Selective Halogen–Lithium Exchange in Bromophenylalkyl Halides[1]

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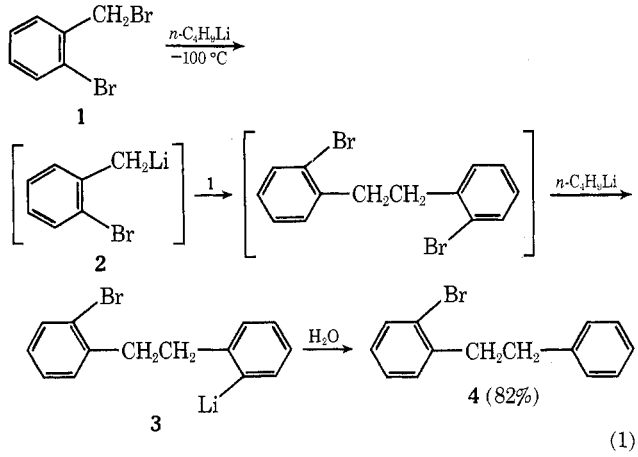
Received October 21, 1975

Halogen–metal exchange with a variety of bromophenylalkyl halides at low temperature (−100 °C) is selective and the order of exchange is $ArCH_2Br > ArBr > ArCH_2CH_2Br > Ar(CH_2)_nCl$. Thus, stable lithioaryl derivatives, which can be elaborated by addition of E^+, are obtained from *o*-bromobenzyl chloride, β-(*o*-bromophenyl)ethyl bromide, and γ-(*o*-bromophenyl)propyl chloride. Intramolecular cyclization occurs rapidly at −100 °C with γ-(*o*-bromophenyl)propyl bromide. Coupling occurs by primary benzylbromine–metal exchange with benzyl bromides. Attempts to prepare benzocyclopropene from *o*-lithiobenzyl chloride leads instead to 9,10-dihydroanthracene. A number of synthetic applications are discussed including a new, convenient synthesis of benzocyclobutene.

The success achieved for the elaboration of aryl bromides containing functional groups[2] that are normally reactive to alkyl- or aryllithium reagents by halogen–metal exchange at very low temperature (−100 °C) has prompted us to examine related reactions with aryl bromides containing haloalkyl functional groups. Complete selectivity has been observed and the order of halogen–metal exchange has been found to be $ArCH_2Br > ArBr > ArCH_2CH_2Br > Ar(CH_2)_nCl$. Halogen–metal exchange reactions were generally conducted at −100 °C in tetrahydrofuran–hexane with *n*-butyllithium. The course of reactions was followed by quenching aliquots with water and examining products both by NMR and by comparing GLC retention times with those of authentic samples, and subsequently by isolation of products.

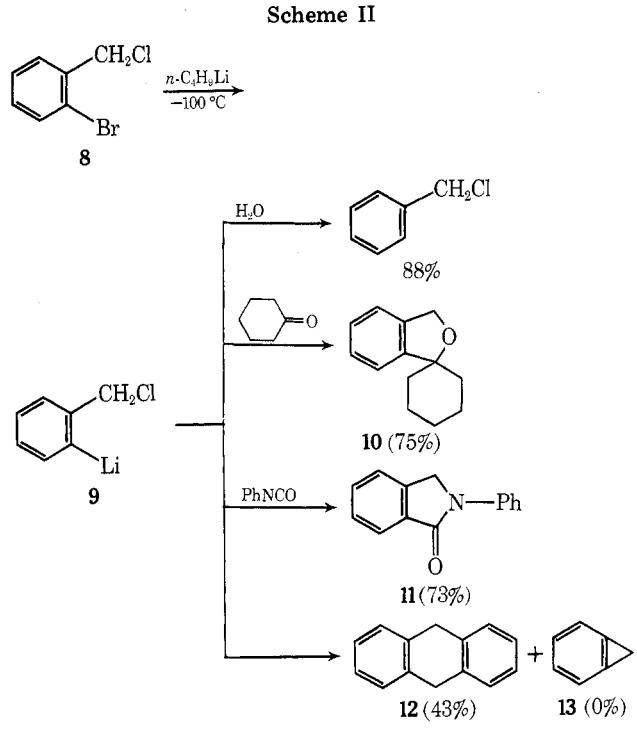
***o*-Bromobenzyl Bromide and *o*-Iodobenzyl Bromide.** Reaction of *o*-bromobenzyl bromide with 1 equiv of *n*-butyllithium gave 2-bromobibenzyl (**4**, 82% isolated yield) which is consistent with initial bromine–metal exchange at the benzyl bromide function as shown in Scheme I (eq 1).

Scheme I



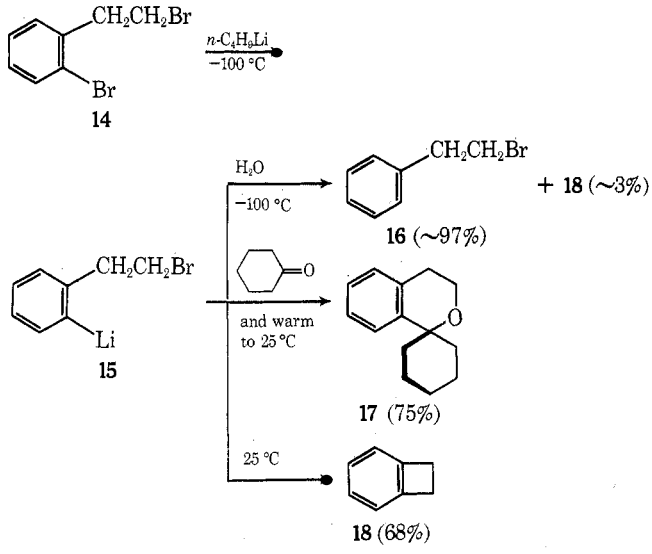
This was unexpected in view of the earlier report[3] which suggested that halogen–metal exchange occurred at the aryl halide function in a similar reaction with *p*-bromobenzyl bromide. When excess (2 equiv) of *n*-butyllithium was employed the product was bibenzyl, the product expected by complete halogen–metal exchange in **3** prior to the addition of water. Similar results were obtained with *o*-iodobenzyl iodide (**5**); however, the distribution of products (**6**, 30%; **7**, 37%) was different from that obtained with **1** when 1 equiv of *n*-butyllithium was employed.

Scheme II



***o*-Bromobenzyl Chloride (8).** Reaction of **8** follows a dramatically different course of reaction than that observed for **1**; *o*-lithiobenzyl chloride (**9**) is formed exclusively at −100 °C after approximately 5 min when 1 equiv of *n*-butyllithium is employed. *o*-Lithiobenzyl chloride is stable in solution at −100 °C and can be elaborated as shown in Scheme II: (a) by conversion to benzyl chloride (88% isolated yield) by addition of water, (b) by conversion to spiro[cyclohexane-1,1′-phthalan] (**10**, 75% isolated yield) by addition of cyclohexanone, and (c) by conversion to *N*-phenylphthalimidine (**11**, 73% isolated yield) by addition of phenyl isocyanate. Considerable effort was made to determine whether **9** might be converted to benzocyclopropene (**13**), particularly since Radlick and Crawford[4] have observed formation of benzocyclopropene by a similar process involving *o*-bromobenzyl methyl ether and *n*-butyllithium at −40 °C. Samples of **9** in the tetrahydrofuran–hexane solvent mixture were allowed to warm to room temperature prior to decomposition with water.[5] The product was pro-

Scheme III



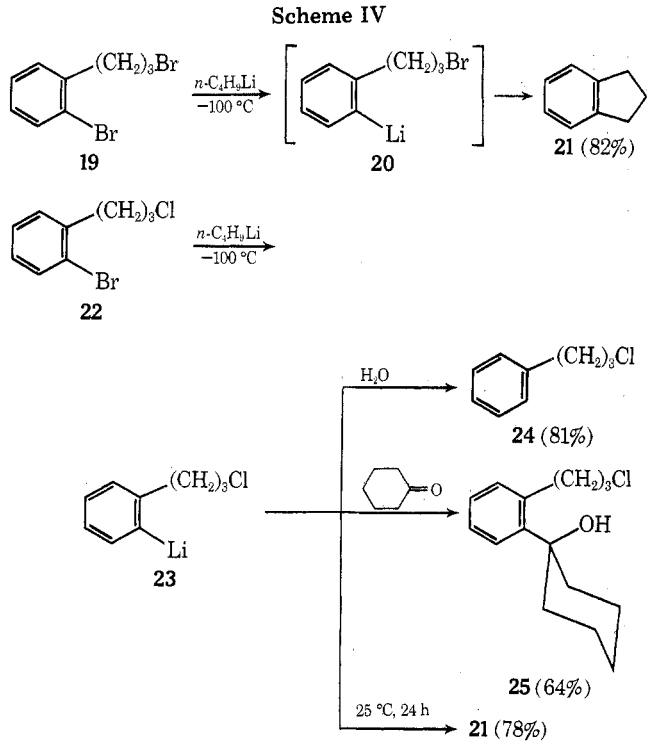
cessed at room temperature to minimize possible decomposition of **13**; however, only benzyl chloride, 9,10-dihydroanthracene (**12**, 43% isolated yield), and higher condensation products were detected. Similar results were obtained when **9** was formed in more dilute solutions of solvent.

β-(*o*-Bromophenyl)ethyl Bromide (14). Aryl halogen–metal exchange by reaction of **14** with *n*-butyllithium is selective at −100 °C; the lithio derivative **15** is formed rapidly (approximately 5 min) and can be elaborated as shown in Scheme III. The intramolecular cylization of **15**, which occurs when **15** is warmed, constitutes a new and highly efficient synthesis of benzocyclobutene[6] (**18**).

γ-(*o*-Bromophenyl)propyl Bromide (19). While one can anticipate selectivity in halogen–metal exchange similar to that described for **14** for *m*- and *p*-bromoalkyl halides, certain ortho isomers, such as **19**, present a new problem since entropy factors are favorable for intramolecular cyclization. In order to test this possibility the reactions of **19** and **22** with *n*-butyllithium at −100 °C were examined (Scheme IV). Only indan (**21**, 82% isolated yield) was detected (NMR) when **20** was formed and quenched at −100 °C with water. By contrast, γ-(*o*-lithiophenyl)propyl chloride (**23**) is formed selectively and is stable at −100 °C, and can be elaborated as shown by (a) its conversion to γ-phenylpropyl chloride (**24**, 81% isolated yield) by addition of water, and (b) by formation of **25** (64% isolated yield) by addition of cyclohexanone. When the solution containing **23** is warmed to room temperature, intramolecular cyclization occurs giving indan (**21**, 78% isolated yield).

These results suggest a broad spectrum of utility in synthesis for lithioarylalkyl halides formed at low temperature from bromoarylalkyl halides.

Scheme IV



Experimental Section

General Procedure for Halogen–Metal Exchange. Reaction of haloarylalkyl halides (0.02 mol) with *n*-butyllithium (1 molar equiv) in dry tetrahydrofuran (~130 ml)–hexane[7] (~40 ml) was carried out similar to that described for bromobenzoic acids[2a] and bromobenzonitriles.[2d] Aliquots were examined as described in ref 8.

Reaction of *o*-Bromobenzyl Bromide (1) with *n*-Butyllithium. Examination of an aliquot[8] showed complete disappearance of **1** after 30 min. The solution was stirred for a total of 1 h at −100 °C and was poured into dilute hydrochloric acid (~100 ml). The organic product, obtained from the dried ($MgSO_2$) ether extract, was essentially pure (GLC) 2-bromobibenzyl[9] (**4**, 82% yield). The analytical sample was collected by preparative GLC [20% SE-30 on Chromosorb W (60/80 mesh), 6 ft × 0.25 in., 185 °C, 90 ml/min He]: NMR ($CDCl_3$) δ 2.95 (m, 4, CH_2), 7.25 (m, 9, aromatic H).

Anal. Calcd for $C_{14}H_{13}Br$: C, 64.38; H, 5.02. Found: C, 64.17; H, 5.03.

When reaction was effected with 2 equiv of *n*-butyllithium, the only product detected was bibenzyl [**7**, 86% yield, mp 50.5–52 °C (lit.[10] mp 51.5–52.5 °C); NMR ($CDCl_3$) δ 2.95 (s, 4, CH_2), 7.25 (m, 10, aromatic H)].

Reaction of *o*-iodobenzyl bromide[11] with *n*-butyllithium was carried out as for **1**, except that the reaction mixture was stirred for 30 min at −100 °C prior to quenching with water (~75 ml) and ether (~100 ml). The dried ($MgSO_4$) organic extracts were concentrated (rotary evaporation) to afford 3.21 g of yellow oil. The crude product was distilled in vacuo to give (a) 0.57 g [37%, bp 76–86 °C (0.03 Torr)] of nearly pure (GLC, coinjection of an authentic sample) bibenzyl, and (b) 1.57 g [bp 95–110 °C (0.03 Torr)] of impure 2-iodobibenzyl. The material was obtained pure by recrystallization from a mixture (80:20) of petroleum ether[12a] and chloroform to afford 0.78 g of **6** (30%): mp 71.5–75 °C [lit.[13] bp 175 °C (0.5 Torr)]; NMR ($CDCl_3$) δ 3.10 (s, 4, CH_2), 7.25 (m, 9, aromatic H).

Anal. Calcd for $C_{14}H_{13}I$: C, 54.57; H, 4.25. Found: C, 54.48; H, 3.91.

Reactions of *o*-Bromobenzyl Chloride[14] (8). A. Conversion to Benzyl Chloride. Analysis of an aliquot[17] obtained from **8** (0.025 mol) and *n*-butyllithium (0.025 mol) at −100 °C 10 min after mixing showed (NMR) essentially only benzyl chloride. The entire mixture was added to a mixture of water (50 ml) and ether (200 ml). Benzyl chloride [88% yield, bp 177–180 °C (lit.[18] bp 179 °C)] was obtained by distillation of the dried organic extract.

B. Spiro[cyclohexane-1,1′-phthalan] (10). The above mixture prepared from **8** (0.05 mol) was treated at −100 °C with *n*-butyllithium (0.05 mol) followed by cyclohexanone (0.075 mol); the resulting mixture was allowed to warm to 25 °C and was poured into water (~100 ml). The organic material obtained from the dried ether extract was distilled in vacuo to give 7.9 g (84% yield) of **10**: bp 87–89 °C (0.01 Torr); pure by GLC; NMR ($CDCl_3$) δ 1.7 (broad s, 10, aliphatic H), 5.1 (s, 2, CH_2O), 7.2 (m, 4, aromatic H).

Anal. Calcd for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 82.85; H, 8.62.

C. Preparation of *N*-Phenylphthalimidine (11). Reaction was carried out as in A above; the mixture was stirred for 40 min at −105 °C, phenyl isocyanate (5.95 g, 0.05 mol) in hexane[7] (~25 ml) was added, and the reaction mixture was allowed to warm to room temperature. The entire mixture was added to water (~100 ml) and ether (~200 ml) and the dried ($MgSO_4$) organic extracts were concentrated (rotary evaporation) to afford 8.44 g of pink semisolid. The crude product was recrystallized twice from a mixture (80:20) of petroleum ether[12b] and chloroform to give 3.82 g (**11**, 73%, mp 156–158 °C, lit.[19] mp 160 °C) of nearly pure **11**. The material

was obtained pure by two successive recrystallizations; mp 166–167 °C; NMR ($CDCl_3$) δ 4.95 (s, 2, CH_2), 7.80 (m, 9, aromatic H).

Anal. Calcd for $C_{14}H_{11}NO$: C, 80.36; H, 5.30; N, 6.69. Found: C, 80.36; H, 5.38; N, 6.63.

D. Conversion to 9,10-Dihydroanthracene (12). The reaction was carried out as in A above; the mixture was processed by a variety of procedures to detect benzocyclopropene[4,20] (**13**, NMR[21] δ 3.11, CH_2). In a typical experiment the mixture was allowed to warm to 25 °C (~3 h); anions were decomposed by addition of water (~5 ml) and the solution was dried ($MgSO_4$, excess). In one experiment, low-boiling materials (identified by NMR spectral analysis as THF, hexane, and *n*-butyl bromide) were removed at 45 °C (150 Torr). The residue contained 9,10-dihydroanthracene and benzyl chloride in the ratio of 70:30 [NMR ($CDCl_3$) δ 3.9 and 4.5, respectively for CH_2 (singlets)]. Recrystallization of the residue from petroleum ether[12a] or ethanol gave pure 9,10-dihydroanthracene (**12**, 0.97 g, 43% yield, mp[22] and mmp 108–110 °C).

Reactions of *o*-Bromophenethyl Bromide (14). A. Phenethyl Bromide. Reactions of **14**[23] [0.03 mol, prepared in 83% yield by reaction of *o*-bromophenethyl alcohol[24] with hydrobromic acid (48%)] with *n*-butyllithium (0.03 mol) at −100 °C was complete <5 min after mixing. Analysis of aliquots[8] showed only phenethyl bromide[25] and benzocyclobutene, in the ratio of 97:3, to be present.

B. Spiro[cyclohexane-1,1′-isochroman] (17). The solution of **15** (0.03 mol), prepared as in A, above, was treated at −105 °C with cyclohexanone (0.04 mol) and the resulting mixture was allowed to warm to 20 °C. The mixture was added to water (~100 ml) and was extracted with ether. The oil obtained from the dried ($MgSO_4$) ether extract was distilled in vacuo to give pure **17**: bp 110–115 °C (0.07–0.09 Torr); NMR ($CDCl_3$) δ 1.7 (m, 10, aliphatic H), 2.9 (t, 2, $ArCH_2$), 4.05 (t, 2, CH_2O), 7.5 (m, 4, aromatic H)].

Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 82.92; H, 9.13.

C. Benzocyclobutene (18). A solution of **15** (0.0189 mol), prepared as described in A above, was stirred for 0.5 h at −100 °C and allowed to warm to 25 °C. The resulting mixture was added to water (~100 ml) and the organic products were collected by extraction with ether. The crude product (2.67 g) was distilled to give 1.57 g of a clear, colorless oil [bp 77 °C (70 Torr)]. Spectral analysis (NMR) of the oil showed it to be a mixture of benzocyclobutene (**18**, 80%, 68% yield), tetrahydrofuran (5%), and *n*-butyl bromide (15%). Pure benzocyclobutene[6] was collected by preparative GLC [20% SE-30 on Chromosorb W (60/80 mesh), 6 ft × 0.25 in., 150 °C, 90 ml/min He]: NMR ($CDCl_3$) δ 3.18 (s, 4, CH_2), 7.10 (m, 4, aromatic H); ir 1450, 1010, 775, 720 cm^{-1}; molecular ion *m/e* 104; $n^{23}D$ 1.5411 (lit.[26] $n^{25}D$ 1.5409).

Anal. Calcd for C_8H_8: C, 92.96; H, 7.74. Found: C, 92.34; H, 7.70.

Reaction of γ-(*o*-Bromophenyl)propyl Bromide (19) with *n*-Butyllithium. Formation of Indan (21). Reaction of **19** [0.025 mol, prepared from β-(*o*-bromophenyl)propanoic acid[2c] by reduction to γ-(*o*-bromophenyl)propanol (90% yield, bp 100–105° (0.02–0.01 Torr), lit.[27] bp 106–108 °C (0.5 Torr), with lithium aluminum hydride and subsequent conversion of the alcohol to **19** (81% yield, bp 104–108 °C (0.6–0.5 Torr), lit.[27] bp 84–85 °C (0.3 Torr), with hydrobromic acid (48%)] with *n*-butyllithium (1 molar equiv) at −100 °C was complete after 15 min (aliquots[28] indicated only indan). The mixture was decomposed with water (50 ml) and processed by extraction (ether) and the dried ($MgSO_4$) organic extracts were concentrated (rotary evaporation) to give a residue which was distilled in vacuo to afford 2.42 g [**21**, 82% yield, bp 176–177 °C, lit.[29] bp 177 °C (760 mm)] of pure indan: NMR ($CDCl_3$) δ 2.05 (m, 2, $-CH_2$), 2.92 (t, 4, $-CH_2$), 7.2 (m, 4, aromatic H).

Anal. Calcd for C_9H_{10}: C, 91.47; H, 8.53. Found: C, 91.52; H, 8.41.

Reactions of γ-(*o*-Bromophenyl)-1-propyl Chloride[30] (22). A. Conversion to 3-Chloro-1-phenylpropane (24). Studies of aliquots[28] obtained 15 min after the addition of *n*-butyllithium (1 molar equiv) to **22** (1 molar equiv) at −100 °C showed no starting material and only **24**. The entire product was added to water and the organic residue obtained from the dried ($MgSO_4$) ether extract was distilled to give pure **24** (81% yield, bp 218–220 °C, lit.[31] bp 219–220 °C).

B. Conversion to Indan (21). When the solution of **23**, prepared at −100 °C, was warmed to 20 °C (24 h) prior to addition of water, pure indan (**21**, 78% yield, bp 176–177 °C[29]) was obtained.

C. Conversion to 25. The solution of **23** (0.05 mol) prepared as in A was treated at −100 °C with cyclohexanone (2 molar equiv) at −100 to −90 °C and the resulting mixture was allowed to warm to 25 °C (24 h). The crude product (obtained by addition to water with subsequent extraction with ether) was distilled through a short Vigreux column to give cyclohexanone containing some **25** (bp <100°, 0.04 Torr). The column was replaced by a short-path column and nearly pure **25** [8.1 g, 64% yield, bp 140–145 °C (0.04 Torr)] was collected. Fractionation of this material through a short Vigreux column gave the analytical sample: bp 153–156 °C (0.03 Torr); NMR ($CDCl_3$) δ 1.8 (m, 13, aliphatic H), 3.2 (m, 2, $-CH_2$), 3.65 (t, 2, $-CH_2$), 7.35 (m, 4, aromatic H).

Anal. Calcd for $C_{15}H_{21}ClO$: C, 71.21; H, 8.37; Cl, 14.03. Found: C, 71.51; H, 8.48; Cl, 13.75.

Registry No.—**1**, 3433-80-5; **4**, 57918-64-6; **5**, 40400-13-3; **6**, 35444-96-3; **7**, 103-29-7; **8**, 578-51-8; **10**, 171-80-2; **11**, 5388-42-1; **12**, 613-31-0; **14**, 1074-15-3; **15**, 57918-65-7; **17**, 57918-66-8; **18**, 694-87-1; **19**, 1075-28-1; **21**, 496-11-7; **22**, 57918-67-9; **23**, 57918-68-0; **24**, 104-52-9; **25**, 57918-69-1; *n*-butyllithium, 109-72-8; cyclohexanone, 108-94-1; phenyl isocyanate, 103-71-9.

References and Notes

(1) Supported by the U.S. Army Research Office through Grant DAHCO4 74 GD128.
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(11) NMR ($CDCl_3$) δ 4.80 (s, 2, CH_2), 7.70 (m, 4, aromatic H). Prepared (94% yield) from commercial *o*-iodobenzyl alcohol and aqueous hydrobromic acid by conventional procedure; cf. W. S. Rapson and R. G. Shuttleworth, *J. Chem. Soc.*, 487 (1941).
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(14) Prepared [74% yield, bp 73–74 °C (0.2 Torr), lit.[15] bp 110–111 °C (15 Torr)] from *o*-bromobenzyl alcohol[16] by reaction with thionyl chloride.
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(30) Prepared (71% yield) from reaction of γ-(*o*-bromophenyl)propanol[27] with thionyl chloride, bp 90–94 °C (0.3–0.4 Torr). Anal. Calcd for $C_9H_{10}BrCl$: C, 46.28; H, 4.32; Br, 34.22. Found: C, 46.35; H, 4.41; Br, 34.06.
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