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CYCLIZATIONS INVOLVING INTERMEDIATES OBTAINED BY SELECTIVE LITH--ETC(U)
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CONT
CYCLIZATIONS INVOLVING INTERMEDIATES
OBTAINED BY SELECTIVE LITHIATIONS

Final Report
by
Charles K. Bradsher
October 15, 1979

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The findings in this Report are not to be construed as an official Department of Army position, unless so designated by other official documents.
The discovery by Parham, et al. that the halogen-metal exchange reaction at low temperature can be used to generate organolithium reagents bearing electrophilic groups elsewhere in the molecule has been of importance in the development of novel cyclization reactions. If the anionic and electrophilic centers of the functionalized organolithium reagent thus generated are suitably arranged, an external electrophile may react to generate a new anion capable of (over)

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**Title:** Cyclizations Involving Intermediates Obtained by Selective Lithiations

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**Abstract:**

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**Security Classification:** Unclassified

**Distribution Statement:** Approved for public release; distribution unlimited.
FOREWORD

The sudden and untimely death of Professor W. E. Parham on May 21, 1976, left an excellent group of four young graduate students each of whom was determined, if possible, to continue and expand the field of "Parham Chemistry" - the synthesis and elaboration of aryllithium reagents bearing functional groups. Since Dr. Parham's grant DAHC04 74 G0128 expired April 30, 1977, we sought research support for the continuation project. The Army Research Office awarded Duke University the sum of $15,000 (over a two-year period) which was agreed to represent participation by ARO with Duke University in the support of the proposed research. The work described here was carried out by three of the four Parham students, David W. Boykin, David A. Hunt and David C. Reames, each of whom has now completed the requirements for the PhD. degree.
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(Publications acknowledging support of Grant No. DAAG29 77 G0170)


BODY OF REPORT

Halogen-metal exchange has long been known to be a useful method for preparation of organolithium compounds. However, the reaction was at first limited to aryl bromides (or iodides) that contained no electrophilic functional groups; those groups precluded exchange, for they reacted with the exchange agent or with the generated aryllithium reagent. Furham and associates found that this limitation could be removed if exchange was carried out at -100°C. At that temperature, many electrophilic groups (e.g., COOH, COOR, CN, CH₂Cl) were found to be passive toward attack by butyllithium while exchange of the aryl bromide remained facile. Thus, the low temperature exchange reaction provided a route to functionalized organolithium reagents.

To demonstrate the synthetic utility of low temperature exchange, a variety of aryllithium reagents containing electrophilic groups were prepared by exchange at -100°C. These novel reagents were employed in two different synthetic sequences. In the first, the functionalized organolithium reagent was allowed to react with an added electrophile. Several exchange substrates were investigated in reactions of this type:

REATIONS WITH EXTERNAL ELECTROPHILES

1. **Benzyl Halides**

α-Methyl-o-bromobenzyl chloride (1₃, R = H) and α,α-dimethyl-o-bromobenzyl chloride (1₄, R = CH₃) were both found to undergo selective exchange to the o-lithio derivatives (2₃ and
2b) when treated with butyllithium at -100°C. These reagents reacted with cyclohexanone, an added electrophile, and cyclized to afford phthalans 3a and 3b.

\[
\begin{align*}
\text{Cl} & \quad \text{BuLi} \quad \text{-100°C} \\
\begin{array}{c}
\text{R} \quad \text{CH}_3 \\
\text{Br}
\end{array} & \rightarrow \\
\begin{array}{c}
\text{R} \quad \text{CH}_3 \\
\text{Li}
\end{array} & \rightarrow \\
\begin{array}{c}
\text{R} \quad \text{CH}_3 \\
\text{Cl}
\end{array} & \rightarrow \\
\text{R} & \quad \text{CH}_3 \\
\text{O}
\end{align*}
\]

\(3a \, (R = H); \, 65\%
\)

\(3b \, (R = \text{CH}_3); \, 25\%
\)

2. \(\beta\)-Methyl Oximes of Aromatic Aldehydes

The aldehyde carbonyl remains reactive toward butyllithium even at -100°C and therefore must be protected during exchange. The \(\beta\)-methyl oxime of \(\alpha\)-bromobenzaldehyde (\(\tilde{\Delta}\)) was prepared and subjected to exchange; the organolithium reagent \(\tilde{\Delta}\) was generated and could be trapped as acid \(\tilde{\Delta}\) by carbonation. Surprisingly, when \(\alpha\)-bromobenzaldehyde oxime was subjected to lithiation with two equivalents of butyllithium, exchange preceded abstraction of the weakly acidic oxime proton. An apparent rapid proton transfer then quenched the aryllithium reagent. Thus, the oxime itself was found to be unsatisfactory as an aldehyde protecting group during exchange.

\[
\begin{align*}
\begin{array}{c}
\text{CH}=\text{NOCH}_3 \\
\text{Br} \\
\text{BuLi} \quad \text{-100°C}
\end{array} \rightarrow \\
\begin{array}{c}
\text{CH}=\text{NOCH}_3 \\
\text{Li}
\end{array} & \rightarrow \\
\begin{array}{c}
\text{CH}=\text{NOCH}_3 \\
\text{COOH}
\end{array} \, \text{CO}_2 \, \text{H}^+ \\
\begin{array}{c}
\text{CH}=\text{NOCH}_3 \\
\text{BuLi} \quad \text{-100°C}
\end{array}
\end{align*}
\]

\(\tilde{\Delta}; \, 88\%
\)

Reaction of o-lithiobenzyl chloride (7), prepared from the reaction of the corresponding bromide with n-butyllithium at -100°, with Schiff bases (9) and pyridine-2-carbonyl derivatives (10) proved to be of value in the preparation of 1,2-diarylsindolines (19), acridizinum salts (11), and dihydroisobenzofurans (12). It was found that whether 9 or 10 was prepared from the reaction of 8 with the pyridine-2-carbonyl derivatives (10) was highly temperature dependent.

\[
\text{ArCH=NR}^\prime (8) \xrightarrow{\text{ArCH=NR}^\prime (8)} \text{N-Ar}^\prime
\]

\[
\text{Cl} \xrightarrow{1) \text{EtOH/-78°}} \text{R} \xrightarrow{2) \Delta/\text{HBr}} \text{Ar}
\]

Reaction of o-lithio-8-phenylethyl bromide (13) (prepared from the corresponding bromide) with nitriles proved to be a facile method for the preparation of 1-substituted-3,4-dihydroisooquinolines (14).
4. Reaction of Isopropyl-o-Lithiobenzoate and o-Lithiobenzonitrile with Schiff Bases.

Reaction of isopropyl-o-lithiobenzoate (15) and o-bromobenzonitrile (16) (prepared by the reaction of the corresponding bromides with n-butyl lithium at \(-100^\circ\))\(^6,7\) with Schiff bases (2) proved to be an entry into the 2,3-diaryl phthalimidine system (17).

5. Studies of Bromine-Lithium Exchange with o-Bromoaryl Schiff Bases.

Reaction of n-butyl lithium with Schiff bases of the type \(\text{ArCH}=\text{NAr'}\) gave varying results. In the case of \(\text{ArCH}=\text{NAr'}\), addition to the azomethine linkage occurred in preference to exchange
at -100°. In the case of \(18b\), a limited amount of exchange product could be detected at -100°.

\[
\begin{align*}
\text{\(18a\), } n &= 0 \\
\text{\(18b\), } n &= 1 \\
\text{\(18c\), } n &= 2
\end{align*}
\]

6. Derivatives of Acrylic Acid

The reactivity of derivatives of 2-bromoacrylic acid was investigated in detail. The reaction of \(19a\) with two molar equivalents of \(n\)-butyllithium in tetrahydrofuran at -100°C afforded polymeric material. Compound \(19b\) was found to undergo dehydrobromination to phenylpropynoic acid, even at -140°C. Bromine-lithium exchange was rapid and complete for \(19c\) and \(19d\), which afforded the lithiovinyl derivatives \(20a\) and \(20b\), respectively.

\[
\begin{align*}
19 & \xrightarrow{\text{THF, -100 °C}} 20 \\
\text{\(a\), } R_1 = R_2 &= \text{H} \\
\text{\(b\), } R_1 &= \text{Ph} \quad R_2 = \text{H} \\
\text{\(c\), } R_1 &= \text{CH}_3 \\
\text{\(d\), } R_1 &= \text{Ph}
\end{align*}
\]
These reagents were used to alkylate a variety of electrophiles to afford 2-substituted acids of types 21a and 21b.

<table>
<thead>
<tr>
<th>Electrophile</th>
<th>Product</th>
<th>Isolated Yield, %</th>
</tr>
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<tbody>
<tr>
<td>CH₃CH₂I</td>
<td>21a, E = CH₂CH₃</td>
<td>79</td>
</tr>
<tr>
<td>CH₃OD</td>
<td>D</td>
<td>98</td>
</tr>
<tr>
<td>C₆H₅SSC₆H₅</td>
<td>SC₆H₅</td>
<td>61</td>
</tr>
<tr>
<td>C₆H₅NCO</td>
<td>CONHC₆H₅</td>
<td>58</td>
</tr>
<tr>
<td>CH₃I</td>
<td>21b, E = CH₃</td>
<td>73</td>
</tr>
<tr>
<td>Cyclohexanone</td>
<td>C(OH)(CH₂)₅</td>
<td>62</td>
</tr>
<tr>
<td>C₆H₅SSC₆H₅</td>
<td>SC₆H₅</td>
<td>68</td>
</tr>
<tr>
<td>C₆H₅CH₂SSCH₂C₆H₅</td>
<td>SCH₂C₆H₅</td>
<td>61</td>
</tr>
</tbody>
</table>

The reaction of 3-methyl-2-butenoic acid (22) with n- or tert-butyllithium was found to produce a lithio derivative which underwent α- and γ-alkylation and/or double bond isomerization, a result also obtained by the use of lithium diisopropyl amide with 22.⁹

7. Bromoaryl Compounds

A comparison of the reactivities of the isomeric lithium lithio benzoates and synthetically related organolithium compounds (25, 26, and 27) was made by using the alkylation of chlorosilanes (e.g., (CH₃)₃SiCl) and disulfides (e.g., CH₃SSCH₃) as model reactions. These were prepared by low temperature lithiation of the corresponding bromoaryl compounds (25, 26, 27).³,⁶,⁷ The
The lithioaryl carboxylates \( \text{a} \) and \( \text{b} \) gave variable yields of alkylation products and were generally inferior to the isomer \( \text{c} \). The alkylation of \( \text{d} \) and \( \text{e} \) followed by acid-catalyzed hydrolysis of the tert-butyl group provided an alternative route to acids \( \text{f} \) and \( \text{g} \) \((E = (CH_3)_3Si)\). The lithio derivatives of the isomeric nitriles \( \text{h} \), \( \text{i} \), and \( \text{j} \) were all efficiently alkylated. A variety of \( o \)-substituted benzoic acids \( \text{k} \) and benzonitriles \( \text{l} \) were prepared: \( \text{m} \), \( E = Si(CH_3)_3, Si(CH_3)_2Ph, SCH_2, SPh, SCH_2Ph, SePh, PPh_2, P^+Ph_2CH_3 1^-; \text{n} \), \( E = Si(CH_3)_3, Si(CH_3)_2Ph, SPh, S(CH_3)_2BF_4^-, PPh_2, PO(Ph)_2, F(S)Ph_2, F^+Ph_2CH_3 1^-; \) Other isomers and esters prepared included: \( \text{o} \), \( E = SCH_2, S(CH_3)_2BF_4^-; \text{p} \), \( E = SCH_2, Si(CH_3)_3, 30, E = SCH_2, 30, E = Si(CH_3)_3, 33, E = Si(CH_3)_3, 33, E = SCH_2.\)

- **ortho**: \( \text{q} \)
- **meta**: \( \text{r} \)
- **para**: \( \text{s} \)

\[ \begin{align*}
\text{Br} & \quad \text{C}_4\text{H}_9\text{Li} & \quad \text{Li} & \quad \text{E}^+ \\
\text{R} & \quad \text{R} & \quad \text{R} & \quad \text{R} \end{align*} \]

\[ \begin{align*}
\text{q}, R = \text{CO}_2\text{H} \\
\text{r}, R = \text{CO}_2\text{Li} \\
\text{s}, R = \text{CO}_2\text{CH(CH}_3)_2 \\
\text{t}, R = \text{CO}_2\text{C(CH}_3)_3 \\
\text{u}, R = \text{C} \equiv \text{N} \]
8. Saturated Bromo Acids

11-Bromoundecanoic acid (34) was converted to the trilithio derivative 35 which afforded 11-(phenylthio)undecanoic acid (36) in 52-53% yield.

\[
\text{Br(CH}_2\text{)}_{10}\text{CO}_2\text{H} \rightarrow \text{Li(CH}_2\text{)}_9\text{CH}=\text{CO}_2\text{Li}_2 \rightarrow \text{PhS(CH}_2\text{)}_{10}\text{CO}_2\text{H}
\]

\[
34 \quad 35 \quad 36
\]

REATIONS WITH INTERNAL ELECTROPHILES

In the case of other functionalized organolithium reagents generated by exchange, the electrophilic group was positioned such that it could act as an internal electrophile and afford a cyclic product. This synthetic sequence, the Parham cyclization, was further developed as an alternative to traditional ring closures in investigations on several systems:

1. Acids

Parham, Jones, and Sayed have reported the use of the lithium salt of a carboxylic acid as an internal electrophile in a synthesis of 1-indanone. This cyclization was extended to the preparation of seven-membered ring ketones and heterocyclic ketones. Of particular interest was a novel synthesis of dibenzosuberone (39). o-Bromobenzyl bromide (37) was converted to 2-bromo-2'-lithiobenzyl; carbonation gave salt 38. Exchange and cyclization gave dibenzosuberone (39; 56% from 37) in an efficient, "one-pot" procedure.
2. Epoxides

The epoxide ring was found to be passive toward attack by butyllithium at -100°C; thus, it was possible to generate aryllithium reagents of type \( \frac{41}{42} \). These reagents were particularly interesting, for rings of two different sizes might be formed in the Parham cyclization. However, for a number of examples, the only cyclic product was the 2,3-dihydro-3-benzofuranmethanol (\( \frac{42}{43} \)). No six-membered ring product was detected even in cases where the epoxide carbon nearer the anionic center was fully substituted.

3. Phenoxyalkyl Halides

The Parham cyclialkylation, previously reported only in carbocyclic systems, was extended to the preparation of substituted oxygen heterocycles. Substituted \( \alpha \)-bromophenoxyalkyl bromides such as \( \frac{43}{44} (n = 2-4) \) were found to undergo rapid exchange to intermediates \( \frac{44}{45} (n = 2-4) \). Cyclization of these reagents gave good yields of products (\( \frac{45}{46} \)).
The phenoxyalkyl bromides were also studied as substrates for double lithiations (i.e., two successive selective exchange reactions on one aryl nucleus). For example, compound \( \text{43} \) was found to undergo selective exchange and cyclization to heterocycle \( \text{44} \). Without isolation of \( \text{44} \), a second exchange and a reaction with an added electrophile \( (\text{CO}_2) \) could be carried out, giving acid \( \text{45} \). Additional examples of double lithiations demonstrated the versatility this technique imparts to the exchange process.

\[
\begin{align*}
\text{46} & \quad \text{BuLi} \quad -100^\circ \text{C} \quad \text{Br} \quad \text{Br} \quad \text{Br} \quad \text{BuLi} \quad 1) \text{BuLi} \\
\text{47} & \quad \text{CO}_2 \quad 2) \text{H}^+ \\
\text{48} & \quad \text{HOOC} \quad 3) \text{H}^+ \quad \text{61%}
\end{align*}
\]

4. **Schiff Bases**

The best results were observed for Schiff bases of the type \( \text{49} \). Bromine-lithium exchange occurred readily at \(-100^\circ\), and upon warming the lithio derivative \( \text{49} \) to room temperature, 1-substituted-1,2,3,4-tetrahydroisoquinolines \( \text{50} \) were obtained via intramolecular attack of the "anion" upon the azomethine linkage.

Attempted bromine-lithium exchange by the reaction of \( n \)-butyllithium with bromophthalimides (5.1) and \( o \)-bromo-\( \delta \)-phenylethyl isocyanate (5.2) at \(-100^\circ\) failed in all cases tested, the major product obtained in each case derived from the addition of \( n \)-butyllithium to the \( N-C=O \) linkage.


Bromine-lithium exchange in systems analogous to \( o \)-lithio-\( \delta \)-phenylethyl bromide (1.3) proved to be a valuable technique for the large scale preparation of arylcyclobutenes 5.3 and 5.4.
Additionally, bromine-lithium exchange studies with the arylbromo compound 55 proved to be a new method for the large scale preparation of 1,3,4,5-benzodicyclobutene (56); however, if substituents are placed at the 3- and 6- positions (as in 57), a single exchange occurs, even when treated with two equivalents of n-butyllithium. This phenomenon is presumably due to anion formation in order to relieve steric strain.
BIBLIOGRAPHY


SUPPLEMENTARY

INFORMATION
bromoethyl, cyano, carboxylate, carboalkoxy as well as beta carboxyethyl anion and beta carboxamidoethyl groups.

Functionalized phenyllithium reagents have great synthetic utility. Reaction with electrophiles, such as methyl iodide, bromine, benzophenone, cyclohexone, phthalic anhydride, benzoate esters, diphenyl disulfide or ethylene oxide replaces the aryl lithium atom resulting in a benzene ring with two functional groups.

Usually, allowing the functionalized aryllithium to warm up results in an interaction between the lithium atom and the functional group. A useful example of such an interaction is the self condensation of lithium ortho-lithio benzoates to yield ortho-benzoylbenzoic acid.

A phenyllithium reagent having a functional substituent in the ortho position are frequently useful intermediates for cyclization.