aqueous DMF. The solution was heated at 40 °C for 10 h. The addition of water resulted in the formation of a brown precipitate. The precipitate was redissolved in methylene chloride and the solution dried ($MgSO_4$) and decolorized with neutral Norit. Methylene chloride was removed in vacuo and crystallization from methylene chloride–hexane gave 631 mg (83%) of *m*-cyanobenzyl phenyl sulfone. The product identification was made by comparison with an authentic sample.[2]

Reaction of α-Iodo- and α-Bromobenzyl Phenyl Sulfones with DBN. To 200 mg (0.56 mmol) of α-iodobenzyl phenyl sulfone in 6 ml of 90% aqueous DMF at room temperature was added 200 mg (1.01 mmol) of DBN. The reaction was followed by TLC (silica gel, methylene chloride). After 3 h the reaction was complete. Water was added, and the mixture was extracted twice with 20-ml portions of methylene chloride, washed once with water, and dried ($MgSO_4$). The solvent was removed in vacuo. Crystallization from methylene chloride–hexane gave 80 mg (62%) of benzyl phenyl sulfone. Identification was made by comparison with an authentic sample.[2] Under similar conditions, α-bromobenzyl phenyl sulfone gave only recovered starting material.

Reaction of Benzenesulfonyl Halides in Aqueous DMF. Solutions of benzenesulfonyl chloride and benzenesulfonyl bromide (~0.001 M) in 90% aqueous DMF were monitored in a Freas conductivity cell with conductance readings taken with a Barnstead conductivity bridge, Model PM-70CB.[2] The rate of increase in conductivity for the bromide was too fast to follow at 25 °C and crude data for benzenesulfonyl chloride showed that it reacted $>10^3$ times faster than α-chloro-*p*-nitrobenzyl phenyl sulfone reacted with 0.2 M sodium benzenesulfinate in 90% aqueous DMF at 25 °C.

Acknowledgment. Support from the University of Maryland Computer Science Center is gratefully acknowledged.

Registry No.—1,5-Diazabicyclo[4.3.0]non-5-ene, 3001-72-7; α-iodobenzyl phenyl sulfone, 41037-85-8; α-bromobenzyl phenyl sulfone, 15296-88-5.

References and Notes

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(11) We take this opportunity to note that dehalogenations are not always as straightforward as they might appear. Some time ago, one of us (B.B.J.) attempted to dehydrohalogenate *meso*-1,2-dibromo-1,2-diphenylethane with sodium ethoxide in ethanol–dioxane cosolvent. Unless the reagent grade dioxane had been purified, this reaction led to *trans*-stilbene as the major product. If the dioxane was purified carefully, the normal product, (*E*)-1,2-diphenylbromoethane, was obtained.
(12) H. Oediger, F. Moller, and K. Eiter, *Synthesis*, 591 (1972).
(13) The order of reactivity for nucleophilic attack on a bromine atom vs. an iodine atom is by no means clear cut. Much of the qualitative data in the literature suggests that the ease of reduction for alkyl halides is RI > RBr, and one quantitative study [M. C. Verploegh, L. Donk, H. J. T. Bos, and W. Drenth, *Recl. Trav. Chim. Pays-Bas*, **90**, 765 (1971)] has shown that nucleophilic attack by sulfide ion on the halogen atom in 2-(2-thienyl)-1-haloacetylenes occurs much more readily with the iodides than with the bromides. Note that in our study (Table IV) α-bromo-*p*-cyanobenzyl phenyl sulfone reacts faster than the iodo compound with sodium benzenesulfinate, but α-iodo-*p*-cyanobenzyl phenyl sulfone reacts faster than the bromo analogue with sodium *p*-chlorobenzenesulfinate.
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(25) Originally the aliquots were quenched with water–acetone–nitric acid (1:1:1); however, electrode response was significantly better with water alone.

Displacement of the Nitro Group of Substituted Nitrobenzenes—a Synthetically Useful Process

Nathan Kornblum,* Leung Cheng, Robert C. Kerber, Melvin M. Kestner, Barry N. Newton, Harold W. Pinnick, Ronald G. Smith, and Peter A. Wade

Department of Chemistry, Purdue University, West Lafayette, Indiana 47907

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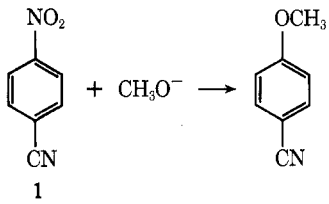
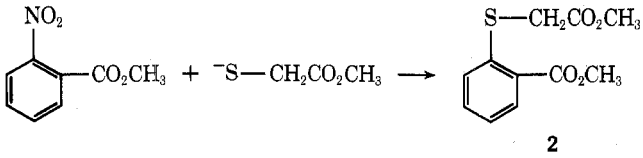
Nitrobenzenes substituted by a variety of electron-withdrawing groups readily undergo nucleophilic displacement of the nitro group at 25°C if the reaction is conducted in hexamethylphosphoramide (HMPA). The yields of pure products are excellent.

Nucleophilic displacement of a nitro group from a benzene ring carrying only one activating group, e.g., the process of eq 1, has, in the past, rarely been observed.[1] Recently, however, Beck and his colleagues[2] have shown that when a dipolar aprotic solvent (DMF) is employed the displacement of a nitro group by mercaptide ions occurs readily at room temperature and that processes such as that of



1 (1)

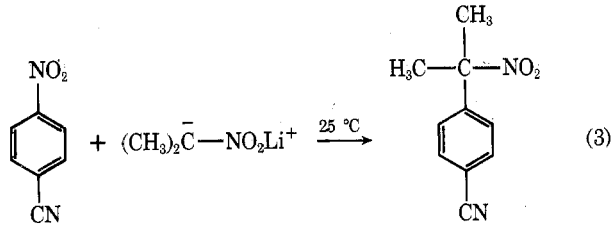
eq 2[3] are synthetically very valuable. In 1974 Knudsen and Snyder[4] reported that anions derived from aldoximes are



2 (2)

able to replace the nitro group of monosubstituted nitrobenzenes, e.g., *p*-nitrobenzonitrile (1), ultimately giving phenols. Here again the reactions are conducted at room temperature in a dipolar aprotic solvent, dimethyl sulfoxide, and the yields are very good.

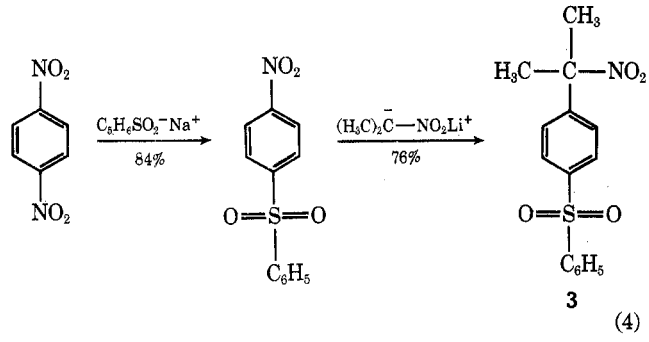
Over the past ten years, in connection with a study of substitution reactions which proceed via radical anion intermediates,[5] a number of otherwise inaccessible compounds have been synthesized in this laboratory from readily available nitroaromatics simply by displacing the nitro group. For example, the reaction of eq 3 is complete in 12 h at 25 °C and gives an 82% yield.



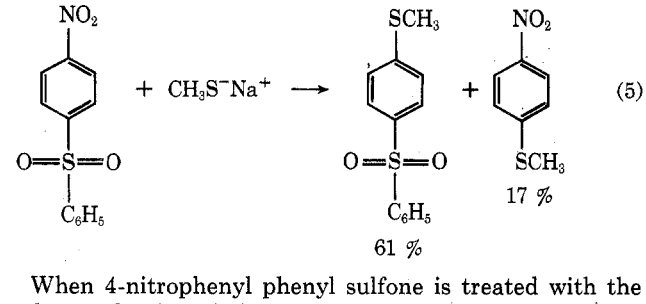
(3)

Nitrobenzenes substituted by six different electron-withdrawing groups have been studied and a variety of nucleophiles have been employed. The use of dipolar aprotic solvents makes it feasible to carry out these reactions at 25 °C and, while the matter has not been studied extensively, it appears that these displacements occur most readily in hexamethylphosphoramide (HMPA), less rapidly in Me_2SO, and still less rapidly in DMF. Our results are summarized in Table I; it should be emphasized that the yields given there refer to pure, isolated, products.

A nice example of the value in synthesis of these processes is the two-step conversion of the readily available *p*-dinitrobenzene into the tertiary nitrosulfone **3** in 64% overall yield (eq 4).



3 (4)



(5)

When 4-nitrophenyl phenyl sulfone is treated with the sodium salt of methyl mercaptan the reaction is complete in 15 min and two products are isolated (eq 5). This is the only instance in which two competitive processes were detected.

Experimental Section[6]

The substituted nitrobenzenes employed in this work were commercial products, purified by recrystallization or sublimation. Crystalline, analytically pure salts were used inasmuch as they were available from other studies; it is highly probable that equally good results will be obtained with salts prepared in situ. The various salts were prepared as described in the literature: the lithium salts of 2-nitropropane and 2-nitrobutane,[7] sodium phenoxide,[8] the sodium salt of methyl mercaptan.[9] The sodium salts of thiophenol and benzyl mercaptan were prepared as described for *p*-chlorothiophenol.[7] Commercial sodium benzenesulfinate was recrystallized from ethanol.[10] As noted above, the success of these reactions is, in good part, due to the use of HMPA as the solvent. HMPA should be handled with great care since it has recently been found to cause cancer in laboratory animals [*Chem. Eng. News*, 17 (Sept 29, 1975)].[11]

General Procedure. The synthesis of *p*-cyano-α-nitrocumene (the reaction of eq 3) is illustrative. Under nitrogen, a mixture of 1.48 g (10 mmol) of *p*-nitrobenzonitrile and 1.90 g (20 mmol) of the lithium salt of 2-nitropropane was dissolved in 20 ml of HMPA and the dark red solution was stirred for 12 h at 25 °C after which it was poured into ice water and extracted with benzene. The benzene extract was washed with water and dried, and the solvent was removed under reduced pressure. The orange residue, mp 55–59 °C, 1.78 g, was chromatographed on acid-washed alumina (Merck) and then recrystallized from pentane. In this way 1.56 g (82% yield) of colorless *p*-cyano-α-nitrocumene, mp 59.5–60.5 °C, was obtained:[12] NMR ($CDCl_3$) δ 2.0 (s, 6 H) and 7.6 (m, 4 H).

Anal. Calcd for $C_{10}H_{10}O_2N_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.22; H, 5.14; N, 14.71.

4-Benzoyl-α-nitrocumene. 4-Nitrobenzophenone (2.06 g, 9.07 mmol), the lithium salt of 2-nitropropane (4.76 g, 50 mmol), 40 ml of HMPA, and a reaction time of 24 h were employed. Workup gave 2.19 g of a dark orange solid, mp 60–69 °C, which was chromatographed on silica gel and then recrystallized from hexane to give 1.91 g (78% yield) of 4-benzoyl-α-nitrocumene: mp 69.5–70.5 °C; NMR ($CDCl_3$) δ 2.0 (s, 6 H), 7.3–7.9 (m, 9 H); ir (KBr) 6.0 (C=O), 6.52 and 7.55 μ (NO_2).

Anal. Calcd for $C_{16}H_{15}O_3N$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.54; H, 5.79; N, 5.33.

4-Phenoxybenzophenone. 4-Nitrobenzophenone (1.18 g, 5 mmol), sodium phenoxide (2.90 g, 25 mmol), and 40 ml of HMPA and a reaction time of 24 h were employed. The crude, an orange oil (1.50 g), when chromatographed on acid-washed alumina, afforded 1.14 g (83% yield) of 4-phenoxybenzophenone, mp 69–70 °C (lit.[13] mp 71 °C).

Anal. Calcd for $C_{19}H_{14}O_2$: C, 83.19; H, 5.14. Found: C, 83.04; H, 4.99.

4-(Thiobenzyl)benzophenone. Here 1.18 g (5 mmol) of 4-nitrobenzophenone, 0.75 g (5.1 mmol) of the sodium salt of benzyl mercaptan, and 10 ml of HMPA (reaction time 10 min) were employed. The crude product was chromatographed on acid-washed alumina and then recrystallized from methanol. An 82% yield (1.25 g) of 4-(thiobenzyl)benzophenone, mp 83–84 °C (lit.[14] mp 84.5–85.4 °C), was obtained.

Anal. Calcd for $C_{20}H_{16}OS$: C, 78.90; H, 5.29; S, 10.53. Found: C, 78.93; H, 5.46; S, 10.32.

Ethyl *p*-Ethoxybenzoate. Ethyl *p*-nitrobenzoate (9.8 g, 50 mmol), sodium ethoxide (3.74 g, 55 mmol), and 50 ml of HMPA were employed; reaction time was 30 min. The crude product was a red oil which on distillation through a short column afforded 7.95 g (81% yield) of ethyl *p*-ethoxybenzoate; bp 79–81 °C (0.22 mm) [lit.[15] bp 145–146 °C (13 mm)], $n^{19}D$ 1.5179 (lit.[16] n ^{20}D 1.5181). Ir and NMR spectra were identical with those in Sadtler.

Ethyl *p*-(Thiobenzyl)benzoate. Ethyl *p*-nitrobenzoate (0.98 g, 5 mmol), sodium benzyl mercaptide (0.80 g, 5.5 mmol), 10 ml of HMPA, and a 30-min reaction time were employed. Chromatography of the crude product (mp 53–56 °C) on silica gel afforded 1.20 g (88% yield) of ethyl *p*-(thiobenzyl)benzoate, mp 57–58 °C (lit.[17] mp 60 °C).

Anal. Calcd for $C_{16}H_{16}O_2S$: C, 70.55; H, 5.92; S, 11.77. Found: C, 70.31; H, 5.88; S, 11.53.

4-Carbomethoxy-α-nitrocumene. Methyl *p*-nitrobenzoate (1.81 g, 10 mmol), the lithium salt of 2-nitropropane (4.75 g, 50 mmol), and 33 ml of HMPA were employed; reaction time was 84

Table I. Compounds Synthesized by the Displacement of an Aromatic Nitro Group at 25 °C[a]

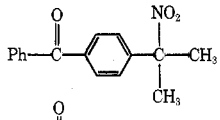
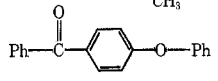
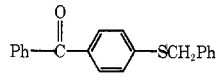
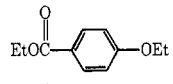
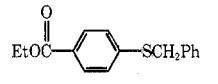
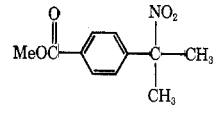
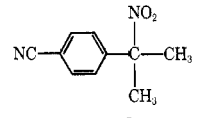
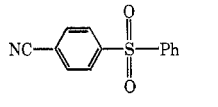
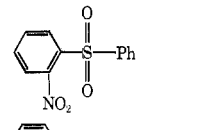
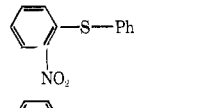
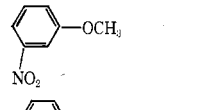
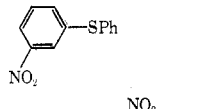
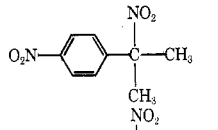
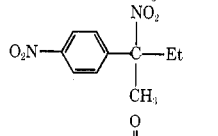
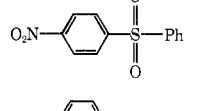
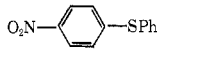
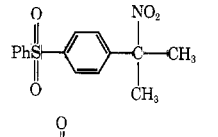
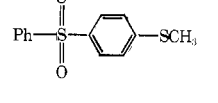
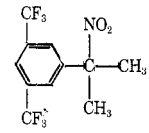
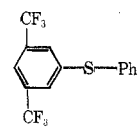
Nitroaromatic employed	Nucleophile employed	Product	Registry no.	Yield, %[b]	Reaction time
4-Nitrobenzophenone	$(CH_3)_2\overline{C}-NO_2Li^+$		58324-79-1	78	24 h
4-Nitrobenzophenone	PhO^-Na^+		6317-73-3	83	24 h
4-Nitrobenzophenone	$PhCH_2S^-Na^+$		26960-79-2	82	10 min
Ethyl *p*-nitrobenzoate	EtO^-Na^+		23676-09-7	81	30 min
Ethyl *p*-nitrobenzoate	$PhCH_2S^-Na^+$		58324-80-4	88	30 min
Methyl *p*-nitrobenzoate	$(CH_3)_2\overline{C}-NO_2Li^+$		58324-81-5	60	84 h
p-Nitrobenzonitrile	$(CH_3)_2\overline{C}-NO_2Li^+$		58324-82-6	82	12 h
p-Nitrobenzonitrile	$PhSO_2^-Na^+$		28525-13-5	67	48 h[c]
o-Dinitrobenzene	$PhSO_2^-Na^+$		31515-43-2	85	1.5 h
o-Dinitrobenzene	PhS^-Na^+		4171-83-9	80	18 h[d]
m-Dinitrobenzene	$CH_3O^-Na^+$		555-03-3	83	16 h
m-Dinitrobenzene	PhS^-Na^+		37984-02-4	88	24 h
p-Dinitrobenzene	$(CH_3)_2\overline{C}-NO_2Li^+$		3276-35-5	75	3 h[e,f]
p-Dinitrobenzene	$CH_3\overline{C}(Et)-NO_2Li^+$		58324-83-7	84	8 h[e]
p-Dinitrobenzene	$PhSO_2^-Na^+$		1146-39-0	84	50 h[e]
p-Dinitrobenzene	PhS^-Na^+		952-97-6	96	24 h[d]
4-Nitrophenyl phenyl sulfone	$(CH_3)_2\overline{C}-NO_2Li^+$		58324-84-8	76	12 h
4-Nitrophenyl phenyl sulfone	$CH_3S^-Na^+$		58324-85-9	61[g]	15 min

Table I (*Continued*)

Nitroaromatic employed	Nucleophile employed	Product	Registry no.	Yield, %[b]	Reaction time
3,5-Bis(trifluoromethyl)-nitrobenzene	$(CH_3)_2\overline{C}-NO_2Li^+$		58324-86-0	70[h]	4 h
3,5-Bis(trifluoromethyl)-nitrobenzene	PhS^-Na^+		58324-87-1	92	6 h[d]

[a] Unless otherwise noted all reactions were carried out in HMPA at 25 °C. [b] Pure, isolated, product. [c] At 80 °C. [d] Reaction probably complete in much shorter time. [e] In Me_2SO. [f] In DMF the reaction requires 65 h. [g] A 17% yield of 4-nitrophenyl methyl sulfide was also isolated. [h] A 5% yield of 3,5-bis(trifluoromethyl)aniline was also isolated.

h. The crude, an orange oil, when chromatographed on silica gel and then recrystallized from pentane afforded 1.34 g (60% yield) of 4-carbomethoxy-α-nitrocumene: mp 50–51 °C; NMR ($CDCl_3$) δ 2.0 (s, 6 H), 3.91 (s, 3 H), 7.5 (d, 2 H), and 8.1 (d, 2 H).

Anal. Calcd for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.27. Found: C, 59.42; H, 5.98; N, 6.17.

4-Cyanophenyl Phenyl Sulfone. Here 1.04 g (7 mmol) of *p*-nitrobenzonitrile, 5.74 g (35 mmol) of sodium benzenesulfinate, 20 ml of HMPA, and a reaction time of 48 h at 80 °C were employed. Workup gave 1.37 g of a brown solid (mp 115–123 °C) which was passed through a short column of acid-washed alumina and then recrystallized from carbon tetrachloride to give 0.95 g of 4-cyanophenyl phenyl sulfone, mp 125–126° (lit.[18] mp 126 °C). The mother liquor was evaporated to dryness and the residue chromatographed to afford an additional 0.18 g of product, mp 124–125 °C. Total yield of 4-cyanophenyl phenyl sulfone was 67%.

Anal. Calcd for $C_{13}H_9O_2NS$: C, 64.20; H, 3.70; N, 5.76; S, 13.16; mol wt, 243.2. Found: C, 64.31; H, 3.63; N, 5.63; S, 13.42; mol wt, 247.1.

2-Nitrophenyl Phenyl Sulfone. Under nitrogen, a mixture of 2.02 g (12 mmol) of *o*-dinitrobenzene and 2.2 g (13.2 mmol) of sodium benzenesulfinate was dissolved in 20 ml of HMPA. The resulting orange solution was stirred for 1.5 h at 25 °C after which it was poured into ice water. The solid collected (mp 142–145 °C) was recrystallized twice from absolute ethanol to afford 2.67 g (85% yield) of 2-nitrophenyl phenyl sulfone, mp 145–146 °C (lit.[19] mp 145 °C).

2-Nitrophenyl Phenyl Sulfide. *o*-Dinitrobenzene (1.01 g, 6 mmol), sodium thiophenoxide (1.58 g, 12 mmol), 10 ml of HMPA, and a reaction time of 18 h were employed. Chromatography of the crude product (mp 70–74 °C) on acid-washed alumina afforded 1.11 g (80% yield) of 2-nitrophenyl phenyl sulfide, mp 78–79 °C (lit.[20] mp 79 °C).

***m*-Nitroanisole.** *m*-Dinitrobenzene (2.01 g, 12 mmol), sodium methoxide (0.82 g, 15 mmol), and 40 ml of HMPA were employed; reaction time was 16 h. Chromatography of the crude product on silica gel afforded 1.52 g (83% yield) of *m*-nitroanisole: mp 36–37 °C; NMR ($CDCl_3$) δ 3.88 (s, 3 H), 7.10–7.92 (m, 4 H).

3-Nitrophenyl Phenyl Sulfide. *m*-Dinitrobenzene (1.01 g, 6 mmol), sodium thiophenoxide (1.58 g, 12 mmol), 60 ml of HMPA, and a reaction time of 24 h were employed. Chromatography of the brown oil on acid-washed alumina afforded 1.21 g (88% yield) of 3-nitrophenyl phenyl sulfide: mp 40.5–41.5 °C (lit.[21] mp 42.5 °C); NMR ($CDCl_3$) δ 7.18–7.62 m, 7 H), 7.76–8.13 (m, 2 H).

α,*p*-Dinitrocumene. *p*-Dinitrobenzene (10.1 g, 60 mmol), the lithium salt of 2-nitropropane (6.3 g, 66 mmol), and 95 ml of Me_2SO were employed; reaction time was 3 h. Two recrystallizations of the crude product (mp 62–67 °C) from hexane–benzene afforded 9.5 g (75% yield) of α,*p*-dinitrocumene, mp 67–68 °C (lit.[22] mp 69–70 °C).

2-(*p*-Nitrophenyl)-2-nitrobutane. *p*-Dinitrobenzene (97.7 g, 0.582 mol), the lithium salt of 2-nitrobutane (68.7 g, 0.624 mol), and 1 l. of Me_2SO were employed as above (reaction time 8 h). Chromatography of the brown oil on acid-washed alumina afforded 109 g (84% yield) of 2-(*p*-nitrophenyl)-2-nitrobutane, mp 44.5–45.5 °C. A sample was distilled for microanalysis, bp 130–131 °C (0.11 mm).

Anal. Calcd for $C_{10}H_{12}N_2O_4$: C, 53.53; H, 5.40; N, 12.49. Found: C, 53.43; H, 5.45; N, 12.47.

4-Nitrophenyl Phenyl Sulfone. *p*-Dinitrobenzene (10.5 g, 62.5 mmol), sodium benzenesulfinate (11.3 g, 68.8 mmol), and 100 ml of Me_2SO were employed as above (reaction time 50 h). Two recrystallizations from absolute ethanol afforded 13.82 g (84% yield) of 4-nitrophenyl phenyl sulfone, mp 139–140 °C (lit.[23] mp 140, 142 °C).

4-Nitrophenyl Phenyl Sulfide. *p*-Dinitrobenzene (1.01 g, 6.0 mmol), sodium thiophenoxide (2.38 g, 18 mmol), and 30 ml of HMPA were employed (reaction time 24 h). Chromatography on acid-washed alumina afforded 1.32 g (96% yield) of 4-nitrophenyl phenyl sulfide: mp 52.5–53 °C (lit.[24] mp 54.5, 55 °C); NMR (CCl_4) δ 7.1 (d, 2 H), 7.4 (s, 5 H), 7.9 (d, 2 H).

4-Phenylsulfonyl-α-nitrocumene. To a solution of 4-nitrophenyl phenyl sulfone (13.15 g, 50 mmol) in 100 ml of HMPA, under nitrogen, was added 9.3 g (98 mmol) of the lithium salt of 2-nitropropane. The deep purple solution was stirred at 25 °C for 13 h after which it was poured into water and extracted with benzene. The benzene extract was washed with water, dried over anhydrous $MgSO_4$, and evaporated. Two recrystallizations from absolute ethanol afforded 11.58 g (76% yield) of 4-phenylsulfonyl-α-nitrocumene, mp 117–117.5 °C.

Anal. Calcd for $C_{15}H_{15}NO_4S$: C 59.03; H, 4.92; N, 4.59; S, 10.49. Found: C, 59.13; H, 4.97; N, 4.50; S, 10.41.

4-Thiomethoxyphenyl Phenyl Sulfone. 4-Nitrophenyl phenyl sulfone (1.58 g, 6 mmol), sodium methyl mercaptide (0.428 g, 6.1 mmol), 15 ml of HMPA, and a reaction time of 15 min were employed. Chromatography on silica gel (benzene–ether fractions) followed by recrystallization from absolute methanol afforded 0.96 g (61% yield) of 4-thiomethoxyphenyl phenyl sulfone: mp 110–111 °C (lit.[25] mp 115 °C); NMR ($CDCl_3$) δ 2.42 (s, 3 H), 7.2–8.05 (m, 9 H).

Anal. Calcd for $C_{13}H_{12}O_2S_2$: C, 59.09; H, 4.58; S, 24.23. Found: C, 59.18; H, 4.54; S, 24.21.

From the hexane–benzene fractions of chromatography was isolated 0.172 g (17% yield) of *p*-nitrophenyl methyl sulfide: mp 69–70 °C (lit.[26] mp 71–72 °C); NMR ($CDCl_3$) δ 2.52 (s, 3 H), 7.3 (d, 2 H), 8.12 (d, 2 H).

Anal. Calcd for C_7H_7NS: C, 49.71; H, 4.17; N, 8.28; S, 18.92. Found: C, 49.84; H, 4.28; N, 8.15; S, 19.01.

3,5-Bis(trifluoromethyl)-α-nitrocumene. 3,5-Bis(trifluoromethyl)nitrobenzene (20.5 g, 80 mmol), the lithium salt of 2-nitropropane (8.2 g, 86 mmol), and 100 ml of HMPA were employed; reaction time was 4 h. The crude product was recrystallized from hexane to give 9.7 g of 3,5-bis(trifluoromethyl)-α-nitrocumene, mp 54.5–55 °C. An additional 6.8 g of product was obtained by chromatographing the residue obtained upon evaporation of the mother liquor on acid-washed alumina; total yield was 70%.

Anal. Calcd for $C_{11}H_9F_6NO_2$: C, 43.87; H, 3.01; N, 4.65; F, 37.84. Found: C, 43.98; H, 3.11; N, 4.65; F, 37.80.

3,5-Bis(trifluoromethyl)phenyl Phenyl Sulfide. 3,5-Bis(trifluoromethyl)nitrobenzene (1.03 g, 4 mmol), sodium thiophenoxide (1.06 g, 8 mmol), and 5 ml of HMPA were employed; reaction time was 6 h. Short-path distillation of the orange oil obtained afforded 1.18 g (92% yield) of pale yellow oil, bp 87–89 °C (0.6 mm), $n^{19}D$ 1.5093.

Anal. Calcd for $C_{14}H_8F_6S$: C, 52.17; H, 2.51; S, 9.94; mol wt, 322.2. Found: C, 52.15; H, 2.55; S, 9.81; mol wt, 324.6.

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Registry No.—4-Nitrobenzophenone, 1144-74-7; ethyl *p*-nitrobenzoate, 99-77-4; methyl *p*-nitrobenzoate, 619-50-1; *p*-nitrobenzonitrile, 619-72-7; *o*-dinitrobenzene, 528-29-0; *m*-dinitrobenzene, 99-65-0; *p*-dinitrobenzene, 100-25-4; 4-nitrophenyl phenyl sulfone, 1146-39-0; 3,5-bis(trifluoromethyl)nitrobenzene, 328-75-6; 2-nitropropane Li salt, 12281-72-0; sodium phenoxide, 139-02-6; benzylmercaptan Na salt, 3492-64-6; sodium ethoxide, 141-52-6; sodium benzenesulfinate, 873-55-2; sodium thiophenoxide, 930-69-8; sodium methoxide, 124-41-4; 2-nitrobutane Li salt, 35818-95-2; sodium methylmercaptide, 5188-07-8; *p*-nitrophenyl methyl sulfide, 701-57-5.

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Substitution Reactions of Specifically Ortho-Metalated Piperonal Cyclohexylimine

Frederick E. Ziegler*[1] and Kerry W. Fowler

Sterling Chemistry Laboratory, Yale University, New Haven, Connecticut 06520

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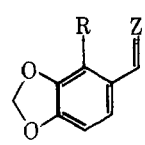
The specific ortho metalation of piperonal and 6-bromopiperonal cyclohexylimine is discussed. Typical reactions of the lithio and cuprous organometallics are explored.

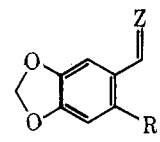
Since the observations of Hauser[2] concerning the stabilizing effect of a neighboring tertiary amine on the stability of ortho-lithiated aryls, this type of reaction has been applied to monosubstituted amides,[3] oxazolines,[4] and imines.[5]. Reiff has observed[5] that when acetophenone cyclohexylimine is treated with *n*-butyllithium (*n*-BuLi) in ether at −78 °C, addition to the imine is the major reaction pathway with minor quantities of dilithioimine derived from metalation at both the methyl group and the ortho position.

We have observed in the instance of piperonal cyclohexylime (**1a**) that reaction with *n*-BuLi in tetrahydrofuran (THF) at 0 °C afforded products of imine addition. When the temperature was lowered to −78 °C, only lithiation at the 2 position (**1b**) was observed, since low-temperature deuteration provided 2-deuteriopiperonal cyclohexylimine (**1d**) with a characteristic ortho-coupling pattern in its NMR spectrum.[6] When 6-bromopiperonal cyclohexylimine (**2e**) was lithiated at −78 °C, the NMR spectrum of the deuterium oxide quenched product indicated that deuteration had occurred exclusively at the 6 position (**2d**). However, when the 6-lithiated imine was allowed to warm to ambient temperature and then quenched with iodine at the same temperature or at −78 °C, only the 2-iodoimine **1f** was observed. Thus, the 2 position of imine **1a** is the site of kinetic and thermodynamic lithiation due to the electron-withdrawing effect of the adjacent oxygen atom. In the latter case, metal–halogen exchange is the kinetic process rather than C-2 deprotonation.[7] The equilibration is thought to be promoted by piperonal cyclohexylimine acting as a proton source. Although a sufficient excess of butyllithium was used in control runs to ensure the metalation of all of the piperonalimine, exchange still occurred. This may imply a disproportionation in which 2 mol of 6-lithiated imine affords 2,6-dilithiated imine and piperonalimine, thereby generating the necessary exchange medium. Alternatively, decomposition (i.e., oxidation and hydrogen abstraction from THF) would also generate piperonalimine.



1

a, R = H; Z = NC_6H_{11}
b, R = Li; Z = NC_6H_{11}
c, R = CuI; Z = NC_6H_{11}
d, R = D; Z = NC_6H_{11}
e, R = Br; Z = NC_6H_{11}
f, R = I; Z = NC_6H_{11}



2

g, R = I; Z = O
h, R = CH_3; Z = O
i, R = $CH_2CH{=}CH_2$; Z = O
j, R = CO_2H; Z = O
k, R = CO_2CH_3; Z = O

Both ortho-lithiated imines were subjected to alkylation with allyl bromide and methyl iodide. The data in Table I under entries A and B indicate that methylation is virtually