Elaboration of Bromoarylnitriles[1]

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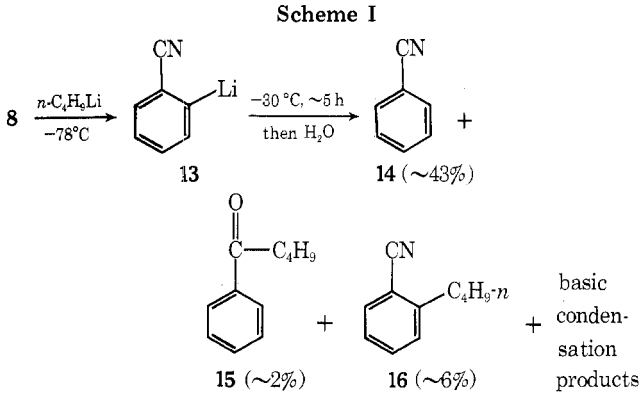
n-Butyllithium reacts selectively at −100 °C with the isomeric bromobenzonitriles by halogen–metal exchange. The resulting lithiobenzonitriles are stable at −100 °C and can be elaborated with electrophiles to give good yields of substituted benzonitriles, or, in the case of *o*-bromobenzonitrile, cyclic products derived from them. Studies of reactions of bromobenzylnitriles and bromophenylpropionitriles with *n*-butyllithium at −100 °C are also described.

The preparation of aryllithium reagents from isomeric bromobenzonitriles by halogen–metal exchange with *n*-butyllithium has been reported;[2] however, such derivatives have not been useful as synthetic intermediates. The low yields[2] of functionalized products obtained by reaction of such lithioarene intermediates with electrophiles are due, at least in part, to the reactivity of the nitrile function with organometallic reagents. The recent observation that bromine–lithium exchange can be effected selectively at −100 °C with aryl bromides containing carboxylate[3a] and, with limitations,[3b] methyl ester functions suggested that bromobenzonitriles could be efficiently elaborated at very low temperature. This has been shown to be the case.

The isomeric bromobenzonitriles were treated in tetrahydrofuran–hexane with *n*-butyllithium at −100 °C. In the case of *o*-bromobenzonitrile, essentially identical results were obtained at −78 °C; halogen–metal exchange was complete[4a] in 5 min at −100 °C. The derived lithioarene intermediates were then functionalized by addition of suitable electrophiles. The results, summarized in Table I, are self-explanatory; however, attention should be called to the fact that intramolecular cyclizations of product anions with the adjacent nitrile functions generally occurred in the ortho series.

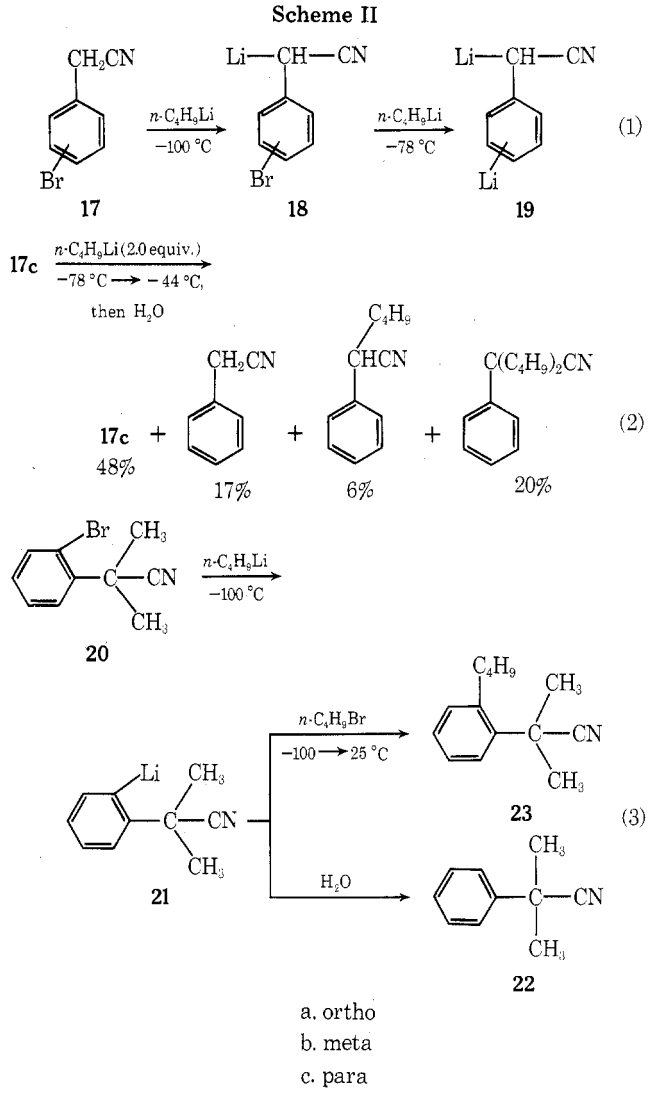
The stability of the derived lithiobenzonitriles was examined briefly by warming *o*-lithiobenzonitrile, subsequent to its formation at −78 °C, for 5 h at −30 °C prior to the addition of water. The products, shown in Scheme I,

Scheme I



suggest that (1) the lithium derivative, once formed, is reasonably stable (~43% of **14**), and (2) reaction of the lithium reagent with *n*-butyl bromide, formed during the exchange reaction, becomes significant (~6% of **16** plus butylated condensation products) at higher temperatures. The formation of significant quantities of higher molecular weight basic condensation products is assumed to result, in part, by condensation of **13** with **16** and with itself. While the mixture of condensation products was not resolved,[6] samples were hydrolyzed with hydrochloric acid and with alkali. No anthraquinone was detected in the resulting products.[7]

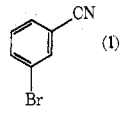
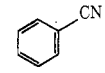
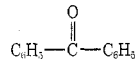
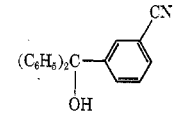
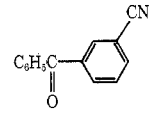
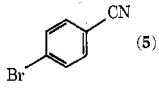
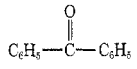
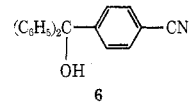
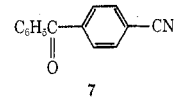
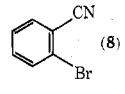
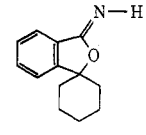
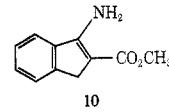
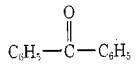
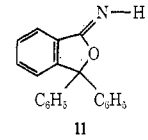
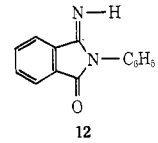
Scheme II



a. ortho
b. meta
c. para

It was of interest to determine whether or not anions derived from homologous bromobenzylnitriles would undergo halogen–metal interchange (Scheme II). Reaction of **17** with *n*-butyllithium at −100 °C gave **18**;[8] however, the anionic character of the benzylic carbon in **18** inhibited halogen–metal exchange in **18** at −100 °C with excess *n*-butyllithium. Examination of aliquots[4a] treated with water after 1 h at −100 °C obtained when excess *n*-butyllithium was employed showed ratios of benzylnitrile to unchanged bromobenzylnitrile of 3.5/97, 1/99, and 0.5/99.5 for **17a**, **17b**, and **17c**, respectively. There was no appreciable change in their ratios after an additional 2 h at −100 °C. Exchange was also slow at −78 °C (6.2, 7.2, and 5.0%, respectively for

Table I. Reaction of Isomeric Lithiobenzonitriles

Substrate	Reactant	Product	Isolated yield, %
 (1)	H_2O	 2	72
1		 3	86
1	$C_6H_5CO_2CH_3$	 4	33
 (5)	H_2O	**2**	82
5		 6	83
5	$C_6H_5CO_2CH_3$	 7	47[a]
 (8)		 9	82[b]
8	$CH_2{=}CHCO_2CH_3$	 10	9[c,d]
8		 11	50
8	C_6H_5NCO	 12	75[e]

[a] The order of addition of the lithiobenzonitrile and methyl benzoate did not affect the yield appreciably.[5] [b] Compound 9 was converted in high yield into the corresponding lactone by reaction with (a) hydrochloric acid, or (b) dilute aqueous sodium hydroxide followed by acidification. [c] Compound 10 was anticipated by intramolecular cyclization of the 1,4 adduct with subsequent enolization of the derived imino function. [d] The major organic residue was polymer, assumed to be formed from the product derived subsequent to 1,2 addition to the ester carbonyl group. [e] Compound 12 was isolated as *N*-phenylphthalimide.

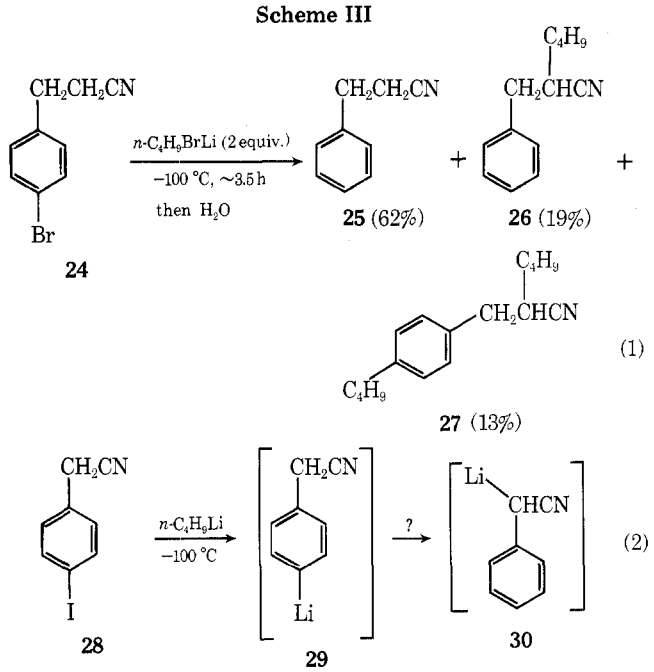
17a, 17b, and **17c** after ~4.5 h);[4a] however, some butylation occurred, presumably by reaction of **18** or **19** with *n*-butyl bromide, at −78 °C.

When reaction of **17** with *n*-butyllithium is carried out at higher temperatures (−44 °C), halogen–metal exchange is significantly increased; however, butylation of derived anions by *n*-butyl bromide, formed by exchange, becomes a significant side reaction. Thus, warming the product of reaction of **17c** with 2 equiv of *n*-butyllithium, formed at −78 °C, to −44 °C gave a product containing nitriles in the ratios shown in eq 2, together with three other components which were not examined.

When benzylic anion formation is disallowed, as in **20,** halogen–metal exchange is rapid (~100% yield after 10 min) and complete.[4a] Formation of α,α-dimethylbenzonitrile (**22,** ~100% yield) by addition of water to **21** suggests that bromobenzylic nitriles with no benzylic protons can be conveniently elaborated through the aryllithium intermediate. This was demonstrated by allowing the mixture prepared from **20** to warm to room temperature; α,α-dimethyl(*o*-butylbenzyl)nitrile (**23**) was formed by reaction of **21** with *n*-butyl bromide, formed by exchange, and was isolated pure in 74% yield.

When the alkylnitrile function in the arene is not benzylic, then halogen–metal exchange occurs readily (Scheme III). While the primary reaction of **24** with 1 equiv of *n*-butyllithium is anion formation at the methylene group adjacent to the nitrile function,[9] the anionic center is suffi-

Scheme III



ciently removed to permit complete halogen–metal exchange with the second equivalent of *n*-butyllithium. Such reactions are not, however, of synthetic interest since there are two anionic centers available for reaction with E^+. Such reactions are further complicated by the fact that appreciable butylation[10] occurs (**26** and **27**) even at −100 °C. It is also of interest to note that iodine–lithium exchange is sufficiently more rapid than bromine–lithium exchange to permit appreciable halogen–metal exchange in **28** (80%) in preference to proton removal with only 1 equiv of *n*-butyllithium (eq 2, Scheme III);[11] however, attempts to elaborate **29** and/or **30** formed from **28** and 1.5 equiv of *n*-butyllithium at −100 °C, with cyclohexanone, led to a complex unresolved mixture containing butylated products.

Experimental Section

Isomeric Bromobenzonitriles. General Procedure. Conversion of *m*-Bromobenzonitrile (1) to Benzonitrile (2). *m*-Bromobenzonitrile[12] (5.00 g, 0.0275 mol), tetrahydrofuran (~125 ml, freshly distilled over lithium aluminum hydride), and dry hexane[13] (~35 ml) were introduced, under nitrogen, into a three-neck flask equipped with a low-temperature thermometer, addition funnel, mechanical stirrer, and nitrogen inlet tube. The reaction mixture was cooled to −100 °C (liquid nitrogen–diethyl ether bath) and *n*-butyllithium (11.9 ml, 0.0275 mol, 2.3 M solution in hexane) was added rapidly (the rate of addition was adjusted such that the temperature did not momentarily exceed −92 °C). Examination of aliquots[4a] showed that halogen–metal exchange was complete <5 min after the addition of *n*-butyllithium (1 equiv). The reaction mixture was poured into water (~200 ml). The organic layer was separated, and the aqueous layer was extracted with three 100-ml portions of ether. The organic extracts were combined, dried ($MgSO_4$), and concentrated (rotary evaporation) to afford 3.10 g of light, yellow oil. This material was distilled to give 2.03 g [72%, bp 188–191 °C, lit.[14] bp 190.6 °C (760 mm)] of pure (GLC)[4a] benzonitrile.

Preparation of Diphenyl(*m*-cyanophenyl)carbinol (3). Reaction of 1 (0.0275 mol) in a mixture of THF (~125 ml)–hexane[13] (~35 ml) with *n*-C_4H_9Li (0.0275 mol) was carried out as described in the general procedure. Benzophenone (0.0275 mol) in dry THF (~30 ml) was added; the reaction mixture was warmed to 20 °C and poured into water (100 ml). The organic layer was separated and the aqueous layer was extracted once with ether (100 ml). The organic extracts were combined, dried ($MgSO_4$), and concentrated to afford 8.65 g of yellow oil. The material was recrystallized once from petroleum ether[15a] to give 6.76 g (86% mp 87–92 °C) of nearly pure **3**. Elution of a portion (400 mg) of this material on a preparative silica gel plate (fluorescent indicator) with a mixture (80:20) of petroleum ether[15c] and ether afforded pure **3** (380 mg, 82%, mp 96.5–98.5 °C); ir ν_{OH} 3330, ν_{CN} 2170 cm^{-1}.

Anal. Calcd for $C_{20}H_{15}NO$: C, 84.18; H, 5.30; N, 4.91. Found: C, 84.23; H, 5.36; N, 4.85.

Preparation of 3-Cyanobenzophenone (4). Reaction of 1 (0.0275 mol) in a mixture of THF (~125 ml)–hexane[13] (~30 ml) with *n*-C_4H_9Li was carried out as described above. The reaction mixture was stirred at −100 °C for 10 min; an aliquot (~10 ml) was quenched with water and dried ($MgSO_4$), and examination of the residue by GLC (5% SE-30 on Chromosorb W, 3 ft × 0.25 in., 105 °C, 45 ml/min He] indicated complete conversion of **1** to 3-lithiobenzonitrile.[4a] Methyl benzoate (0.029 mol) in dry THF (~25 ml) was added; the reaction mixture was warmed to 25 °C and poured into water (100 ml). Ether extraction of the aqueous layer and concentration of the organic extracts afforded 5.72 g of yellow oil. The material was recrystallized twice from methanol to give 1.7 g [33%, mp 90–92 °C (lit.[16] mp 92 °C)] of pure 3-cyanobenzophenone.

Conversion of *p*-Bromobenzonitrile (5)[12] to Benzonitrile (2). Reaction of **5** (0.0275 mol) in a mixture of dry THF (~125 ml)–hexane[13] (~35 ml) with *n*-C_4H_9Li (0.0275 mol) and subsequent decomposition of *p*-lithiobenzonitrile with water was carried out as described for **1**. Distillation of the residue (3.02 g) gave 2.33 g (82%) of pure (GLC)[4a] benzonitrile.

Preparation of Diphenyl(*p*-cyanophenyl)carbinol (6). The procedure, starting with **5**, was essentially identical with that described for **3**. The crude product was crystallized from a mixture (85:15) of petroleum ether[15b] and chloroform to give 6.54 g (83% yield, mp 90–93 °C) of nearly pure **6** (mp 92–93.5 °C; ir (KBr) ν_{OH} 3300, ν_{CN} 2200 cm^{-1}).

Anal. Calcd for $C_{20}H_{15}NO$: C, 84.18; H, 5.30; N, 4.91. Found: C, 83.97; H, 5.31; N, 4.80.

Preparation of 4-Cyanobenzophenone (7). The procedure, starting with **5**, was essentially identical with that described for **4**. One recrystallization of the crude product from methanol gave pure **7** (mp 115–116 °C, lit.[17] mp 107–108 °C).

Anal. Calcd for $C_{14}H_9NO$: C, 81.14; H, 4.38; N, 6.76. Found: C, 81.43; H, 4.41; N, 6.66.

Conversion of *o*-Bromobenzonitrile (8)[12] to Phthalan 9. Reaction of **8** (0.0275 mol) in THF (~125 ml)–hexane[13] (~40 ml) mixture with *n*-C_4H_9Li (0.0275 mol) was carried out as described in the general procedure, except that the reaction mixture was maintained at −78 °C (dry ice–acetone bath). Examination (GLC)[4a] of an aliquot (~10 ml) indicated only *o*-lithiobenzonitrile. Cyclohexanone (0.0296 mol) in THF (~20 ml) was added; the reaction mixture was warmed to 5 °C and was poured into ice-cold water (100 ml). Rapid extraction (chloroform) of the aqueous layer, followed by concentration of the organic extracts, gave 6.97 g of yellow oil. The crude product was distilled in vacuo to afford 4.5 g [82%, bp 104–105 °C (0.03 Torr)] of pure iminophthalan **9**: ir ν 1660 cm^{-1}; NMR ($CDCl_3$) δ 1.8 (broad s, 10 aliphatic H), 6.75 (broad s, 1, NH), 7.4 (m, 3, aromatic H), 7.85 (m, 1, aromatic H).

Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.39; H, 7.35; N, 6.88.

Acid (concentrated hydrochloric) or base (10% sodium hydroxide) hydrolysis of phthalan **9** gave the corresponding known lactone[18] (mp, mmp 80–82 °C) in high yield.

Preparation of 2-Carbomethoxy-3-aminoindene (10). Reaction of **8** (0.0275 mol) in a THF (~125 ml)–hexane[13] (~40 ml) mixture with *n*-C_4H_9Li (0.0275 mol) was carried out as described above. Methyl acrylate[19] (0.030 mol) in dry hexane[13] (~25 ml) was added; the reaction mixture was warmed to 0 °C and poured into water (~100 ml). The crude product was distilled in vacuo to afford 1.47 g of yellow oil. The oil was recrystallized once from petroleum ether[15a] to give 0.45 g (9%, mp 103.5–105 °C) of pure **10**: NMR ($CDCl_3$) δ 3.62 (s, 2, benzylic H), 3.90 (s, 3, $-OCH_3$), 6.0 (broad s, 2, $-NH_2$), 7.5 (m, 4, aromatic H).

Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found: C, 70.09; H, 5.63; N, 7.30.

The distillation residue appeared to be polymeric.

Preparation of Phthalan 11. Reaction of **8** (0.0275 mol) in a THF (~125 ml)–hexane[13] (~35 ml) mixture with *n*-C_4H_9Li (0.0275 mol) was carried out as described in the general procedure. Benzophenone (0.028 mol) in THF (~25 ml) was added, and the reaction mixture was warmed to 0 °C and poured into cold water (~100 ml). Rapid extraction (ether) of the aqueous layer and concentration (rotary evaporation) of the organic extracts afforded 8.38 g of yellow solid. The crude product was recrystallized from petroleum ether[15a] to give 3.93 g (50%, mp 106–107.5 °C) of nearly pure iminophthalan **11**. One further recrystallization of this material gave the pure product, 2.56 g (33%, mp 108.5–109.5 °C); ir ν 1660 cm^{-1}.

Anal. Calcd for C_9H_8BrN: C, 51.45; H, 3.84; N, 6.67. Found: C, 51.31; H, 3.88; N, 6.70.

Preparation of *N*-Phenylphthalimide (12). Reaction of 8 (0.275 mol) in a THF (~125 ml)–hexane[13] (~35 ml) mixture with n-C_4H_9Li (0.0275 mol) was carried out as described above, except that the reaction mixture was maintained at −78 °C. Phenyl isocyanate (0.03 mol) was added; the reaction mixture was warmed to 25 °C and poured into dilute aqueous hydrochloric acid (5% ~150 ml) and the resulting mixture was allowed to stand for 2 h. Extraction (chloroform) of the aqueous layer and concentration of the organic extracts afforded 6.19 g of yellow semisolid. The crude product was recrystallized once from a mixture (85:15) of absolute alcohol and chloroform to give 4.6 g (75%, mp 206–210 °, lit.[20] mp 208 °C) of **12.**

Reaction of *o*-Bromobenzonitrile and *n*-Butyllithium at −30 °C. The reaction mixture, prepared as described in the general procedure using 1 equiv of n-C_4H_9Li at −78 °C, was allowed to warm to ~−30 °C and was maintained at this temperature for 5 h. The resulting product was added to cold concentrated hydrochloric acid (~200 ml) and separated into neutral and basic components by conventional methods. The isolated neutral component was analyzed by GLC [20% SE-30 on Chromosorb W (60/80 mesh), 6 ft × 0.25 in., 180 °C, 80 ml/min He; the components were identified by coinjection of authentic materials and/or by isolation] and was found to contain benzonitrile (1.13 min, ~43% yield), *o*-butylbenzonitrile [**16,** ~6% yield, 2.94 min; NMR ($CDCl_3$) δ 0.95 (t, 3, CH_3), 1.5 (m, 4, CH_2), 2.85 (t, 2, $ArCH_2$), 7.4 (m, 4, aromatic H); ir ν_{CN} 2200 cm^{-1}] and valerophenone [**15,** ~4% yield, 3.13 min; NMR ($CDCl_3$) δ 0.7–1.95 (m, 6, aliphatic H), 3.0 (t, 2, $ArCH_2$), 7.45 (m, 3, aromatic H), 8.00 (m, 2, aromatic H)]. The dark green solid (1.74 g) obtained by neutralization of the acidic fraction was multicomponent; attempts (recrystallization, TLC) to resolve this mixture into pure components were unsuccessful. Hydrolysis of the presumed imino functions with both ethanolic potassium hydroxide–water and with dilute hydrochloric acids gave mixtures (five colored bands on TLC); however, TLC experiments showed that no anthraquinone was present.

Preparation of the Isomeric Bromobenzylnitriles. *o*-Bromobenzylnitrile[21] [**17a,** NMR ($CDCl_3$) δ 3.82 (s, 2, CH_2)], *m*-bromobenzylnitrile[21] [**17b,** NMR ($CDCl_3$) δ 3.82 (s, 2, CH_2)], and *p*-bromobenzylnitrile[21] [**17c,** NMR ($CDCl_3$) δ 3.70 (s, 2, CH_2)] were prepared in good yield by conventional procedures from the corresponding bromobenzyl bromides. The bromobenzyl bromides were prepared from the corresponding bromotoluenes by bromination with *N*-bromosuccinimide[22] or from the corresponding bromobenzyl alcohol[23a] by reaction with aqueous hydrobromic acid (48%).[23b] The latter process was preferable since the nitriles obtained were free of trace impurities as determined by NMR and GLC analysis.

α,α-Dimethyl-*o*-bromobenzylnitrile (20). *o*-Bromobenzonitrile (**17a,** 20.0 g, 0.103 mol) dissolved in dimethylformamide (40 ml) was added slowly, under nitrogen, to a mixture of sodium hydride (5.2 g, 0.12 mol), dimethylformamide (40 ml), and benzene (20 ml) at 0 °C. The mixture was stirred for 0.5 h at 0 °C and methyl iodide (17 g, 0.12 mol) was added slowly. The resulting mixture was warmed to 25 °C (~0.5 h) and poured into water (100 ml) and the aqueous layer was extracted with four 60-ml portions of chloroform. The oil [bp 103 °C (0.2 Torr)] obtained from the dried chloroform was dissolved in dimethylformamide (40 ml) and re-treated, as above, with sodium hydride and methyl iodide. The oil, obtained as described above, was distilled to give pure **20** [19.5 g, 87% yield; bp 95–105 °C (~0.03 Torr); NMR ($CDCl_3$) δ 1.9 (s, 6, CH_3), 7.4 (m, 4, aromatic H)].

Anal. Calcd for $C_{10}H_{10}BrN$: C, 53.60; H, 4.50; Br, 35.66; N, 6.25. Found: C, 53.43; H, 4.37; Br, 35.53; N, 6.15.

α-Butylphenylacetonitrile and α,α-Dibutylphenylacetonitrile. n-Butyllithium (13.3 ml, 0.032 mol, 2.4 M solution in hexane) was added dropwise to a cold (−78 °C, dry ice–acetone bath), stirred solution of phenylacetonitrile (7.5 g, 0.064 mol) in THF (100 ml, freshly distilled from lithium aluminum hydride) under an atmosphere of nitrogen. n-Butyl bromide (3.44 ml, 0.032 mol) was added rapidly. The mixture was warmed to 0 °C (5 min) and cooled to −78 °C, and the treatment with n-butyllithium and n-butyl bromide was repeated; the resulting mixture was warmed to room temperature and stirred for 7 h. The mixture was poured into water (60 ml) and the organic layer was collected in ether. Analysis of the oil (11.2 g) obtained from the dry ($MgSO_4$) ether extract by GLC [20% SE-30 on Chromosorb W (60/80 mesh), 6 ft × 0.25 in., 230 °C, 70 ml/min He] indicated three components in the ratio of 74:21:5 [phenylacetonitrile (1.31 min, ~7.5% yield), α-butylphenylacetonitrile (3.12 min, ~75% yield), and α,α-dibutylphenylacetonitrile (6.19 min, ~16% yield)]. The oil was fractionated and the fraction [6.54 g, bp 83–86 °C (0.07 Torr)] rich in butylated material was resolved by preparative GLC (column as described above) to give the following.

α-Butylphenylacetonitrile [NMR ($CDCl_3$) δ 0.6–2.0 (m, 9, aliphatic H), 3.7 (t, 1, methine H), 7.3 (s, 5, aromatic H)].

Anal. Calcd for $C_{12}H_{15}N$: C, 83.19; H, 8.73. Found: C, 83.27; H, 8.19.

α,α-Dibutylphenylacetonitrile [NMR ($CDCl_3$) δ 0.6–2.0 (m, 18, aliphatic H), 7.3 (s, 5, aromatic H)].

Anal. Calcd for $C_{16}H_{23}N$: C, 83.79; H, 10.11. Found: C, 83.88; H, 10.06.

Reactions of Isomeric Bromobenzylnitriles (17a–c) with *n*-Butyllithium. These reactions were carried out essentially as described for the isomeric bromobenzonitriles. Progress of reactions was followed by examining aliquots.[4a]

At −100 °C with 1 equiv of n-C_4H_9Li there was no evidence of halogen–metal exchange; only anions **18** were formed. Thus, addition of water to the product obtained from **17a** (5.0 g) resulted in recovery of only *o*-bromobenzylnitrile (4.52 g, 92% yield). Addition of methyl iodide (1 equiv) with subsequent warming of the mixture to 25 °C (2 h) gave, subsequent to distillation [bp 70–72 °C (0.05 Torr)] nearly pure (79%) 2-(*o*-bromophenyl)propionitrile. Analysis of the product by GLC [5% SE-30 on Chromosorb W (60/80 mesh), 3 ft × 0.25 in., 140 °C, 45 ml/min He] showed *o*-bromobenzylnitrile (trace) and α,α-dimethyl-*o*-bromobenzylnitrile (5%). Pure **2-(*o*-bromophenyl)propionitrile** [NMR ($CDCl_3$) δ 1.59 (d, 3, CH_3), 1.39 (q, 1, CH), 7.35 (m, 2, aromatic H), 7.65 (m, 2, aromatic H)] was collected by preparative GLC [20% SE-30 on Chromosorb W (60/80 mesh), 6 ft × 0.25 in., 170 °C, ~90 ml/min He].

Anal. Calcd for C_9H_8BrN: C, 51.46; H, 3.84; N, 6.66. Found: C, 51.40; H, 4.02; N, 6.63.

Reaction of 17 with 2 Equiv of n-C_4H_9Li. Results at −100 and −78 °C are described in the discussion. At higher temperatures extensive butylation of derived anions resulted. Examination of the product obtained by reaction of *p*-bromobenzylnitrile with n-butyllithium (2 equiv; initial reaction at −78 °C, then aged 90 min at −53 °C and 30 min at −44 °C) by GLC [5% SE-30 on Chromosorb W (60/80 mesh), 3 ft × 0.25 in., 130 °C, 45 ml/min He] obtained subsequent to the addition of water showed at least seven components. Four of these, together with their ratio, were identified by NMR and by coinjection of authentic samples (see eq 2, Scheme II, in the discussion).

Reaction of α,α-Dimethyl-*o*-bromobenzylnitrile (20) with n-C_4H_9Li. The reaction was carried out at −100 °C as described for **1.** Examination of aliquots (GLC) showed that halogen–metal exchange was complete in <10 min [the product obtained subsequent to addition of water was essentially pure α,α-dimethylbenzylnitrile (**22,** 100% yield)].[24] The solution was allowed to warm to room temperature and was stirred at 25 °C for 0.5 h prior to quenching with water. The oil, obtained in the usual way from the reaction mixture, was distilled to give essentially pure α,α-dimethyl-*o*-butylbenzylnitrile (**23**): bp 79 °C (0.02 Torr); molecular ion *m/e* 201; ir ν_{CN} 2200 cm^{-1}; NMR ($CDCl_3$) δ 0.85–1.75 (m, 7, aliphatic H), 1.65 (s, 6, CH_3), 2.15 (m, 2, CH_2), 7.95 (m, 4, aromatic H). The sample submitted for analysis was collected by GLC [20% SE-30 on Chromosorb W (60/80 mesh), 6 ft × 0.25 in., 180 °C, 70 ml/min He].

Anal. Calcd for $C_{14}H_{19}N$: C, 83.53; H, 9.51. Found: C, 83.76; H, 9.66.

β-(*p*-Bromophenyl)propionamide was prepared from β-(*p*-bromophenyl)propionic acid[26] in a conventional way with thionyl chloride followed by ammonium hydroxide (85%, mp 138.5–141.5 °C). An analytical sample was obtained pure by recrystallization from a mixture (80:20) of petroleum ether[15a] and chloroform, mp 147–148 °C.

Anal. Calcd for $C_9H_{10}BrNO$: C, 47.39; H, 4.42; N, 6.14; Br, 35.04. Found: C, 47.11; H, 4.40; N, 6.14; Br, 35.22.

β-(*p*-Bromophenyl)propionitrile (24) was prepared from the corresponding amide by dehydration with thionyl chloride [7 h reflux, 84% yield, bp 116 °C (0.05 Torr)].

Anal. Calcd for C_9H_8BrN: C, 51.45; H, 3.84; N, 6.67. Found: C, 51.31; H, 3.88; N, 6.70.

Reaction of β-(*p*-Bromophenyl)propionitrile (24) with n-C_4H_9Li. The reaction was carried out at −100 °C as described for **1.** Aliquots were decomposed with water and the products were analyzed by GLC [20% SE-30 on Chromosorb W (60/80 mesh), 6 ft × 0.25 in., 195 °C, 90 ml/min He]. With ~1 equiv of n-C_4H_9Li, the

ratio of **25/24** was 17/83 after 15 min; the ratio did not change after an additional 40 min at −100 °C. An additional 1.1 equiv of *n*-butyllithium was added. After 15 min the above ratio was 75/16; compound **26** was also detected. The mixture was continually stirred at −100 °C; examination of aliquots showed that the amount of **24** decreased while the amount of butylated products (**26** and **27**) increased. The mixture was quenched with water after a total of 4 h after the second addition of n-C_4H_9Li. The mixture of products obtained contained phenylpropionitrile (**25**, 62%), α-butyl-β-phenylpropionitrile (**26**, 19%), α-butyl-β-(*p*-butylphenyl)propionitrile (**27**, 13%), and an unidentified product. Products were collected by preparative GLC.

α-Butyl-β-phenylpropionitrile (26): NMR ($CDCl_3$) δ 0.9 (t, 3, aliphatic H), 1.55 (m, 6, aliphatic H), 2.9 (m, 3, aliphatic H), 7.3 (m, 5, aromatic H).

Anal. Calcd for $C_{13}H_{17}N$: C, 83.37, H, 9.15; N, 7.48. Found: C, 83.55; H, 9.05; N, 7.55.

α-Butyl-β-(*p*-butylphenyl)propionitrile (27): NMR ($CDCl_3$) δ 0.70–1.9 (m, 16, aliphatic H), 2.2 (m, 2, CH_2), 2.85 (m, 3, aliphatic H), 7.2 (m, 4, aromatic H).

Anal. Calcd for $C_{17}H_{25}N$: C, 83.89; H, 10.35. Found: C, 83.79; H, 10.60.

***p*-Iodobenzylnitrile (28).** Examination[4b] of an aliquot, quenched with water taken after 15 min from reaction of **28**[27] with 1 equiv of n-C_4H_9Li at −100 °C, showed the ratio of benzylnitrile to starting material (**28**) to be 80/20; starting material immediately disappeared upon addition of an additional 0.5 equiv of n-C_4H_9Li. Attempts to trap the anionic products from the reaction mixture with cyclohexanone gave a multicomponent mixture (GLC) which was not resolved.

Registry No.—**1**, 6952-59-6; **2**, 100-47-0; **3**, 57775-02-7; **4**, 6136-62-5; **5**, 623-00-7; **6**, 57808-43-2; **7**, 1503-49-7; **8**, 2042-37-7; **9**, 57775-03-8; **10**, 28873-85-0; **11**, 57775-04-9; **12**, 34446-14-5; **15**, 1009-14-9; **16**, 57775-05-0; **17a**, 19472-74-3; **17b**, 31938-07,5; **17c**, 16532-79-9; **20**, 57775-06-1; **23**, 57775-07-2; **24**, 57775-08-3; **26**, 54321-42-5; **27**, 57775-09-4; **28**, 51628-12-7; *n*-butyllithium, 109-72-8; benzophenone, 119-61-9; methyl benzoate, 93-58-3; cyclohexanone, 108-94-1; methyl acrylate, 96-33-3; phenyl isocyanate, 103-71-9; phenylacetonitrile, 140-29-4; *n*-butyl bromide, 109-65-9; α-butylphenylacetonitrile, 3508-98-3; α,α-dibutylphenylacetonitrile, 3508-99-4; 2-(*o*-bromophenyl)propionitrile, 57775-10-7; β-(*p*-bromophenyl)propionamide, 57775-11-8; β-(*p*-bromophenyl)propionic acid, 1643-30-7.

References and Notes

(1) Supported by U.S. Army Research Office, Grant DAHCO4 74 GD128.
(2) H. Gilman and G. Melstrom, *J. Am. Chem. Soc.*, **70**, 4177 (1948).
(3) (a) W. E. Parham and Y. A. Sayed, *J. Org. Chem.*, **39**, 2051 (1974); (b) *ibid.*, **39**, 2053 (1974).
(4) The degree of metalation was determined by treating aliquots with water and analyzing the dried organic products by (a) GLC [20% SE-30 on Chromosorb W (60/80 mesh), 6 ft × 0.25 in., or 5% SE-30 on Chromosorb W (60/80 mesh), 3 ft × 0.25 in., including injection of authentic starting halides and reduced products], (b) NMR, the benzylic protons of *p*-iodobenzyl nitrile and benzyl nitrile appear as sharp singlets at δ 3.75 and 3.65, respectively.
(5) Dr. Robert Piccirilli, Duke University, private communication.
(6) Thin layer chromatography showed it to be multicomponent.
(7) Imino anthraquinones (or *N*-butyl derivatives) were anticipated as possible products of self-condensation of **13** by analogy to products of self-condensation of lithium *o*-lithiobenzoates (cf. ref 3b).
(8) Reaction of **18a**, formed from **17a** and 1 equiv of *n*-butyllithium, with methyl iodide, gave a 79% yield of nearly pure 2-(*o*-bromophenyl)propionitrile (see Experimental Section).
(9) Analysis of the organic products obtained by decomposition of aliquots with water showed 17% halogen–metal exchange after 0.5 h with 1 equiv of *n*-butyllithium.
(10) Butylation is assumed to occur by reaction of *n*-butyl bromide, formed by exchange, with the dilithio derivative formed from **24**.
(11) Studies of aliquots showed that 80% iodine–lithium exchange occurs when **28** is treated with 1 equiv of *n*-butyllithium.
(12) *o*-, *m*-, and *p*-bromobenzonitrile are commercially available.
(13) Practical grade stored over molecular sieves.
(14) G. W. A. Kahlbaum and G. von Wirkner, *Ber.*, **27**, 1894 (1894).
(15) (a) bp 90–110 °C; (b) bp 60–90 °C; (c) bp 30–60 °C.
(16) L. Novak and M. Protiva, *Collect. Czech. Chem. Commun.*, **24**, 3966 (1959).
(17) F. Ahrens, *Ber.*, **20**, 2957 (1887).
(18) W. H. Puterbaugh and C. R. Hauser, *J. Org. Chem.*, **29**, 853 (1964).
(19) Freshly distilled from hydroquinone.
(20) M. P. H. van der Meulen, *Recl. Trav. Chim. Pays-Bas*, **15**, 282 (1896).
(21) (a) C. L. Jackson and J. F. White, *Am. Chem. J.*, **2**, 315 (1880); (b) N. Campbell and J. E. McKail, *J. Chem. Soc.*, 1251 (1948).
(22) R. C. Fuson et al., *J. Org. Chem.*, **23**, 1161 (1958).
(23) (a) W. E. Parham and D. C. Egberg, *J. Org. Chem.*, **37**, 1545 (1972); (b) L. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. I, Wiley, New York, N.Y., 1967, p 450.
(24) Shown by coinjection of an authentic sample prepared from benzyl nitrile (1 equiv), sodium hydride (2 equiv), and methyl iodide (2 equiv) in dimethylformamide; bp 226 °C (754 mm); $n^{25}D$ 1.5016 (lit.[25] bp 232 °C; n_D 1.50665).
(25) O. Wallach, *Chem. Zentralbl.*, 1047 (1899).
(26) (a) S. Gabriel and Z. Zimmerman, *Ber.*, **13**, 1683 (1880); (b) J. V. Braun and J. Nelles, *Chem Ber.*, **66**, 1464 (1933).
(27) (a) C. F. Maybery and C. L. Jackson, *Am. Chem. J.*, **2**, 253 (1880); (b) C. L. Jackson, *ibid.*, **1**, 100 (1879).

Ring Cleavage Rearrangements of 2-Bicyclo[3.2.0]heptyl and Related Grignard Reagents

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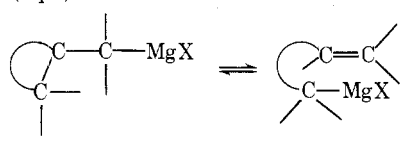
The Grignard reagent (**12**) from 2-bromobicyclo[3.2.0]heptane undergoes a ring cleavage rearrangement to cyclopentenylethyl (**13**) and cycloheptenyl (**14**) Grignard reagents. Grignard **14** is slowly converted to **13**. The rate of rearrangement of **12** is thought to be somewhat retarded by geometric restrictions introduced by the bicyclic skeleton. The facility of the rearrangement of **12** → **14** may indicate that the preferred transition state for rearrangement is nonplanar. Rearrangement of the Grignard reagent **25** from 3-chlorotricyclo[5.3.0.$0^{2,6}$]decane occurs in analogous fashion. Grignard reagents **31** from 2-bromo-6-alkoxybicyclo[3.2.0]heptanes decompose with elimination of the alkoxy group and ring cleavage to 3-vinylcyclopentene and 1,4-cycloheptadiene.

The rearrangement of appropriate organomagnesium compounds, either by cleavage of a strained ring or its reverse (intramolecular addition to a multiple bond), is well established (eq 1):[2]



(1)

Experimental results have been interpreted as being most consistent with a synchronous four-center process for this rearrangement.[2-4] In the present paper, we report Grignard cleavage studies in the bicyclo[3.2.0]heptyl and tricyclo[5.3.0.$0^{2,6}$]decyl systems. These studies were undertaken to probe the effects of geometric constraints imposed on the transition state by the bicyclic system, and to assess the influence of a polar substituent, an alkoxy group.

Preparation of Halides. Bicyclo[3.2.0]heptan-2-ol (**1**)