<td>70</td>
</tr>
<tr>
<td>95</td>
<td>108</td>
<td>71</td>
</tr>
<tr>
<td>97</td>
<td>100</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>109</td>
<td>32</td>
</tr>
<tr>
<td>103a</td>
<td>110</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>111</td>
<td>25</td>
</tr>
</tbody>
</table>

a Isolated yields.
The structure of all products were deduced from analytical and spectral (\textsuperscript{1}H NMR, IR, MS) data.

The isolation of 107\textsubscript{a} confirmed the preparation of carbamate derivatives 85e, 85f and 85g which were discussed earlier (Section 2.3.1). Formation of the product 107\textsubscript{b} also confirmed the regiospecific anion generation as was evidenced from the formation of 1,2,4-isomeric derivative 85h by THSCl trapping.

Exclusive isolation of the known product 108 confirmed the lithiation of 1-naphthyl carbamate at the 2-position under these potentially equilibrating conditions. On the other hand, the 2-0-naphthyl carbamate underwent the anionic ortho-Fries rearrangement to afford a mixture of hydroxy naphthamides 100 and 109 in a ratio of 48:32. Compound 100 is known (See Section 2.2.2) while product 109 was identified by comparison of its \textsuperscript{1}H NMR and IR spectra and physical properties with authentic material prepared from 101 by metal-halogen exchange followed by anionic ortho-Fries rearrangement (Scheme 33).

\begin{center}
\textbf{Scheme 33}
\end{center}

The ortho-methyl carbamate 103\textsubscript{a} was found to undergo both aromatic and benzylic metalation to give products 110 and 111 in a ratio of 56:25.
Product 110 is a known compound while 111 is easily identified by the methylene peak (δ 3.73) in its ¹H NMR spectrum which is characteristically downfield form the methyl peak (δ 2.26).

2.2.5. MECHANISM OF THE ANIONIC ORTHO-FRIES REARRANGEMENT

In order to distinguish between an intra- or intermolecular anionic 1,3-carbamoyl migration, a mixture of one equivalent each of N,N-diethyl 0-4-tolyl carbamate 84e and N,N-dimethyl 0-phenyl carbamate 102 was lithiated with two equivalent of base and allowed to warm to room temperature. The identified products were the corresponding salicylamide derivative 107c and 104 (Scheme 34) with no evidence for cross over products thus suggesting an intramolecular mechanism for the anionic carbamoyl migration which therefore presumably proceeds

Scheme 34

转化模式：

\[
\begin{align*}
\text{OCONEt}_2 + \text{OCONMe}_2 & \xrightarrow{RLI (2.0 \text{ equiv})} \text{OH} \\
\text{Me} + \text{Me} & \xrightarrow{-95^\circ C \rightarrow RT} \text{OH} \\
\text{84e} + \text{102} & \rightarrow \text{107c, 70%} + \text{104, 75%}
\end{align*}
\]

via the intermediacy of a tetrahedral intermediate 112 (Scheme 35).
The intermediacy of a similar cyclobutane type intermediate formed from the attack on a carbonyl group by an ortho phenyl anion has been proposed\textsuperscript{77} (Scheme 36).

The formation of a tetrahedral intermediate would be expected to be faster for the \textit{N},\textit{N}-dimethyl carbamoyl group compared to the corresponding \textit{N},\textit{N}-diethyl function because of the smaller steric bulk of the former.
2.2.6. COMPETITIVE METALATION: RELATIVE ORTHO DIRECTING ABILITIES OF CARBAMATE, AMIDE AND METHOXYMETHOXY GROUPS

The N,N-diethylcarbamoyloxy group is a very recent addition to the known directed ortho metalation groups\(^6,^8\). The efficiency of this group as an ortho director has been successfully demonstrated in work described in the previous sections. However, its ortho directing capability in comparison to other known ortho directing groups required exploration.

Fraser's\(^7^8\) \(pK_a\) results indicate that the N,N-diethylcarbamoyloxy group possesses an extremely strong thermodynamic acidifying effect of an ortho hydrogen in an aromatic substrate.

In our study, the relative ortho directing ability of carbamate in both inter- and intramolecular reactions with N,N-diethylamide and methoxymethoxy groups was compared. The comparison with the tertiary amide is valuable in view of the work of Beak\(^4^7\) and Meyers\(^4^6\) which demonstrated its very powerful directing ability. The comparison with OCH\(_2\)OMe offers evaluation of two phenol protecting groups.

2.2.6.1. RELATIVE DIRECTED METALATION ABILITIES OF CARBAMATE AND TERTIARY AMIDE FUNCTIONS

In an intermolecular competition experiment, 1.0 equiv of each of the carbamate \(84a\) and the amide \(45a\) was allowed to react with 1.0 equiv. of s-BuLi/ TMEDA in THF solvent (Scheme 37) and the lithiated species were treated with several different electrophiles. The results are collected in Table 16.
Scheme 37

Table 16  Competition between 84a and 45a for 1.0 Equiv of s-BuLi/TMEDA

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lithiation Temp (°C)/Time</th>
<th>Electrophile</th>
<th>Product, yield(^a),%</th>
<th>Starting Material, Yield(^a),%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>113  114  58(^b)</td>
<td>84a  45a</td>
</tr>
<tr>
<td>1</td>
<td>-78/1h</td>
<td>EtOD</td>
<td>62(^c) 36(^c)  7</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>-78/1h</td>
<td>MeI</td>
<td>48  21  15  38  26</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>-78/1h</td>
<td>(MeS)(_2)</td>
<td>40  13  20  30  17</td>
<td></td>
</tr>
<tr>
<td>4(^d)</td>
<td>-100/15 min</td>
<td>MeI</td>
<td>46  33  4  54  62</td>
<td></td>
</tr>
<tr>
<td>5(^d)</td>
<td>-100/15 min</td>
<td>(MeS)(_2)</td>
<td>30  21  6  70  73</td>
<td></td>
</tr>
<tr>
<td>6(^d)</td>
<td>-100/15 min</td>
<td>Et(_2)NCOCl</td>
<td>40  31  9  60  60</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Since 84a, 113, and 45a, 114 mixtures were inseparable, products ratios were established by \(^1\)H NMR and GC comparison with authentic samples (See
Experimental).

Product 58 was isolated and identified by comparing with authentic materials (1H NMR, IR, GC, MS).

Deuterium content calculated from 1H NMR and MS. Chemical yields were 113: 85%; 114: 87%.

Ratios of products determined by GC comparison with authentic materials (see Experimental).

The results from these intermolecular competition experiments indicate that the carbamate is a somewhat better ortho directing group than the tertiary amide varying from 3:2 to 1.2:1 (entries 1-3). In an attempt to suppress the formation of 58, the lithiation was carried out at -100°C for 15 min (entries 4-7). However, complete suppression could not be achieved.

2.2.6.2. RELATIVE DIRECTED METALATION ABILITIES OF CARBAMOYLOXY, TERTIARY AMIDE AND METHOXYMETHOXY GROUPS BY INTRAMOLECULAR COMPETITION EXPERIMENTS

The intramolecular competition in metalation of methoxymethoxy and the CONEt2 positioned ortho, meta, and para with respect to a carbamoyloxy group was examined. Lithiation of the substituted O-aryl carbamate derivatives 115, 118 and 121 was carried out under standard conditions (s-BuLi/TMEDA/THF/-78°C) and the lithiated species were treated with an electrophile (MeOD, ClCONEt2) (Scheme 38). The results are summarized in Table 17.
Scheme 38

\[ \text{OCONET}_2 \text{Z} \xrightarrow{1) \text{RLi} \atop 2) \text{E}^+} \]

\[ \begin{align*}
\text{II5} & \quad \text{II6} + \text{II7} \\
\text{Z} & \quad \text{E} \\
a & : \text{CONET}_2 \\
b & : \text{OCH}_2\text{OMe} \\
\text{II8} & \quad \text{II9 a, c} + \text{II0 d, e} \\
\text{Z} & \quad \text{E} \\
a & : \text{CONET}_2 \\
b & : \text{OCH}_2\text{OMe} \\
\text{II7 b} & \\
\end{align*} \]
\[
\begin{align*}
\text{121 } & a-b \\
\text{122 } & a-d \\
\text{123 } & a-b \\
\end{align*}
\]
### Table 17: Intramolecular Competition in Metalation between Carbamate and Tertiary Amide and Methoxymethoxy Functions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Electrophile</th>
<th>Product Ratio</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>115a</td>
<td>MeOD</td>
<td>116 a</td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td>115a</td>
<td>Et₂NCOCL</td>
<td>82 18</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>115b</td>
<td>MeOD</td>
<td>a</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>115b</td>
<td>Et₂NCOCl</td>
<td>100 0</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>118a</td>
<td>MeOD</td>
<td>119 100 0</td>
<td>85</td>
</tr>
<tr>
<td>6</td>
<td>118a</td>
<td>Et₂NCOCl</td>
<td>120 31 69</td>
<td>23</td>
</tr>
<tr>
<td>7</td>
<td>118b</td>
<td>MeOD</td>
<td>122 100 0</td>
<td>96</td>
</tr>
<tr>
<td>8</td>
<td>118b</td>
<td>Et₂NCOCl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>118a</td>
<td>--</td>
<td>123 -- 100</td>
<td>30</td>
</tr>
<tr>
<td>10</td>
<td>121a</td>
<td>MeOD</td>
<td>124 a</td>
<td>85</td>
</tr>
<tr>
<td>11</td>
<td>121a</td>
<td>Et₂NCOCl</td>
<td>125 61 39</td>
<td>68</td>
</tr>
<tr>
<td>12</td>
<td>121b</td>
<td>MeOD</td>
<td>a</td>
<td>87</td>
</tr>
<tr>
<td>13</td>
<td>121b</td>
<td>Et₂NCOCl</td>
<td>126 100 0</td>
<td>70</td>
</tr>
</tbody>
</table>

*a Ratio could not be obtained as loss in peak intensity could not be measured exactly.

The extent of deuteration was estimated by ¹H NMR and mass spectrometry (Table 18).
Table 18: $^1$H NMR and Mass Spectral Data of Carbamates 115, 118, 121 and Their Deuterated Derivatives.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Hydrogens</th>
<th>Chemical Shift, δ</th>
<th>% d₁</th>
<th>MS δ, c</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Protio (Intensity)</td>
<td>Deutero (Intensity)</td>
<td></td>
</tr>
<tr>
<td>115a (116a) (117a)</td>
<td>3,4,5,6</td>
<td>7.2-7.3(4)</td>
<td>7.2-7.4(3.2)</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td></td>
<td><img src="image" alt="Diagram" /></td>
<td><img src="image" alt="Diagram" /></td>
<td><img src="image" alt="Diagram" /></td>
</tr>
<tr>
<td>115b (116c) (117c)</td>
<td>3,4,5,6</td>
<td>7.0-7.16(4)</td>
<td>7.0-7.25(3.37)</td>
<td>63</td>
</tr>
<tr>
<td>118a (119a)</td>
<td>2,4,5,6</td>
<td>7.1-7.36(4)</td>
<td>7.1-7.36(3.36)</td>
<td>64</td>
</tr>
<tr>
<td>118b (119c)</td>
<td>2,4,6</td>
<td>6.7-6.9(3)</td>
<td>6.8-6.9(2.3)</td>
<td>70</td>
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<tr>
<td></td>
<td></td>
<td>6.7-6.9(3)</td>
<td>6.8-6.9(2.3)</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7.0-7.24(1)</td>
<td>7.1-7.26(1)</td>
<td><img src="image" alt="Diagram" /></td>
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</table>
Table 18 (continued)

<p>| | | | | |</p>
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</thead>
<tbody>
<tr>
<td>121a</td>
<td>(122a)</td>
<td>2,6</td>
<td>7.0-7.19(2)</td>
<td>7.1-7.2(1.27)</td>
</tr>
<tr>
<td></td>
<td>(123a)</td>
<td>3,5</td>
<td>7.0-7.19(2)</td>
<td>7.33-7.44(1.7)</td>
</tr>
</tbody>
</table>

121b | (122c) | 2,6 | 7.0(4) | 7.0(3.03) | 97 | 54 |
|     | (123c) | 3,5 |

\[
\text{Am} = \text{CONEt}_2 \quad \text{MOM} = \text{OCH}_2\text{OCH}_3
\]

\(a\) Integral area vs 8.0 for the four methylenes of the carbamate and amide groups in the carbamate-amide derivatives and integrated area vs 2.0 for the methylene of the methoxymethoxy groups in carbamate-methoxymethoxy derivatives.

\(b\) The values of deuterium content as estimated by \(^1\text{H NMR}\) and MS were found to differ largely from each other. Some of the reactions were repeated but the results remained almost the same.

\(c\) The deuterium content as calculated from MS are considered to be more reliable.

The sites of lithiation were determined by analysis of the \(^{13}\text{C NMR}\) spectra which show a reduction in intensity of the signal for the substituted carbon(s) in the products compared to the corresponding signal in the starting materials according to the method of Beak.\(^{47}\) The position of substitution was assigned by using established additivity of individual \(^{13}\text{C NMR}\) substituent chemical shifts either from the literature\(^{76}\) or as determined (Table 19). The shift value expresses the direction and magnitude of a carbon's chemical shift difference from 128.5 ppm, the shift
for benzene.\textsuperscript{76} The experimental chemical shift difference of aromatic carbons of O-phenyl carbamate were found to fit reasonably well with the chemical shift difference of aromatic carbons of phenyl acetate. These findings were also confirmed by comparing the \textsuperscript{13}C NMR spectrum of N,N-diethyl O-(4-N,N-diethyl carbamoyl) phenyl carbamate following the method of Beak.\textsuperscript{47} This method was found to work satisfactorily when applied to other substitution patterns. Similarly, the aromatic carbon chemical shift difference of methoxymethoxybenzene was determined by comparison with the p-methoxymethoxy carbamate derivative (Table 19).

\par
\textbf{Table 19}: \textsuperscript{13}C NMR Substituent Shifts (\(\Delta\delta\)) of Monosubstituted Benzenes Relative to Benzene (128.5 ppm) in CDCl\textsubscript{3}.

<table>
<thead>
<tr>
<th>Z</th>
<th>Carbon (\Delta\delta) values\textsuperscript{a}</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ipso</td>
<td>ortho</td>
</tr>
<tr>
<td>CONEt\textsubscript{2}</td>
<td>+8.8</td>
<td>-2.2</td>
</tr>
<tr>
<td>OCONEt\textsubscript{2}</td>
<td>+22.9</td>
<td>-7.0</td>
</tr>
<tr>
<td>OMe</td>
<td>+31.4</td>
<td>-14.4</td>
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<tr>
<td>OCH\textsubscript{2}OMe</td>
<td>+29.5</td>
<td>-11.26</td>
</tr>
<tr>
<td>Cl</td>
<td>+6.2</td>
<td>+0.4</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Positive \(\Delta\delta\) values correspond to downfield shift.

\textsuperscript{b} Experimental values
The observed chemical shifts and relative intensities of the peaks for the aromatic carbons of the carbamate derivatives, as well as calculated chemical shifts determined by using the substituent shift (Table 19), are collected in Tables 20 and 21.

**Table 20** Calculated and Experimental Aromatic $^{13}$C NMR Shifts for Deuterated Carbamate Derivatives

<table>
<thead>
<tr>
<th>Compound H (D)</th>
<th>Carbon</th>
<th>$\delta$ ppm</th>
<th>H Exptl (rel. intensity)</th>
<th>D Exptl (rel. intensity)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Calcd</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>115a(116a)</strong></td>
<td>1</td>
<td>149.2</td>
<td>147.4 (39)</td>
<td>147.4 (40)</td>
</tr>
<tr>
<td>(117a)</td>
<td>2</td>
<td>130.3</td>
<td>130.6 (28)</td>
<td>129.5 (47)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>126.7</td>
<td>126.6 (95)</td>
<td>126.8 (100)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>124.7</td>
<td>124.9 (83)</td>
<td>125.0 (77)</td>
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<td></td>
<td>5</td>
<td>129.5</td>
<td>129.4 (83)</td>
<td>129.4 (67)</td>
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<td></td>
<td>6</td>
<td>121.4</td>
<td>123.2 (100)</td>
<td>123.2 (56)</td>
</tr>
<tr>
<td><strong>115b(116c)</strong></td>
<td>1</td>
<td>140.1</td>
<td>141.4 (30)</td>
<td>141.6 (9)</td>
</tr>
<tr>
<td>(117c)</td>
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<td>151.0</td>
<td>149.2 (35)</td>
<td>149.4 (12)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>117.6</td>
<td>116.3 (91)</td>
<td>116.5 (68)</td>
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<tr>
<td></td>
<td>4</td>
<td>125.6</td>
<td>125.9 (100)</td>
<td>126.1 (100)</td>
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<td></td>
<td>5</td>
<td>122.3</td>
<td>122.0 (96)</td>
<td>122.1 (94)</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>123.9</td>
<td>123.3 (95)</td>
<td>123.5 (88)</td>
</tr>
<tr>
<td><strong>118a(119a)</strong></td>
<td>1</td>
<td>151.3</td>
<td>151.3 (47)</td>
<td>151.5 (19)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>119.3</td>
<td>119.8 (95)</td>
<td>120.1 (59)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>5</td>
<td>128.8</td>
<td>129.0 (81)</td>
<td>129.3 (86)</td>
</tr>
<tr>
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<td>6</td>
<td>122.1</td>
<td>122.1 (96)</td>
<td>122.4 (94)</td>
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Table 20 (continued)

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<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
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<tbody>
<tr>
<td><strong>118b</strong>&lt;sup&gt;119c&lt;/sup&gt;</td>
<td>152.2</td>
<td>152.4</td>
<td><strong>53</strong></td>
<td>152.4</td>
<td>63</td>
<td></td>
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<tr>
<td></td>
<td>2</td>
<td>110.2</td>
<td>110.1</td>
<td><strong>93</strong></td>
<td>110.1</td>
<td>79</td>
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<td>158.0</td>
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<td>158.0</td>
<td>70</td>
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<tr>
<td></td>
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<td>113.0</td>
<td><strong>97</strong></td>
<td>113.0</td>
<td>100</td>
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<tr>
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<td>151.1</td>
<td>25</td>
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<td></td>
<td><strong>2</strong></td>
<td>121.4</td>
<td>131.3</td>
<td><strong>99</strong></td>
<td>121.6</td>
<td>91</td>
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<td>126.7</td>
<td>127.2</td>
<td><strong>100</strong></td>
<td>127.4</td>
<td>100</td>
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<td></td>
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<td>133.7</td>
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<td>133.9</td>
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<td>145.9</td>
<td>145.9</td>
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<td>146.1</td>
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<td></td>
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<td>122.3</td>
<td><strong>78</strong></td>
<td>122.5</td>
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<tr>
<td></td>
<td>3</td>
<td>116.6</td>
<td>116.6</td>
<td><strong>100</strong></td>
<td>116.9</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>154.3</td>
<td>154.3</td>
<td><strong>24</strong></td>
<td>154.3</td>
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Table 21: Calculated and Experimental Aromatic $^{13}$C NMR Shifts of Carbamate Derivatives 116b, 117b, 116d, 119b, 120d, 122b, 123b, 122d.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Carbon</th>
<th>$\delta$ ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td>116b</td>
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<tr>
<td></td>
<td>2)</td>
<td>130.2</td>
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<tr>
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<tr>
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<td>124.6</td>
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<tr>
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<tr>
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<td>137.9</td>
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<tr>
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<td>125.5</td>
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<tr>
<td></td>
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<td>118.2</td>
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<td>150.9</td>
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<td></td>
<td>122b</td>
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<tr>
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<td>6</td>
<td>122.2</td>
<td>124.0</td>
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</tbody>
</table>

It was observed from the deuteriation results (Table 20) that for the ortho-carboxamido carbamate 115a, the lithiation occurs predominantly ortho to the carbamoyloxy group as judged by the loss of intensity of the
signal for C-6. However, the ratio of the products could not be estimated. For compound 115b, it is difficult to arrive at any conclusion. For compounds 121a and 121b, although the intensity of the signals for carbons ortho to the carbamoyloxy functions is less than the carbons ortho to the competing groups, the ratio of products could not be estimated and hence no conclusive statement could be made. However, when the carbamate and the competing groups are meta-related as in compounds 118a and 118b, the metatation was found to occur almost exclusively at the position between the two groups as evidenced by the loss of intensity of the signal for C-2 with a trace reduction in intensity of the signal for C-6.

In view of the above results which failed to provide conclusive evidence regarding the site of lithiation and therefore extent of competition, trapping experiments with another electrophile, diethylcarbamoyl chloride were undertaken (Table 17). Examination of the $^{13}$C spectra of the derived products 116b, 116d, 117b, 119b, 120d, 120e, 122b, 122d and 123b (Table 21), the site and extent of lithiation and thus the ratio of the products (see Table 17) were determined which ultimately provided evidence that the lithiation takes place preferentially ortho to the carbamate functionality when the competing group is a tertiary amide and exclusively when the competing group is methoxymethoxy. For compound 115a and 121a where the amide is at ortho- and para-positions to carbamate respectively, predominant metatation occurs ortho to the carbamate (Table 17, entries 2 and 11). Two products 116b and 117b were obtained from 115a in a ratio of 82:18 (overall yield 80%). The structure
of compound 117b was confirmed by comparison with authentic material prepared by another route (see Experimental). Likewise 121a afforded 122b and 123b in a ratio of 61:39. In a separate experiment, 115a was shown to undergo the ortho-Fries rearrangement to give 124 in 60% yield (Scheme 39).

![Scheme 39]

For compounds 115b and 121b, where the methoxymethoxy group is at the ortho- and para-position with respect to carbamate respectively, single products 116d (50%) and 122d (70%) respectively, were obtained indicating exclusive metalation ortho to the carbamate function.

For compound 118a in which carbamate and amide functionalities are meta-related, reaction with Et₂NCOCl appeared sluggish and led to 119b and rearranged product 120d in a ratio of 31:69 and low combined yield. The reason for low incorporation of the CONEt₂ function into the site common to the two directing groups may be attributed to a steric effect which retards intermolecular reaction with Et₂NCOCl and allows the presumably faster intramolecular migration of CONEt₂ to dominate. No products arising from C-4 or C-6 metalation were isolated. For compound 118b, metalation again
occurred exclusively between the two directing groups but the anionic Fries rearrangement product 120e again dominated supposedly for the same reason.

These above results demonstrate the superiority of the carbamate function as an ortho director over tertiary amide and methoxymethoxy groups. It would appear therefore that the carbamoyloxy is the functionality of choice among the oxygen based directed metatalation groups.

Finally we have carried out lithiation of N,N-diethyl O-(3-N,N-diethylcarbamoyloxy)phenyl carbamate 125 in order to determine metatalation regioselectivity of two juxtaposed carbamates. Lithiation of 125 for 45 min followed by treatment with Et₂NCOCl afforded only the rearranged product 126 in high yield suggesting that the anionic ortho-Fries rearrangement is very fast even at -78°C. Without added electrophile, 125 underwent the ortho-Fries rearrangement to give 126 in similar yield (Scheme 40). However, under shorter lithiation times (10 min) followed by quenching with a small electrophile (MeOD), the rearrangement is minimized (11%) leading mainly to deuterated product 127.
Scheme 40

1) RLi / 45 min.
2) Et₂NCOCl
86%

RLi / -78° → RT
83%

1) RLi / 10 min.
2) MeOD
11%

126 + 127

76% (66% d₁)

¹H and ¹³C NMR spectral examination of 126 and 127 reveal that lithiation occurs exclusively in between the two carbamate functions. For compound 126, ¹H NMR indicates a 1,2,3-aromatic hydrogen substitution pattern (δ 6.72, J=7.8, 1.17 and δ 6.76, J=8.2, 1.7 indicate H-4 and H-6. δ 7.17, J=7.8, 8.2 indicates H-5). The ¹³C NMR spectral data (Table 22) confirmed the structures of the products and hence the site of lithiation.
Table 22: Calculated and Experimental Aromatic $^{13}$C NMR Chemical Shifts of 125, 126, 127.

<table>
<thead>
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<th>Compound</th>
<th>Carbons</th>
<th>$\delta$ ppm</th>
</tr>
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<tbody>
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<td></td>
<td>Calcd</td>
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<tr>
<td></td>
<td>6</td>
<td>113.5</td>
</tr>
</tbody>
</table>

$^a$ These values could be reversed.

As a sequel to ongoing work on dilithiated 0-aryl biscarbamates,$^{54,79}$ 125 was subjected to dilithiation conditions (2.0 equiv s-BuLi/TMEDA/THF/-78°C) and the presumed resulting lithiated species was allowed to warm to room temperatures. A mixture of mono- and bis-migrated products 126 and 128 were isolated in a ratio of 40:60 (Scheme 41). Variation of the conditions, using up to 4.0 equiv of s-BuLi or subjecting 125 to a one pot two-step metalation gave the same mixture of products in almost an identical ratio. However, when purified 126 was subjected to metalation (3.0 equiv s-BuLi) followed by warming to room temperature, 128 was
obtained in quantitative yield.

Scheme 41

2.2.7. ITERATIVE METALATION

Iterative metalation procedures for O-aryl carbamates may be envisaged by considering the anionic introduction of electrophilic groups (E⁺) which direct further ortho metalation (Scheme 42). In this manner, very short, preferably one pot, methods for the synthesis of polysubstituted aryl carbamates might be achieved. Towards this end, several experiments were performed (Scheme 43).
Scheme 42

\[ \text{E}_1 = \text{Non-directing group} \]
\[ \text{E}_2,\text{E}_3 = \text{Directed metalation group} \]
\[ \text{E}_4 = \text{Directed or non-directing metalation group} \]

\[ \text{R} = \text{Non-directing or weakly directing group} \]
\[ \text{E}_1,\text{E}_2 = \text{Directed metalation group} \]
\[ \text{E}_3 = \text{Directed or non-directing group} \]
Scheme 43

84a

1) RLi
2) TMSCl
3) RLi
4) Et₂NCOCl

129
54%

1) RLi
2) Et₂NCOCl

TMS

130
75%

84b

1) RLi
2) Et₂NCOCl
3) RLi
4) CH₃I

131
66%
Sequential metation, silylation, metation, carbamoylation of 84a in one pot provided the trisubstituted system 129 in reasonable yield. More than two metation in the same pot proved unsatisfactory as seen from the further attempted conversion of 129 into 130 without isolation of 129. However, after purification, 129 underwent metation and electrophilic quench to afford the contiguously tetrasubstituted carbamate derivative 130 in good yield. This compound may be amenable to further metation although this was not tested.

Compound 84b also underwent two sequential metalations and electrophile quenches in one pot to give the tetrasubstituted product 131. Therefore, it may be concluded that contiguously polysubstituted carbamate derivatives may be prepared by iterative metation tactics.

2.3.8. SYNTHESSES OF 2(3H)-BENZOFURANONE

Encouraged by the exclusive metation at the benzylic position of 81 with LDA as evidenced by electrophilic trapping experiments (Section 2.2.1), attempts to induce an 1,4-0 to C carbamoyl migration to the benzylic site were undertaken (Scheme 44). In the event, when 81 was subjected to metation followed by warming to room temperature (the same conditions as those used for the anionic ortho-Fries rearrangement), the ortho-hydroxy phenylacetamides 132, 133 were obtained in useful yields. Compound 132 was easily cyclized under acid-catalysed conditions (1M HCl/
C₆H₆/Δ/40 h or p-TsOH/C₆H₆/Δ/4 d) to the benzofuranone 134.

Scheme 44

The product 133 appeared to be formed from 132 via the generation of a second benzylic anion followed by intermolecular migration of the CONEt₂ group. Compound 133 was also found to undergo facile hydrolysis and
decarboxylation to give ortho-hydroxyphenylcetic acid 135 which also underwent cyclization to 134.

This methodology could be useful for the synthesis of substituted benzofuranone derivatives with substituent patterns difficult to obtain by other means. For instance, 7-chloro-, 7-methoxy-, and 6-methyl-2(3H)benzofuranones have been prepared by our coworkers\textsuperscript{54,30} following the methodology described above.
3.1. INTRODUCTION

Although the aromaticity of pyridine has been indicated by valence bond and molecular orbital treatments, the electron distribution around the pyridine ring, unlike benzene, is not uniform due to the higher electronegativity of nitrogen compared to carbon thereby causing electron withdrawal particularly from the 2- and 4-positions towards nitrogen. The distribution of electron density as estimated by a molecular orbital treatment is shown below (Fig. 2) for illustration. The nonuniformity of electron density in pyridine also affects C-C bond lengths and bond angles (Fig. 2).

Figure 2a. The Distribution of Electron Density in Pyridine as Estimated by Molecular Orbital Treatment.

\[
\begin{array}{c}
0.955 \\
0.987 \quad 0.987 \\
0.962 \quad 0.962 \\
1.147 \\
136
\end{array}
\]

Figure 2b. Bond Lengths and Bond Angles in Pyridine

\[
\begin{align*}
1.40 \text{Å} & \quad \angle C-2 = 124^\circ \\
1.39 \text{Å} & \quad \angle C-3 = 118^\circ 36' \\
1.34 \text{Å} & \quad \angle C-4 = 118^\circ 06'
\end{align*}
\]
Therefore pyridine, in principle, is less reactive towards electrophilic reagents and more reactive towards nucleophilic reagents than benzene in ordinary chemical reactions. Also the hydrogens in pyridine are more acidic than in benzene and can be abstracted by basic reagents as will be discussed in Section 3.1.2.

3.1.1. REACTION OF PYRIDINE WITH NUCLEOPHILIC BASES

Early reports established that treatment of pyridine with nucleophilic bases results in an overall addition-elimination reaction at the 2- and 4-positions\textsuperscript{84} (Scheme 45).

\begin{scheme}
\begin{align*}
\text{137} \quad \xrightarrow{\text{Nu}} \quad \text{138} \quad \xrightarrow{\Delta \text{ or } O_2} \quad \text{139} \\
\text{140} \quad \xrightarrow{\text{Nu}} \quad \text{141} \quad \xrightarrow{\Delta \text{ or } O_2} \quad \text{142}
\end{align*}
\end{scheme}
\[ X = \text{H, Cl, OMe, NO}_2 \quad R = \text{H, Na, K} \]

\[ \text{Nu} = \text{NH}_3, \text{KNH}_2, \text{NaNH}_2 \]

\[ \text{C}_6\text{H}_5\text{SH, NaOH} \]

\( X = \text{H}, \ \text{Nu} = \text{NH}_2 = \text{Chichibabin reaction} \)

The nucleophilic reactivity of the pyridine nucleus is enhanced by the presence of a good leaving group at the 2- and 4-positions. Protonation, quaternization and N-oxide formation also enhance nucleophilic attack at these positions.\(^{85}\)

Comparatively new reports that alkyl- and aryllithium and Grignard reagents add to the 2- and 4-positions parallel the previous results (Scheme 46).\(^{86,87,88,89}\) The predominant addition of these basic reagents takes place at the 2-position which may be accounted for by invoking initial complexation of the reagent with the nitrogen followed by intramolecular attack at the 2-position.\(^{85}\) Benzyllithium and benzylmagnesium chloride, on the other hand, afford predominantly 4-benzylpyridine. This may be considered to reflect the greater stability and selectivity of the benzyl anion.

**Scheme 46**

\[ \begin{align*}
\text{136} & \xrightarrow{RM} \text{143} + \text{144} \\
M &= \text{Li, MgX} \\
R &= \text{Alkyl, Aryl, Benzyl}
\end{align*} \]
The alkylation and arylation of the pyridine ring at the 2- and 4-positions with RLi, RMgX or R Cu has been reported very recently through the quaternization of the nitrogen with acyl chloride, ethyl- or phenyl chloroformate and t-butyldimethyl silyltriflate (Scheme 47). 90,91,92,93 Alkyl or aryllithiums and aryl Grignard reagents add mainly to the 2-position. Alkyl Grignards, however, gives a mixture of 1,2- and 1,4-addition products. Alkyl and aryl Grignards in presence of copper iodide, and lithium dialkylcuprates or R Cu BF3 reagents add regioselectively to the 4-position of 1-acyl pyridinium salts.

Scheme 47

R = R''CO

O2 or Δ

R' = Alkyl, Aryl

M = Li, MgX,
3.1.2. METALATION OF PYRIDINE

A complete H-D exchange of pyridine was reported by Zoltewicz when pyridine is heated to 200°C in NaOD-D₂O (Scheme 48) and a positional exchange ratio of 1:2.3:3 for the protons (2+6): (3+5): 4 has been estimated from this reaction.

Scheme 48

Zoltewicz later reported a relative acidity ratio of 1:9.3:12 for the protons (2+6): (3+5): 4 from the NaOMe catalysed H-D exchange reaction of pyridine in MeOD at 165°C. Although the two reports differ from each other with respect to reaction conditions and results, both indicate a slower exchange rate at the 2-position. An explanation based on the relative acidity of different pyridine ring protons was proposed by Zoltewicz who considered two factors to account for the decreased reactivity of positions adjacent to nitrogen (2 and 6) relative to more distant centres (3 as well as 4): i) decreased s-character of the C₂-H bond due to the increased bond angle at C-2 of pyridine in comparison to benzene resulting in the reduced acidity of C-2 hydrogen; ii) electrostatic
repulsion between the electron pair on coplaner nitrogen and the (developing) carbanion formed by deprotonation. A very recent result on the metalation of pyridine followed by treatment with different electrophiles to give 2-, 3- and 4-substituted pyridines has been reported by Brandsma\textsuperscript{95} (Scheme 49).

Scheme 49

\begin{center}

\begin{tikzpicture}

\node (cu) at (0,0) {
\begin{tabular}{c}
\textbf{1) BuLi-KO\textsubscript{Bu}(1:1) THF-hexane(2:1)}
\end{tabular}
};

\node (arrow) at (2,0) {
\begin{tabular}{c}
\textbf{\textendash}105\textdegree C/90 min
\end{tabular}
};

\node (n) at (4,0) {
\begin{tabular}{c}
\textbf{2) E\textsuperscript{+}}
\end{tabular}
};

\node (arrow) at (6,0) {
\begin{tabular}{c}
\textbf{90\textendash}94\%}
\end{tabular}
};

\node (end) at (9,0) {
\begin{tabular}{c}
\textbf{151}
\end{tabular}
};

\node (n1) at (0,0) {
\begin{tabular}{c}
\textbf{136}
\end{tabular}
};

\node (n2) at (9,0) {
\begin{tabular}{c}
\textbf{E \equiv D, MeS, TMS}
\end{tabular}
};

\end{tikzpicture}

\end{center}

A kinetic acidity ratio of 6:1:6 for the protons (2+6): (3+5): 4 has been estimated from the deuteriation reaction which is in contrast with the results by Zoltewicz.\textsuperscript{94} Brandsma\textsuperscript{95} also noted that when pyridine was treated with BuLi - Bu0K in Et\textsubscript{2}0, 2-potassiopyridine was obtained in 85\% yield, whereas in a more polar solvent (THF, HMPT) about 90\% yield of 4-potassiopyridine was obtained. So, it is apparent that different regioisomers can be obtained depending on the nature of solvent and base used.
3.1.3. METALATION OF PYRIDINE BY METAL-HALOGEN EXCHANGE

Formation of lithiated pyridine by metal-halogen exchange is well documented and takes place very readily under mild conditions.\textsuperscript{96,97} Two examples are cited below for illustration (Scheme 50).\textsuperscript{98,99} The first example shows that deprotonation of the highly acidic hydrogens on the \( o \)-methyl group does not compete with metal-halogen exchange.\textsuperscript{98}
Although this method is synthetically useful, it depends entirely on the availability of suitably substituted halopyridines.

3.1.4. DIRECTED ORTHO METALATION OF PYRIDINES

Deprotonation reactions of $\pi$-deficient heterocycles has been an unexplored area for a long period of time perhaps due to the discouraging results of the addition reactions described in Section 3.1.1.

With the demonstration that the aromatic directed metalation reaction is a powerful synthetic tool for synthesis of polysubstituted aromatics\(^8\), there has been a resurgence of interest in applying this chemistry to heteroaromatic substrates.

Towards this end, an increasing number of directing groups have been attached to the pyridine nucleus for testing the ortho metation methodology (Table 23).

Table 23: Metatation of Pyridine Bearing Ortho Directing Groups

\[
\begin{align*}
\text{DMG} & \quad \text{Metalation Conditions} & \quad \text{Position of Metalation} & \quad \text{Ref} \\
4-\text{CONEt}_2 & s-\text{BuLi/TMEDA/THF/-78}$^\circ$C & 3 & 45 \\
2-\text{CON(iPr)}_2 & \text{LDA/THF/-78}$^\circ$C & 3 & 26,100 \\
3-\text{CON(iPr)}_2 & \text{LDA/THF/-78}$^\circ$C & 4 & 26,100 \\
\end{align*}
\]

DMG = Directed Metation Group
Table 23 - continued

<table>
<thead>
<tr>
<th>Compound</th>
<th>Reagents</th>
<th>n</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-CON(iPr)₂</td>
<td>LDA/THF/-78°C</td>
<td>3</td>
<td>26,100</td>
</tr>
<tr>
<td>4</td>
<td>MeLi/THF/-78°C</td>
<td>3</td>
<td>101</td>
</tr>
<tr>
<td>2-Br,Cl,F</td>
<td>LDA/THF/-78°C</td>
<td>3</td>
<td>102</td>
</tr>
<tr>
<td>3-Br,Cl,F</td>
<td>LDA/THF/-78°C</td>
<td>4</td>
<td>102</td>
</tr>
<tr>
<td>4-Br,Cl,F</td>
<td>LDA/THF/-78°C</td>
<td>3</td>
<td>102</td>
</tr>
<tr>
<td>3-OEt</td>
<td>n-BuLi/TMEDA/THF/-40°C</td>
<td>2</td>
<td>103</td>
</tr>
<tr>
<td>3-OCH₂OMe</td>
<td>t-BuLi/Et₂O/-78°C</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>3-SO₂N</td>
<td>LDA/Et₂O/-70°C</td>
<td>4</td>
<td>104</td>
</tr>
<tr>
<td>2-NHCOt-Bu</td>
<td>n-BuLi/THF/0°C</td>
<td>3</td>
<td>105</td>
</tr>
<tr>
<td>2-CONHCH₂R</td>
<td>n-BuLi/THF/-78°C</td>
<td>3</td>
<td>106</td>
</tr>
<tr>
<td>(R=H, Ph)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Two synthetic applications are quoted below to illustrate the utility of this methodology. A short synthesis of ellipticine (163), an antitumor alkaloid has been reported from our laboratory based on the initial lithiation of isonicotinamide 160 (Scheme 51). 45
Iwao\textsuperscript{107} reported the synthesis of sesbanine (166) using lithiation of nicotinamide 164 as a starting point (Scheme 52).
3.1.5. **N,N-DIETHYL O-PYRIDYL CARBAMATES. MASKED PYRIDINOLS OR PYRIDONES**

Polysubstituted 2- and 4-pyridones and 3-hydroxypyridine derivatives are usually prepared by classical methods involving ring forming reactions.\(^{108}\) One example is shown below (Scheme 53).

Scheme 53

These systems are also available from the parent systems by electrophilic substitution reactions although these procedures are invariably non-regioselective.\(^{109}\) For example, 2-pyridone gives a mixture of 5-chloro and 3,5-dichloro-2-pyridone when treated with chlorine while 3-hydroxypyridine affords the 2-bromopyridine derivative or a dihalo derivative with excess halogen by classical bromination.\(^{110}\)
Previous to our work, two examples of metalation of pyridine bearing an oxygen-based directed metalation group (3-0Et, 3-0CH2OMe) had been reported (See Table 23). 103,104

Following the successful demonstration of the N,N-diethylcarbamoyloxy group as an ortho director69 and cognizant of the greater thermodynamic acidity of OCONEt2 compared with other directed metalation groups78 (Chapter II, Section 2.2.4), we decided to test the ortho metalation directing ability of this functionality on the pyridine nucleus. The aim was to develop new methodology for the regioselective synthesis of polysubstituted hydroxypyridine derivatives. O-Pyridyl carbamates are easily prepared111 compounds with a long history.
in medicinal chemistry. Substituted 3-pyridinol carbamates and their N-alkylated derivatives are parasympathomimetic substances and are capable of inhibiting cholinesterase.112

This part of the thesis will deal with a) the ortho lithiation of N,N-diethyl 0-pyridyl carbamates; b) iterative metalation of these systems; c) anionic ortho Fries rearrangement leading to the synthesis of nicotinamide and isonicotinamide derivatives; d) ipso carbodestannylation reactions; and e) reductive elimination of the carbamate directing group.113

3.2. RESULTS AND DISCUSSION

3.2.1. PREPARATION OF 0-ARYL CARBAMATES

0-Pyridyl-3-carbamate was prepared according to a literature procedure111,112 (Scheme 55).

![Scheme 55](image)

Although 0-pyridyl-2-carbamate (176) was prepared following the above procedure from 2-pyridone, the N-acylated derivative was obtained as a minor product from 4-pyridone under identical reaction conditions (Scheme 56).
The O-Pyridyl-4-carbamate 179, however, was obtained following the method outlined in Scheme 57.

Scheme 57

\[ \text{NaH/DMF} \]

178 \[ \rightarrow \] 179

\[ \text{Et}_2\text{NCOCl} \]

Reflux, 8h \[ 66\% \]
3.2.2. SYNTHESIS OF POLYSUBSTITUTED O-PYRIDYL CARBAMATES

All the isomeric N,N-diethyl O-pyridyl carbamates (176, 177, 179) were shown to undergo smooth metalation under the standard conditions (s-BuLi/TMEDA/THF/-78°C) used for aromatic amide and carbamate metalation as evidenced by reaction with a variety of electrophiles to give substituted pyridines (Scheme 58).

Scheme 58

```
176 + RLi → Li + 181
              E
```

a b c d e f
---
E D Me CONEt2 TMS Br I

```
177 + RLi → Li + 182
              E
```

a b c d e f g h
---
E D Me CONEt2 TMS Br I SO2NMe2 CO2H
Metalation followed by electrophilic quench of 0-pyridyl-2-carbamate 176 gave 3-substituted products 181. Under identical conditions, the 3-carbamate 177 afforded only 4-substituted products 182 and the 4-carbamate 179 gave 3-substituted pyridine derivatives 183. The results of these methodological studies using the three isomeric 0-pyridyl carbamates are summarized in Table 24.
Table 24: Synthesis of Substituted O-Pyridyl Carbamates 181, 182, 183

<table>
<thead>
<tr>
<th>E⁺</th>
<th>E, Yield (%)</th>
<th>E, Yield (%)</th>
<th>E, Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeOD</td>
<td>D, 87 (56%d₁)</td>
<td>D, 82 (51%d₁)</td>
<td>D, 75 (37%d₁)</td>
</tr>
<tr>
<td>MeI</td>
<td>Me, 72</td>
<td>Me, 83</td>
<td>Me, 72</td>
</tr>
<tr>
<td>Et₂NCOCl</td>
<td>CONEt₂, 66</td>
<td>CONEt₂, 64</td>
<td>CONEt₂, 69</td>
</tr>
<tr>
<td>TMSCl</td>
<td>TMS, 52 (62)a</td>
<td>TMS, 69 (82)a</td>
<td>TMS, 67</td>
</tr>
<tr>
<td>Br(CH₂)₂Br</td>
<td>Br, 59</td>
<td>Br, 71</td>
<td>Br, 60</td>
</tr>
<tr>
<td>I₂</td>
<td>I, 68</td>
<td>I, 89</td>
<td>I, 60</td>
</tr>
<tr>
<td>ClSO₂NMe</td>
<td>SO₂NMe₂, 81</td>
<td></td>
<td>SO₂NMe₂, 60</td>
</tr>
<tr>
<td>CO₂</td>
<td>CO₂H, 60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ClSnMe₃</td>
<td>SnMe₃, 82</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ClSn(n-Bu)₃(MeS)₂</td>
<td>Sn(n-Bu)₃, 50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MeCHO</td>
<td>CHOH(Me), 50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C₆H₅CHO</td>
<td>CHOH(C₆H₅), 75</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* a Using LDA/THF/-78°C Conditions.
The low deuterium incorporation into all O-pyridyl carbamates in comparison
to the high yield of products with other electrophiles is difficult to
explain. Similar results, however, have been reported by others.\textsuperscript{26,100}
Lithiation of O-pyridyl carbamates \textit{176} and \textit{177} can also be effected by
using LDA and, as seen from the Table \textit{24}, the yield of the
products \textbf{181d} and \textbf{182d} were even better despite the decreased thermodynamic
basicity of LDA in comparison to alkyllithiums. This observation may be
accounted for by considering greater compatibility of
TMS\textsubscript{Cl} with LDA than with alkyllithiums.\textsuperscript{114} The products from the three
isomeric carbamates \textit{176}, \textit{177} and \textit{179} have been identified by examination of
\textsuperscript{1}H NMR spectra, particularly the aromatic region, which show a distinct,
well-separated peak pattern for differently substituted carbamate
derivatives \textbf{181}, \textbf{182} and \textbf{183}. For example, a 1,2,3-type aromatic
substitution pattern was observed for product \textbf{181d} and 1,2,4-substitution
patterns were observed for \textbf{182b} and \textbf{183c} (Table \textit{25}).
Table 25: Aromatic $^1$H NMR Chemical Shifts of 181d, 182b, 183c

<table>
<thead>
<tr>
<th>Compound</th>
<th>Chemical Shift</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\delta$(ppm) (multiplicity, Coupling Const.) $J$ in Hz</td>
<td></td>
</tr>
<tr>
<td><strong>181d</strong></td>
<td>7.20 (dd, J = 7.2, 4.8)</td>
<td>H-5</td>
</tr>
<tr>
<td></td>
<td>7.89 (dd, J = 7.2, 2.19)</td>
<td>H-4</td>
</tr>
<tr>
<td></td>
<td>8.40 (dd, J = 4.8, 2.19)</td>
<td>H-6</td>
</tr>
<tr>
<td><strong>182b</strong></td>
<td>7.14 (d, J = 4.9)</td>
<td>H-5</td>
</tr>
<tr>
<td></td>
<td>8.30 (d, J = 4.9)</td>
<td>H-6</td>
</tr>
<tr>
<td></td>
<td>8.33 (s)</td>
<td>H-2</td>
</tr>
<tr>
<td><strong>183c</strong></td>
<td>7.32 (d, J = 5.6)</td>
<td>H-5</td>
</tr>
<tr>
<td></td>
<td>8.51 (s)</td>
<td>H-2</td>
</tr>
<tr>
<td></td>
<td>8.58 (d, J = 5.6)</td>
<td>H-6</td>
</tr>
</tbody>
</table>
In some cases, chemical corroboration has also been achieved by basic hydrolysis into known compounds\textsuperscript{115} (Scheme 59) and details are provided in the Experimental Section.

Scheme 59

\[
\begin{align*}
\text{Br} & \quad \text{NaOMe/MeOH} \quad \Delta / 40h \\
\text{Br} & \quad \text{NaOMe/MeOH} \quad \Delta / 40h \\
\text{Me} & \quad \text{NaOMe/MeOH} \quad \Delta / 12h \\
\end{align*}
\]
Although the 3-ethoxypyridine was found to undergo metatation at the 2-position (Table 23), the N,N-diethyl 0-pyridyl-3-carbamate 177 was found to metatalate exclusively at the 4-position under the specific conditions of the reaction. Although we do not expect the relative acidity of C-2 and C-4 hydrogens would be identical due to the presence of a directing group at the 3-position, the exclusive 4-metatalation is surprising in view of Brandsma's result.\textsuperscript{95} This may be rationalized by assuming a conformation of the carbamate which allows coordination of the directing group with the base in such a way so that it places the anionic part of the base closest to the C-4 hydrogen ultimately affording the 4-lithiated-3-carbamate (Scheme 60).

\begin{center}
\textbf{Scheme 60}
\end{center}

However, in the absence of conformation information on pyridyl carbamates, a similar coordination and deprotonation at the 2-position cannot be argued against. A tentative argument against 2-deprotonation may be the instability of the developing 2-carbanion due to electronic repulsion with the lone pair electrons of the ring nitrogen.\textsuperscript{94}

The efficient and regiospecific formation of a variety of substituted 0-pyridyl carbamates via this metatation methodology (Table 24) opens door to new synthetic pyridine chemistry. The regiospecific formation of monohalo (bromo/iodo) pyridones and hydroxyxypyrindines underscores the advantage and of this methodology with the electrophilic substitution
approach since the latter usually does not lead to monohalo derivatives with positional selectivity (see Section 3.1.5, Scheme 54).

3.2.3. ITERATIVE METALATION OF O-PYRIDYL CARBAMATES

Following the concept demonstrated for O-aryl carbamates (Chapter II, Section 2.2.7), O-pyridyl carbamates have been subjected to iterative metalation in order to synthesize contiguously trisubstituted pyridine derivatives. In addition this study has allowed the evaluation of relative directing abilities of different groups in pyridine systems (Scheme 61).

Scheme 61

In each of the cases depicted schematically, if OCONEt₂ group is a better ortho directing than E₁, then the predominant product from the subsequent lithiation would be expected to be the one in which E₂ is ortho to it. Several experiments were carried out to this end on substituted carbamates 182c, 182e and 183c (Scheme 62).
Lithiation at the 5-position of 182c was evidenced by the formation of product 187 upon TMSCl quench. Likewise, compounds 182e and 183c afforded products 188 and 189 respectively. Lithiation of 182e was carried out using LDA following the method of Gribble\textsuperscript{102} and Queguiner.\textsuperscript{103} These results show that irrespective of the nature of the directing groups, the
2-position of the pyridyl carbamates is inherently reluctant to undergo metation in competition with metation ortho to CONEt$_2$, Br and OCONEt$_2$ substituents. Further confirmation of these observations was achieved by unsuccessful attempts to metate 182d under a variety of conditions (Scheme 63) using the trimethyl silyl group to block the more reactive metation sites.$^{116}$ In all cases, starting material was recovered in almost quantitative yield.

**Scheme 63**

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Base</th>
<th>Lithiation Temp (0°C)</th>
<th>$E^+$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$s$-BuLi/TMEDA/THF</td>
<td>-78 --&gt; RT</td>
<td>-</td>
</tr>
<tr>
<td>$s$-BuLi/TMEDA/THF</td>
<td>-78</td>
<td>MeOD</td>
</tr>
<tr>
<td>LDA/THF</td>
<td>-78</td>
<td>MeOD</td>
</tr>
<tr>
<td>LiTMP/THF</td>
<td>-78</td>
<td>TMSCl</td>
</tr>
<tr>
<td>$n$-BuLi/TMEDA/Et$_2$O</td>
<td>-60 --&gt; 40</td>
<td>MeI</td>
</tr>
</tbody>
</table>
3.2.4. ANIONIC ORTHO FRIES REARRANGEMENT. SYNTHESIS OF ISONICOTINAMIDES AND NICOTINAMIDES

By analogy with O-aryl carbamates\textsuperscript{69}, the lithiated species of pyridyl carbamates 177, 179, 183b and 183d, when allowed to warm to room temperature over a period of 8h, underwent the anionic Fries rearrangement to give the isonicotinamide 190 and nicotinamides 191a, 191b, 191c respectively (Scheme 64). The results are summarized in Table 26.

Scheme 64

\[
\begin{align*}
\text{CONEt}_2 & \xrightarrow{RLI} \xrightarrow{-78^\circ C \rightarrow RT} \text{CONEt}_2 \\
\text{CONEt}_2 & \xrightarrow{RLI} \xrightarrow{-78^\circ C \rightarrow RT} \text{CONEt}_2
\end{align*}
\]
Table 26: Synthesis of Isonicotinamide (190) and Nicotinamides (191) via Anionic Fries Rearrangement.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>E</th>
<th>Product</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>177</td>
<td>-</td>
<td>190</td>
<td>40</td>
</tr>
<tr>
<td>179</td>
<td>H</td>
<td>191a</td>
<td>74</td>
</tr>
<tr>
<td>183b</td>
<td>Me</td>
<td>191b</td>
<td>80</td>
</tr>
<tr>
<td>183d</td>
<td>TMS</td>
<td>191c</td>
<td>60</td>
</tr>
</tbody>
</table>

The products were identified by $^1$H NMR spectroscopy by comparing the chemical shifts of ring protons in structures 191 with the chemical shifts of the known 3-methyl-4-pyridone. Signals for pyridone hydrogens are characteristically distinct from a heteroaromatic ring protons.\textsuperscript{117}

3.2.5. CARBAMATE AS REMOVABLE DIRECTING GROUP

The reductive conversion of hydroxypyridines to the corresponding pyridines via their chloro or bromo derivatives has been known for a long time. An example is shown in Scheme 65. \textsuperscript{118}
Scheme 65

Hence the substituted pyridine derivatives 181, 182, 183 and 190, 191 may be considered as precursors to differently substituted pyridines in which the carbamate serves its function in the introduction of an electrophile and then may be removed or, in some cases, rearranged to amide derivatives. To establish this principle, the substituted 4-pyridone 191b was converted into the 4-chloropyridine 195 which, on hydrogenolysis was transformed into 5-methylnicotinamide (196) (Scheme 66).
The reaction time of pyridone 191b with phosphoryl chloride must be limited to 10 min as indicated because no identifiable product has been isolated when the reaction time was longer. Since most of the substituted carbamate derivatives are hydrolyzable into pyridone or hydroxy pyridine derivatives, this sequence may be useful for the synthesis of diversely substituted pyridines.

3.2.6. ELECTROPHILE-INDUCED IPSO-DESTANNYLATION

Yamamoto and coworkers\textsuperscript{43, 119} have shown that stannylated pyridine derivatives undergo electrophile-induced ipso-destannylation to give iodopyridine and acylpyridines (Scheme 67).

![Scheme 67](image)

The formation of 198, \( E = \text{COMe} \) is significant since the direct acylation of hydroxy pyridines and pyridines with an acyl chloride using Friedel Crafts reaction conditions has been reported to be unsuccessful.\textsuperscript{120} Encouraged by the observations of Yamamoto,\textsuperscript{43, 119} the stannylated derivatives 1821 was
MeCOCl to afford iodocarbamate 182f and acylcarbamate 199 respectively (Scheme 68). The product 182f was shown to be identical with that obtained by directed ortho lithiation methodology (Section 3.2.2) whereas the structure of 199 was established by examination of its NMR spectrum. In comparison, the tri-\textsubscript{n}-butylstannylated derivative 182j failed to undergo this ipsoestannylation reaction upon treatment with I\textsubscript{2} presumably owing to the steric bulk of the \textsubscript{n}-butyl group.

This preliminary study points to the potential of coupling directed metalation and electrophilic substitution chemistries on pyridine carbamates for the goal of preparation of unusual polysubstituted systems.
3.2.6. CONCLUSION

An efficient, practical, and short method for the synthesis of diversely substituted 2- and 4-pyridones and 3-pyridinols via 0-pyridyl carbamates has been developed by using directed ortho metalation chemistry. This work further underscores the advantage and effectiveness of directed metalation methodology in pyridine metalation.
4.0 EXPERIMENTAL

4.1 GENERAL METHODS

Melting points were determined in a Buchi model SMP-20 instrument and are uncorrected. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tennessee. $^1$H NMR spectra were determined with Bruker WP-80 and Bruker AM-250 spectrometers in CDCl$_3$ with 1% tetramethyilsilane as an internal standard unless indicated otherwise. Spectra listed follow the order: chemical shift ($\delta$, ppm), (multiplicity, coupling constants J in Hz, number of protons and/or assignment). $^{13}$C NMR spectra were recorded with Bruker WP-80 and AM-250 instruments in CDCl$_3$ referenced to CHCl$_3$ at 77.0 ppm. Infrared spectra were recorded on a Beckman model Acculab 10 or Perkin-Elmer 983 spectrophotometers. High resolution mass spectra were determined on a VG 7070F instrument and low resolution mass spectra were determined either on a VG 7070F or a Varian MAT CH7 mass spectrometers. Analytical gas liquid chromatography (GLC) was performed on a Hewlett Packard 5840A instrument fitted with a flame ionization detector using a commercially available 10% SE 30 column. Column chromatography was performed using silica gel 60 (0.04-0.063 mm and 0.063-20 mm) with hexane/ethyl acetate as eluent (1:1 to 9:1) unless stated otherwise.
The phrase "workup in the usual manner" or "standard workup" refers to treatment of the reaction mixture with saturated aqueous NH₄Cl followed by extraction with CH₂Cl₂ or Et₂O, drying of the organic extract over Na₂SO₄ and evaporation to dryness under reduced pressure to afford the crude product. Subsequent chromatography and/or recrystallization and/or distillation of the crude material afforded pure products.

All dry solvents employed were obtained by refluxing over and distilling from an appropriate drying agent. Diethyl ether (Et₂O), benzene and tetrahydrofuran (THF) were freshly distilled from sodium-benzophenone ketyl prior to use. All lithiations were performed using syringe-septum cap techniques in oven-dried glassware under an atmosphere of dry high purity nitrogen. Solutions of the butyllithium reagents were stored in septum-capped bottles inside plastic bags containing CaCl₂. The n-BuLi was stored at ambient temperature, whereas s-BuLi and t-BuLi were stored at 0°C. The titre of all commercially available alkyllithium reagents was determined with 2,5-dimethoxybenzyl alcohol as standard. DMF was dried and distilled over CaH₂ and stored over NaH. Diisopropylamine (DIA), triethylamine, tetramethylethylenediamine (TMEDA) were dried and distilled over CaH₂ and stored over 4A molecular sieves in brown bottles which were kept in a dessicator containing CaCl₂. All other liquid reagents were dried according to literature procedures and distilled prior to use.
4.1.1. STANDARD PROCEDURE FOR CHAPTER I

A. General Transmetalation Procedure of Benzamides

A solution of the appropriate benzamide (1.0 equiv) in anhydrous THF (5 mL) was added by syringe injection to a stirred solution of s-BuLi (1.1 equiv) and TMEDA (1.1 equiv) in anhydrous THF at -78°C under nitrogen. MgBr₂·2Et₂O (3.0 equiv) was added after 30 min which produced a colorless precipitate. The reaction mixture was warmed to room temperature to give a clear solution which was cooled again to -78°C and stirred for 40 min. The electrophile (2.0 equiv) was added and the solution was allowed to warm to room temperature overnight. Standard workup afforded the crude product.

B. General Procedure for the Preparation of Phthalides

The crude hydroxyamide derivative obtained from the reaction of 47 (generated according to procedure A) and an aldehyde was not purified but was subjected to cyclization in refluxing toluene in presence of catalytic amount of p-toluenesulfonic acid monohydrate for 20-24 h. Workup in the usual manner gave the crude product.

C. General Procedure for the Preparation of 3,4-Dihydroisocoumarins

The required allylbenzamide was refluxed in 6N aqueous HCl for 20-90 h. The reaction mixture was diluted by adding aqueous NH₄Cl solution and was extracted with CH₂Cl₂. The CH₂Cl₂ solution was washed with water, dried (Na₂SO₄) and CH₂Cl₂ evaporated under
vacuum to give crude product.

4.1.2. PREPARATION OF TERTIARY BENZAMIDES, OXAZOLINE AND 
METHOXYMETHOXYBENZENE

All the benzamides were prepared by reacting the required acid 
chloride (obtained from carboxylic acid and SOCl₂) with an excess 
of the appropriate amine.¹²⁵ Oxazoline was prepared from the 
reaction of benzoylchloride with 2-amino-2-methylpropan-1-ol 
followed by cyclization of the resulting amide by refluxing with 
SOCl₂.¹²⁶ Methoxymethoxybenzene was obtained from the reaction of 
the required Na-phenoxide with chloromethyl methyl ether.¹²⁷ All 
these compounds were purified either by microdistillation or 
Kugelrohr distillation or recrystallization. Unless indicated 
otherwise, these compounds showed spectral (IR, NMR, MS) 
properties consistent with their assigned structures.

N,N-Diethylbenzamide 45a: bp 78°C/0.04 mm (lit.¹²⁸ bp 
150-151°C/15 mm).

N,N-Diethyl-2-methoxybenzamide 45b: bp 105-106°C/0.25 mm 
(lit.¹²⁵ bp 100-104°C/1 mm).

N,N-Diethyl-3-methoxybenzamide 45c: bp 110-112°C/0.05 mm 
(lit.¹²⁹ bp 177°C/14 mm).

N,N-Diethyl-2,5-dimethoxybenzamide 45d: mp 78-80°C/EtOAc) 
(lit.¹³⁰ bp 125°C/0.35 mm)

N,N-Diethyl-2,3,4-trimethoxybenzamide 45e: bp 115-120°C/0.2 mm;

IR (CHCl₃) νmax 1620 cm⁻¹; ¹H NMR (CDCl₃) δ 1.04, 1.24 (2 t, J =
7, 6H, 2 CH₃), 3.18, 3.55 (2 q, J = 7, 4H, 2 CH₂), 3.87, 3.88, 3.90 (3 s, 9H, 3 OCH₃), 6.66 (d, J = 8.5, 1H, H-6), 6.91 (d, J = 8.5, 1H, H-5); MS m/e 267 (M⁺); satisfactory analytical data (C, H, N) were not obtained.

**N,N-Dimethyl-2,3,4-trimethoxybenzamide 52:** mp 65-66°C
(CH₂Cl₂-hexane); IR (CHCl₃) ν max 1615 cm⁻¹; ¹H NMR (CDCl₃) δ 2.87 (s, 3H, CH₃), 3.10 (s, 3H, CH₃), 3.88 (s, 9H, 3 OCH₃), 6.67 (d, J = 8.2, 1H, H-6), 6.94 (d, J = 8.2, 1H, H-5); MS m/e 239 (M⁺);
Anal. Calcd for C₁₂H₁₇NO₄: C, 60.24; H, 7.16; N, 5.85. Found: C, 59.77; H, 7.34; N, 6.29.

**N,N-Diethyl-2-bromobenzamide:** bp 140-142°C/0.30 mm (lit.¹²⁵ bp 138-140°C/2mm); IR (CHCl₃) ν max, 1620 cm⁻¹; ¹H NMR (CDCl₃) δ 1.06, 1.27 (2 t, J = 7, 6H, 2 CH₃), 3.15, 3.75 (2 q, J = 7, 4H, 2 CH₂), 7.16-7.60 (m, 4H, ArH).

**2-Phenyl-4,4-dimethyloxazoline 61:** bp 63-65°C/1.0 mm (lit.¹²⁶ 112-114°C/14 mm).

**4-Methoxymethoxyanisole 63:** bp 55-58°C/0.05 mm (lit.¹²⁷ 114°C/0.1 mm).
4.1.3. EXPERIMENTAL DETAILS

3-n-Propylphthalide (50a).

According to general transmetalation procedure (procedure A) N,N-diethyl-o-(bromomagnesio)benzamide 47a was generated from N,N-diethylbenzamide 45a (500 mg, 2.82 mmol), s-BuLi (2.82 mL, 3.10 mmol), TMEDA (0.47 mL, 3.10 mmol), MgBr₂Et₂O (3.21 mL, 8.47 mmol) and was treated with n-butyraldehyde (407 mg, 5.65 mmol). Standard workup gave the crude hydroxylamide derivative which was cyclized according to the procedure for the preparation of phthalide (Procedure B) to afford after column chromatography (1:9 EtOAc-hexane as eluent) 310 mg (64% overall) of compound 50a as an oil; IR (neat) νₘₐₓ 1750 cm⁻¹; NMR (CDCl₃) δ 0.97 (t, J = 7, 3H, CH₃), 1.29-2.1 (complex m, 4H, CH₂CH₂), 5.49 (m, 1H, CH), 7.37-7.96 (m, 4H, ArH); MS m/e 176 (M⁺).

3-Methylphthalide (50b).

According to procedure A, N,N-diethyl-o-(bromomagnesio)-benzamide 47a was generated from N,N-diethylbenzamide 45a (500 mg, 2.82 mmol) as in the previous experiment and was treated with freshly distilled acetaldehyde (248 mg, 5.65 mmol). The crude
hydroxymamide obtained after usual workup was subjected to cyclization according to procedure B to give after purification by column chromatography (1:9 EtOAc-hexane as eluent) 251 mg (61% overall) of compound 50b, bp 60-65°C/ 0.03 mm (lit57 101°C/0.9 mm); IR (neat) \( \nu_{\text{max}} \) 1750 cm\(^{-1}\); NMR (CDCl\(_3\)) \( \delta \) 1.65 (d, J = 6.6, 3H, CH\(_3\)), 5.57 (q, J = 6.6, 1H, CH), 7.62 (m, 4H, ArH); MS m/e 148.

7-Methoxy-3-n-propylphthalide (50c).

According to procedure A, the appropriate bromomagnesiobenzamide 47 was generated from N,N-diethyl-2-methoxybenzamide 45b (500 mg, 2.41 mmol), s-BuLi (2.21 mL, 2.65 mmol), TMEDA (0.40 mL, 2.65 mmol), MgBr\(_2\).2Et\(_2\)O (2.75 mL, 7.24 mmol) and was treated with n-butyraldehyde (347 mg, 4.82 mmol). Standard workup gave crude hydroxymamide derivative which was cyclized according to procedure B. Workup in the usual manner followed by column chromatography (1:9 EtOAc-hexane as eluent) afforded 300 mg (60% overall) of compound 50c, bp 97-101°C/0.01 mm; IR (neat) \( \nu_{\text{max}} \) 1750 cm\(^{-1}\); NMR (CDCl\(_3\)) \( \delta \) 0.96 (t, J = 6.5, 3H, CH\(_3\)), 1.24-2.02 (m, 4H, CH\(_2\)CH\(_2\)), 3.99 (s, 3H, OCH\(_3\)), 5.39 (m, 1H, CH), 6.95 (d, J = 8.4, 1H, H-4 or H-6), 6.99 (d, J = 7.6, 1H, H-4 or H-6), 7.63 (dd, J = 7.6, 8.4, 1H, H-5); MS m/e 206 (M\(^+\)); Anal. Calcd for C\(_{12}\)H\(_{14}\)O\(_3\): C, 69.88; H, 6.84. Found: C, 69.49; H, 7.16.

4-Methoxy-3-n-propylphthalide (50d).

According to procedure A, the required bromomagnesiobenzamide 47 was generated from N,N-diethyl-3-methoxybenzamide 45c
(582 mg, 2.82 mmol), s-BuLi (3.16 mL, 3.10 mmol), TMEDA (0.47 mL, 3.10 mmol), MgBr₂₂Et₂O (3.21 mL, 8.47 mmol) and was treated with n-butyraldehyde (407 mg, 5.65 mmol). Standard workup gave the crude hydroxyamide derivative which was cyclized according to procedure B to give after purification by column chromatography (1:9 EtOAc-hexane as eluent) 342 mg (59% overall) of the desired product 50d, mp 76-77°C (CH₂Cl₂-hexane); IR (CHCl₃) νmax 1750 cm⁻¹; NMR (CDCl₃) δ 0.95 (t, J = 7, 3H, CH₃), 1.2-2.2 (m, 4H, CH₂CH₂), 3.92 (s, 3H, OCH₃), 5.5 (m, 1H, CH), 7.1-7.45 (m, 3H, ArH); MS m/e 206(M⁺); Anal. Calcd for C₁₂H₁₄O₃: C, 69.88; H, 6.84. Found: C, 69.73; H, 6.64.

4,7-Dimethoxy-3-n-propylphthalide (50e).

According to procedure A, the appropriate bromomagnesiobenzamide 47 was generated from N,N-diethyl-2,5-dimethoxybenzamide 45d (1.34 g, 5.64 mmol), s-BuLi (6.34 mL, 6.20 mmol), TMEDA (0.94 mL, 6.20 mmol), MgBr₂₂Et₂O (6.4 mL, 16.92 mmol) and was treated with n-butyraldehyde (814 mg, 11.28 mmol). Workup in the usual manner gave the crude hydroxyamide which was subjected to cyclization according to procedure B. Standard workup followed by column chromatography (1:9 EtOAc-hexane as eluent) afforded 981 mg (74% overall) of the desired product 50e, mp 128°C (Et₂O-hexane); IR (CHCl₃) νmax 1750 cm⁻¹; NMR (CDCl₃) δ 0.95 (t, J = 7, 3H, CH₃), 1.2-2.2 (m, 4H, CH₂CH₂), 3.84, 3.92 (2 s, 6H, 2 OCH₃), 5.42 (m, 1H, CH), 6.83 (d, J = 8.8, 1H, H-5 or H-6), 7.05 (d, J = 8.8, 1H, H-5 or H-6); MS m/e 236(M⁺); Anal. Calcd for C₁₃H₁₆O₄: C, 66.10; H, 6.82. Found: C, 66.18; H, 6.72.
3-(2-Pyridyl)phthalide (50f).

According to procedure A, the o-(bromomagnesio)benzamide 47a - was generated from N,N-diethylbenzamide 45a (500 mg, 2.82 mmol) as described for the preparation of 50a and was quenched with pyridine-2-carboxaldehyde (604 mg, 5.64 mmol). Workup in the usual manner and cyclization of the crude hydroxyamide obtained according to procedure B afforded after purification by column chromatography 524 mg (88%) of compound 50f, mp 83-84°C (EtOAC-Et₂O); IR (CHCl₃) ν_max 1765 cm⁻¹; NMR (CDCl₃) δ 6.52 (s, 1H, CH), 7.18-7.99 (m, 7H, ArH) 8.64 (m, 1H, ArH); MS m/e 211 (M⁺); Anal. Calcd for C₁₃H₉N₂: C, 73.93; H, 4.29; N, 6.63. Found: C, 73.69; H, 4.28, N, 6.30.

N,N-Diethyl-2-allylbenzamide (51a).

According to the procedure A, N,N-diethyl-o-(bromomagnesio)-benzamide 47a was produced from 45a (500 mg, 2.82 mmol), s-BuLi (2.82 mL, 3.10 mmol), TMEDA (0.47 mL, 3.10 mmol), MgBr₂.2Et₂O (3.21 mL, 8.47 mmol) and was treated with allyl bromide (683 mg, 5.64 mmol). Workup in the usual manner followed by purification by column chromatography using 1:5 (v/v) EtoAc-hexane as eluent yielded 435 mg (71%) of the desired product 51a, bp 90-94°C/0.1 mm; IR (neat) ν_max 1620 cm⁻¹; NMR (CDCl₃) δ 1.05, 1.26 (2 t, J = 7, 6H, 2 CH₃), 3.15 (q, J = 7, 2H, CH₂), 3.35 (m, 2H, CH₂CH=), 3.35-3.38 (br, 2H, CH₂), 4.9-5.25 (m, 2H, CH=CH₂), 5.7-6.2 (m, 1H, CH=CH₂), 7.1-7.3 (m, 4H, ArH) MS m/e 217 (M⁺); Anal. Calcd for C₁₄H₁₉NO: C, 77.41; H, 8.75; N, 6.45; Found: C, 76.98; H, 8.87; N, 6.36.
N,N-Diethyl-2-allyl-6-methoxybenzamide (51b).

According to procedure A, the required 47 was generated from N,N-diethyl-2-methoxybenzamide 45b (1.0 g, 4.83 mmol), s-BuLi (4.21 mL, 5.31 mmol), TMEDA (0.80 mL, 5.31 mmol), MgBr₂.2Et₂O (5.5 mL, 14.49 mmol) and was quenched with allyl bromide. Standard (1:5 EtOAc-hexane as eluent) workup gave the crude product which upon column chromatography afforded 665 mg (55%) of compound 51b, bp 110-114°C/0.35 mm, IR (neat) ν max 1620 cm⁻¹; NMR (CDCl₃) δ 1.02 1.28 (2 t, J = 7, 6H, 2 CH₃), 3.12, 3.48 (2 q, J = 7, 4H, 2 CH₂), 3.32 (br, 2H, CH₂CH=), 3.78 (s, 3H, OCH₃), 4.92-5.25 (m, 2H, CH=CH₂), 5.7-6.2 (m, 1H, CH=CH₂), 6.80 (m, 2H, ArH), 7.25 (m, 1H, ArH); MS m/e 247 (M⁺); Anal. Calcd for C₁₅H₂₁NO₂: C, 72.84; H, 8.53; N, 5.67. Found: C, 72.43; H, 8.35; N, 6.05.

N,N-Diethyl-2-allyl-3-methoxybenzamide (51c).

According to procedure A, the o-(bromomagnesio)benzamide 47c was generated from N,N-diethyl-3-methoxybenzamide 45c (1.169 g, 5.64 mmol), s-BuLi (6.34 mL, 6.21 mmol), TMEDA (0.94 mL, 6.21 mmol), MgBr₂.2Et₂O (6.43 mL, 16.92 mmol) and was treated with allyl bromide (1.36 g, 11.28 mmol). Workup in the usual manner and purification by column chromatography (1:5 EtOAc-hexane as eluent) yielded 1.11 g(80%) of compound 51c, bp 115-118°C/0.2 mm; IR (neat) ν max 1620 cm⁻¹; NMR (CDCl₃) δ 1.02, 1.28 (2 t, J = 7, 6H, 2 CH₃), 3.09, 3.38 (2 q, J = 7, 4H, (s, 3H, OCH₃), 4.85-5.10 (m, 2H, CH=CH₂), 5.77-5.89 (m, 1H, CH=), 6.71-6.90 (m, 2H, ArH), 7.11-7.30
(m, 1H, ArH); MS m/e 247 (M⁺); Anal. Calcd for C₁₅H₂₁NO₂: C, 72.84; H, 8.53; N, 5.67; Found: C, 72.94; H, 8.46; N, 5.52.

**N,N-Diethyl-2-allyl-3,6-dimethoxybenzamide (51d).**

According to procedure A, the o-(bromomagnesio)benzamide 47d was produced from N,N-diethyl-2,5-dimethoxybenzamide 45d (1.33 g, 5.61 mmol), s-BuLi (6.42 mL, 6.17 mmol), TMEDA (0.94 mL, 6.17 mmol), MgBr₂.2Et₂0 (6.43 mL, 16.83 mmol) and was treated with allyl bromide (1.36 g, 11.22 mmol). Standard workup and column chromatography (1:5 EtOAc-hexane as eluent) afforded 991 mg (63%) of compound 51d, bp 128-129°C/0.25 mm; IR (neat) ν max 1620 cm⁻¹; NMR (CDCl₃) δ 1.02, 1.28 (2 t, J = 7, 6H, 2 CH₃), 3.10, 3.38 (2 q, J = 7, 4H, 2 CH₂), 3.32 (m, 2H, CH₂CH=), 3.72, 3.78 (2 s, 6H, 2 OCH₃), 4.87-5.10 (m, 2H, CH=CH₂), 5.70-6.10 (m, 1H, CH=), 6.68 (d, J = 9, 1H, H-5 or H-6); 6.81 (d, J = 9, 1H, H-5 or H-6); MS m/e 277 (M⁺); Anal. Calcd for C₁₆H₂₃NO₃: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.05; H, 8.41; N, 5.09.

**N,N-Diethyl-2-allyl-4,5,6-trimethoxybenzamide (51e).**

According to procedure A, the o-(bromomagnesio)benzamide 47e was generated from N,N-diethyl-2,3,4-trimethoxybenzamide 45e (500 mg, 1.87 mmol), s-BuLi (2.1 mL, 2.06 mmol), TMEDA (0.31 mL, 2.06 mmol), MgBr₂.2Et₂0 (2.13 mL, 5.61 mmol) and was treated with allyl bromide (453 mg, 3.74 mmol). Standard workup followed by purification of the crude product by column chromatography (1:5 EtOAc-hexane as eluent) afforded 378 mg (66%) of compound 51e, bp
110-112°C/0.07 mm; IR (neat) \nu_{\text{max}}

1620 cm\(^{-1}\); NMR (CDCl\(_3\)) \delta 1.05, 1.25 (2 t, J = 7, 6H, 2 CH\(_3\)), 3.15, 
3.58 (2 q, J = 7, 4H, 2CH\(_2\)), 3.30 (br, 2H, CH\(_2\)CH=), 3.85 (s, 6H, 2 
OCH\(_3\)), 3.88 (s, 3H, OCH\(_3\)), 4.98-5.20 (m, 2H, CH=CH\(_2\)), 5.70-6.20 
(m, 1H, CH=), 6.53 (s, 1H, ArH); MS m/e 307 (M\(^+\)); satisfactory 
analytical data were not obtained.

N,N-Dimethyl-2-allyl-4,5,6-trimethoxybenzamide (54).

The general transmetalation procedure was modified for the 
preparation of compound 54 as follows:

N,N-Dimethyl-2,3,4-trimethoxybenzamide 52 (500 mg, 2.1 mmol) 
was lithiated with s-BuLi (1.91 mL, 2.30 mmol) and TMEDA (0.35 mL, 
2.30 mmol) at -90°C for 1.5 h and then warmed to -78°C over 30 
min. MgBr\(_2\)2Et\(_2\)O (2.39 mL, 6.30 mmol) was added and after 30 min 
the mixture was allowed to warm to room temperature to give a 
clear solution, again cooled to -78°C. After 1h, allyl bromide 
(508 mg, 4.2 mmol) was added. Standard workup followed by column 
chromatography yielded 465 mg (77%) of compound 54, bp 
95-98°C/0.02 mm; IR (neat) \nu_{\text{max}} 1620 cm\(^{-1}\); NMR (CDCl\(_3\)) \delta 2.81 (s, 
3H, CH\(_3\)), 3.11 (s, 3H, CH\(_3\)), 3.30 (m, 2H, CH\(_2\)CH=), 3.86, 3.89, 
3.91 (3 s, 9H, 3 OCH\(_3\)), 4.97-5.2 (m, 2H, CH=CH\(_2\)), 5.7-6.2 (m, 1H, 
CH=), 6.54 (s, 1H, ArH); MS: mass spectrum showed that 
compound 54 was contaminated by traces of a compound, ms m/e 319 
(M\(^+\)), which might be formed from the benzylic allylation 
of 54 which could not be isolated, therefore satisfactory 
analytical (C, H, N) data were not obtained.
3-Methyl-3-[2-(diethylcarbamoyl)phenyl]phthalide (57).

According to procedure A, N,N-diethyl-o-Bromomagnesio)benzamide 47a was generated from N,N-diethylbenzamide 45a (500 mg, 2.82 mmol), s-BuLi (3.17 mL, 3.10 mmol), TMEDA (0.47 mL, 3.10 mmol), MgBr₂₂Et₂O (3.21 mL, 8.47 mmol) and was treated with freshly distilled ethyl acetate (497 mg, 5.65 mmol), standard workup followed by column chromatography afforded 320 mg (35%) of compound 57, mp 126-127°C (Et₂O); IR (CHCl₃) ν max 1750, 1615 cm⁻¹; NMR (CDCl₃) δ 0.97-1.57 (m, 6H, 2 CH₃), 2.05 (2 s, 3H, singlet in Me₂SO-d₆, CH₃), 3.07-3.81 (m, 4H, 2 CH₂), 7.26-7.93 (m, 8H, ArH); MS m/e 323 (M⁺); Anal. Calcd for C₂₀H₂¹NO₃: C, 74.28; H, 6.54; N, 4.33. Found: C, 74.35; H, 6.41; N, 4.60.

2-(Diethylcarbamoyl)benzophenone (58) from N,N-Diethylbenzamide (45a).

According to procedure A, N,N-diethyl-o-(bromomagnesio)benzamide 47a was generated from N,N-diethylbenzamide 45a (500 mg, 2.82 mmol), s-BuLi (3.17 mL, 3.10 mmol), TMEDA (0.47 mL, 3.10 mmol), MgBr₂₂Et₂O (3.21 mL, 8.47 mmol) allowed to warm to room temperature and quenched with water. Workup in the usual manner and column chromatography (using 1:4 and 1:1 (v/v) EtOAc-hexane as eluent) gave starting material (325 mg, 65%) and 150 mg (19%) of compound 58, bp 100-105°C/0.15 (lit. 59 mp 76-77°C); IR (CHCl₃) ν max 1655, 1620 cm⁻¹; NMR (CDCl₃) δ 0.98-1.19 (m, 6H, 2 CH₃),
3.13-3.56 (m, 4H, 2 CH₂), 7.28-7.86 (m, 9H, ArH); MS m/e 281 (M⁺).

**Preparation of Compound 58 from N,N-diethyl-2-bromobenzamide.**

N,N-Diethyl-2-bromobenzamide (500 mg, 1.95 mmol) in THF (5 mL) was added with stirring to finely divided, triply sublimed magnesium (85 mg, 3.5 mmol) under nitrogen in THF solution (20 mL) containing 2 drops of 1,2-dibromoethane and the reaction mixture was refluxed for 2.5 h, cooled to 0°C and quenched with aqueous NH₄Cl solution. Standard workup followed by column chromatography afforded N,N-diethylbenzamide (60%) and compound 58 (10%) which was identical (IR, NMR) with the compound 58 obtained as described in the previous experiment.

**3-Methyl-3,4-dihydroisocoumarin-1-one (59a).**

According to procedure C, N,N-diethyl-2-allylbenzamide 51a - (462 mg, 2.13 mmol) was refluxed in 6N aqueous HCl (30 mL) for 20 h. Standard workup followed by column chromatography using 1:9 (v/v) EtOAc-hexane as eluent afforded 321 mg (93%) of compound 59a 64 as an oil; IR (neat) νₓₐₙₐ₆ 1720 cm⁻¹; NMR (CDCl₃) δ 1.52 (d, J = 6.8, 3H, CH₃), 2.94 (d, J = 6.8, 2H, CH₂), 4.68 (m, 1H, CH), 7.17-7.65 (m, 3H, ArH), 8.06-8.20 (m, 1H, ArH); MS m/e 162 (M⁺).
8-Hydroxy-3-methyl-3,4-dihydroisocoumarin-1-one (Mellein) (59b).

According to procedure C, N,N-Diethyl-2-allyl-6-methoxybenzamide 51b (350 mg, 1.42 mmol) was refluxed in 6N aqueous HCl (30 mL) for 4 days. Standard workup followed by column chromatography using 1:4 (v/v) EtOAc-hexane as eluent gave 181 mg (75%) of mellein (59b), mp 38°C (CH₂Cl₂-hexane) (lit.62 mp 38-38.5°C); IR (CHCl₃) ν_max 3200, 1675 cm⁻¹; NMR (CDCl₃) δ 1.52 (d, J = 6.2, 3H, CH₃), 2.92 (d, J = 7, 2H, CH₂), 4.68 (m, 1H, CH), 6.68 (d, J = 8.2, H-5 or H-7), 6.84 (d, J = 8.2, H-5 or H-7), 7.40 (dd, J = 8.2, H-6), 11.02 (s, 1H, OH); MS m/e 178 (M⁺).

3-Methyl-5-methoxy-3,4-dihydroisocoumarin-1-one (59c), 3-Methyl-5-hydroxy-3,4-dihydroisocoumarin-1-one (59d), and 4-(Diethylcarbamoyl)-2-methyl-2,3-dihydrobenzo[b]furan (60).

According to procedure C, N,N-Diethyl-2-allyl-3-methoxybenzamide 51c (551 mg, 2.23 mmol) was refluxed in 6N aqueous HCl (25 mL) for 18 h. Workup in the usual manner and column chromatography using 1:9 and 1:3 (v/v) EtOAc-hexane as eluent afforded 210 mg (49%) of compound 59c, mp 83-84°C (Et₂O-hexane) (lit.131 mp 83°C); IR (CHCl₃) ν_max 1720 cm⁻¹; NMR (CDCl₃) δ 1.52 (d, J = 6.2, 3H, CH₃), 2.62 (dd, J = 17, 11, 1H, H-C-H), 3.17 (dd, J = 17, 3.5, 1H, H-C-H), 3.88 (s, 3H, OCH₃), 4.49-4.76 (m, 1H, CH), 7.00-7.43 (m, 2H, ArH), 7.66-7.77 (m, 1H, ArH), MS m/e 192 (M⁺); 72 mg (16%) of compound 59d, mp 173-174°C (EtOAc-Et₂O) (lit.131 176-177°C); IR
(CHCl₃) ν max 3200, 1715 cm⁻¹; NMR (CDCl₃) δ 1.47 (d, J = 6.2, 3H, CH₃), 2.62 (dd, J = 17, 11, 1H, H-C-H), 3.19 (dd, J = 17, 3.5, 1H, H-C-H), 4.55-4.63 (m, 1H, CH), 7.08-7.47 (m, 2H, ArH), 7.50-7.59 (m, 1H, ArH), 8.8 (br, 1H, OH); MS m/e 178 (M⁺); and 60 mg (13%) of compound 60, bp 75-80/0.02 mm; IR (neat) ν max 1620 cm⁻¹; NMR (CDCl₃) δ 0.88-1.25 (m, 6H, 2 CH₃), 1.45 (d, J = 5.8, 3H, CH₃), 2.61-3.12 (m, 2H, CH₂), 3.24-3.48 (m, 4H, 2 CH₂), 4.79-5.08 (m, 1H, CH), 6.68-7.39 (m, 3H, ArH); MS m/e 233 (M⁺); Anal. Calcd for C₁₄H₁₉NO₂: C, 72.07; H, 8.20; N, 6.00. Found: C, 71.91; H, 8.30; N, 6.08.

6,7-Dimethoxy-8-hydroxy-3-methyl-3,4-dihydroisocoumarin-1-one (Kigelin) (59e).

N,N-Dimethyl-2-allyl-4,5,6-trimethoxybenzamide 54 (115 mg, 0.39 mmol) in 6N aqueous HCl (15 mL) was heated to 80°C and stirred for 24 h under nitrogen. Workup in the usual manner followed by preparative TLC using 3:1 (v/v) EtOAc-hexane as eluent gave 25 mg (27%) of Kigelin (59e), mp 141-142°C (CH₂Cl₂-hexane) (lit, 63 mp 142-143°C); IR (CHCl₃) ν max 3200, 1680 cm⁻¹; NMR (CDCl₃) δ 1.52 (d, J = 6.7, 3H, CH₃), 2.88 (d, J = 7.5, 2H, CH₂), 3.88, 3.92 (2 s, 6H, 2 OCH₃), 4.5-4.8 (m, 1H, CH), 6.3 (s, 1H, ArH), 11.00 (br, 1H, OH).
2-[(1-Hydroxybutyl)phenyl]-4,4-dimethyloxazoline (62).

s-BuLi (3.5 mL, 3.38 mmol) was added to a stirred THF solution (50 mL) of 2-phenyl-4,4-dimethyloxazoline 61 (500 mg, 2.85 mmol) at -78°C under nitrogen and after 2.75 h, the reaction mixture was warmed to 0°C and quenched with freshly distilled n-butyraldehyde (411 mg, 5.7 mmol). The resulting solution was allowed to warm to room temperature overnight. Workup in the usual manner and column chromatography using 1:4 (v/v) EtOAc-hexane as eluent afforded 467 mg (65%) of compound 62, bp 78-82°C/0.01 mm; IR (CHCl₃) νmax 3300, 1640 cm⁻¹; NMR (CDCl₃) δ 0.93 (t, J = 6.6, 3H, (CH₂)₂(CH₃), 1.39 (s, 6H, 2 CH₃), 1.50-2.20 (m, 4H, CH₂CH₂), 4.11 (s, 2H, OCH₂), 4.69 (m, 1H, CH), 7.20-7.39 (m, 3H, ArH), 7.70-7.90 (m, 1H, ArH); MS m/e 247 (M⁺); Anal. Calcd for C₁₅H₂₁NO₂: C, 72.82; H, 8.56; N, 5.67. Found: C, 72.92; H, 8.87; N, 5.79.

Following the transmetalation procedure compound 62 was prepared in 68% yield.

3-[(1-Hydroxybutyl)-4-(methoxymethoxy)anisole (64).

t-BuLi (1.78 mL, 3.26 mmol) was added to a stirred ether solution (50 mL) of 4-(methoxymethoxy)anisole 63 (500 mg, 2.97 mmol) at 0°C under nitrogen and after 2.5 h n-butyraldehyde (429 mg, 5.95 mmol) was added. The resulting solution was allowed to warm to room temperature overnight. Workup in the usual manner and column chromatography using 1:4 (v/v) EtOAc-hexane afforded 272 mg of compound 64, bp 82-86°C/0.01 mm; IR (CHCl₃) νmax 3400
cm⁻¹; NMR (CDCl₃) δ 0.93 (t, J = 6.6, 3H, (CH₂)₂CH₃), 1.20-1.90 (m, 4H, CH₂CH₂), 2.58 (br, 1H, OH), 3.47 (s, 3H, OCH₃), 3.75 (s, 3H, OCH₃), 4.93 (m, 1H, CH), 5.12 (s, 2H, OCH₂), 6.63-7.10 (m, 3H, ArH); MS m/e 240 (M⁺); Anal. Calc'd for C₁₂H₁₈O₃:  C, 64.98; H, 8.39.  Found: C, 65.01; H, 8.27.

Following the general transmetalation method compound 64 was prepared in 66% yield.
4.2. STANDARD PROCEDURE FOR CHAPTER II

4.2.1.A. LITHIATION OF 0-ARYL CARBAMATES WITH s-BuLi

A solution of the carbamate in dry THF (5-10 mL) was added dropwise by syringe injection to a stirred solution of a 1:1 s-BuLi-TMEDA complex in dry THF at -78°C (or -90°C) under nitrogen. After a reaction period (5 min to 1h), the mixture was treated with an electrophile. The resulting solution was then allowed to warm to room temperature over 8h after which a few mL of aqueous NH₄Cl solution was added and the THF was removed in vacuo. Subsequent standard workup gave the crude product. The details of the lithiation procedure which follow the above standard procedure are summarized in the order as follows: name and number of molar equivalents of alkyllithium reagent used, reaction temperature, lithiation time and name and number of molar equivalents of electrophile used.

B. LITHIATION OF O-ARYL CARBAMATES WITH LDA

To a THF solution of freshly distilled diisopropylamine (1.1 equiv) was added n-BuLi (1.1 equiv) at 0°C under nitrogen and was stirred for 30 min. The resulting solution of lithium diisopropylamide was cooled to -78°C and the required carbamate (1.0 equiv) in THF (5 mL) was injected by syringe injection. After 1h, an electrophile was added and the resulting solution was
allowed to warm to room temperature over 8h and processed in the normal manner (as described in procedure A) to give the crude product.

C. ORTHO-FRIES REARRANGEMENT. 1,3 OR 1,4 O --> C CARBAMOYL MIGRATION

Lithiation of the appropriate carbamate was carried out with s-BuLi (procedure A) or LDA (procedure B) and the resulting lithiated carbamate was allowed to warm to room temperature over 8h. Processing in usual manner as described in procedure A gave the crude product.

4.2.2. PREPARATION OF N,N-DIALKYL O-PHENYL CARBAMATE DERIVATIVES

The carbamates were prepared under standard conditions by treatment of the corresponding phenol with N,N-diethylcarbamoyl chloride (Et₂NCOCl) in refluxing pyridine\textsuperscript{132} for 4-6h, purified by distillation and/or recrystallization and kept in an airtight container. The yields were 70-96%. The phenolic derivatives N,N-Di-ethylhydroxybenzamides and N,N-diethyl O-(hydroxy)phenylcarbamates were obtained from the demethylation\textsuperscript{133} of the corresponding N,N-diethyl methoxybenzamide and N,N-diethyl O-(methoxy)phenyl carbamate with boron tribromide (BBr₃) in anhydrous CH₂Cl₂ at -78°C and purified by recrystallization. Yields were 83-93%.
The methoxymethoxy-carbamate derivatives were prepared by the reaction of the corresponding N,N-diethyl O-(hydroxy)phenylcarbamate with sodium hydride (NaH) in dimethylformamide (DMF) followed by treatment of the sodium phenoxide with chloromethyl methyl ether at 0°C. The crude products were purified by distillation. Yields were 84-95%.

All the products showed spectral (IR, NMR and MS) properties consistent with their assigned structures.

**N,N-Diethyl O-Phenylcarbamate (84a):**

bp 88-90°C/0.3 mm (lit\(^{134}\) 107-108°C/1.0 mm); IR (neat) \(\nu_{\text{max}}\) 1715 cm\(^{-1}\); NMR (CDCl\(_3\)) \(\delta\) 1.23 (t, J = 7, 6H, 2 CH\(_3\)), 3.42 (q, J = 7, 4H, 2 CH\(_2\)), 7.05-7.39 (m, 5H, ArH); MS m/e 193 (M\(^+\)).

**N,N-Diethyl O-2-anisylcarbamate (84b):**

bp 110-115°C/0.05 mm; IR (neat) \(\nu_{\text{max}}\) 1710 cm\(^{-1}\); NMR (CDCl\(_3\)) \(\delta\) 1.23 (t, J = 7, 6H, 2 CH\(_3\)), 3.42 (q, J = 7, 4H, 2 CH\(_2\)), 3.82 (s, 3H, OCH\(_3\)), 6.90-7.17 (m, 4H, ArH); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) (relative intensity) 13.3 (19, 2 CH\(_3\)), 42.0 (89, 2 CH\(_2\)), 55.7 (98, OCH\(_3\)), 112.4 (66, C-3), 120.4 (88, C-5), 123.1 (89, C-6), 125.8 (100, C-4), 140.7 (10, C-1), 153.8 (11, C-2), 151.6 (12, OCO); MS m/e 223 (M\(^+\)); Anal. Calcd for C\(_{12}\)H\(_{17}\)NO\(_3\): C, 64.55; H, 7.67; N, 6.27. Found: C, 64.46; H, 7.78; N, 6.16.

**N,N-Diethyl O-(2-Chloro)phenylcarbamate (84c):**

bp 88-90°C/0.02 mm; IR (neat) \(\nu_{\text{max}}\) 1720 cm\(^{-1}\); NMR (CDCl\(_3\)) \(\delta\) 1.1-1.26 (m, 6H, 2 CH\(_3\)), 3.34-3.49 (m, 4H, 2 CH\(_2\)), 7.03-7.45 (m, 4H,
ArH); $^{13}$C NMR (CDCl$_3$) $\delta$ (relative intensity) 13.1 (23, CH$_3$), 14.0 (21, CH$_3$), 42.0 (31, CH$_2$), 42.2 (31, CH$_2$), 124.0 (87, C-6), 126.03 (100, C-4), 127.0 (13, C-2), 127.3 (86, C-5), 129.8 (97, C-3), 147.6 (8, C-1), 152.8 (8, OCO); MS m/e 227 (M$^+$); Anal. Calcd for C$_{11}$H$_{14}$ClNO$_2$: C, 58.02; H, 6.19; N, 6.15. Found: C, 58.32; H, 6.46; N, 6.08.

**N,N-Diethyl 0-2-tolylcarbamate (81):**

bp 94-95°C/0.2 mm; IR (neat) $\nu_{\max}$ 1710 cm$^{-1}$; NMR (CDCl$_3$) $\delta$1.23 (t, J = 7, 6H, 2 CH$_3$), 2.21 (s, 3H, CH$_3$), 3.42 (q, J = 7, 4H, 2 CH$_2$), 7.06-7.24 (m, 4H, ArH); MS m/e 207 (M$^+$); Anal. Calcd for C$_{12}$H$_{17}$NO$_2$: C, 69.54; H, 8.26; N, 6.75. Found: C, 69.03; H, 8.38; N, 6.93.

**N,N-Diethyl 0-3-tolylcarbamate (84d):**

bp 88-89°C/ 0.02 mm; IR (neat) $\nu_{\max}$ 1715 cm$^{-1}$; NMR (CDCl$_3$) $\delta$1.21 (t, J = 7, 6H, 2 CH$_3$), 2.34 (s, 3H, CH$_3$), 3.40 (q, J = 7, 4H, 2 CH$_2$), 6.86-7.33 (m, 4H, ArH); MS m/e 207 (M$^+$); Anal. Calcd for C$_{12}$H$_{17}$NO$_2$: C, 69.54; H, 8.26; N, 6.75. Found: C, 69.27; H, 8.32; N, 7.02.

**N,N-Diethyl 0-4-tolylcarbamate (84e):**

bp 84-85°C/0.05 mm; IR (neat) $\nu_{\max}$ 1710 cm$^{-1}$; NMR (CDCl$_3$) $\delta$1.21 (t, J = 7, 6H, 2 CH$_3$), 2.32 (s, 3H, CH$_3$), 3.40 (q, J = 7, 4H, 2 CH$_2$), 6.97 (d, J = 8.6, 2H, ArH), 7.15 (d, J = 8.6, 2H, ArH); MS m/e 207 (M$^+$); Anal. Calcd for C$_{12}$H$_{17}$NO$_2$: C, 69.54; H, 8.26; N, 6.75. Found: C, 69.57; H, 8.40; N, 6.90.
N,N-Diethyl 0-3-anisylcarbamate (84f):
bp 122-124°/0.12 mm (lit.\textsuperscript{135} 138-140°/2.0 mm); IR (neat) $\nu_{\text{max}}$
1715 cm$^{-1}$; NMR (CDCl$_3$) $\delta$ 1.22 (t, J = 7, 6H, 2 CH$_3$), 3.40 (q, J =
7, 4H, 2 CH$_2$), 3.78 (s, 3H, OCH$_3$), 6.63-6.79 (m, 3H, ArH),
7.12-7.34 (m, 1H, ArH); MS m/e 223 (M$^+$).

N,N-Diethyl 0-1-naphthylcarbamate (95):
bp 135-140°/0.1 mm (lit.\textsuperscript{136} 201-202°/10-11 mm); IR (neat) $\nu_{\text{max}}$
1710 cm$^{-1}$; NMR (CDCl$_3$) $\delta$ 1.29 (m, 6H, 2 CH$_3$), 3.51 (m, 4H, 2 CH$_2$),
7.28-7.98 (m, 7H, ArH); MS m/e 243 (M$^+$).

N,N-Diethyl 0-2-naphthylcarbamate (97):
bp 120-122°/0.04 mm (lit.\textsuperscript{136} 203-205°/11 mm); IR (neat) $\nu_{\text{max}}$
1710 cm$^{-1}$; NMR (CDCl$_3$) $\delta$ 1.23 (t, J = 7, 6H, 2 CH$_3$), 3.43 (q, J =
7, 4H, 2 CH$_2$), 7.2-7.97 (m, 7H, ArH); MS m/e 243 (M$^+$).

N,N-Diethyl 0-(1-bromo)-2-naphthylcarbamate (101):
mp 77-78° (hexane); IR (CHCl$_3$) $\nu_{\text{max}}$ 1710 cm$^{-1}$; NMR (CDCl$_3$) $\delta$
1.15-1.42 (m, 6H, 2 CH$_3$), 3.30-3.59 (m, 4H, 2 CH$_2$), 7.23-7.85 (m, 5H, ArH), 8.19-8.31 (m, 1H, ArH); MS m/e 322, 324 (M$^+$); Anal.
Calcd for C$_{15}$H$_{16}$BrNO$_2$:  C, 55.91; H, 5.0; N, 4.34. Found: C, 55.97; H, 5.16; N, 4.28.

N,N-Dimethyl 0-phenylcarbamate (102):
bp 79-80°/0.04 mm (mp 43-44°) (lit.\textsuperscript{137} mp 45°C); IR (CHCl$_3$)
$\nu_{\text{max}}$ 1715 cm$^{-1}$; NMR (CDCl$_3$) $\delta$ 2.98, 3.05 (2s, 6H, 2 CH$_3$), 7.02-7.46
(m, 5H, ArH); MS m/e 165 (M$^+$).
N,N-Diethyl O-(2-N,N-diethylcarbamoyl)phenylcarbamate (115a):
bp 160-165°C/0.15 mm (lit134 180-185°C/1 mm); IR (neat) v max 1710, 1622 cm⁻¹; NMR (CDCl₃) δ 0.96-1.27 (m, 12H, 4 CH₃), 3.07-3.64 (m, 8H, 4 CH₂), 7.19-7.50 (m, 4H, ArH); ¹³C NMR (CDCl₃) δ (relative intensity) 11.8 (19, CH₃), 12.7 (84, CH₃), 13.4 (40, CH₃), 13.8 (88, CH₃), 42.1 (118, 2 CH₂), 42.8 (78, 2 CH₂), 123.2 (100, C-6), 124.9 (83, C-4), 126.6 (95, C-3), 129.4 (83, C-5), 130.6 (28, C-2), 147.4 (39, C-1), 153.45 (18, OCO), 167.59 (26, CO); MS m/e 292 (M⁺).

Compound 115a was also prepared from the lithiation of N,N-diethyl 0-phenylcarbamate 84a (s-BuLi-TMEDA) followed by quenching with N,N-diethylcarbamoyl chloride.⁶⁹

N,N-Diethyl O-(3-N,N-diethylcarbamoyl)phenylcarbamate (118a):
bp 130-135°C/0.03 mm; IR (neat) v max 1710 cm⁻¹; NMR (CDCl₃) δ 1.12-1.29 (m, 12H, 4 CH₃), 3.26-3.52 (m, 8H, 4 CH₂), 7.10-7.36 (m, 4H, ArH); ¹³C NMR (CDCl₃) δ (relative intensity) 13.4 (83, 4 CH₃), 39.8 (17, CH₂), 40.7 (16, CH₂), 41.2 (18, CH₂), 42.0 (21, CH₂), 119.8 (95, C-2), 122.1 (96, C-6), 122.5 (100, C-4), 129.0 (81, C-5), 138.1 (44, C-3), 151.3 (47, C-1), 153.6 (27, OCO), 170.0 (38, CO); MS m/e 292 (M⁺); Anal. Calcd for C₁₆H₂₄N₂O₃: C, 65.73; H, 8.27; N, 9.58. Found: C, 65.54; H, 8.29, N, 9.74.
N,N-Diethyl O-(4-N,N-diethylcarbamoyl)phenylcarbamate (121a):
bp 100-105°C/0.02 mm (lit\textsuperscript{134} 180-190°C/1 mm); IR (neat) $\nu_{\text{max}}$
1710, 1620 cm\textsuperscript{-1}; NMR (CDCl\textsubscript{3}) $\delta$1.08-1.31 (m, 12H, 4 CH\textsubscript{3}), 3.28-3.54
(m, 8H, 4 CH\textsubscript{2}), 7.15 (d, J = 8.5, 2H, H-2 and H-6), 7.39 (d, J =
8.5, 2H, H-3 and H-5); $^{13}$C NMR (CDCl\textsubscript{3}) $\delta$(relative intensity)
13.4 (69, 4 CH\textsubscript{3}), 42.0 (70, 4 CH\textsubscript{2}), 121.3 (99, C-2 and C-6),
127.2 (100, C-3 and C-5), 133.7 (32, C-4), 151.9 (28, C-1), 153.4
(16, OCO), 170.3 (24, CO); MS m/e 292 (M\textsuperscript{+}).

N,N-Diethyl O-(3-N,N-diethylcarbamoyloxy)phenylcarbamate (125):
bp 180-185°C/0.04 mm; IR (neat) $\nu_{\text{max}}$ 1715 cm\textsuperscript{-1}; NMR (CDCl\textsubscript{3}) $\delta$1.21
(t, J = 7, 12H, 4 CH\textsubscript{3}), 3.39 (q, J = 7, 8H, 4 CH\textsubscript{2}), 6.88-9.96 (m,
3H, ArH), 7.0-7.42 (m, 1H, ArH); $^{13}$C NMR (CDCl\textsubscript{3}) $\delta$(relative
intensity) 13.5 (53, 4 CH\textsubscript{3}), 41.9 (138, 4 CH\textsubscript{2}), 115.3 (64, C-2),
118.0 (100, C-4 and C-6), 128.8 (64, C-5), 151.7 (55, C-1 and
C-3), 153.5 (52, 2 OCO); MS m/e 308 (M\textsuperscript{+}); Anal. Calcd for
C\textsubscript{16}H\textsubscript{24}N\textsubscript{2}O\textsubscript{4}: C, 62.32; H, 7.84; N, 9.08. Found: C, 62.23; H,
7.80; N, 9.17.

N,N-Diethyl-2-hydroxybenzamide:
mp 99-100°C (CH\textsubscript{2}Cl\textsubscript{2}-hexane) (lit\textsuperscript{138} 104°C).

N,N-Diethyl-3-hydroxybenzamide:
mp 80-82°C (C\textsubscript{6}H\textsubscript{6}-hexane) (lit\textsuperscript{139} 84°C).

N,N-Diethyl-4-hydroxybenzamide:
mp 119-121°C (CH\textsubscript{2}Cl\textsubscript{2}-hexane) (lit\textsuperscript{138} 121-123°C).
N,N-Diethyl O-(2-hydroxy)phenylcarbamate:
mp 71-73°C (C6H6-hexane) (lit. 75°C); IR (CHCl3) νmax 3300, 1700 cm⁻¹; NMR (CDCl3) δ 1.13-1.31 (m, 6H, 2 CH3), 3.28-3.37 (m, 4H, 2 CH2), 6.51-7.17 (m, 4H, ArH); MS m/e 209 (M⁺).

N,N-Diethyl O-(3-hydroxy)phenylcarbamate:
mp 61-63°C (Et2O-hexane) (lit. mp 64-66°C); IR (CHCl3) νmax 3300, 1695 cm⁻¹; NMR (CDCl3) δ 1.12-1.36 (m, 6H, 2 CH3), 3.28-3.51 (m, 4H, 2 CH2), 6.87-7.27 (m, 4H, ArH); MS m/e 209 (M⁺). Anal. Calcd for C11H15NO3: C, 63.14; H, 7.22; N, 6.69. Found: C, 63.18; H, 7.36; N, 6.63.

N,N-Diethyl O-(4-hydroxy)phenylcarbamate:
mp 92-93°C (C6H6); IR (CHCl3) νmax 3200, 1700 cm⁻¹; NMR (CDCl3) δ 1.21 (t, J = 7, 6H, 2 CH3), 3.40 (q, J = 7, 4H, 2 CH2), 6.50-6.88 (ABq, J = 8.9, 4H, ArH), 7.24 (s, 1H, OH exchanged with D2O); MS m/e 209 (M⁺). Anal. Calcd for C11H15NO3: C, 63.14; H, 7.22; N, 6.69. Found: C, 63.49; H, 7.29; N, 6.69.

N,N-Diethyl O-(2-methoxymethoxy)phenylcarbamate (115b):
bp 75-78°C/0.1 mm; IR (neat) νmax 1710 cm⁻¹; NMR (CDCl3) δ 1.23 (t, J = 6.9, 6H, 2 CH3), 3.43 (q, J = 6.9, 4H, 2 CH2), 3.47 (s, 3H, OCH3), 5.15 (s, 2H, OCH2O), 6.99-7.16 (m, 4H, ArH); 13C NMR (CDCl3) δ (relative intensity) 13.6 (96, 2 CH3), 42.1 (157, 2 CH2), 56.0 (74, OCH3), 95.0 (87, OCH2O), 116.3 (91, C-3), 122.0 (95, C-5), 123.3 (96, C-6), 125.9 (100, C-4), 141.4 (30, C-1), 149.2 (35, C-2), 153.8 (26, COO). MS m/e 253 (M⁺);
Anal. Calcd for C_{13}H_{19}NO_4: C, 61.64; H, 7.56; N, 5.52. Found: C, 61.94; H, 7.67; N, 5.25.

**N,N-Diethyl 0-(3-methoxymethoxy)phenylcarbamate:**
mp 80-84°C/0.1 mm; IR (neat) \( \nu_{\text{max}} \) 1710 cm\(^{-1}\); NMR (CDCl\(_3\)) \( \delta \) 1.21 (t, J = 7, 6H, 2 CH\(_3\)), 3.42 (q, J = 7, 4H, 2 CH\(_2\)), 3.45 (s, 3H, OCH\(_3\)), 5.15 (s, 2H, OCH\(_2\)), 6.72-7.26 (m, 4H, ArH); \(^{13}\)C NMR (CDCl\(_3\)) \( \delta \) (relative intensity) 13.9 (55, 2 CH\(_3\)), 42.1 (126, 2 CH\(_2\)), 56.0 (83, OCH\(_3\)), 94.5 (88, OCH\(_2\)), 110.1 (93, C-2), 113.0 (97, C-4), 115.2 (90, C-6), 129.5 (100, C-5), 152.4 (53, C-1), 158.0 (47, C-3), 154.0 (35, OCO); MS m/e 253 (M\(^+\)); Anal. Calcd for C\(_{13}H_{19}NO_4\): C, 61.64; H, 7.56; N, 5.52. Found: C, 61.65; H, 7.76; N, 5.26.

**N,N-Diethyl 0-(4-methoxymethoxy)phenylcarbamate (121b):**
bp 85-88°C/1.0 mm; IR (neat) \( \nu_{\text{max}} \) 1710 cm\(^{-1}\); NMR (CDCl\(_3\)) \( \delta \) 1.21 (t, J = 7, 6H, 2 CH\(_3\)), 3.41 (q, J = 7, 4H, 2 CH\(_2\)), 3.45 (s, 3H, OCH\(_3\)), 5.13 (s, 2H, OCH\(_2\)), 7.01 (s, 4H, ArH); \(^{13}\)C NMR (CDCl\(_3\)) \( \delta \) (relative intensity) 13.6 (24, 2 CH\(_3\)), 41.8 (55, 2 CH\(_2\)), 55.5 (35, OCH\(_3\)), 94.6 (45, OCH\(_2\)), 116.6 (100, C-3 and C-5), 122.3 (78, C-2 and C-6), 146.0 (32, C-1), 154.3 (24, C-4), 154.1 (20, OCO); MS m/e 253 (M\(^+\)); Anal. Calcd for C\(_{13}H_{19}NO_4\): C, 61.64; H, 7.56; N, 5.52. Found: C, 61.81; H, 7.72; N, 5.25.

**4.2.3. EXPERIMENTAL DETAILS ON LITHIATION**

**N,N-Diethyl-0-(2-deutero)phenylcarbamate (85a).**

According to procedure A, lithiation of N,N-diethyl-0-phenylcar-
bamate 84a (2.0 g, 10.36 mmol), s-BuLi (8.97 mL, 11.39 mmol),
TMEDA (1.72 mL, 11.39 mmol), -78°C, 1h, ethanol-d₄ (0.67 mL, 11.39
mmol) and standard workup followed by column chromatography using
1:4 (v/v) EtOAc-hexane afforded 1.9 g (95%) of compounds 85a
(4%d₀, 96% d₁), bp 65-70°C/0.25 mm; IR (neat) νₓ max 1710 cm⁻¹; NMR
(CDCl₃) δ 1.22 (t, J = 7.5, 6H, 2 CH₃), 3.40 (q, J = 7.5), 7.0-7.4
(m, 4H, ArH); MS m/e 194 (M⁺).

N,N-Diethyl 0-(2-allyl)phenylcarbamate (85b).

According to procedure A, lithiation of N,N-Diethyl 0-phenylcarb-
amate 84a (700 mg, 3.59 mmol), s-BuLi (3.02 mL, 3.98 mmol), TMEDA
(0.60 mL, 3.98 mmol), -78°C, 1h, allyl bromide (0.34 mL, 3.98
mmol) and standard workup followed by column chromatography using
1:9 (v/v) EtOAc-hexane as eluent gave 633 mg (75%) of compound, bp
75-78°C/0.25 mm; IR (neat) νₓ max 1710 cm⁻¹; NMR (CDCl₃) δ 1.33-1.69
(m, 6H, 2 CH₃), 3.30-3.64 (m, 4H, 2 CH₂ and 2H, CH₂-CH=), 4.90-
5.26 (m, 2H, CH=CH₂), 5.70 -6.20 (m, 1H, CH=), 6.98-7.54 (m, 4H,
ArH); Anal. Calcd for C₁₄H₁₉NO₂: C, 72.07; H, 8.20; N, 6.00.
Found: C, 71.62; H, 8.47; N, 6.14.

N,N-Diethyl 0-(2-methoxy-6-trimethylsilyl)phenylcarbamate (85c).

According to procedure A, lithiation of N,N-diethyl-0-2-anisylcarb-
amate 84b (500 mg, 2.24 mmol), s-BuLi (1.94 mL, 2.46 mmol), TMEDA
(0.37 mL, 2.46 mmol), -78°C, 1h, TMSCl (0.31 mL, 2.46 mmol, and
standard workup followed by column chromatography using 1:5 (v/v)
EtOAc-hexane as eluent afforded 449 mg (65%) of compound 85c, bp
108-112°C/0.1 mm; IR (neat) νₓ max 1710 cm⁻¹; NMR (CDCl₃) δ 0.03
(s, 9H, Si(CH₃)₃), 1.1-1.45 (m, 6H, 2 CH₃), 3.25-3.65 (m, 4H, 2 CH₂), 3.85 (s, 3H, OCH₃), 6.90-7.30 (m, 3H, ArH); ¹³C NMR (CDCl₃) δ (relative intensity) 0.79 (199, Si(CH₃)₃), 13.3 (47, 2 CH₃), 14.0 (46, 2 CH₃), 41.9 (70, 2 CH₂), 42.0 (67, 2 CH₂), 55.9 (91, OCH₃), 113.8 (82, C-3), 125.7 (76, C-4), 125.8 (100, C-5), 133.21 (13, C-6), 145.50 (7, C-1), 151.3 (14, C-2), 153.9 (10, OCO); MS m/e 295 (M⁺); Anal. Calcd for C₁₅H₂₅NO₂Si: C, 60.98; H, 8.52; N, 4.74. Found: C, 60.70; H, 8.59; N, 4.62.

N,N-Diethyl O-(2-N,N-diethylcarbamoyl-6-methoxy)phenylcarbamate (85d).

According to procedure A, lithiation of N,N-diethyl 0-2-anisylcarbamate 84b (500 mg, 2.24 mmol), s-BuLi (2.07 mL, 2.46 mmol), TMEDA (0.37 mL, 2.46 mmol), -78°C, 1h, N,N-diethylcarbamoyl chloride (0.30 mL, 2.46 mmol) and workup in the usual manner followed by column chromatography using 1:4 (v/v) EtOAc-hexane as eluent afforded 648 mg (90%) of compound 85d, bp 135-138°C/0.1 mm; IR (neat) νmax 1715, 1620 cm⁻¹; NMR (CDCl₃) δ 0.88-1.32 (m, 12H, 4 CH₃), 3.10-3.75 (m, 8H, 4 CH₂), 3.80 (s, 3H, OCH₃), 6.82 (dd, J = 7.3, 1.7, H-3), 6.95 (dd, J = 8.2, 1.7, H-5), 7.18 (dd, J = 7.3, 8.2, H-4); ¹³C NMR (CDCl₃) δ (relative intensity) 12.6 (91, 2 CH₃), 13.8 (104, 2 CH₃), 38.5 (90, CH₂), 42.3 (112, 2 CH₂), 42.8 (82, CH₂), 56.2 (98, OCH₃), 112.8 (80, C-5), 118.1 (86, C-3), 126.0 (100, C-4), 132.5 (30, C-2), 137.0 (15, C-1), 152.4 (26, C-6), 153.2 (22, OCO), 167.3 (25, CO); MS m/e 322
(M\(^+\)); Anal. Calcd for C\(_{17}\)H\(_{26}\)N\(_2\)O\(_4\): C, 63.39; H, 8.15; N, 8.69. Found: C, 63.51; H, 8.28, N, 9.12.

**N,N-Diethyl O-(2-chloro-6-trimethylsilyl)phenyl carbamate (85e).**

According to procedure A, lithiation of N,N-diethyl 0-(2-chloro)phenyl carbamate 84e (500 mg, 2.19 mmol), s-BuLi (1.90 mL, 2.41 mmol), TMEDA (0.36 mL, 2.41 mmol), -78°C, 1 h, TMSCl (0.30 mL, 2.41 mmol) and standard workup followed by column chromatography using 1:4 (v/v)EtOAc-hexane as eluent afforded 520 mg (79%) of compound 85e, bp 78-80°C/0.02 mm; IR (neat) \(\nu_{\text{max}}\) 1720 cm\(^{-1}\); NMR (CDCl\(_3\)) \(\delta\) 0.12 (s, 9H, 3 Si(CH\(_3\))\(_3\)), 1.01-1.29 (m, 6H, 2 CH\(_3\)), 3.26-3.45 (m, 4H, 2 CH\(_2\)), 6.97 (dd, J = 7.6, H-4), 7.18 (dd, J = 7.6, 1.5, H-5), 7.25 (dd, J = 7.6, 1.5, H-3), MS m/e 284, 286 (M\(^+\)-CH\(_3\)), 264 (9.69), 186 (0.34), 184 (0.88), 100 (100, 72 (59.4)); Anal. Calcd for C\(_{14}\)H\(_{22}\)ClN\(_2\)O\(_2\)Si: C, 56.06; H, 7.39; N, 4.67. Found: C, 56.14; H, 7.52; N, 4.57.

**N,N-Diethyl O-(2-chloro-6-iodo)phenyl carbamate (85f).**

According to procedure A, lithiation of N,N-diethyl 0-(2-chloro)phenyl carbamate 84e (500 mg, 2.19 mmol), s-BuLi (1.90 mL, 2.41 mmol), TMEDA (0.36 mL, 2.41 mmol), -78°C, 1 h, iodine (624 mg, 2.41 mmol), standard workup and purification by column chromatography (1:4 EtOAc-hexane as eluent) gave 722 mg (93%) of compound 85f, bp 85-9°C/0.05 mm; IR (neat) \(\nu_{\text{max}}\) 1720 cm\(^{-1}\); NMR (CDCl\(_3\)) \(\delta\) 1.14-1.71 (m, 6H, 2 CH\(_3\)), 3.28-3.66 (m, 4H, 2 CH\(_2\)), 6.86 (t, J = 7.8, 1H, H-4), 7.39 (dd, J = 7.8, 1.56, 1H, H-5), 7.69 (dd, J = 7.8, 1.56, 1H, H-3); HRMS m/e 352.9678; Calc. for C\(_{11}\)H\(_{13}\)ClINO\(_2\): 352.9680.
N,N-Diethyl O-(2-N,N-diethylcarbamoyl-6-chloro)phenyl carbamate (85g).

According to procedure A, lithiation of N,N-diethyl O-(2-chloro)phenyl carbamate 84c (500 mg, 2.19 mmol), s-BuLi (1.90 mL, 2.41 mmol), TMEDA (0.36 mL, 2.41 mmol), -78°C, 1h, N,N-diethylcarbamoyl chloride (0.30 mL, 2.41 mmol), standard workup and purification by column chromatography (1:1 EtOAc-hexane as eluent) afforded 559 mg (78%) of compound 85g, bp 130-3°C/0.04 mm; IR (neat) ν max 1720 1630 cm⁻¹; NMR (CDCl₃) δ 0.96-1.34 (m, 12H, 4 CH₃), 3.18-3.56 (m, 8H, 4 CH₂), 7.14-7.20 (m, 2H, ArH), 7.41 (m, 1H, ArH); ¹³C NMR (CDCl₃) δ (relative intensity) 12.6 (86, CH₃), 13.4 (58, CH₃), 13.9 (85, CH₃), 14.1 (59, CH₃), 38.7 (86, CH₃), 42.4 (66, CH₂), 42.6 (65, CH₂), 42.9 (96, CH₂), 124.9 (86, C-3), 126.3 (93, C-4), 129.0 (15, C-6), 130.4 (100, C-5), 133.6 (13, C-2), 145.0 (7, C-1), 153.0 (9, OC=O), 167.0 (12, CO); MS m/e 326, 328 (M⁺); Anal. Calcd for C₁₆H₂₃ClN₂O₃: C, 58.79; H, 7.09; N, 8.57. Found: C, 58.71; H, 7.12; N, 8.79.

N,N-Diethyl O-(3-methyl-6-trimethylsilyl)phenyl carbamate (85h).

According to procedure A, lithiation of N,N-diethyl 0-3-tolyl carbamate 84d (620 mg, 2.99 mmol), s-BuLi (2.61 mL, 3.29 mmol), TMEDA (0.49 mL, 3.29 mmol), -78°C, 1h, TMSCl (0.42 mL, 2.99 mmol), standard workup and column chromatography using 1:9 EtOAc-hexane as eluent afforded 646 mg (77%) of compound 85h, bp 88-92°C/0.1 mm; IR (neat) ν max 1710 cm⁻¹; NMR (CDCl₃) δ 0.30 (s, 9H, Si (CH₃)₃), 1.05-1.45 (m, 6H, 2 CH₃), 2.35 (s, 3H, CH₃), 3.25-3.65
(m, 4H, CH₃), 6.85 (s, H-6), 7.05 (d, J = 7.5, H-3), 7.38 (d, J = 7.5, H-4); MS m/e 279 (M⁺). Anal. Calcd for C₁₅H₂₅NO₂Si: C, 64.47; H, 9.01; N, 5.01. Found: C, 64.76; H, 9.03; n, 4.90.

Compound 84d when subjected to lithiation using LDA, according to procedure B, the product 85h was obtained in only 39% yield.

**N,N-Diethyl O-(4-methyl-6-trimethylsilyl)phenyl carbamate (85i).**

According to procedure A, lithiation of N,N-diethyl O-4-tolyl carbamate 84e (500 mg, 2.41 mmol), s-BuLi (2.10 mL, 2.65 mmol), TMEDA (0.40 mL, 2.65 mmol), -78°C, 1h, TMSCl (0.34 mL, 2.65 mmol), standard workup followed by recrystallization afforded 559 mg (83%) of compound 85i, mp 53-54°C (hexane); IR (CHCl₃) ν max 1710 cm⁻¹; NMR (CDCl₃) δ 0.29 (s, 9H, Si (CH₃)₃), 1.18-1.36 (m, 6H, 2 CH₃), 2.35 (s, 3H, CH₃), 3.37, 3.55 (m, 4H, 2 CH₂), 6.92 (d, J = 8.2, 1H, H-6), 7.16 (dd, J = 8.2, 1.8, 1H, H-5), 7.22 (d, J = 1.8, 1.8, 1H, H-3); MS m/e 279 (M⁺); Anal. Calcd for C₁₅H₂₅NO₂Si: C, 64.47; H, 9.01; N, 5.01. Found: C, 64.63; H, 9.10; N, 5.07.

When 84e (500 mg, 2.41 mmol) was subjected to lithiation using LDA (2.65 mmol), -78°C, 1h, TMSCl (0.34 mL, 2.65 mmol), according to procedure B, 105 mg (16%) of the product 85i was obtained which was shown to be identical with the material prepared by the method described above.

**N,N-Diethyl O-(3-methoxy-2-methyl)phenyl carbamate (85j) and N,N-Diethyl O-(3-methoxy-6-methyl)phenyl carbamate (85k).**

According to procedure A, lithiation of N,N-Diethyl O-3-anisyl carbamate (1.52 g, 6.79 mmol), s-BuLi (6.61 mL, 7.47 mmol), TMEDA
(1.13 mL, 7.47 mmol), -78°C, 1h, methyl iodide (1.5 mL, excess) and standard workup gave 1.50 g (93%) of product consisting of 85j and 85k in the ratio of 73:27 (by interaction of the CH₃ signal at 1.95 and 2.1 in ¹H NMR). The two isomers were unresolved by G.C. Purification by column chromatography (1:9 (v/v) EtOAc-hexane as eluent) followed by recrystallization gave pure 85j, mp 58-60°C (hexane); IR (CHCl₃) ν_max 1710 cm⁻¹; NMR (DMSO-d₆) δ 1.00-1.40 (m, 6H, 2 CH₃), 1.95 (s, 3H, CH₃), 3.10-3.60 (m, 4H, 2 CH₂), 3.79 (s, 3H, OCH₃), 6.66 (d, J = 8.0 1H, H-6), 6.82 (d, J = 8.0, 1H, H-4), 7.163 (dd, J = 8.0, 1H, H-4) MS m/e 237 (M⁺); Anal. Calcd for C₁₃H₁₉N₀₃: C, 65.80; H, 8.07; N, 5.90. Found: C, 66.09; H, 8.19; N, 5.96.

Compound 85k was contaminated with 85j which could not be removed. Therefore satisfactory spectral and analytical data for - 85k were not obtained.

**N,N-Diethyl O-(2- N,N-diethylcarbamoyl)-1-naphthylcarbamate (96).**

According to procedure A, lithiation of N,N-diethyl 0-1-naphthylcarbamate 95 (500 mg, 2.05 mmol), s-BuLi (1.88 mL, 2.26 mmol), TMEDA (0.34 mL, 2.26 mmol), -78°C, 1h, N,N-diethylcarbamoyl chloride, standard workup and purification by column chromatography (1:1 EtOAc-hexane as eluent) yielded 550 mg (78%) of compound 96, bp 170-180°C/0.3 mm; IR (neat) ν_max 1710, 1620 cm⁻¹; NMR (CDCl₃) δ 0.98-1.44 (m, 12H, 4 CH₃), 3.26-3.68 (m, 8H, 4 CH₂), 7.33 (d, J = 8.4, H-3), 7.44-7.90 (m, 5H, ArH); Ms m/e 342 (M⁺); Anal. Calcd for C₂₀H₂₆N₂O₃: C, 70.15; H, 7.65; N, 8.18. Found: C, 70.14; H, 7.75; N, 8.20.
N,N-Diethyl 0-(3-trimethylsilyl)-2-naphthylcarbamate (98a),
N,N-Diethyl 0-(1-trimethylsilyl)-2-naphthylcarbamate (99a) and
N,N-Diethyl-3-hydroxy-2-naphthamide (100).

According to procedure A, lithiation of N,N-diethyl 0-2-naphthyl-
carbamate 97 (500 mg, 2.05 mmol), s-BuLi (1.78 mL, 2.26 mmol),
TMEDA (0.34 mL, 2.26 mmol), -78°C, 1h, THSCL (0.29 mL, 2.25 mmol),
standard workup and column chromatography (1:9 EtOAc-hexane as
eluent) gave a mixture of compound 98a and its isomer 99a (62%
overall) in a ratio of 70:30 (by NMR, δ of Si(CH₃)₃ 0.30 & 0.55)
and the rearranged product 100 (20%). The compound 98a was
isolated from 99a by fractional recrystallization, mp 63-64°C
(hexane); IR (CHCl₃) ν max 1710 cm⁻¹; NMR (CDCl₃) δ 0.30 (s, 9H,
Si(CH₃)₃), 1.09-1.37 (m, 6H, 2 CH₃), 3.34-3.53 (m, 4H, 2 CH₂),
7.20-7.89 (m, 6H, ArH); MS m/e 315 (M⁺); Anal. Calcd for
C₁₈H₂₅NO₂Si: C, 68.57; H, 7.98; N, 4.43. Found: C, 69.00; H,
8.15; N, 4.72.

Compound 99a was contaminated with 98a, so satisfactory spectral
data were not obtained.

Compound 100, mp 169-171°C (C₆H₆-hexane) (lit.¹⁴₀ mp 170-171°C);
IR (CHCl₃) ν max 3200, 1620 cm⁻¹; NMR (CDCl₃) δ 1.32 (t, J = 7,
6H, 2 CH₃), 3.59 (q, J = 7, 4H, 2 CH₂), 7.25-7.78 (m, 6H, ArH),
8.96 (br, 1H, OH, exchanged with D₂O); MS m/e 243 (M⁺).

Compound 99a was, however, prepared from N,N-diethyl 1-(bromo)-2-
naphthylcarbamate 101 by metal halogen exchange as follows:
t-BuLi (0.90 mL, 1.70 mmol) was injected to a stirred THF solution
(50 mL) of N,N-diethyl 0-(1-bromo)-2-naphthylcarbamate 101 (500
mg, 1.55 mmol) at -78°C under nitrogen and after 1 h, TMSCl (0.22 mL, 1.70 mmol) was added. Workup in the usual manner and purification by column chromatography afforded 398 mg (81%) of compound-99a as an oil whose spectral (NMR, GC) data were shown to be non-identical to those for 98a; IR (neat) νmax 1710 cm⁻¹; NMR (CDCl₃) δ 0.55 (Si(CH₃)₃), 1.02-1.42 (m, 6H, 2 CH₃), 3.35-3.70 (m, 4H, 2 CH₂), 7.08-8.30 (m, 6H, ArH); MS m/e 315 (M⁺).

**N,N-Diethyl O-(3-N,N-diethylcarbamoyl)-2-naphthylcarbamate (98b).**

According to procedure A, lithiation of N,N-diethyl O-2-naphthylcarbamate 97 (500 mg, 2.05 mmol), s-BuLi (1.78 mL, 2.26 mmol), TMEDA (0.34 mL, 2.26 mmol), -78°C, 1 h, N,N-diethylcarbamoyl chloride (0.28 mL, 2.26 mmol), standard workup and purification by column chromatography using 1:1 (v/v) EtOAc-hexane as eluent afforded 358 mg (51%) of compound 98b as a viscous oil, IR (neat) νmax 1710, 1625 cm⁻¹; NMR (CDCl₃) δ 0.83-1.43 (m, 12H, 4 CH₃), 3.07-3.83 (m, 8H, 4 CH₂), 7.33-7.90 (m, 6H, ArH); HRMS m/e 342.1926; Calcd for C₂₀H₂₆N₂O₃: 342.1944; and compound 100 (25%).

**N,N-Diethyl O-(1-N,N-diethylcarbamoyl)-2-naphthylcarbamate (99b).**

t-BuLi (0.90 mL, 1.70 mmol) was injected to a stirred THF solution (50 mL) of N,N-diethyl O-(1-bromo)-2-naphthylcarbamate 101 (500 mg, 1.55 mmol) at -78°C and after 1 h, N,N-diethylcarbamoyl chloride (0.21 mL, 1.70 mmol) was added. Standard workup followed by column chromatography using 1:1 EtOAc-hexane as eluent afforded 165 mg (31%) of compound 99b, IR (neat) νmax 1710, 1620 cm⁻¹; NMR (CDCl₃) δ 0.844-1.42 (m, 12H, 4 CH₃), 3.07-3.82 (m, 8H, 4 CH₂), 7.32-7.90 (m, 6H, ArH); MS m/3 342 (M⁺).
The spectral data (NMR, GC) of 99b was shown to be non identical to those of 98b described in the previous experiment.

**N,N-Dimethyl O-2-tolylicarbamate (103a).**

According to procedure, lithiation of N,N-dimethyl O-phenylcarbamate 102 (500 mg, 3.03 mmol), s-BuLi (2.97 mL, 3.33 mmol), TMEDA (0.50 mL, 3.33 mmol), -95°C, 10 min, methyl iodide (0.5 mL, excess), standard workup and purification by column chromatography using 1:9 (v/v) EtOAc-hexane as eluent afforded 485 mg (90%) of compound 103a, bp 80-81°C/0.05 mm (lit. 115-117°C/0.3 mm); IR (neat) ν<sub>max</sub> 1710 cm<sup>-1</sup>; NMR (CDCl<sub>3</sub>) δ 2.20 (s, 3H, CH<sub>3</sub>), 3.01, 3.09 (2 s, 6H, 2 CH<sub>3</sub>), 7.0-7.23 (m, 4H, ArH); MS m/e 179 (M<sup>+</sup>).

**N,N-Dimethyl O-(2-N,N-diethylcarbamoyl)phenylcarbamate (103b).**

According to procedure A, lithiation of N,N-dimethyl O-phenylcarbamate 102 (500 mg, 3.03 mmol), s-BuLi (2.90 mL, 3.33 mmol), TMEDA (0.50 mL, 3.33 mmol), -95°C, 10 min, N,N-diethylcarbamoyl chloride (0.41 mL, 3.33 mmol), standard workup followed by column chromatography using 1:1 (v/v) EtOAc-hexane as eluent afforded 626 mg (78%) of compound 103b, bp 110-114°C/0.05 mm; IR (neat) ν<sub>max</sub> 1710, 1620 cm<sup>-1</sup>; NMR (CDCl<sub>3</sub>) δ 0.95-1.3 (n, 6H, 2 CH<sub>3</sub>), 3.0 and 3.08 (2 s, 6H, 2 CH<sub>3</sub>), 3.08 - 3.8 (m, 4H, 2 CH<sub>2</sub>), 7.05 - 7.5 (m, 4H, ArH); MS m/e 264 (M<sup>+</sup>): Anal. Calcd for C<sub>14</sub>H<sub>20</sub>N<sub>2</sub>O<sub>3</sub>: C, 63.62; H, 7.62; N, 10.59. Found: C, 63.77; H, 7.65; N, 10.30.

**N,N-Dimethyl O-(2-deutero)phenylcarbamate (103c).**

According to procedure A, lithiation of N,N-dimethyl O-phenylcarbamate 102 (500 mg, 3.03 mmol), s-BuLi (2.27 mL, 3.33 mmol), TMEDA
(0.50 mL, 3.33 mmol), -95°C, 10 min, ethanol-d$_1$ 0.5 mL, excess), standard workup and column chromatography using 1:9 (v/v) EtOAc-hexane as eluent afforded 415 mg (83%) of compound 103c (47% d$_0$, 53% d$_1$); bp 88-92°C/0.1 mm; IR (neat) $\nu_{\text{max}}$ 1710 cm$^{-1}$; NMR (CDCl$_3$) $\delta$ 2.98, 3.05 (2 s, 6H, 2 CH$_3$), 7.06-7.32 (m, 4H, ARH); MS m/e 166 (M$^+$).

**N,N-Dimethyl O-(2-trimethylsilyl)phenyl carbamate (103d).**

According to procedure A, lithiation of N,N-dimethyl 0-phenylcarbamate 102 (500 mg, 3.03 mmol), s-BuLi (2.97 mL, 3.33 mmol), TMEDA (0.50 mL, 3.33 mmol), -95°C, 10 min, TMSCl (0.43 mL, 3.33 mmol), standard workup and purification by column chromatography using 1:9 (v/v) EtOAc-hexane as eluent afforded 630 mg (88%) of compound 103d, bp 70-75°C/0.01 mm; IR (neat) $\nu_{\text{max}}$ 1715 cm$^{-1}$; NMR (CDCl$_3$) $\delta$ 0.26 (s, 9H, Si(CH$_3$)$_3$), 2.98, 3.04 (2 s, 6H, 2 CH$_3$), 7.13-7.24 (m, 4H, ArH); MS m/e 222 (M$^+-\text{CH}_3$); HRMS m/e 222.0948; Calcd. for C$_{11}$H$_{16}$NO$_2$Si: 222.095 (M$^+-\text{CH}_3$).

**N,N-Dimethyl-2-hydroxybenzamide (104).**

According to procedure C, lithiation of N,N-dimethyl 0-phenylcarbamate 102 (500 mg, 3.03 mmol), s-BuLi (2.64 mL, 3.33 mmol), TMEDA (0.50 mL, 3.33 mmol), -95°C, 5.5h, and quenching at -95°C with saturated aqueous MH$_4$Cl solution gave after standard workup 491 mg of a crude product which upon recrystallization afforded 430 mg (86%) of compound 104, mp 155-156°C (CH$_2$Cl$_2$) (lit. 142, 161-164°C); IR (CHCl$_3$) $\nu_{\text{max}}$ 3200, 1620 cm$^{-1}$; NMR (CDCl$_3$) $\delta$ 3.16 (s, 6H, 2 CH$_3$), 6.73-7.42 (m, 4H, ArH), 9.96 (br s, 1H, OH exchanged with D$_2$O); MS m/e 165 (M$^+$).
N,N-Diethyl-2-hydroxy-3-chlorobenzamide (107a).

According to procedure C, lithiation of N,N-diethyl 0-(2-chloro)phenyl carbamate 84c (500 mg, 2.19), s-BuLi (1.90 mL, 2.41 mmol), TMEDA (0.36 mL, 2.41 mmol), -78°C, standard workup and column chromatography using 1:1 (v/v) EtOAc-hexane as eluent afforded 364 mg (72%) of compound 107a, bp 105-108°C/0.25 mm; IR (neat) ν_max 3200, 1610 cm⁻¹; NMR (CDCl₃) δ 1.25 (t, J = 7, 6H, 2 CH₃), 3.49 (q, J = 7, 2 CH₂), 6.81 (dd, J = 7.8, H-5), 7.18 (dd, J = 7.82, 1.56, H-6), 7.38 (dd, J = 7.8, 1.56, H-4), 9.58 (br s, 1H, OH, exchanged with D₂O); MS m/e 227, 229 (M⁺); Anal. Calcd for C₁₁H₁₄ClN₂O: C, 58.01; H, 6.19; N, 6.15. Found: C, 58.32; H, 6.23; N, 6.04.

N,N-Diethyl-2-hydroxy-4-methylbenzamide (107b).

According to procedure C, lithiation of N,N-diethyl 0-(3-methyl)phenyl carbamate 84d (500 mg, 2.41 mmol), s-BuLi (1.82 mL, 2.65 mmol), TMEDA (0.40 mL, 2.65 mmol), -78°C, standard workup followed by column chromatography using 1:1 (v/v) EtOAc-hexane as eluent afforded 240 mg (48%) of compound 107b, np 104-105°C (CH₂Cl₂/hexane), IR (CHCl₃) ν_max 3200, 1630 cm⁻¹; NMR (CDCl₃) δ 1.26 (t, J = 7, 6H, 2 CH₃), 2.31 (s, 3H, CH₃), 3.51 (q, J = 7, 4H, 2 CH₂), 6.60 (s, H-3), 6.75 (d, J = 8.2, H-5), 7.16 (d, J = 8.2, H-6), 9.6 (br, 1H, OH, exchanged with D₂O); MS m/e 207 (M⁺); Anal. Calcd for C₁₂H₁₇NO₂: C, 69.54; H, 8.26; N, 6.75. Found: C, 69.24; H, 7.92; N, 6.85.
N,N-Diethyl-2-hydroxy-5-methylbenzamide (107c).
According to procedure C, lithiation of N,N-diethyl-0-(4-methyl)-phenyl carbamate 84e (500 mg, 2.41 mmol), s-BuLi (2.06 mL, 2.65 mmol), TMEDA (0.40 mL, 2.65 mmol), -78°C, standard workup and purification by column chromatography using 1:1 EtOAc-hexane as eluent afforded 350 mg (70%) of compound 707c, mp 110-111°C (benzene); IR (CHCl₃) ν_max 3200, 1630 cm⁻¹; NMR (CDCl₃) δ 1.28 (t, J = 7, 6H, 2 CH₃), 2.28 (s, 3H, CH₃), 3.52 (q, J = 7, 2 CH₂), 6.88 (d, J = 7, H-4), 7.05 (s, H-6), 7.20 (d, J = 7, H-3); 9.20 (br s, 1H, OH, exchanged with D₂O); MS m/e 207 (M⁺); Anal. Calcd for C₁₂H₁₇NO₂: C, 69.54; H, 8.26; N, 6.75. Found: C, 69.56; H, 8.00; N, 6.62.

N,N-Diethyl-1-hydroxy-2-naphthamide (108).
According to procedure C, lithiation of N,N-diethyl 0-2-naphthyl carbamate 95 (850 mg, 3.08 mmol), s-BuLi/3.20 mL, 3.39 mmol), TMEDA (0.51 mL, 3.39 mmol), -78°C, standard workup followed by column chromatography using 1:4 (v/v) EtOAc-hexane as eluent afforded 535 mg (715) of compound 108, bp 120-125/0.1 mm (lit. 143 130-133°C/1 mm); IR (neat) ν_max 3200, 1620 cm⁻¹; NMR (CDCl₃) δ 1.30 (t, J = 7, 6H, 2 CH₃), 3.55 (q, J = 7, 4H, 2 CH₂), 7.2-7.8 (m, 5H, ArH), 8.25-8.45 (m, 1H, H-8), 11.3 (br, 1H, OH, exchanged with D₂O); MS m/e 243 (M⁺).

N,N-Diethyl-3-hydroxy-2-naphthalamide (100) and N,N-Diethyl-2-hydroxy-1-naphthamide (109).
According to procedure C, lithiation of N,N-diethyl 0-2-naphthyl
carbamate 97 (500 mg, 2.05 mmol), s-BuLi (1.78 mL, 2.26 mmol), TMEDA (0.34 mL, 2.26 mmol), -78°C, standard workup and column chromatography using 1:1 (v/v) EtOAc-hexane as eluent afforded 215 mg (43%) of compound 100 140 and 185 mg (37%) of compound 109, mp 198-200°C (CH₂Cl₂); IR (CHCl₃) ν max 3200, 1620 cm⁻¹; NMR (CDCl₃) δ 1.06-1.24 (m, 6H, 2 CH₃), 3.15-3.68 (m, 4H, 2 CH₂), 6.73-7.74 (m, 6H, ArH), 8.52 (br, 1H, OH, exchanged with D₂O); MS m/e 243 (M⁺);
Anal. Calcd for C₁₅H₁₇N₂O₂: C, 74.05; H, 7.04; N, 5.75. Found: C, 73.82; H, 7.1; N, 5.83. Compound 109 was found to be identical with authentic sample prepared as described below.

t-BuLi (0.75 mL, 1.39 mmol) was injected to a stirred THF solution (50 mL) of N,N-diethyl 0-(1-bromo)-2-naphthyl carbamate (450 mg, 1.39 mmol) at -78°C under nitrogen. The stirred solution was then allowed to warm to room temperature over 8h. Standard workup followed by recrystallization gave 350 mg (77%) of compound 109 (by mp, H NMR, G.C.).

N,N-Dimethyl-2-hydroxy-3-methylbenzamide (110) and N,N-Dimethyl-2--(2-hydroxyphenyl)acetamide (111).

According to procedure C, lithiation of N,N-dimethyl 0-2-tolyllcarbamate 103a (677 mg, 3.78 mmol), s-BuLi (3.27 mL, 4.16 mmol), TMEDA (0.63 mL, 4.16 mmol), -100°C, warming to room temperature, standard workup and column chromatography using 1:1 (v/v) EtOAc-hexane as eluent chromatography afforded compound 110 (56%), mp 45°C (CH₂Cl₂); IR (neat) ν max 3200, 1620 cm⁻¹; NMR (CDCl₃) δ 2.26 (s, 3H, CH₃), 3.14 (s, 6H, 2 CH₃), 6.73 (dd, J = 7.7, 1H, H-5),
7.16 (m, 2H, H-4 and H-6), 10.10 (br s, 1H, OH exchanged with D$_2$O); MS m/e 179 (M$^+$); Anal. Calcd for C$_{10}$H$_{13}$NO$_2$: C, 67.02; H, 7.31; N, 7.81; Found: C, 67.23; H, 7.46; N, 7.46 and compound 111 (25%), mp 85-86°C (Et$_2$O); IR (CHCl$_3$) ν max 3200, 1620 cm$^{-1}$; NMR (CDCl$_3$) δ 2.97 (s, 3H, CH$_3$), 3.18 (s, 3H, CH$_3$), 3.73 (s, 2H, CH$_2$), 6.81-7.19 (m, 4H, ArH), 9.99 (s, 1H, OH exchanged with D$_2$O); MS m/e 179 (M$^+$); Anal. Calcd for C$_{10}$H$_{13}$NO$_2$: C, 67.02; H, 7.31; N, 7.81. Found: C, 67.07; H, 7.21; N, 7.62.

**Lithiation and anionic ortho Fries rearrangement of a mixture of N,N-diethyl-0-4-tolyl carbamate (84e) and N,N-dimethyl 0-phenyl carbamate (102).**

According to procedure C, lithiation of a 1:1 (molar equiv) mixture of N,N-diethyl 0-4-tolyl carbamate 84e (500 mg, 2.41 mmol) and N,N-dimethyl 0-phenyl carbamate 103 (398 mg, 2.41 mmol), s-Buli (4.14 mL, 5.30 mmol), TMEDA (0.8 mL, 5.30 mmol), -95°C, 5h, warming to room temperature, standard workup and column chromatography using 1:9 and 1:4 (v/v) EtOAc-hexane as eluent gave 350 mg (70%) of compound 107c and 0.295 mg (75%) of compound 104.

**Lithiation of a 1:1 molar equivalent mixture of N,N-diethyl 0-phenyl carbamate 84a and N,N-diethylbenzamide 45a with 1.1 equivalent of s-Buli and treatment with different electrophiles.**

**Expt. I:** According to procedure A, lithiation of a mixture of N,N-diethyl 0-phenyl carbamate 84a (545 mg, 2.82 mmol) and N,N-diethylbenzamide 45a (500 mg, 2.82 mmol), s-Buli (2.70 mL, 3.1 mmol), TMEDA (0.47 mL, 3.1 mmol), -78°C, 15 min, ethanol-d$_4$ (0.18
mL, 3.1 mmol), standard workup and column chromatography using 1:5 and 1:3 (v/v) EtOAc-hexane as eluent yielded 113 (85%, E = D, 62% d$_1$ by mass spectroscopy), 114 (87%, E = D, 36% d$_1$ by mass spectroscopy), and 2-N,N-diethylcarbamoyl benzophenone 58 (7%) which was shown to be identical with authentic material (1H NMR, IR, MS, GC).

**Expt. II:** According to procedure A, lithiation of a mixture of 84a (0.545 mg, 2.82 mmol) and 45a (500 mg, 2.82 mmol), s-BuLi (2.70 mL, 3.1 mmol), TMEDA (0.47 mL, 3.1 mmol), -78°C, 1h, methyl iodide (0.5 mL, excess), standard workup and column chromatography using 1:9 and 1:4 (v/v) EtOAc-hexane as eluent gave 113 (48%, E = Me), 114 (21%, E = Me) and 58 (15%). The products 113 and 114 were inseparable from their respective starting materials, so product ratio as indicated above was established by 1H NMR and GC comparison with authentic samples (both starting materials and products). When the lithiation was carried out at -100°C for 15 min, the ratio of the products as determined by GC comparison with authentic samples was 113 (46%), 114 (33%) and 58 (4%).

**Expt. III:** According to procedure A, lithiation of 84a (545 mg, 2.82 mmol) and 45a (500 mg, 2.82 mmol), s-BuLi (2.70 mL, 3.1 mmol), TMEDA (0.47 mL, 3.1 mmol), -78°C, 1h, methyl disulfide (0.28 mL, 3.1 mmol), standard workup and column chromatography using 1:9 and 1:4 (v/v) EtOAc-hexane as eluent afforded 113 (40%, E = SMe), 114 (13%, E = SMe) and 58 (20%). Products ratio was determined as described in Expt. II.
When the lithiation was carried out at -100°C for 15 min, the ratio of the products was 113 (30%), 114 (21%) and 58 (6%).

**Expt. IV:** According to procedure A, lithiation of 84a (545 mg, 2.82 mmol) and 45a (500 mg, 2.82 mmol), s-BuLi (2.70 mL, 3.1 mmol), TMEDA (0.47 mL, 3.1 mmol), -100°C, 15 min, N,N-diethylcarbamoyl chloride (0.38 mL, 3.1 mmol), standard workup and column chromatography using 1:5 and 1:2 (v/v) EtOAc: hexane as eluent gave 113 (40%, E = CONEt₂), 114 (31%, E = CONEt₂) and 58 (9%).

N,N-Diethyl 0-(2-N,N-diethylcarbamoyl-6-deuterio)phenyl carbamate (116a) and/or N,N-Diethyl 0-(2-N,N-diethylcarbamoyl-3-deuterio)-phenyl carbamate (117a).

According to procedure A, lithiation of N,N-diethyl 0-(2-N,N-diethylcarbamoyl)phenyl carbamate 115a (320 mg, 1.07 mmol), s-BuLi (0.05 mL, 1.18 mmol), TMEDA (0.18 mL, 1.18 mmol), -78°C, 1h, methanol-d₄ (0.5 mL, excess), standard workup and column chromatography using 1:1 (v/v)EtOAc-hexane as eluent afforded 275 mg (86%) of compounds 116a and/or 117a (55% d₁, 45% d₀), bp 140-144°C/0.1 mm; IR (neat) ν max 1710, 1630 cm⁻¹; ¹H NMR (CDCl₃) δ 0.95-1.36 (m, 12H, 4 CH₃), 3.06-3.60 (m, 8H, 4 CH₂), 7.17-7.29 (m, 3.2H, ArH); ¹³C NMR (CDCl₃) δ(relative intensity) 12.1 (61, CH₃), 13.43 (28, CH₃), 13.92 (71, CH₃) 14.2 (22, CH₃), 38.8 (100, 2 CH₂), 42.2 (99, CH₂), 42.9 (99, CH₂), 123.3 (56, C-6), 125.03 (77, C-4), 126.9 (100, C-3), 129.5 (47, C-2), 129.6 (67, C-5), 147.4 (40, C-1), 153.5 (20, OC0), 167.6 (30, CO); MS m/e 293 (M⁺).
N,N-Diethyl 0-(2,6-bis-N,N-diethylcarbamoyl)phenylcarbamate (116b) and N,N-Diethyl 0-(2,3-bis-N,N-diethylcarbamoyl)phenylcarbamate (117b).

According to procedure A, lithiation of N,N-diethyl 0-(2-N,N-diethylcarbamoyl)phenylcarbamate 115a (485 mg, 1.66 mmol), s-BuLi (1.47 mL, 1.66 mmol), TMEDA (0.25 mL, 1.66 mmol), -78°C, 1h, N,N-diethylcarbamoyl chloride (0.21 mL, 1.66 mmol), standard workup and sequential column chromatography using EtOAc as eluent and preparative TLC (EtOAc as eluent) afforded 428 mg (66%) of compound 116b, IR (neat) ν max 1710, 1620 cm⁻¹; NMR (CDCl₃) δ 0.97-1.34 (m, 18H, 6 CH₃), 3.24-3.98 (m, 12H, 6 CH₂), 7.24-7.31 (m, 3H, ArH); ¹³C NMR (CDCl₃) δ (relative intensity), 12.7 (80, 2 CH₃), 13.5 (35, CH₃), 14.0 (95, 2 CH₃), 14.3 (39, CH₃), 38.8 (91, 2 CH₂), 42.5 (72, 2 CH₂), 43.0 (91, 2 CH₂), 125.2 (44, C-4), 127.4 (100, C-3 & C-5), 132.5 (30, C-2 & C-6), 145.0 (4, C-1), 152.0 (4, OCO), 167.1 (29, 2 CO); MS m/e 391.2476; Calcd for C₂₁H₃₃N₃O₄: 391.2472 and 92 mg (14%) of compound 117b, IR (CHCl₃) ν max 1710, 1620 cm⁻¹; NMR (CDCl₃) δ 0.98-1.26 (m, 18H, 6 CH₃), 3.13-3.71 (m, 12H, 6 CH₂), 7.06-7.40 (m, 3H, ArH); ¹³C NMR (CDCl₃) δ (relative intensity) 12.8 (136, 2 CH₃), 13.5 (117, 2 CH₃), 14.0 (60, CH₃), 14.2 (31, CH₃), 38.8 (98, CH₂), 39.2 (56, CH₂), 41.8 (21, CH₂), 42.0 (39, CH₂), 42.4 (41, CH₂), 43.5 (123, CH₂), 122.5 (100, C-6), 123.3 (98, C-4), 127.6 (23, C-2), 129.1 (96, C-5), 136.1 (30, C-3), 147.4 (21, C-1), 153.2 (18, OCO), 165.8 (21 CO), 168.7 (19, CO); MS m/e 391.2476; Calcd for C₂₁H₃₃N₃O₄: 391.2472.

Compound 117b was also prepared from N,N-diethyl 0-(2,3-bis-N,N-
diethylcarbamoyl-6-trimethylsilyl)-phenyl carbamate 130 by CsF induced desilylation method as follows.

Compound 130 (97 mg, 0.21 mmol) was taken in DMF (10 mL) moistened with 2 drops of water and catalytic amount of CsF was added to it and the resulting mixture was refluxed for 17 h. Standard workup and purification by preparative TLC (EtOAc as eluent) afforded 51 mg (62%) of a compound which was shown to be identical (by R_f, NMR) with compound 117b obtained above.

N,N-Diethyl O-(2-methoxymethoxy-6-deuterio)phenyl carbamate (116c) and/or N,N-Diethyl O-(2-methoxymethoxy-3-deuterio)phenyl carbamate (117c).

According to procedure A, lithiation of N,N-diethyl-0-(2-methoxymethoxy)phenylcarbamate 115b (320 mg, 1.26 mmol), s-BuLi (1.0 mL, 1.39 mmol), TMEDA (0.21 mL, 1.39 mmol), -78°C, 1 h, methanol-d_4 (0.5 mL, excess), standard workup and column chromatography using 1:9 (v/v) EtOAc-hexane as eluent gave 280 mg (88%) of compounds 116c and/or 117c, bp 95-100°C/0.25 mm; IR (neat) ν max 1715 cm⁻¹; NMR (CDCl_3) δ 1.23 (t, J = 7, 2 CH₃), 3.39 (q, J = 7, 2 CH₂), 3.47 (s, 3H, OCH₃), 5.16 (s, 2H, OCH₂0), 7.0-7.25 (m, 3.37H, ArH); ¹³C NMR (CDCl_3) δ (relative intensity) 13.1 (7, CH₃), 13.6 (35, CH₃), 13.7 (35, CH₃), 13.8 (34, CH₃), 42.5 (130, 4 CH₂), 56.1 (67, OCH₃), 95.2 (74, OCH₂0), 116.5 (69, C-3), 122.2 (94, C-5), 123.51 (88, C-6), 126.1 (100, C-4), 141.6 (9, C-1), 149.4 (12, C-2), 154.0 (11, OCO); MS m/e 254 (M⁺).
N,N-Diethyl O-(2-N,N-diethylcarbamoyl-6-methoxymethoxy)phenyl carbamate (116d).

According to procedure A, lithiation of N,N-diethyl O-(2-methoxymethoxy)phenyl carbamate 115b (500 mg, 1.97 mmol), s-BuLi (1.99 mL, 2.17 mmol), TMEDA (0.33 mL, 2.17 mmol), -78°C, 1h, N,N-diethylcarbamoyl chloride (0.27 mL, 2.17 mmol), standard workup followed by column chromatography using 3:1 (v/v) EtOAc-hexane as eluent afforded 280 mg (48%) of compound 116d, bp 125-130°C/0.05 mm; IR (CDCl₃) νmax 1710, 1625 cm⁻¹, ¹H NMR (CDCl₃) δ 0.97-1.27 (m, 12H, 4 CH₃), 3.21-3.82 (m, 8H, 4 CH₂), 3.46 (s, 3H, OCH₃), 5.16 (s, 2H, OCH₂O), 6.82-7.27 (m, 3H, ArH); ¹³C NMR (CDCl₃) δ (relative intensity) 12.6 (102, 2 CH₃), 13.8 (138, 2 CH₃), 38.5 (79, CH₂), 41.4 (33, CH₂), 42.3 (180, CH₂), 42.7 (92, CH₂), 56.0 (79, OCH₃), 94.9 (78, OCH₂O), 116.2 (87, C-5), 119.2 (95, C-3), 125.9, (100, C-4), 132.6 (37, C-2), 137.5 (25, C-1), 149.8 (35, C-6), 153.1 (25, OCO), 167.1 (28, C0); MS m/e 352 (M⁺); Anal. Calcd for C₁₈H₂₈N₂O₅: C, 61.34; H, 8.00; N, 7.94. Found: C, 61.11; H, 8.08; N, 7.74.

N,N-Diethyl O-(2-deuterio-3-N,N-diethylcarbamoyl)phenyl carbamate (119a).

According to procedure A, lithiation of N,N-diethyl-0-(3-N,N-diethylcarbamoyl)phenyl carbamate 118a (313 mg, 1.07 mmol), s-BuLi (0.85 mL, 1.18 mmol), TMEDA (0.18 mL, (1.18 mmol), -78°C, 1h, methanol-d₁ (0.5 mL, excess), standard workup and column chromatography (1:1 EtOAc-hexane as eluent) afforded 267 mg (85%)
of compound 119a (33% d₁, 67% d₀), bp 155-160°C/0.1 mm; IR (neat) ν max 1715, 1630 cm⁻¹; NMR (CDCl₃) δ 0.95-1.31 (m, 12H, 4 CH₃), 3.27-3.54 (m, 8H, 4 CH₂), 7.10-7.36 (m, 3.36H, ArH); ¹³C NMR (CDCl₃) δ (relative intensity) 13.5 (H, 2CH₃), 14.3 (27, 2 CH₃), 42.1 (31, 2 CH₂), 42.3 (30, 2 CH₂), 120.1 (59, C-2), 122.4 (84, C-6), 122.8 (100, C-4), 129.3 (86, C-5), 138.3 (20, C-3), 151.5 (19, C-1), 153.9 (14, OCO), 170.4 (16, CO); MS m/e 293 (M⁺).

N,N-Diethyl 0-(2,3-bis-N,N-diethylcarbamoyl)phenyl carbamate (117b) and 1,2-Bis-N,N-diethyl-3-hydroxyphthalimide (120d).

According to procedure A, lithiation of N,N-diethyl 0-(3-N,N-diethylcarbamoyl)phenyl carbamate 118a (400 mg, 1.36 mmol), s-BuLi (1.06 mL, 1.50 mmol), TMEDA (0.23 mL, 1.50 mmol), -78°C, 1h, N,N-diethylcarbamoyl chloride (0.18 mL, 1.50 mmol), standard work-up followed by preparative TLC using EtOAc as eluent afforded 35 mg (7%) of compound 117b and 65 mg (16%) of compound 120d. Compound 120d, IR (neat) ν max 3200, 1620 cm⁻¹; NMR (CDCl₃) δ 0.95-1.25 (m, 12H, 4 CH₃), 3.09-3.58 (m, 8H, 4 CH₂), 6.70 (dd, J = 7.6, 1.17, 1H, H-4), 6.86 (dd, J = 7.6, 1.17, 1H, H-6), 7.11 (dd, J = 7.6, 1H, H-5); ¹³C NMR (CDCl₃) δ (relative intensity) 12.9 (92, CH₃), 13.4 (119, CH₃), 13.9 (76, CH₃) m, 14.0 (88, CH₃), 39.4 (70, CH₂), 41.6 (106, 2, CH₂), 43.5 (77, CH₂), 117.1 (92, C-4), 117.6 (96, C-6), 121.8 (69, C-2), 129.8 (100, C-5), 135.7 (86, C-1), 153.3 (87, C-3), 169.4 (77, 2CH₀); MS m/e 292 (M⁺); satisfactory analytical data (C,H,N) were not obtained.
N,N-Diethyl O-(2-deuterio-3-methoxymethoxy)phenyl carbamate (19c).

According to procedure A, lithiation of N,N-diethyl 0-(3-methoxymethoxy)phenyl carbamate 118b (300 mg, 1.18 mmol), s-BuLi (0.95 mL, 1.30 mmol), TMEDA (0.20 mL, 1.30 mmol), -78°C, 15 min, methanol-d₄ (0.4 mL, excess), standard workup and column chromatography using 1:4 EtOAc-hexane as eluent afforded 290 mg (96%) of compound 119c (55% d₄, 45% d₀); bp 95-100°C/0.2 mm; IR (neat) ν max 1715 cm⁻¹; NMR (CDCl₃) δ 1.21 (t, J = 7, 6H, 2 CH₃), 3.39 (q, J = 7, 4H, 2 CH₂), 3.47 (s, 3H, OCH₃), 5.16 (s, 2H, OCH₂O), 6.81-7.30 (m, 3.3H, ArH); ¹³C NMR (CDCl₃) δ (relative intensity) 14.1 (100, 2 CH₃), 42.1 (156, 2 CH₂), 56.1 (98, OCH₃), 94.6 (96, OCH₂O), 110.2 (79, C-2), 113.0 (100, C-4), 115.3 (84, C-6), 129.6 (98, C-5), 152.4 (63, C-1), 158.0 (70, C-3), 154.0 (54, COO); MS m/e 254 (M⁺).

N,N-Diethyl-2-hydroxy-6-methoxymethoxybenzamide (120e).

According to procedure A, lithiation of N,N-diethyl 0-(3-methoxymethoxy)phenyl carbamate 118b (500 mg, 1.97 mmol), s-BuLi (1.81 mL, 2.16 mmol), TMEDA (0.33 mL, 2.16 mmol), -78°C, 45 min, N,N-diethylcarbamoyl chloride (0.27 mL, 2.16 mmol), standard workup and column chromatography using 1:1 EtoAc-hexane as eluent afforded 338 mg (68%) of the rearranged product 120e, mp 76-77°C (C₆H₆-hexane); IR (CHCl₃) ν max 3200, 1620 cm⁻¹; NMR (CDCl₃) δ 1.07-1.25 (m, 6H, 2 CH₃), 3.22-3.68 (m, 4H, 2 CH₂), 3.45 (s, 3H, OCH₂), 5.36 (s, 2H, OCH₂O), 6.57 (d, J = 8.2, 1H, H-4 or
H-6), 6.61 (d, J = 8.2, 1H, H-4 or H-6), 7.10 (dd, J = 8.2, 1H, 
H-5); MS m/e 253 (M+); Anal. Calcd for C$_{13}$H$_{19}$NO$_4$: C, 61.64; H, 
7.56; N, 5.52. Found: C, 61.57; H, 7.36; N, 5.45.

N,N-Diethyl O-(2-deuterio-4-N,N-diethylcarbamoyl)phenyl carbamate 
(122a), and/or N,N-Diethyl O-(3-deuterio-4-N,N-diethylcarbamoyl)-
phenyl carbamate (123a).

According to procedure A, lithiation of N,N-diethyl O-(4-N,N-
diethylcarbamoyl)phenyl carbamate 121a (335 mg, 1.14 mmol), 
_s-BuLi (0.92 mL, 1.26 mmol), TMEDA (0.19 mL, 1.26 mmol), -78°C, 
1h, methanol-d$_1$ (0.5 mL, excess), standard workup and column 
chromatography using 1:1 (EtOAc-hexane as eluent afforded 284 mg 
(85%) of compounds 122a and/or 123a (66% d$_1$, 34% d$_0$), bp 
135-140°C/0.2 mm; IR (neat) $\nu_{max}$ 1710, 1625 cm$^{-1}$; NMR (CDCl$_3$) $\delta$
1.08-1.31 (m, 12H, 4 CH$_3$), 3.29-3.55 (m, 8H, 4 CH$_2$), 7.08-7.44 (m, 
3H, ArH); $^{13}$C NMR (CDCl$_3$) $\delta$ (relative intensity) 13.6 (78, 4 CH$_3$), 
42.2 (91, 4 CH$_2$), 121.6 (91, C-2 and C-6), 127.5 (100, C-3 and 
C-5), 133.9 (26, C-4), 152.1 (25, C-1), 153.8 (23, CO), 170.7 
(28, C0); MS m/e 293 (M+).

N,N-Diethyl O-(2,4-bis-N,N-diethylcarbamoyl)phenyl carbamate 
(122b) and N,N-Diethyl O-(3,4-bis-N,N-diethylcarbamoyl)phenyl 
carbamate (123b).

According to procedure A, lithiation of N,N-diethyl O-(4-N,N-
diethylcarbamoyl)phenyl carbamate 121a (512 mg, 1.75 mmol), 
_s-BuLi (1.78 mL, 1.92 mmol), TMEDA (0.29 mL, 1.92 mmol), -78°C, 
1h, N,N-diethylcarbamoyl chloride (0.24 mL, 1.92 mmol), standard 
workup and column chromatography using 1:1 EtOAc-hexane as eluent
afforded 278 mg (41%) of compound 122b; IR (neat) ν max 1710, 1620 cm⁻¹; NMR (CDCl₃) δ 0.96-1.29 (m, 18H, 6 CH₃), 3.08-3.42 (m, 12H, 6 CH₂), 7.28-7.37 (m, 3H, ArH); ¹³C NMR (CDCl₃) δ (relative intensity) 12.8 (113, 2 CH₃), 13.7 (121, 2 CH₃), 14.0 (149, 2 CH₃), 38.9 (92, 2 CH₂), 42.3 (133, 2 CH₂), 43.0 (94, 2 CH₂), 123.3 (100, C-6), 125.4 (98, C-3), 127.8 (94, C-5), 130.8 (69, C-2), 134.3 (71, C-4), 148.2 (69, C-1), 153.2 (48, OCO), 166.98 (46, k CО), 170.0 (63, CО); HRMS m/e 391.2487; Calcd for C₂₁H₃₃N₃O₄: 391.2472 and 123b (28%); IR (neat) ν max 1710, 1620 cm⁻¹; NMR (CDCl₃) δ 1.02-1.31 (m, 18, 6 CH₃), 3.15-3.60 (m, 12H, 6 CH₂), 7.08 (d, J = 2.2, H-2), 7.17 (dd, J = 8.3, 2.2, H-6), 7.27 (d, J = 8.3, H-5); ¹³C NMR (CDCl₃) δ (relative intensity) 12.73 (126, 2 CH₃), 13.4 (44, CH₃), 13.9 (112, 2 CH₃), 14.3 (41, CH₃), 39.2 (85, 2 CH₂), 42.0 (45, CH₂), 42.4 (43, CH₂), 42.5 (137, 2 CH₂), 119.5 (96, C-2), 121.5 (96, C-6), 127.0 (100, C-5), 131.7 (33, C-4), 136.2 (28, C-3), 151.2 (33, C-1), 153.4 (16, OCO), 168.6 (20, CО), 169.1 (26, CО); HRMS m/e 391.2483; Calcd for C₂₁H₃₃N₃O₄: 391.2472.

N,N-Diethyl 0-(2-deutério-4-methoxymethoxy)phenyl carbamate (122c) and/or N,N-Diethyl 0-(3-deutério-4-methoxymethoxy)phenyl carbamate (123c).

According to procedure A, lithiation of N,N-diethyl 0-(4-methoxymethoxy)phenyl carbamate 121b (500 mg, 1.97 mmol), s-BuLi (2.05 mL, 2.17 mmol), TMEDA (0.33 mL, 2.17 mmol), -78°C, 1h, ethanol-d₁ (0.5 mL, excess), standard workup followed by column
chromatography using 1:5 EtOAc-hexane as eluent yielded 430 mg (86%) of compound 122c and/or 123c (56% d₁, 44% d₀), bp 98-100°C/2.0 mm; IR (neat) νmax 1710 cm⁻¹; NMR (CDCl₃) δ 1.21 (t, J = 7.0, 6H, 2 CH₃), 3.39 (q, J = 7.0 4H, 2 CH₂), 3.45 (s, 3H, OCH₃), 5.12 (s, 2H, OCH₂0), 7.01 (s, 3H, ArH); ¹³C NMR (CDCl₃) δ (relative intensity) 13.8 (50, 2 CH₃), 42.04 (90, 2 CH₂), 55.8 (34, OCH₃), 94.9 (60, OCH₂0), 116.9 (100, C-3, C-5), 122.5 (92, C-2, C-6), 146.1 (29, C-1), 154.3 (24, C-4), 154.5 (24, OCO); Ms m/e 254 (M⁺).

N,N-Diethyl O-(2-N,N-diethylcarbamoyl-4-methoxymethoxy)phenyl carbamate (122d).

According to procedure A, lithiation of N,N-diethyl O-(4-methoxymethoxy)phenyl carbamate 121b (500 mg, 1.97 mmol), s-BuLi (2.05 mL, 2.17 mmol), TMEDA (0.33 mL, 2.17 mmol), -78°C, 1h, N,N-diethylcarbamoyl chloride (0.27 mL, 2.17 mmol), standard workup and column chromatography using 3:2 (v/v) EtOAc-hexane as eluent gave 485 mg (70%) of compound 122d, bp 130-135°C/0.05 mm; IR (neat) νmax 1710, 1620 cm⁻¹; NMR (CDCl₃) δ 0.97-1.28 (m, 12H, 4 CH₃), 3.17-3.39 (m, 8H, 4 CH₂), 3.45 (s, 3H, OCH₃), 5.13 (s, 2H, CH₂), 6.94-7.08 (m, 3H, ArH); ¹³C NMR (CDCl₃) δ (relative intensity) 12.50 (86, 2 CH₃), 13.6 (108, 2 CH₃), 38.5 (73, CH₃), 41.91 (117, 2 CH₂), 42.6 (74, CH₂), 55.7 (110, OCH₃), 94.7 (85, OCH₂0), 114.2 (97, C-3), 117.3 (88, C-5), 124.0 (100, C-6), 131.2 (65, C-2), 141.7 (63, C-2), 153.6 (40, OCO), 154.1 (85, C-4), 167.0 (32, CO): MS m/e 308 (M⁺); Anal. Calcd for
C_{18}H_{28}N_{2}O_{5}:  C, 61.34; H, 8.00; N, 7.94. Found:  C, 61.19; H, 8.13; N, 8.21.

1,3-Bis-N,N-diethyl-2-hydroxyisophthalamide (124).

According to procedure C, lithiation of N,N-diethyl 0-(2-N,N-diethylcarbamoyl)phenyl carbamate 115a (454 mg, 1.55 mmol), s-BuLi (1.37 mL, 1.70 mmol), TMEDA (0.23 mL, 1.70 mmol), -78°C, warming to room temperature, standard workup followed by column chromatography using 1:2 (v/v) EtOAc-hexane as eluent afforded 136 mg (30%) of compound 124, mp 86-87°C (C_{6}H_{6}-hexane); IR (CHCl₃) ν_{max} 3200, 1620 cm⁻¹; NMR (CDCl₃) δ 1.13 (t, J = 7, 12H, 4 CH₃), 3.37 (q, J = 7, 8H, 4 CH₂), 6.86 (dd, J = 7.4, 1H, H-5), 7.28 (d, J = 7.4, 2H, H-4 and H-6), 10.03 (br, 1H, OH exchanged with D₂O); MS m/e 292 (M⁺); Anal. Calcd for C_{16}H_{24}N_{2}O_{3}:  C, 65.73; H, 8.27; N, 9.58. Found:  C, 65.94; H, 8.31; N, 9.60.

N,N-Diethyl 0-(2-N,N-diethylcarbamoyl-3-hydroxy)phenyl carbamate (126).

According to procedure C, lithiation of N,N-diethyl-0-(3-N,N-diethylcarbamoyloxy)phenyl carbamate 125 (700 mg, 2.27 mmol), s-BuLi (2.05 mL, 2.49 mmol), TMEDA (0.38 mL, 2.49 mmol), -78°C, warming to room temperature, standard workup followed by recrystallization gave 600 mg (86%) of compound 126, mp 130-131°C (C_{6}H_{6}-hexane); IR (CHCl₃) ν_{max} 3200, 1710, 1620 cm⁻¹; NMR (CDCl₃) δ 1.031.24 (m, 12H, 4 CH₃), 3.23-3.40 (m, 8H, 4 CH₂), 6.72 (dd, J
= 8.2, 1.17, 1H, H-6), 6.76 (dd, J = 7.8, 1.17, 1H, H-4), 7.17
(dd, J = 7.8, 8.2, (1H, H-5); 13C NMR (CDCl3) δ (relative intensity) 13.4 (178, 2 CH₃), 14.2 (60, 2 CH₃), 41.3 (58, 2 CH₂), 42.2
(118, 2 CH₂), 113.6 (100, C-4), 113.8 (100, C-6), 117.7 (64, C-2), 129.9 (82, C-5), 148.1 (71, C-1), 153.5 (58, OC0), 154.8
(49, C-3), 166.8 (67, CO): MS m/e 308 (M+); Anal. Calcd for
C₁₆H₂₄N₂O₄: C, 62.32; H, 7.84; N, 9.08. Found: C, 62.30; H,
8.0; N, 9.01.

N,N-Diethyl O-(2-deuterio-3-N,N-diethylcarbamoyloxy)phenyl
carbamate (127).

According to procedure A, lithiation of N,N-diethyl O-(3-N,N-
diethylcarbamoyloxy)phenyl carbamate 125 (700 mg, 2.27 mmol),
s-BuLi (2.05 mL, 2.49 mmol), TMEDA (0.38 mL, 2.49 mmol), -78°C, 10
min, methanol-d₄ (0.5 mL, excess), standard workup followed by
column chromatography using 2:3 (v/v) EtOAc-hexane as eluent gave
80 mg (11%) of compound 126 and 530 mg (76%) of compound 127
(64%, d₄), bp 190-194°C/0.1 mm; (IR (neat) νmax 1715 cm⁻¹; NMR
(CDCl3) δ 1.21 (t, J = 7.0, 12H, 4 CH₃), 3.39 (q, J = 7.0, 8H, 4
CH₂), 6.91-7.00 (m, 2H, ArH), 7.2-7.3 (m, 1H, ArH); 13C NMR
(CDCl3) δ (relative intensity) 13.9 (52, 4 CH₃), 42.1 (126, 4 CH₂),
115.6 (21, C-2), 118.3 (100, C-4, C-6), 129.1 (50, C-5), 151.9
(45, C-1, C-3), 153.8 (39, OC0); MS m/e 309 (M+).
1,3-Bis-N,N-diethyl-2,4-dihydroxyisophthalamide (128).

According to procedure C, lithiation of N,N-diethyl O-(2-N,N-diethylcarbamoyl-3-hydroxy)phenyl carbamate 126 (400 mg, 1.29 mmol), s-BuLi (3.27 mL, 3.99 mmol), TMEDA (0.61 mL, 3.99 mmol), -78°C, warming to room temperature, standard workup followed by recrystallization afforded 372 mg (93%) of compound 128, mp 122-124°C (CH2Cl2-hexane); IR (CHCl3) ν max 3200, 1608 cm⁻¹; NMR (CDCl3) δ 1.09-1.35 (m, 12H, 4 CH3), 3.33-3.62 (m, 8H, 4 CH2), 6.41 (d, J = 8.6, H-6), 7.16 (d, J = 8.6, H-5); MS m/e 392 (M⁺);
Anal. Calcd for C16H24N2O4: C, 62.32; H, 7.84; N, 9.08. Found: C, 62.26; H, 7.96; N, 8.76.

N,N-Diethyl O-(2-N,N-diethylcarbamoyl-6-trimethylsilyl)phenyl carbamate (129).

To a stirred THF solution (60 mL) of s-BuLi (2.17 mL, 2.59 mmol) and TMEDA (0.39 mL, 2.59 mmol) at -78°C under nitrogen was added by syringe injection N,N-diethyl O-phenyl carbamate 84a (500 mg, 2.59 mmol) in THF (5 mL). After 1 h, TMSCl (0.33 mL, 2.59 mmol) was added and the solution was stirred at -78°C for 1 h. Second portion of s-BuLi (2.17 mL, 2.59 mmol) and TMEDA (0.39 mL, 2.59 mmol) were likewise injected followed after 1 h by N,N-diethylcarbamoyl chloride (0.32 mL, 2.59 mmol). The resulting solution was allowed to warm to room temperature over 8 h. Standard workup followed by column chromatography (1:2 EtOAc-hexane as eluent) afforded 510 mg (54%) of compound 129, mp 53-54°C.
(hexane); IR (CHCl₃) νₘₐₓ 1710, 1620 cm⁻¹; NMR (CDCl₃) δ 0.30 (s, 9H, Si(CH₃)₃), 1.03-1.38 (m, 12H, 4 CH₃), 3.16-3.61 (m, 8H, 4 CH₂), 7.18-7.56 (m, 3H, ArH); MS m/e 364 (M⁺); Anal. Calcd. for C₁₉H₃₂N₂O₃Si: C, 62.60; H, 8.84; N, 7.68; Found: C, 62.80; H, 9.0; N, 7.68.

**N,N-Diethyl 0-(2,3-bis-N,N-diethylcarbamoyl-6-trimethylsilyl)phenyl carbamate (130).**

According to procedure A, lithiation of N,N-diethyl 0-(2-N,N-diethylcarbamoyl-6-trimethylsilyl)phenyl carbamate 129 (500 mg, 1.37 mmol), s-BuLi (1.08 mL, 1.37 mL), TMEDA (0.21 mL, 1.37 mmol), -78°C, 1h, N,N-diethylcarbamoyl chloride (0.17 mL, 1.37 mmol), standard workup and purification by column chromatography (1:1 EtOAc-hexane as eluent) yielded 475 mg (75%) of compound 130, bp 157-160°C/0.1 mm; IR (neat) νₘₐₓ 1720, 1645, 1625 cm⁻¹; NMR (CDCl₃) δ 0.18 (s, 9H, Si(CH₃)₃), 0.83-1.25 (m, 18H, 6 CH₃), 3.0-3.52 (m, 12H, 6 CH₂), 7.02, (d, J = 7.6, 1H, H-6); MS m/e 463 (M⁺); Anal. Calcd for C₂₆H₄₁N₃O₄Si: C, 62.16; H, 8.91; N, 9.06. Found: C, 62.04; H, 9.03; N, 8.94.

**N,N-Diethyl 0-(2-N,N-diethylcarbamoyl-3-methyl-6-methoxy)phenyl carbamate (131).**

To a stirred THF solution (60 mL) of s-BuLi (2.07 mL, 2.46 mmol) and TMEDA (0.37 mL, 2.46 mmol) at -78°C under nitrogen was added by syringe injection N,N-diethyl 0-2-anisyl carbamate (500
mg, 2.24 mmol in THF (5 mL). After 1 h, N,N-diethylcarbamoyl
chloride (0.30 mL, 2.46 mmol) was added and the solution was stir-
red for 1 h at -78°C. Again s-BuLi (2.07 mL, 2.46 mmol) and TMEDA
(0.37 mL, 2.46 mmol) were added to the reaction flask. After 1 h,
methyl iodide (0.5 mL, excess) was added and the resulting solu-
tion was allowed to warm to room temperature over 8 h. Standard
workup and column chromatography afforded 460 mg (66%) of
compound 131, IR (neat) ν max 1715, 1625 cm⁻¹; NMR (CDCl₃) δ
0.88-1.42 (m, 12H, 4 CH₃), 2.21 (s, 3H, CH₃), 3.04-3.73 (m, 8H, 4
CH₂), 3.79 (s, 3H, OCH₃), 6.82, 7.0 (2 d, J = 8.6, 2H, H-4, H-5);
MS m/e 336 (M⁺); Anal. Calcd for C₁₈H₂₈N₂O₄: C, 64.26; H, 8.38;
N, 8.32. Found: C, 63.90; H, 8.10; N, 7.99.

N,N-Diethyl-2-(2-hydroxy)phenyl acetamide (132) and
Bis-N,N-diethyl-2-(2-hydroxy)phenyl malonamide (133).

According to procedure C, lithiation of N,N-diethyl 0-2-tolyl
carbamate 81 (500 mg, 2.41 mmol), LDA (1.2 equiv, prepared accord-
ing to procedure B), -78°C, warming to room temperature over 8 h,
standard workup and column chromatography using 1:2 (v/v) EtOAc-
hexane as eluent afforded 300 mg (60%) of compound 132, mp
87-89°C (CH₂Cl₂-hexane); IR (CHCl₃) ν max 3400, 1610 cm⁻¹; NMR
(CDCl₃) δ 0.95-1.37 (m, 6H, 2 CH₃), 3.21-3.63 (m, 4H, 2 CH₂), 3.71
(s, 2H, CH₂), 6.72-7.26 (m, 4H, ArH), 10.43 (s, 1H, OH exchanged
with D₂O). MS m/e 207 (M⁺); Anal. Calcd for C₁₂H₁₇NO₂: C, 69.54;
H, 8.26; N, 6.75. Found: C, 69.32; H, 8.41; N, 6.93; and 59 mg
(8%) of compound 133, mp 148-149°C (C₆H₆); IR (CHCl₃) ν max 3200,
1625 (cm⁻¹; NMR (CDCl₃) δ 0.93-1.23 (m, 12H, 4 CH₃), 3.12-3.51 (m, 8H, 4 CH₂), 4.95 (s, 1H, CH), 6.70-7.35 (m, 4H, ArH), 10.8 (s, 1H, OH, exchanged with D₂O); MS m/e 306 (M⁺); Anal. calcd for C_{17}H_{26}N₂O₃: C, 66.64; H, 8.55; N, 9.14. Found: C, 66.49; H, 8.86; N, 9.03.

2(3H)-Benzofuranone (134).

Method I: N,N-Diethyl-2-(2-hydroxy)phenyl acetamide 132 (190 mg, 0.92 mmol) dissolved in benzene (20 mL) was refluxed in presence of 1 M HCl (2 mL) for 40 h. Standard workup followed by purification by column chromatography using 1:9 (v/v) EtOAc-hexane as eluent afforded 115 mg (94%) of compound 134, mp 47-49°C (CH₂Cl₂-hexane) (lit.¹⁴⁴ 49-50°C); IR (CHCl₃) ν_max 1800 cm⁻¹; NMR (CDCl₃) δ 3.70 (s, 2H, CH₂), 6.99-7.42 (m, 4H, ArH); MS m/e 134 (M⁺).

Method II: Compound 132 (250 mg, 1.20 mmol) was refluxed in benzene in presence of p-toluene sulfonic acid hydrate (100 mg) for 4 days. Workup and purification as above gave 115 mg (72%) of compound 134.

Preparation of ortho-hydroxyphenylacetic acid (135) from (133).

Compound 133 (150 mg) was refluxed in HCl for 18 h. Workup in the usual manner followed by recrystallization afforded 54 mg (69%) of compound 135, mp 146°C (Et₂O-hexane) (lit.¹⁴⁵ 149-150°C).
4.3 STANDARD PROCEDURE FOR CHAPTER III.

4.3.1. LITHIATION OF O-PYRIDYL CARBAMATES WITH \text{\textit{s-BuLi}}

A. The procedure for lithiation of 0-pyridyl carbamate with \text{\textit{s-BuLi-TMEDA}} complex was similar to procedure A for the lithiation of 0-aryl carbamate as described in Section 4.2.1.A.

B. The procedure for lithiation of 0-pyridyl carbamate with LOA was similar to procedure B for the lithiation of 0-aryl carbamate as described in Section 4.2.1.B.

C. The procedure for anionic ortho-Fries rearrangement of 0-pyridyl carbamate was similar to procedure C for anionic ortho-Fries rearrangement of 0-aryl carbamate as described in Section 4.2.1.C.

4.3.2. PREPARATION OF O-PYRIDYL CARBAMATES

\text{\textit{N,N-Diethyl 0-pyridyl-2-carbamate and N,N-diethyl 0-pyridyl-3-carbamate}} were prepared according to literature procedure from the reaction of 2-pyridone and 3-pyridinol respectively with \text{\textit{N,N-diethylcarbamoyl chloride (1.1 equiv) in presence of triethylamine (1.1 equiv) in refluxing benzene for 6-8 h.}} \text{\textit{N,N-diethyl 0-pyridyl-4-carbamate}} was prepared from the reaction of 4-pyridone with \text{\textit{N,N-diethylcarbamoyl chloride (1.1 equiv) in presence of sodium hydride (1.5 equiv) in refluxing DMF for 8h.}} All three 0-pyridyl carbamates were purified by distillation.
**N,N-Diethyl 0-pyridyl-2-carbamate (176):**

bp 98-100°C/0.1 mm; IR (neat) $\nu_{\text{max}}$ 1719 cm$^{-1}$; NMR (CDCl$_3$) $\delta$

1.16-1.31 (m, 6H, 2 CH$_3$); 3.37-3.50 (m, 4H, 2 CH$_2$), 7.06-7.24 (m, 2H, H-3 and H-5), 7.75 (doublets of triplet (dt), J = 7.63, 2.05, H-4), 8.37 (ddd, J = 4.7, 2.05, 0.88, H-5); MS m/e 194 (M$^+$);

Anal. Calcd for C$_{10}$H$_{14}$N$_2$O$_2$: C, 61.84; H, 7.26; N, 14.42. Found:

C, 61.71; H, 7.32; N, 14.02.

**N,N-Diethyl 0-pyridyl-3-carbamate (177):**

bp 89-91°C/0.05 mm (lit.$^{111}$ bp 91-93°C/3.5 mm); IR (neat) $\nu_{\text{max}}$

1723 cm$^{-1}$; NMR (CDCl$_3$) $\delta$ 1.23 (t, J = 7, 6H, 2 CH$_3$), 3.38 (q, J = 7, 4H, 2 CH$_2$), 7.29 (dd, J = 7.8, 4.7, H-5), 7.5 (ddd, J = 7.8, 2.05, 1.46, H-4), 8.39-8.46 (m, H-2 and H-6); MS m/e 194 (M$^+$).

**N,N-Diethyl 0-pyridyl-4-carbamate (179):**

bP 95-98°C/0.25 mm; IR (neat) $\nu_{\text{max}}$ 1728 cm$^{-1}$; NMR 9CDCl$_3$ $\delta$

1.21 (t, J = 7.08, 6H, 2 CH$_3$), 3.39 (q, J = 7.08, 4H, 2 CH$_2$), 7.14 (dd, J = 4.64, 1.46, H-3 and H-5), 8.56 (dd, J = 4.64, 1.7, H-2 and H-6); MS m/e 194 (M$^+$); Anal. Calcd for C$_{10}$H$_{14}$N$_2$O$_2$: C, 61.84; H, 7.26; N, 14.42. Found: C, 61.41; H, 7.35; N, 13.81.
4.3.3. EXPERIMENTAL DETAILS

N,N-Diethyl 0-(3-deuterio)pyridyl-2-carbamate (181a).

According to Procedure A, lithiation of N,N-diethyl 0-pyridyl-2-carbamate 176 (400 mg, 2.06 mmol), s-BuLi (1.84 mL, 2.2 mmol), TMEDA (0.34 mL, 2.2 mmol), -78°C, 10 min, methanol-d₁ (0.5 mL, excess), standard workup and purification by column chromatography afforded 350 mg (87%) of compound 181a (56% d₁, 44% d₀), bp 108-110°C/0.15 mm; IR (neat) ν max 1717 cm⁻¹; NMR (CDCl₃) δ 1.01-1.31 (m, 6H, 2 CH₃), 3.42-3.50 (m, 4H, 2 CH₂), 7.06-7.28 (m, residual H-3 and H-5), 7.6-7.8 (m, H-4), 8.37 (dd, J = 4.7, 2.05, H-6); MS m/e 195 (M⁺).

N,N-Diethyl 0-(3-methyl)pyridyl-2-carbamate (181b).

According to Procedure A, lithiation of carbamate 176 (860 mg, 4.43 mmol), s-BuLi (4.35 mL, 4.87 mmol), TMEDA (0.74 mL, 4.87 mmol), -78°C, 10 min, methyl iodide 6.3 mL, 4.87 (mmol), standard workup and column chromatography using 1:2 (EtOAc-hexane as eluent afforded 662 mg (72%) of compound 181b, bp 125-130°C/0.2 mm; IR (neat) ν max 1719 cm⁻¹; NMR (CDCl₃) δ 0.90-1.40 (m, 6H, 2 CH₃), 2.22 (s, 3H, CH₃), 7.06 (dd, J = 7.4, 4.7, H-5 and residual H-3), 7.5-7.6 (m, H-4), 8.18 (dd, J = 4.8, 1.46, H-6); MS m/e 208 (M⁺). Compound 181b was contaminated with a trace of starting material (by GC) which could not be removed and therefore satisfactory analytical data (C, H, N) were not obtained.
N,N-Diethyl O-(3-N,N-diethylcarbamoyl)pyridyl-2-carbamate (181c).

According to Procedure A, lithiation of carbamate 176 (500 mg, 2.57 mmol), s-BuLi (2.33 mL, 2.83 mmol), TMEDA (0.43 mL, 2.83 mmol), -78°C, 10 min, N,N-diethylcarbamoyl chloride (0.35 mL, 2.83 mmol), standard workup and column chromatography afforded 468 mg (66%) of compound 181c, bp 155-160°C/0.1 mm; IR (neat) νmax 1718, 1636 cm⁻¹; NMR (CDCl₃) δ 1.06-1.30 (m, 12H, 4 CH₃), 3.19-3.56 (m, 8H, 4 CH₂), 7.21 (dd, J = 7.4, 4.9, H-5), 7.68 (dd, J = 7.4, 2.05, H-4), 8.42 (dd, J = 4.9, 2.05, H-6); HRMS m/e 293.1762; Calcd. for C₁₅H₂₃N₃O₃: 293.1740.

N,N-Diethyl O-(3-trimethylsilyl)pyridyl-2-carbamate (181d).

According to Procedure A, lithiation of carbamate 176 (700 mg, 3.60 mmol), s-BuLi (3.1 mL, 3.96 mmol), TMEDA (0.6 mL, 3.96 mmol), -78°C, 10 min, TMSCl (0.5 mL, 3.96 mmol), standard workup and column chromatography using 2:3 EtOAc-hexane as eluent afforded 460 mg (52%) of compound 181d, bp 95-100°C/0.3 mm; IR (neat) νmax 1725 cm⁻¹; NMR (CDCl₃) δ 0.38 (s, 9H, Si(CH₃)₃), 1.03-1.43 (m, 6H, 2 CH₃), 3.35-3.69 (m, 4H, 2 CH₂), 7.20 (dd, J = 7.2, 4.88, H-5), 7.89 (dd, J = 7.2, 2.2, H-4), 8.40 (dd, J = 4.88, 2.2, H-6); MS m/e 266 (M⁺); Anal. Calcd for C₁₃H₂₂N₂O₂Si: C, 58.61; H, 8.32; N, 10.51. Found: C, 58.80; H, 8.28, N, 10.42.

When 176 was subjected to lithiation with LDA, according to procedure B, compound 181d was obtained in 62% yield.
N,N-diethyl O-(3-bromo)pyridyl-2-carbamate (181e).

According to Procedure A, lithiation of carbamate 176 (0.752 g, 3.87 mmol), s-BuLi (4.02 mL, 4.26 mmol), TMEDA (0.64 mL, 4.26 mmol), -78°C, 10 min, 1,2-dibromoethane (0.67 mL, 7.72 mmol), standard workup and column chromatography using 1:9 EtOAc-hexane as eluent gave 600 mg (59%) of compound 181e, bp 118-122°C/0.1 mm; IR (neat) \( \nu_{\text{max}} \) 1722 cm\(^{-1} \); NMR (CDCl\(_3\)) \( \delta \) 1.10-1.40 (m, 6H, 2 CH\(_3\)), 3.38-3.54 (m, 4H, 2 CH\(_2\)), 7.08 (dd, J = 7.8, 4.69, H-5), 7.95 (dd, J = 7.8, 1.76, H-4), 8.33 (dd, J = 4.69, 1.76, H-6); HRMS m/e 272.0152 and 274.0138; Calcd for C\(_{10}\)H\(_{13}\)BrN\(_2\)O\(_2\): 272.0160 and 274.0160.

N,N-Diethyl O-(3-iodo)pyridyl-2-carbamate (181f).

According to Procedure A, lithiation of carbamate 176 (600 mg, 3.09 mmol), s-BuLi (2.76 mL, 3.39 mmol), TMEDA (0.51 mL, 3.39 mmol), -78°C, 10 min iodine (864 mg, 3.39 mmol), standard workup and column chromatography using 1:2 EtOAc-hexane as eluent afforded 672 mg (68%) of compound 181f, bp 134-138°C/0.2 mm; IR (neat) \( \nu_{\text{max}} \) 1725 cm\(^{-1} \); NMR (CDCl\(_3\)) \( \delta \) 1.01-1.45 (m, 6H, CH\(_3\)), 3.29-3.63 (m, 4H, 2 CH\(_2\)), 6.93 (dd, J = 7.6, 4.69, H-5), 8.15 (dd, J = 7.6, 1.76, H-4), 8.34 (dd, J = 4.69, 1.76, H-6); MS m/e 320, 322 (M\(^+\)); Anal. Calcd for C\(_{10}\)H\(_{13}\)IN\(_2\)O\(_2\): C, 37.52; H, 4.09; N, 8.75. Found: C, 37.80; H, 4.24; N, 8.80.
N,N-Diethyl O-(4-deuterio)pyridyl-3-carbamate (182a).

According to Procedure A, lithiation of N,N-diethyl O-pyridyl-3-carbamate 177 (600 mg, 3.09 mmol), s-BuLi (2.63 mL, 3.39 mmol), TMEDA (0.51 mL, 3.39 mmol), -78°C, 40 min, methanol-d$_1$ (0.5 mL, excess), standard workup and column chromatography using 1:1 EtOAc-hexane as eluent afforded 489 mg (82%) of compound 182a (51% d$_1$, 49% d$_0$), bp 101-104°C/0.15 mm; IR (neat) $\nu_{\text{max}}$ 1700 cm$^{-1}$; NMR (CDCl$_3$) $\delta$ 1.23 (t, J = 7.04, 6H, 2 CH$_3$), 3.38 (q, J = 7.04, 4H, 2 CH$_2$), 7.25-7.37 (m, H-5), 7.45-7.61 (m, residual H-4), 8.42 (d, J = 4.7, H-6), 8.45 (s, H-2); MS m/e 195 (M$^+$).

N,N-Diethyl O-(4-methyl)pyridyl-3-carbamate (182b).

According to Procedure A, lithiation of carbamate 177 (860 mg, 4.43 mmol), s-BuLi (4.35 mL, 4.87 mmol), TMEDA (0.74 mL, 4.87 mmol), -78°C, 40 min, methyl iodide (0.30 mL, 4.87 mmol), standard workup and column chromatography using 1:1 EtOAc-hexane as eluent afforded 762 mg (83%) of compound 182b, bp 98-102/0.15 mm; IR (neat) $\nu_{\text{max}}$ 1719 cm$^{-1}$; NMR (CDCl$_3$) $\delta$ 1.16-1.33 (m, 6H, 2 CH$_3$), 2.24 (s, 3H, CH$_3$), 3.40-3.48 (m, 4H, 2 CH$_2$), 7.14 (d, J = 4.98, H-5), 8.30 (d, J = 4.98, H-6), 8.33 (s, H-2); MS m/e 208 (M$^+$). Anal. Calcd for C$_{11}$H$_{16}$N$_2$O$_2$: C, 63.44, H, 7.74; N, 13.45. Found: C, 63.61; H, 7.58; N, 13.61.
N,N-Diethyl O-(N,N-diethylcarbamoyl)pyridyl-3-carbamate (182c).

According to Procedure A, lithiation of carbamate 177 (600 mg, 3.09 mmol), s-BuLi (2.75 mL, 3.40 mmol), TMEDA (0.51 mL, 3.40 mmol), -78°C, 40 min, N,N-Diethylcarbamoyl chloride (0.42 mL, 3.40 mmol), standard workup and column chromatography using 1:1 EtOAc-hexane as eluent gave 580 mg (64%) of compound 182c, bp 140-143°C/0.2 mm; IR (neat) $\nu_{\text{max}}$ 1725, 1640 cm$^{-1}$; NMR (CDCl$_3$) $\delta$ 0.99-1.29 (m, 12H, 4 CH$_3$), 3.05-3.66 (m, 8H, 4 CH$_2$), 7.20 (d, J = 4.7, H-5), 8.47 (d, J = 4.7, H-6), 8.55 (s, H-2); MS m/e 293 (M$^+$); Anal. calcd for C$_{15}$H$_{23}$N$_3$O$_3$: C, 61.41; H, 7.90; N, 14.32. Found: C, 60.92; H, 7.89; N, 13.92.

N,N-Diethyl O-(4-trimethylsilyl)pyridyl-3-carbamate (182d).

According to Procedure A, lithiation of carbamate 177 (2.00 g, 10.30 mmol), s-BuLi (9.86 mL, 11.34 mmol), TMEDA (1.71 mL, 11.34 mmol), -78°C, 40 min, TMSCl (1.44 mL, 11.34 mmol), standard workup and column chromatography using 1:4 EtOAc-hexane as eluent afforded 1.88 g (69%) of compound 182d, bp 53-55°C/0.04 mm; IR (neat) $\nu_{\text{max}}$ 1722 cm$^{-1}$; NMR (CDCl$_3$) $\delta$ 0.33 (s, 9H, Si(CH$_3$)$_3$), 1.08-1.43 (m, 6H, 2 CH$_3$), 3.30-3.65 (m, 4H, 2 CH$_2$), 7.36 (d, J = 4.7, H-5), 8.35 (s, H-2), 8.42 (d, J = 4.7, H-6); MS m/e 266 (M$^+$); Anal. Calcd for C$_{13}$H$_{22}$N$_2$O$_2$Si: C, 58.61; H, 8.32; N, 10.51. Found: C, 58.59; H, 8.21; N, 10.39. Compound 182d was obtained in 82% yield from the lithiation of carbamate 177 with LDA according to Procedure B.
N,N-Diethyl O-(4-bromo)pyridyl-3-carbamate (182e).

According to Procedure A, lithiation of carbamate 177 (2.00 g, 10.30 mmol), s-BuLi (10.84 mL, 11.34 mmol), TMEDA (1.71 mL, 11.34 mmol), -78°C, 30 min, 1,2-dibromoethane (1.86 mL, 21.65 mmol), standard workup and column chromatography using 1:4 EtOAc-hexane as eluent afforded 1.70 g (71%) of compound **182e**, bp 130-135°C/0.1 mm (with decomposition); IR (neat) ν max 1726 cm⁻¹; NMR (CDCl₃) δ 1.10-1.50 (m, 6H, 2 CH₃), 3.25-3.70 (m, 4H, 2 CH₂), 7.54 (d, J = 5.2, H-5), 8.25 (d, J = 5.2, H-6), 8.47 (s, H-6); MS m/e 272, 274 (M⁺). Compound **182e** was found to be very unstable and a sample for analysis could not be obtained.

N,N-Diethyl O-(4-iodo)pyridyl-3-carbamate (182f).

According to Procedure A, lithiation of carbamate 177 (635 mg, 3.27 mmol), s-BuLi (3.05 mL, 3.60 mmol), TMEDA (0.54 mL, 3.60 mmol), -78°C, 40 min, iodine (914 mg, 3.60 mmol), standard workup and column chromatography using 3:2 EtOAc-hexane as eluent gave 680 mg (65%) of compound **182f**; IR (neat) ν max 1725 cm⁻¹; NMR (CDCl₃) δ 1.15-1.41 (m, 6H, 2 CH₃), 3.37-3.57 (m, 4H, 2 CH₂), 7.76 (d, J = 4.98, H-5), 8.05 (d, J = 4.98; H-6), 8.38 (s, H-2); MS m/e 320 (M⁺).

Compound **182f** decomposed on heating or standing at room temperature for a few days. Therefore, an analytical sample could not be obtained.
N,N-Diethyl O-(4-N,N-dimethylsulfonyl)pyridyl-3-carbamate (182g).

According to Procedure A, lithiation of carbamate 177 (500 mg, 2.57 mmol), s-BuLi (2.75 mL, 2.83 mmol), TMEDA (0.43 mL, 2.83 mmol), -78°C, 45 min, N,N-dimethylsulfonyl chloride (0.130 mL, 2.83 mmol), standard workup and column chromatography (2:1 EtOAc-hexane as eluent) yielded 625 mg (81%) of compound 182g, bp 95-100°C/0.05 mm; IR (neat) νmax 1725 cm⁻¹; NMR (CDCl₃) δ 1.13-1.38 (m, 6H, 2 CH₃), 2.81 (s, 6H, 2 CH₃), 3.27-3.53 (m, 4H, 2 CH₂), 7.37 (d, J = 5.2, H-5), 8.35 (d, J = 5.2, H-6), 8.49 (s, H-2); MS m/e 256 (M⁺-NMe₂); Anal. Calcd for C₁₂H₁₉N₃O₄S: C, 47.83; H, 6.35; N, 13.94; Found: C, 48.18; H, 5.97; N, 13.56.

N,N-Diethyl O-(4-carboxy)pyridyl-3-carbamate (182h).

According to Procedure A, lithiation of carbamate 177 (528 mg, 2.72 mmol), s-BuLi (2.23 mL, 2.99 mmol), TMEDA (0.45 mL, 2.23 mmol), -78°C, 45 min, CO₂, standard workup followed by recrystallization afforded 387 mg (60%) of compound 182h, mp 143-145°C (CH₂Cl₂-hexane); IR (CHCl₃) νmax 3200-2500, 1726 cm⁻¹; NMR (CHCl₃) δ 1.11-1.50 (m, 6H, 2 CH₃), 3.26-3.79 (m, 4H, 2 CH₂), 7.91 (d, J = 5, H-5), 8.59 (m, H-2 and H-6); MS m/e 238 (M⁺); Anal. Calcd for C₁₁H₁₄N₂O₄: C, 55.46; H, 5.92; N, 11.75; Found: C, 55.79; H, 6.09; N, 11.74.
N,N-Diethyl O-(4-trimethylstamyl)pyridyl-3-carbamate (182i).

According to Procedure A, lithiation of carbamate 177 (1.50 g, 7.73 mmol), s-BuLi (7.26 mL, 8.5 mmol), TMEDA (1.28 mL, 8.5 mmol), -78°C, 45 min, trimethyltin chloride (1.69 g, 8.5 mmol), standard workup and column chromatography using 3:1 EtOAc-hexane as eluent afforded 2.23 g (82%) of compound 182i, bp 130-134°C/0.2 mm; IR (neat) ν_{max} 1721 cm^{-1}; NMR (CDCl₃) δ 0.33 (s, 9H, Sn(CH₃)_3), 1.12-1.35 (m, 6H, 2 CH₃), 3.27-3.51 (m, 4H, 2 CH₂), 7.37 (d, J = 4.8, H-5), 8.33 (s, H-2), 8.36 (d, J = 4.8, H-6); MS m/e 357 (M⁺); Anal. Calcd for C₁₃H₂₂N₂O₂Sn: C, 43.73; H, 6.21; N, 7.84. Found: C, 43.77; H, 6.03; N, 7.70.

N,N-Diethyl O-(4-tributylstannyl)pyridyl-3-carbamate (182j).

According to Procedure A, lithiation of carbamate 177 (528 mg, 2.72 mmol), s-BuLi (2.23 mL, 2.99 mmol), TMEDA (0.45 mL, 2.99 mmol), -78°C, 45 min, tributyltin chloride (0.81 mL, 2.99 mmol), standard workup and column chromatography 1:2 EtOAc-hexane as eluent afforded 640 mg (50%) of compound 182j, bp 135-140°C/0.05 mm; IR (neat) ν_{max} 1720 cm^{-1}; NMR (CDCl₃) δ 0.80-1.10 (m, 6H, 2 CH₃), 1.18-1.88 (m, 27H, Sn(Bu)_3), 3.27-3.51 (m, 4H, 2 CH₂), 7.35 (d, J = 4.7, H-5), 8.31 (s, H-2), 8.33 (d, J = 4.7, H-6); MS m/e 425 (M⁺-(C₂H₅)₂). Satisfactory analytical data were not obtained.
N,N-Diethyl O-(4-thiomethyl)pyridyl-3-carbamate (182k).

According to Procedure A, lithiation of carbamate 177 (600 mg, 3.09 mmol), s-BuLi (2.76 mL, 3.39 mmol), TMEDA (0.51 mL, 3.39 mmol), -78°C, 40 min, methyldisulfide (0.31 mL, 3.39 mmol), standard workup and column chromatography using 1:2 EtOAc-hexane as eluent gave 370 mg (50%) of compound 182k, bp 135-140°C/0.15 mm; IR (neat) ν_max 1720 cm⁻¹; NMR (CDCl₃) δ 1.22-1.38 (m, 6H, 2 CH₃), 2.44 (s, 3H, SCH₃), 3.30-3.60 (m, 4H, 2 CH₂), 7.08 (d, J = 4.8, H-5), 8.30 (s, H-2), 8.32 (d, J = 4.8, H-6); MS m/e 240 (M⁺); Anal. calcd for C₁₁H₁₆N₂O₂S: C, 54.97; H, 6.71; N, 11.65. Found: C, 54.89; H, 6.70; N, 11.41.

N,N-Diethyl O-[4-(1-hydroxy)ethyl]pyridyl-3-carbamate (182l).

According to Procedure A, lithiation of carbamate 177 (600 mg, 3.09 mmol), s-BuLi (3.30 mL, 3.39 mmol), TMEDA (0.51 mL, 3.39 mmol), -78°C, 40 min, acetaldehyde (0.19 mL, 3.39 mmol) (and after 1h, aqueous NH₄Cl solution was added at -78°C), standard workup and column chromatography afforded 350 mg (48%) of compound 182l, bp 155-160°C/0.05 mm; IR (neat) ν_max 3406, 1719 cm⁻¹; NMR (CDCl₃) δ 1.21-1.36 (m, 6H, 2 CH₃), 1.44 (d, J = 6.4, CH₃), 3.27-3.51 (m, 4H, 2 CH₂), 4.35 (br, 1H, OH), 4.98 (q, J = 6.4, CH), 7.50 (d, J = 4.7, H-5), 8.23-8.40 (br, H-2 and H-6); MS m/e 238 (M⁺); Anal. Calcd for C₁₂H₁₈N₂O₃: C, 60.43; H, 7.61; N, 11.75. Found: C, 59.98; H, 7.23; N, 11.40.
N,N-Diethyl 0-[4-(1-hydroxy-1-phenyl)methyl]pyridyl-3-carbamate (182m).

According to Procedure A, lithiation of carbamate 177 (500 mg, 2.57 mmol), s-BuLi (2.75 mL, 2.83 mmol), TMEDA/0.43 mL, 2.83 mmol), -78°C, 40 min, benzaldehyde (0.29 mL, 2.83 mmol) (and after 1h, aqueous NH₄Cl solution was added at -78°C), standard workup and column chromatography using 1:9 EtOAc-hexane as eluent afforded 580 mg (75%) of compound 182m as a viscous oil; IR (neat) \( \nu_{\text{max}} \) 3408, 1719 cm\(^{-1} \); NMR (CDCl\(_3\)) \( \delta \) 1.03-1.24 (m, 6H, 2 CH\(_3\)), 3.28-3.37 (m, 4H, 2 CH\(_2\)), 4.11 (br, 1H, OH), 5.92 (s, 1H, CH), 7.30 (s, 5H, ArH), 7.43 (d, J = 4.9, H-5), 8.31 (s, H-2), 8.40 (d, J = 4.9, H-6); MS m/e 300 (M\(^+\)); Anal. Calcd for C\(_{17}\)H\(_{20}\)N\(_2\)O\(_3\): C, 67.98; H, 6.71; N, 9.32. Found: C, 67.94; H, 7.11; N, 9.17.

N,N-Diethyl 0-(3-deuterio)pyridyl-4-carbamate (183a).

According to Procedure A, lithiation of N,N-diethyl 0-pyridyl-4-carbamate 179 (313 mg, 1.61 mmol), s-BuLi (1.54 mL, 1.77 mmol), TMEDA (0.27 mL, 1.77 mmol), -78°C, 40 min, methanol-d\(_1\) (0.3 mL, excess), standard workup and column chromatography using 1:2 EtOAc-hexane as eluent afforded 236 mg (75%) of compound 183a (37% d\(_1\), 63% d\(_0\)), bp 80-85°C/0.15 mm; IR (neat) \( \nu_{\text{max}} \) 1725 cm\(^{-1} \); NMR (CDCl\(_3\)) \( \delta \) 1.23 (t, J = 7.04, 6H, 2 CH\(_3\)), 3.41 (q, J = 7.04, 4H, 2 CH\(_2\)), 7.14 (dd, J = 4.7, 1.46, H-5 and residual H-3), 8.57 (dd, J = 4.7, 1.46, H-2 and H-6); MS m/e 195 (M\(^+\)).
N,N-Diethyl O-(3-methyl)pyridyl-4-carbamate (183b).

According to Procedure A, lithiation of carbamate 179 (1.268 g, 6.53 mmol), s-BuLi (6.30 mL, 7.18 mmol), TMEDA (1.1 mL, 7.18 mmol), -78°C, 40 min, methyl iodide (1.0 mL, excess), standard workup and column chromatography using 3:1 EtOAc-hexane as eluent gave 1.15 g (84%) of compound 183b, bp 105-110°C/0.1 mm; IR (neat) $\nu_{\text{max}}$ 1710 cm$^{-1}$; NMR (CDCl$_3$) $\delta$ 1.23 (t, J = 7.04, 6H, 2 CH$_3$), 2.22 (s, 3H, CH$_3$), 3.41 (q, J = 7.04, 4H, 2 CH$_2$), 7.14 (d, J = 4.9, H-5), 8.41 (d, J = 4.9, H-6), 8.44 (s, H-2); MS m/e 208 (M$^+$); Anal. Calcd for C$_{11}$H$_{16}$N$_2$O$_2$: C, 63.44; H, 7.74; N, 13.45. Found: C, 63.24; H, 7.94; N, 13.54.

N,N-Diethyl O-(3-N,N-diethylcarbamoyl)pyridyl-4-carbamate (183c).

According to Procedure A, lithiation of carbamate 179 (1.130 g, 5.82 mmol), s-BuLi (5.81 mL, 6.40 mmol), TMEDA (0.96 mL, 6.40 mmol), -78°C, 40 min, N,N-diethylcarbamoyl chloride (0.77 mL, 6.40 mmol), standard workup and column chromatography using EtOAc as eluent afforded 1.160 g (69%) of compound 183c, bp 132-135°C/0.25 mm; IR (neat) $\nu_{\text{max}}$ 1726, 1637 cm$^{-1}$; NMR (CDCl$_3$) $\delta$ 1.00-1.40 (m, 12H, 4 CH$_3$), 3.1-3.68 (m, 8H, 4 CH$_2$), 7.32 (d, J = 5.6, H-5), 8.51 (s, H-2), 8.58 (d, J = 5.6, H-6); HRMS m/e 293.1731. Calcd. for C$_{15}$H$_{23}$N$_3$O$_3$: 293.1740.
N,N-Diethyl O-(3-trimethylsilyl)pyridyl-4-carbamate (183d).

According to Procedure A, lithiation of carbamate 179 (520 mg, 2.68 mmol), s-BuLi (2.56 mL, 2.94 mmol), TMEDA (0.44 mL, 2.94 mmol), -78°C, 40 min, TMSCl (0.37 mL, 2.94 mmol), standard workup and column chromatography using 1:1 EtOAc-hexane as eluent gave 473 mg (67%) of compound 183d, mp 52-54°C; IR (CHCl₃) νmax 1722 cm⁻¹; NMR (CDCl₃) δ 0.30 (s, 9H, Si(CH₃)₃), 1.11-1.32 (m, 6H, 2 CH₃), 3.26-3.58 (m, 4H, 2 CH₂), 7.04 (d, J = 5.6, H-5), 8.55 (d, J = 5.6, H-6), 8.58 (s, H-2); MS m/e 266 (M⁺); Anal. Calcd for C₁₃H₂₂N₂O₂Si: C, 58.61; H, 8.32; N, 10.51. Found: C, 58.95; H, 7.97; N, 10.20.

N,N-Diethyl O-(3-bromo)pyridyl-4-carbamate (183e).

According to Procedure A, lithiation of carbamate 179 (720 mg, 3.71 mmol), s-BuLi (3.85 mL, 4.08 mmol), TMEDA (0.62 mL, 4.08 mmol), -78°C, 40 min, 1,2-dibromoethane (0.66 mL, 7.42 mmol), standard workup and column chromatography (1:5 EtOAc-hexane as eluent) afforded 605 mg (60%) of compound 183e, bp 125-130°C/0.20 mm; IR (neat) νmax 1732 cm⁻¹; NMR (CDCl₃) δ 1.0-1.37 (m, 6H, 2 CH₃), 3.36-3.53 (m, 4H, 2 CH₂), 7.34 (d, J = 5.4, H-5), 8.47 (d, J = 5.4, H-6), 8.72 (s, H-6); MS m/e 272, 274 (M⁺); Anal. Calcd for C₁₀H₁₃BrN₂O₂: C, 43.95; H, 4.79; N, 10.25. Found: C, 43.90; H, 5.17; N, 10.24.
N,N-Diethyl O-(3-iodo)pyridyl-4-carbamate (183f).

According to Procedure A, lithiation of carbamate 179 (500 mg, 2.57 mmol), s-BuLi (2.57 mL, 2.83 mmol), TMEDA (0.43 mL, 2.83 mmol), -78°C, 40 min, iodine (720 mg, 2.83 mmol), standard workup and column chromatography (1:1 EtOAc-hexane as eluent) afforded 485 mg (60%) of compound 183f, bp 132-136°C/0.2 mm; IR (neat) ı̅{max} 1734 cm⁻¹; NMR (CDCl₃) δ 0.90-1.41 (m, 6H; 2 CH₃), 3.03-3.66 (m, 4H, 2 CH₂), 7.33 (d, J = 5.5, H-5), 8.48 (d, J = 5.5, H-6), 8.90 (s, H-2); MS m/e 320 (M⁺); Anal. Calcd. for C₁₁H₁₃IN₂O₂: C, 37.52; H, 4.09; N, 8.75. Found: C, 37.51; H, 4.30; N, 8.66.

N,N-Diethyl O-(3-N,N-dimethylsulfonyl)pyridyl-4-carbamate (183g).

According to Procedure A, lithiation of carbamate 179 (418 mg, 2.15 mmol), s-BuLi (2.30 mL, 2.37 mmol), TMEDA (0.36 mL, 2.37 mmol), -78°C, 45 min, N,N-Dimethylsulfonyl chloride (0.25 mL, 2.37 mmol), standard workup and column chromatography (2:1 EtOAc-hexane as eluent) afforded 385 mg (60%) of compound 183g, bp 85-90°C/0.05 mm; IR (neat) ı̅{max} 1720 cm⁻¹; NMR (CDCl₃) δ 1.10-1.40 (m, 6H, 2 CH₃), 2.8 (s, 6H, 2 NCH₃), 3.20-3.60 (m, 4H, 2 CH₂), 7.32 (d, J = 5.6, H-5), 8.45 (d, J = 5.6), 8.6 (s, H-2); MS m/e 257 (M⁺(301)-NMe₂); Anal. Calcd. for C₁₂H₁₉N₃O₄S: C, 47.83; H, 6.35; N, 13.94. Found: C, 48.14; H, 6.23; N, 12.92.
3-Bromo-2-pyridone (184).

N,N-Diethyl O-(3-bromo)pyridyl-2-carbamate 181e (300 mg, 1.1 mmol) was refluxed in methanol (10 mL) in presence of sodium methoxide (118 mg, 2.2 mmol) for 40 h. The reaction mixture was made acidic (pH=6) by adding 2M HCl and further workup in the usual manner gave crude product which upon recrystallization afforded 170 mg (90%) of compound 184, mp 175-179°C (CH$_2$Cl$_2$) (lit.$^{115}$ 181-187°C); IR (CHCl$_3$) $\nu_{\text{max}}$ 3250, 1630 cm$^{-1}$; NMR (CHCl$_3$) $\delta$ 6.23 (dd, J = 7, H-5), 7.45 (dd, J = 7, 1.7, H-4), 7.87 (dd, J = 7, 1.7, H-6); MS m/e 173, 175 (M$^+$).

4-Methyl-3-hydroxypyridine (185).

N,N-Diethyl O-(4-methyl)pyridyl-3-carbamate 182b (600 mg, 2.88 mmol) was refluxed in methanol 15 mL) in presence of sodium methoxide (311 mg, 5.76 mmol) for 12 h. Workup in the usual manner as described in the previous experiment followed by recrystallization gave 248 mg (80%) of compound 185, mp 114-115°C (C$_6$H$_6$-hexane) (lit.$^{115}$ 117-119°C); IR (CHCl$_3$) $\nu_{\text{max}}$ 3400 cm$^{-1}$; NMR (CDCl$_3$) $\delta$ 2.35 (s, 3H, CH$_3$), 7.25 (d, J = 4.7, H-5), 8.0 (d, J = 4.7, H-6), 8.3 (br S, H-2), 9.6 (br, 1H, OH).

3-Methyl-4-pyridone (186).

N,N-Diethyl O-(3-methyl)pyridyl-4-carbamate 183b (450 mg, 2.16 mmol) was refluxed in methanol in presence of sodium methoxide (233 mg, 4.32 mmol) for 20 h. Usual workup as described in the
previous experiment followed by recrystallization afforded 198 mg (85%) of compound 186, mp 92-93°C (CH₂Cl₂-hexane) (lit. 115 92-94°C), IR (CHCl₃) ν̂max 3227, 1637 cm⁻¹; NMR (CDCl₃) δ 2.12 (s, 3H, CH₃), 6.56 (d, J = 6.7, H-5), 7.73 (m, 2H, H-2 and H-6), 9.53 (br, 1H, OH).

N,N-Diethyl O-(4-N,N-diethylcarbamoyl-5-trimethylsilyl)pyridyl-3-carbamate (187).

According to Procedure A, lithiation of N,N-Diethyl O-(4-N,N-diethylcarbamoyl)pyridyl-3-carbamate 182c (255 mg, 0.87 mmol), s-BuLi (1.36 mL, 1.82 mmol), TMEDA (0.27 mL, 1.82 mmol), -78°C, 45 min, TMSCl (0.12 mL, 0.95 mmol), standard workup and column chromatography using 3:1 EtOAc-hexane afforded 210 mg (66%) of compound 187, bp 160-164°C/0.05 mm; IR (neat) ν̂max 1725, 1640 cm⁻¹; NMR (CDCl₃) δ 0.34 (s, 9H, Si(CH₃)₃), 0.92-1.36 (m, 12H, 4 CH₃), 3.01-3.65 (m, 8H, 4 CH₂), 8.56, 8.59 (2 s, 2H, H-2 and H-6); HRMS m/e 365.2126; Calcd. for C₁₈H₃₁N₃O₃Si: 365.2132.

N,N-Diethyl O-(4-bromo-5-trimethylsilyl)pyridyl-3-carbamate (188).

According to Procedure B, lithiation of N,N-diethyl O-(4-bromo)pyridyl-3-carbamate 182e (610 mg, 2.23 mmol), LDA (1.1 equiv, 2.83 mmol), -78°C, 25 min, TMSCl (0.31 mL, 2.45 mmol),
standard workup and column chromatography using 1:2 EtOAc-hexane 
as eluent gave 500 mg (65%) of compound **188** as an oil; IR (neat) 
\[ \nu_{\text{max}} \ 1730 \ \text{cm}^{-1}; \ \text{NMR (CDCl}_3) \ \delta 0.43 \ (s, \ 9H, \ Si(CH}_3)_3, \ 1.14-1.31 \ (m, \ 6H, \ 2 \ CH_3), \ 3.30-3.64 \ (m, \ 4H, \ 2 \ CH_2), \ 8.32, \ 8.41 \ (12 \ s, \ H-2 \ \text{and} \ H-6); \ MS \ m/e \ 345, \ 347 \ (M^+). \]  
Compound **188** was found to decompose on standing at 0°C for a few days and an analytical sample could not be obtained.

**N,N-Diethyl 0-(3-N,N-diethylcarbamoyl-5-trimethylsilyl)pyridyl-4-carbamate (189).**

According to Procedure A, lithiation of N,N-diethyl 0-(3-N,N-diethylcarbamoyl)pyridyl-4-carbamate **183c** (53 mg, 0.87 mmol), n-BuLi (1.36 mL, 1.82 mmol), TMEDA (0.27 mL, 1.82 mmol), –78°C, 45 mm, TMSCl (0.12 mL, 0.95 mmol), standard workup and column chromatography using 3:1 EtOAc-hexane as eluent afforded 215 mg (66%) of compound **189**, bp 155-160°C/0.05 mm; IR (neat) \[ \nu_{\text{max}} \ 1725, \ 1636 \ \text{cm}^{-1}; \ \text{NMR (CDCl}_3) \ \delta 0.93-1.26 \ (m, \ 12 \ H, \ 4 \ CH_3), \ 3.13-3.39 \ (m, \ 8H, \ 4 \ CH_2), \ 8.5, \ 8.6 \ (2 \ s, \ 2H, \ H-2 \ \text{and} \ H-6); \ \text{HRMS} \ m/e \ 365.2130; \ \text{Calcd. for} \ C_{18}H_{31}N_3O_3Si: \ 365.2132.\]

**N,N-Diethyl-3-hydroxyisonicotinamide (190).**

According to Procedure C, lithiation of N,N-diethyl 0-pyridyl-3-carbamate **177** (600 mg, 3.09 mmol), n-BuLi (2.83 mL,
3.40 mmol), TMEDA (0.51 mL, 3.40 mmol), -78°C and warming to room temperature over 8h, standard workup and purification by preparative TLC using EtOAc as eluent afforded 240 mg (40%) of compound 190 as a viscous oil; IR (CHCl₃) ν max 1625 cm⁻¹; NMR (CDCl₃) δ 1.18 (t, J = 7, 6H, 2 CH₃), 3.41 (q, J = 7, 4H, 2 CH₂), 7.10 (d, J = 4.7, H-5), 8.06 (d, J = 4.7, H-6), 8.24 (br, H-2); HRMS m/e 194.1051 Calcd. for C₁₀H₁₄N₂O₂: 194.1056.

3-N,N-Diethylcarbamoyl-4-pyridone (191a).

According to Procedure C, lithiation of N,N-diethyl 0-pyridyl-4-carbamate 179 (409 mg, 2.10 mmol), s-BuLi (1.89 mL, 2.31 mmol), TMEDA (0.35 mL, 2.31 mmol), -78°C and warming to room temperature over 8h, standard workup followed by recrystallization gave 300 mg (74%) of compound 191a, mp 98-100°C (C₆H₆-CH₂Cl₂); IR (CHCl₃) ν max 3220, 1641, 1618 cm⁻¹; NMR (CDCl₃) δ 1.14 (t, J = 7, 6H, 2 CH₃), 3.38 (q, J = 7, 4H, 2 CH₂), 6.49 (d, J = 7, H-5), 7.68 (d, J = 7, H-6), 7.76 (s, H-2); HRMS m/e 194.1047; Calcd. for C₁₀H₁₄N₂O₂: 194.1056.

3-N,N-Diethylcarbamoyl-5-methyl-4-pyridone (191b).

According to Procedure C, lithiation of N,N-diethyl 0-((3-methyl)pyridyl-4-carbamate 183b (300 mg, 1.44 mmol), s-BuLi (2.65 mL, 3.02 mmol), TMEDA (0.45 mL, 3.02 mmol), -78°C, and warming to room temperature over 8 h, standard workup and
purification by preparative TLC using EtOAc as eluent afforded 238 mg (80%) of compound 191b, IR (neat) \( \nu_{\text{max}} \) 3419, 1641 cm\(^{-1}\); NMR (CDCl\(_3\)) \( \delta \) 1.0-1.5 (m, 6H, 2 CH\(_3\)), 2.05 (s, 3H, CH\(_3\)), 2.95-3.50 (m, 4H, 2 CH\(_2\)), 7.6, 7.7 (2 s, 2H, H-2 and H-6); HRMS m/e 208.1209; Calcd for C\(_{11}\)H\(_{16}\)N\(_2\)O\(_2\): 208.1212.

3-N,N-Diethylcarbamoyl-5-trimethylsilyl-4-pyridone (191c).

According to Procedure C, lithiation of N,N-diethyl 0-(3-trimethylsilyl)pyridyl-4-carbamate 183d (250 mg, 0.93 mmol), s-BuLi (0.84 mL, 1.12 mmol), TMEDA (0.17 mL, 1.12 mmol) -78°C, and warming to room temperature over 8h, standard workup and recrystallization afforded compound 191c, mp 198-201°C (CH\(_2\)Cl\(_2\)-hexane); IR (CHCl\(_3\)) \( \nu_{\text{max}} \) 3208, 1632 cm\(^{-1}\); NMR (CDCl\(_3\)) \( \delta \) 0.22 (s, 9H, Si(CH\(_3\))\(_3\)), 1.06-1.50 (m, 6H, 2 CH\(_3\)), 3.30-3.70 (m, 4H, 2 CH\(_2\)), 7.7 (br, 2H, H-2 and H-6); MS m/e 266 (M\(^+\)); Anal. Calcd for C\(_{13}\)H\(_{22}\)N\(_2\)O\(_2\)Si: C, 58.61; H, 8.32; N, 10.54. Found: C, 58.66; H, 8.15; N, 10.06.

N,N-Diethyl-4-chloro-5-methylnicotinamide (195).

3-N,N-Diethylcarbamoyl-5-methyl-4-pyridone 191b (91 mg 0.44 mmol), was refluxed with phosphoryl chloride (2 mL) for 10 min. Excess phosphoryl chloride was removed under vacuo followed by standard workup gave crude product which upon purification by preparative TLC using EtOAc as eluent afforded 49 mg (50%) of compound 195 as an oil; IR (neat) \( \nu_{\text{max}} \) 1636 cm\(^{-1}\); NMR
(CDCl₃) δ 1.00-1.37 (m, 6H, 2 CH₃), 2.41 (s, 3H, CH₃), 3.02-3.8 (m, 4H, 2 CH₂), 8.21-8.6 (br, 2H, H-2 and H-6); HRMS m/e 226.0865 and 228.0844; Calcd. for C₁₁H₁₅ClN₂O: 226.0874 and 228.0844.

**N,N-Diethyl-5-methylnicotinamide (196).**

Hydrogen was passed through a stirred solution of N,N-diethyl-4-chloro-5-methylnicotinamide 195 (40 mg, 0.18 mmol) in ethanol (5 mL) for 16 h in presence of catalytic amount of palladium-barium sulfate catalyst. Usual workup followed by purification by preparative TLC (EtOAc as eluent) afforded 30 mg (90%) of compound 196 as an oil; IR (neat) ν max 1630 cm⁻¹; NMR (CDCl₃) δ 1.12-1.27 (m, 6H, 2 CH₃), 2.37 (s, 3H, CH₃), 3.37-3.53 (m, 4H, 2 CH₂), 7.54 (br, H-4), 8.46 (br, 2H, H-2 and H-6); HRMS 192.1263. Calcd. for C₁₁H₁₆N₂O: 192.1263.

**N,N-Diethyl 0-(4-iodopyridyl-3-carbamate (182f) from N,N-diethyl 0-(4-trimethylstannyl)pyridyl-3-carbamate (182i).**

Iodine (237 mg, 0.92 mmol) was added to a solution of stannylated carbamate 182i (152 mg, 0.42 mmol) in chloroform (10 mL) and the mixture was stirred for 5h at room temperature under nitrogen. The reaction mixture was washed with aqueous sodium thiosulfite solution and water and the chloroform solution was
dried (Na₂SO₄) and concentrated to give crude product which upon column chromatography afforded 136 mg (90%) of compound 182f which was shown to be identical (by NMR, GC) with a sample obtained through ortho lithiation reaction of 177.

**N,N-Diethyl O-(4-acetyl)pyridyl-3-carbamate (199).**

The stannylated carbamate 182i (312 mg, 0.87 mmol) was taken in benzene (15 mL) and acetyl chloride (0.25 mL, 3.50 mmol) was added to it and the resulting solution was heated at reflux for 40 h under nitrogen. The reaction mixture was washed with aqueous sodium bicarbonate solution and water and the benzene solution was dried (Na₂SO₄) and concentrated to give crude product which was purified by preparative TLC (EtOAc as eluent) to afford 207 mg (57%) of compound 199 as an oil; IR (neat) vₓₓ 1726 cm⁻¹; NMR (CDCl₃) δ 1.12-1.55 (m, 6H, 2 CH₃), 2.55 (s, 3H, CH₃), 3.25-3.64 (m, 4H, 2 CH₂), 7.50 (d, J = 4.9, H-5), 8.51 (s, H-2), 8.56 (d, J = 4.9, H-6); MS m/e 237 (M⁺). Compound 199 was found contaminated with a trace of starting material (by mass spectrum) which could not be removed and an analytical sample was not obtained.
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