Selective Lithiation of Bromoarylalkanoic Acids and Amides at Low Temperature. Preparation of Substituted Arylalkanoic Acids and Indanones

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Studies of \( p \)-bromophenylpropanoic acid suggest that \( p \)- and presumably \( m \)-, bromoarylalkanoic acids can be conveniently elaborated by selective halogen-metal exchange with \( n \)-butyllithium at \(-100^\circ C\) followed by reaction with \( E^+ \). Metal-halogen exchange is also selective for ortho-substituted acids, however, \( \alpha \)-bromoarylalkanoic acids lead directly to indanones in high yield. Amide anions have been shown to be less reactive toward organo-lithium derivatives than carboxylates; consequently, by masking the carboxylic acid group by conversion to the amide anion, indanone formation can be obviated and elaboration of \( \alpha \)-bromoarylalkanoic acid can be achieved. \( \alpha \)-Bromophenylacetic acid (3) reacts with \( n \)-butyllithium at \(-100^\circ C\) or at \(-78^\circ C\) to give the dilithio derivative 21; the trilithio derivative 23 results (see Scheme 2). Similar results were obtained with \( \alpha \)-bromophenylacetamide (4); however, in contrast to the results obtained with the amide anion, alkylation of intermediate anions with \( n \)-butyl bromide, formed during metal interchange, occurs which detracts from synthetic applications in the latter case.

Although Grignard (or lithium) reagents of aryl halides are useful intermediates for formation of aryl-carbon bonds, utilization of such derivatives has been of limited value for aromatic nuclei containing sensitive electron-withdrawing groups. Meyers and Temple\(^2\) have obviated the generality of the above method for the elaboration of alkanoic acids. Acid 1 was selected as a model for the behavior expected for a broad series of para- and meta-substituted bromoarylalkanoic acids. Limitations for utilization of bromoarylalkanoic acids were anticipated where functional groups were expected to react with lithium reagents. Mel"nikov and coworkers\(^1\) showed that halogen-lithium exchange was \(-80\%\) after 30 min and the ratio did not change appreciably after an additional 90 min at \(-100^\circ C\). Additional \( n \)-butyllithium (up to 0.4 to 1 equiv) increased the degree of exchange only slightly (ratio of 1:6 was \(-85\%\)) however, with excess \( n \)-butyllithium and time, small quantities of butylated products were detected (NMR) in the neutral component of the aliquots. In subsequent experiments 2.2 equiv of \( n \)-butyllithium was employed and the mixture was stirred at \(-100^\circ C\) for 45 min prior to quenching. In one experiment (see Scheme 1) the mixture was quenched with water; the yield of 1 was recovered as a product.  

References and Notes


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Scheme I

\[ nC_\text{H}_L i (2.2 \text{equiv}) \rightarrow 90 \text{ to } -100^\circ \]

\[ \text{CH}_\text{CH}_\text{COOH} \]

\[ \text{CH}_\text{CH}_\text{COOH} \]

of 6, isolated pure by distillation, was 86%. The residual acidic product was a mixture of 1, 6, and a trace of butylated acid. In another experiment 5 was quenched with cyclohexanone; the yield of nearly pure 7 was 67% (59% pure). In no case was there any evidence that 5 self-condensed at -100°. It was concluded, therefore, that, except for the limitations described in B and C (below), the procedure described should prove to be a useful one for the elaboration of \( m \)- and \( p \)-arylalkanoic acids.

B. \( \beta \)-\( \alpha \)-Bromophenylpropionic Acid (2). This acid was chosen for study since it was anticipated that favorable entropy considerations may lead to self-condensation of 8, leading to indanone (9).

Scheme II

Reaction of 2 with \( n \)-butyllithium was indeed selective at -100° in that halogen-metal exchange occurred without proton abstraction from the methylene group or without addition of \( n \)-butyllithium to carboxylate; however, as anticipated, cyclization occurred at -100° to give indanone. Reaction of 2 with \( n \)-butyllithium at -100° leads directly to indanone (61% yield by isolation). By contrast, reaction of the unsubstituted amide 14 with 2 equiv of \( n \)-butyllithium leads to the dilithio derivative 15, which does not cyclize at -100°. Reaction with acid gave 16 in 81% yield (isolated); amide 17 was isolated pure in 40% yield when 15 was quenched with cyclohexanone. Use of such amides appears attractive as masking agents of carboxyl functions in such reactions.

C. \( \alpha \)-Bromophenylacetic Acid (3). Halogen-metal interchange in \( \alpha \)-bromophenylacetic acid is more complex owing to trianion formation (23) and incomplete halogen-metal exchange; however, by utilizing "anion decay" (see below), reasonable yields of elaborated products (24) can be obtained. Results of these studies, which are summarized in Scheme IV, have led us to the following conclusions and comments.
1. Metalation of the rapidly formed salt 18 with the second equivalent of n-butyllithium was slow at -100° and leads to the dilithio derivative 21 and presumably to the trilithio derivative 23. Whether 19 is formed at all, or whether it was unreactive owing to solubility or steric reasons, was not determined; however, no products derived from 19, other than recovered 3, were obtained in subsequent reactions. Examination of aliquots which were quenched with dilute acid showed no change in degree of metalation (ratio of o-bromophenylacetic acid to phenylacetic acid 36:64) after 4 hr.

2. The salt 19, if formed, does not undergo appreciable further metalation. Addition of a third equivalent of n-butyllithium changed the above ratio to 30:70; however, further addition of n-butyllithium (up to 6 equiv) caused no appreciable further change in this ratio, and in the amount of o-bromophenylacetic acid recovered.

3. The dilithio derivative 21 does react with n-butyllithium to give the trilithio derivative 23; however, 23 is unstable at -100° and reacts with solvent to regenerate 21. Thus, addition of additional n-butyllithium has little effect on the ultimate composition of the mixture; 23 is formed from 21, which decays back to 21, and this process is repeated by addition of additional n-butyllithium.

4. The dilithio derivative 21 reacts with cyclohexanone by addition to give, subsequent to acidification, lactone 24, and undoubtedly some phenylacetic acid by enolate formation with the ketone. Maximum yield of lactone 24 (42%, 60% based on converted 3) was obtained when a mixture of o-bromophenylacetic and 3 equiv of n-butyllithium was stirred at -100° for 5 hr, to permit decay of 23 to 21, prior to addition of excess cyclohexanone. The only other acids formed in this reaction were o-bromophenylacetic acid and phenylacetic acid (ratio 40:60).

5. The trilithio derivative 23 reacts with cyclohexanone to give hydroxy acid 27; in no case was hydroxy acid 25 detected. The anion 23 rapidly decays to 21 and after 4-5 hr at -75 to -100° is completely converted to 21. Thus, if cyclohexanone is added only 1 hr after addition of the third equivalent of n-butyllithium to the reaction mixture obtained from 3 and 2 equiv of n-butyllithium (7 hr, -100°), 23 is present. Under these conditions hydroxy acid 27 is formed which was isolated in 39% yield; lactone 24 was isolated in 24% yield. If this solution is aged prior to addition of cyclohexanone (see 4, above), no hydroxy acid 27 is produced. The lifetime of 23 was examined (in separate experiments) by adding cyclohexanone after different time intervals following the addition of the third equivalent of n-butyllithium. The maximum yield of 27 (54%, 77% based on converted 3) was obtained by adding excess cyclohexanone to an aged mixture (14 hr) prepared from 3 and 3 equiv of n-butyllithium 15 min after addition of a fourth equivalent of n-butyllithium; 10% yield of lactone 24 was also isolated in this case. Failure to isolate the disubstituted product 25 from the trilithio derivative is interpreted to mean that either (1) reaction with ketone occurred preferentially at the anion adjacent to carbonyl, and that the derived aryllithium intermediate 26 does not react further with cyclo-
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hexanone for steric reasons, or (2) that the aryllithium in 26 is lost and converted to the salt of 27 by reaction with solvent. It is of interest to note that the corresponding trilithio derivative 30 obtained from the para isomer reacts with cyclohexanone at both carbon anionic centers.

6. Loss of trilithio derivative 23 is a function of concentration and temperature. Reaction of 3 under identical conditions described in 5 (above), but at one-fourth the molar concentration (i.e., more concentrated in solvent tetrahydrofuran), led to greater loss of 23. The yield of 27 decreased from 39% to 26% while the yield of lactone derived from 24 increased from 24% to 30% (by isolation). Furthermore, addition of cyclohexanone to a mixture prepared from 3 (2 equiv of n-butyllithium) 3 hr after adding the third molar equivalent of n-butyllithium at −100° led to a 13% yield of 27, but to no 27 when the extra 3 hr of aging was at −75°.

7. An alternate pathway for the formation of 27 as shown in Scheme V is rejected. If this process was of significance, then aging prior to addition of cyclohexanone should result in an increase in yield of 27, which is in complete contradiction to the results observed.

Studies of metalation of p-bromophenylacetic acid (4) gave similar results and provided more conclusive evidence for formation of products derived from the trilithio derivative 30 (Scheme VI); however, the reaction products were more complex than those obtained from 3. The following observations were made.

1. The degree of halogen–lithium interchange was 40% with 2 equiv of n-butyllithium after 2 hr and this value was unchanged after additional 4 hr. The degree of halogen–lithium interchange decreased in more concentrated solutions. Thus, under similar conditions but at four times the molar concentration of 4 in solvent, the degree of halogen–lithium interchange was only 20%. This decrease is attributed to insolubility of the carboxylate salt of 4. The maximum degree of halogen–lithium interchange (60%) was achieved by addition of 3 equiv of n-butyllithium to 4 and stirring the resulting mixture (~17 hr). The solution was a mixture containing 28 and 30. The degree of halogen–lithium interchange was unchanged by addition of a fourth equivalent of n-butyllithium.

2. The trilithio derivative 30, like the analogous salt 23, decays to dilitthio derivative 28 with time by reaction with solvent. Thus, addition of a fourth equivalent of n-butyllithium to a mixture prepared from 4 and 3 equiv of n-butyllithium gave a mixture rich in 30 relative to 28. When excess cyclohexanone was added 15 min after addition of the fourth equivalent of n-butyllithium, the product mixture contained little 29 which would be derived from the dilitthio derivative 28. The acidic products were separated by preparative plate chromatography. The principal products were (a) an oil (~25% crude yield), the NMR spectrum of which was consistent with 31a (this product could not be induced to crystallize and was not characterized by composition analysis), and (b) alcohol 32a (~25% crude yield) which was obtained pure.

In contrast, when the above solution was aged for 12 hr at −75°, there was considerable loss of trilithio derivative 30 to dilitthio derivative 28. In this case, addition of excess cyclohexanone led to a significant quantity (~33% crude yield) of 29b. Chromatography of the mixed acids gave, in addition to 29b, products derived from the trilithio derivative 30 but in reduced yields: (a) diol 31b (~16% yield) which was obtained pure, and (b) a mixture (by NMR spectral analysis) of 32a and 32b (~16% total yield) which was not resolved.

3. Alkylation of lithium derivatives derived from 4 by n-butyl bromide formed during halogen–lithium exchange, to give products of type 31, detract from the synthetic utility of such syntheses with p-bromophenylacetic acid, an observation in sharp contrast to that observed with o-bromo-
phenylacetic acid. We currently believe, but have not established, that alkylation at $-100^\circ$ occurs only with the very reactive trianion 30, a process which is sterically inhibited with the ortho isomer 23; consequently, we believe that significant amounts of alkylation at $-100^\circ$ will be encountered only in the phenylacetic acid series (meta or para).

While some exceptions have been defined, notably p-bromophenylacetic acid, the procedures described in A-C (above) offer useful routes for the elaboration of a seemingly broad variety of types of bromoalkanoids.

Experimental Section

A. Conversion of $\beta$-(p-Bromophenyl)propanoic Acid (1) to Phenylacetic Acid. $\beta$-(p-Bromophenyl)propanoic acid$^{1\text{a}}$ (2.29 g, 0.01 mol), mp 137-138$^\circ$ (lit.$^{1\text{b}}$ mp 138$^\circ$), tetrahydrofuran ($\sim$125 ml, freshly distilled over lithium aluminum hydride), and dry hexane$^{1\text{c}}$ (25 ml) introduced, under nitrogen, into a three-neck flask equipped with a low-temperature thermometer, addition funnel, and nitrogen inlet tube. The reaction mixture was cooled to $-100^\circ$ and treated with n-butyllithium (0.02 mol) in THF (125 ml)--hexane$^{1\text{a}}$ (25 ml as described in A. An aliquot (25 ml) taken after 30 min at $-100^\circ$ was quenched with water; NMR analysis showed only 3-phenylpropanoic acid. The mixture was quenched with water, and the crude product obtained by extraction with ether was re-crystallized from water to give 1.22 g (81% yield) of pure 3-phenylpropanoic acid (mp and nmp$^{1\text{a}}$ 104-105$^\circ$).

B. Preparation of $\beta$-(p-Cyclohexenyl)propanoic Acid (7). Reaction of 1 (0.02 mol) in a mixture of THF (250 ml)--hexane$^{1\text{c}}$ (50 ml) with n-butyllithium (0.044 mol) was carried out as in A. Cyclohexanols (0.30 mol) in dry hexane$^{1\text{c}}$ (10 ml) was added; the mixture was warmed to 25$^\circ$ and poured into dilute hydrochloric acid (250 ml). The organic layer was extracted with four 100-ml portions of ether. The ether extracts were combined, dried (MgSO$\text{4}$), and concentrated (rotary evaporation) to afford 1.55 g of light yellow semisolid. This material was distilled to give 1.29 g (66% yield, mp$^{1\text{b}}$ and nmp 45-46$^\circ$) of pure phenylacetic acid (6). The residue (0.28 g) was shown (NMR) to be a mixture of 1, 6, and a small amount of butylic acid (position of butyl group undetermined).

C. Preparations. 1. From $\beta$-(p-Bromophenyl)propanoic Acid$^{1\text{c}}$. (2) Reaction of 2 (0.01 mol, mp 98-101$^\circ$ (lit.$^{1\text{b}}$ mp 98$^\circ$)) in THF (125 ml)--hexane$^{1\text{c}}$ (25 ml) with n-butyllithium (0.02 mol) was carried out as in A; the reaction mixture was stirred for 3 hr at $-100^\circ$.

From 3-o-Bromodipropylamide (13). Amide 13 (0.01 mol, bp 150-160$^\circ$ (0.02-0.01 Torr); 98% yield from 3-o-bromophenylpropanoyl chloride$^{1\text{d}}$ and diisopropylamine in ether) in THF (125 ml)--hexane$^{1\text{c}}$ (25 ml) was allowed to react with n-butyllithium (0.01 mol) as in A. Examination of aliquots by NMR showed that after $-100^\circ$ the reaction product was indanone contaminated with a small amount of butylic material. The mixture was quenched with water and the dried material obtained from the ether extract was distilled to give 0.8 g (61% yield) of pure indanone.

D. Reactions of $\beta$-(p-Bromophenyl)propanoic Acid (18). 1. Conversion to Phenylpropionamide. Amide 14$\text{b}$ (0.01 mol) was treated with n-butyllithium (0.02 mol) in THF (125 ml)--hexane$^{1\text{a}}$ (25 ml) as described in A. An aliquot (25 ml) taken after 30 min at $-100^\circ$ was quenched with water; NMR analysis showed only 3-phenylpropanoic acid. The mixture was quenched with water, and the crude product obtained by extraction with ether was re-crystallized from water to give 1.22 g (81% yield) of pure 3-phenylpropanoic acid (mp and nmp$^{1\text{a}}$ 104-105$^\circ$).

2. Conversion to o-(1-Hydroxycyclohexyl)-3-phenylpropanoic Acid (17). The reaction product was carried out as in D-1 above, and quenched after 30 min with cyclohexanone (0.04 mol) in dry hexane$^{1\text{a}}$ (20 ml) at $-100^\circ$. The crude product (5.5 g) obtained after addition of water and extraction with ether and containing cyclohexane was recrystallized from petroleum ether$^{1\text{b}}$ to give 2.1 g of white solid which was a mixture of 16 and 17. This material was chromatographed on silica gel (300 g). Elution of the column with petroleum ether$^{1\text{b}}$ to give 2.1 g of white solid which was recrystallized from chloroform-petroleum ether to give 0.97 g (40% yield) of pure 17 (mp 148-150$^\circ$).

Anal. Calcd. for C$_8$H$_{12}$O$_2$: C, 73.00; H, 8.42; N, 5.49. Found: C, 73.00; H, 8.42; N, 5.49.

E. Metathesis of o-Bromophenylacetic Acid (3) with n-Butyllithium. 1. Degree of Metal-Halogen Exchange. Reaction of 3$\text{b}$ (0.025 mol) with n-butyllithium (0.05 mol) in THF (150 ml) and hexane$^{1\text{c}}$ (30 ml) was carried out as in B. Examination of an aliquot at 1 hr showed that the ratio of 3 to 2 was 90:10; at 3 hr the ratio of 3 to 2 was 29:71; and at 4 hr the ratio of 3 to 2 was 20:80. Additional reaction time (at $-100^\circ$ and/or further addition of n-butyllithium up to 200% of the original amount) caused no appreciable change in the ratio of 3 to 2.

A third molar equivalent of n-butyllithium was added to the reaction mixture at $-100^\circ$; and the mixture was stirred for an additional 1 hr at $-100^\circ$. Examination of an aliquot (10 ml) showed that the ratio of 3 to 2 was 30:70. Additional reaction time (at $-100^\circ$) and/or further addition of n-butyllithium (up to a total of 6 molar equiv) caused no appreciable change in the above ratio (30:70).

Examination of aliquots from a similar reaction but at $-78^\circ$ (instead of $-100^\circ$) showed no appreciable change in the progress and/or degree of metalation.

Synthesis of Spirolactone. 24. Metallation of o-bromophenylacetic Acid. (5.4 g, 0.025 mol) was treated with n-butyllithium (0.075 mol) as described above. The mixture was aged for 5 hr at $-95$ to $-100^\circ$ (ratio of o-bromophenylacetic acid to phenylacetic acid 30:70 by NMR spectral analysis$^{23}$) and cyclohexanone (9.8 g, 0.1 mol) in hexane (20 ml) was added to the mixture maintained at $-100^\circ$. The resulting mixture was allowed to warm to room temperature and was added to ether (50 ml) and aqueous sodium hydroxide (100 ml, 3%). The two layers were separated and the aqueous layer was extracted with ether (four 100-ml portions). The basic layer containing the salt of 3 was acidified (hydrochloric acid) and treated with n-butyllithium (3.1 g, 4.28 mol), cooled, and extracted with ether to give $0.88 g$ (85% yield) of 3-phenylpropanoic acid (mp$^{1\text{a}}$ and nmp$^{1\text{a}}$ 104-105$^\circ$).
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The NMR spectrum of the acid material (2.2 g) obtained from the alkaline extract showed it to be a mixture of o-bromophenylacetic acid (3) and phenylacetic acid (22) in the ratio 40:60 (20 and 35% yield, respectively).

Preparation of Hydroxy Acid 27. The reaction was conducted as described for 25 with the following modifications. The mixture was stirred for 7 hr after addition of 2 equiv of n-butylithium, but only 15 min after addition of the third equivalent of n-butylithium prior to addition of cyclohexane. The yield of lactone 24 (mp and mmp 105-106°) was 10%.

Concentration of the dried ether extract obtained from the acidified alkaline extract gave a mixture of which suggested that it was crystallized from chloroform, mp 71.77; H, 7.74. Found: C, 71.98; H, 8.00.

F. Reactions of p-Bromophenylacetic Acid (4). 1. Reaction of p-bromophenylacetic acid (5.4 g, 0.025 mol) was carried out exactly as described for 3 except the temperature was -78°4b (Dry Ice-acetone bath). Progress of metation was followed as for 4.