

Tetrakis-sulphoxides: a New Type of Phase-transfer Catalyst for Nucleophilic Displacements and Alkylations

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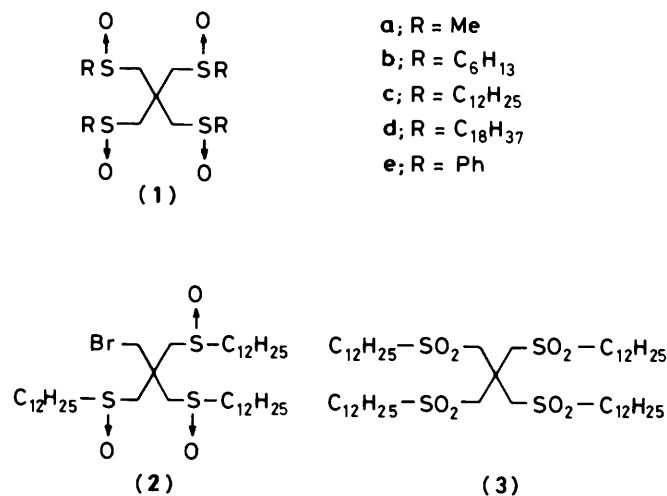
Tetrakis(alkylsulphinylmethyl)methanes have been shown to serve as good phase-transfer catalysts which accelerate S_N2 type displacements of octyl bromide with various nucleophiles (thiocyanate, cyanide, phenoxide, and thiolate) in solid-liquid two-phase systems. Alkylation of phenylacetonitrile with alkyl halides has also been carried out in liquid-liquid two-phase systems in the presence of the above sulphoxides to afford the corresponding mono-alkylated products in high yields.

Phase-transfer catalysis is an important process in synthetic organic chemistry, and various compounds such as onium salts (ammonium or phosphonium), crown ethers, and cryptands have been used as catalysts.¹ A further class of phase-transfer catalysts is represented by neutral open-chain compounds having polyodants, which are called 'octopus molecules'.² An example of these, tetrakis(hydroxymethyl)methane derivatives with three polyoxyethylene moieties, are effective phase-transfer catalysts for simple displacement reactions. However, they do not promote the alkylation of phenylacetone with butyl bromide in liquid-liquid two-phase systems;³ this can be achieved by the use of α -phosphoryl sulphoxides as phase-transfer catalysts. The latter are inefficient catalysts for ordinary displacement reactions.⁴

We have recently reported that methyl 2-pyridyl sulphoxides and related pyridyl derivatives are good phase-transfer catalysts for S_N2 reactions of various primary or secondary alkyl halides in a two-phase reaction system.⁵ The catalytic activity of these sulphoxides can be attributed to initial co-ordination of the metal cation by the sulphinyl oxygen atom and the pyridyl nitrogen atom, resulting in transfer of nucleophiles from an aqueous phase to an organic phase. Thus, the nucleophiles become highly nucleophilic 'naked anions'. As expected, the compounds containing polysulphinyl groups have higher catalytic activities than monosulphinyl compounds. Therefore, we have synthesized tetrakis(alkylsulphinylmethyl)methanes, octopus compounds of a new type, and tested their phase-transfer catalytic activities for simple displacements in a solid-liquid two-phase system, and for alkylations in a liquid-liquid two-phase system. Here we describe the results of these phase-transfer reactions.

Results and Discussion

Synthesis of the Catalysts.—The polysulphoxides (1) and (2), and the sulphone (3) (Scheme 1) were synthesized as illustrated in Scheme 2. Tetrakis(alkyl- or phenyl-thiomethyl) methanes (4) were prepared in nearly quantitative yields by treatment of several sodium thiolates with tetrakis(bromomethyl)methane; the latter was obtained by reaction of tetrakis(hydroxymethyl)methane with phosphorus tribromide. Tris(dodecylthiomethyl)(bromomethyl)methane (8) was prepared in the following manner. Tetrakis(bromomethyl)methane was treated with sodium sulphide to give 2,6-dithiaspiro[3.3]heptane (5) in good yield and an equimolar mixture of this and dodecyl bromide in benzene and ethanol was heated in a sealed tube to give 3-(bromomethyl)-3-(dodecylthiomethyl)thietane (6). 3,3-Bis(dodecylthiomethyl)thietane (7) was obtained in the reaction of (6) with sodium dodecanethiolate in ethanol in ca. 60% yield.

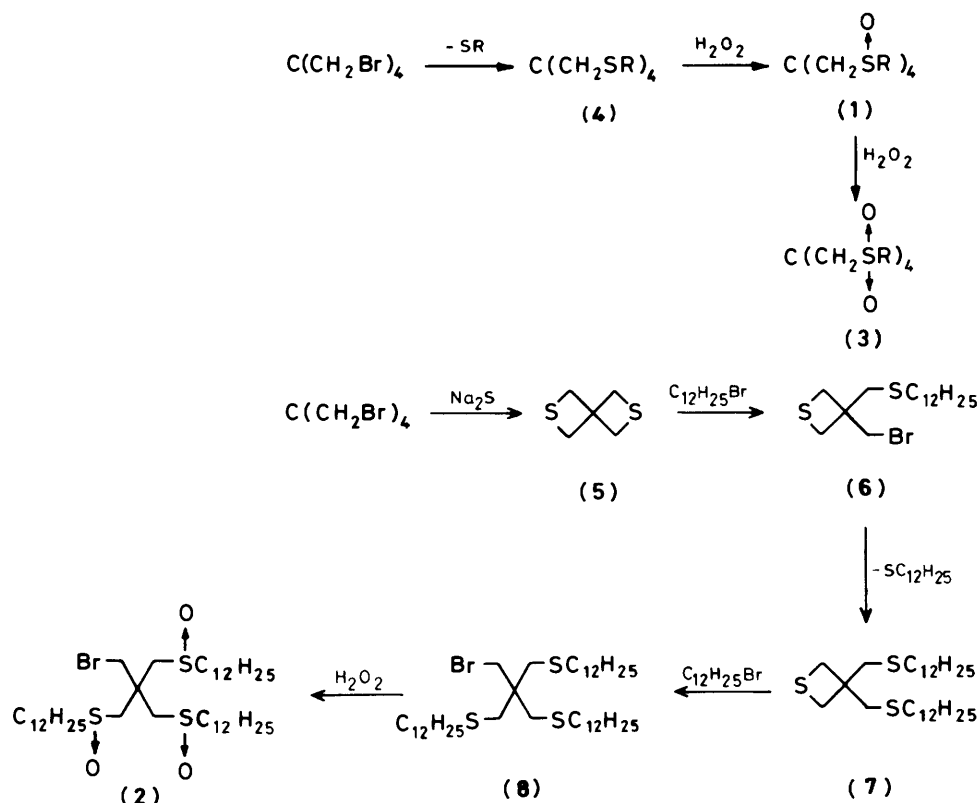


Scheme 1.

The reaction of compound (7) with dodecyl bromide gave tris(dodecylthiomethyl)(bromomethyl)methane (8) in good yield. The sulphoxides (1a–e) and (2), and the sulphone (3) were then obtained by oxidation of the corresponding sulphide with hydrogen peroxide in acetic acid-benzene. The tetrakis-sulphoxides thus obtained seem to be a mixture of several diastereoisomers, since they have broad ranges of melting points; their elemental analyses were however satisfactory (Table 1).

Nucleophilic Substitution under PTC Conditions.—In order to test these sulphoxides as catalysts for nucleophilic substitution, octyl bromide was treated with various nucleophiles in xylene in the presence of the tetrakis-sulphoxides (1a–e). All the reactions were carried out in a solid-liquid two-phase system: in the absence of the sulphoxides as catalysts there was no reaction. The results are summarized in Table 2.

Inspection of the results reveals that the reaction of octyl bromide with potassium thiophenoxide or thiocyanate in the presence of e.g. (1b), in xylene solution, gave either the corresponding sulphide or thiocyanate, in nearly quantitative yield. The yield of octyl phenyl sulphide decreased in xylene-water (liquid-liquid phase). In contrast, the reaction with either potassium cyanide or phenoxide was sluggish and afforded the corresponding product in a low yield. This might be attributed to the low solubility of these reagents in organic solvents.



Scheme 2.

In order to compare the catalytic activity of the tetrakis-sulphoxides (1a–e), the trisulphoxide (2), and the sulphone (3), the reaction of octyl bromide with potassium thiocyanate was carried out in the presence of these catalysts in xylene at 100 °C (see Table 3).

The tetrakis-sulphoxides bearing long alkyl chains, *i.e.* (1b–d), were the most effective catalysts whilst the sulphoxides (1a) and (1e) were ineffective. The ineffectiveness of (1a) is probably accounted for by lack of solubility in the reaction medium, a result of the hydrophilic nature of its methyl group, whilst the phenylsulphinyl group in (1e) may result in reduced chelating ability owing to the presence of a strong electron-withdrawing group. Further, the catalytic activity of the tris-sulphoxide (3) was less than that of the tetrakis-sulphoxide (1c). These results suggest that an increase in the number of sulphinyl groups in the molecule results in an increase in the local concentration of nucleophile around the catalyst and thus, increases its catalytic ability. Unlike the sulphoxides, the sulphone (3) was an ineffective catalyst. This lack of reactivity is believed to be due to the comparatively weak affinity of the sulphonyl groups for the metal cation, a feature which emphasizes the cumulative ability to chelate the metal cation brought about by the presence of four sulphinyl groups.

Alkylation of Active Methylene Compounds under PTC Conditions.—In order to test the tetrakis-sulphoxide (1b) as a phase-transfer catalyst in a liquid–liquid two-phase system, phenylacetonitrile was treated with various alkyl halides in 50% aqueous sodium hydroxide in the presence of the sulphoxide (1b). The alkylations proceeded smoothly at room temperature, (see Table 4). Although phenylacetonitrile reacts with methyl iodide in the absence of catalysts to give, after 24 h, a 12% yield of product, the sulphoxide (1b) markedly improved the yield of

product. Other alkyl halides reacted similarly to give mono-alkylated products. In contrast, mono- and di-methylated products (3:1) were obtained when α -phosphoryl sulphoxides were used as catalysts in the methylation of phenylacetonitrile with methyl iodide in 50% aqueous sodium hydroxide.⁴ The high selectivity for mono-alkylation shown in the present work is, clearly, of synthetic importance. The sulphoxide (1b) was also an effective catalyst for the alkylation of phenylacetone with alkyl halides in aqueous sodium hydroxide.⁶

Experimental

General.—All m.p.s were uncorrected and were taken on a Yanako micro melting-point apparatus. I.r. spectra were obtained on a JASCO A-3 spectrophotometer and n.m.r. spectra were obtained on a Hitachi R-600 FT-NMR spectrometer or a JEOL LNM-MH-100 spectrometer in CDCl_3 using Me_4Si as internal standard. All the reactions were monitored by chromatography, namely t.l.c. (Merck Kieselgel 60-GF₂₅₄) and g.l.c. [Hitachi 163, using a 5% silicon GE-30 on SiO_2 (60–80 mesh) or 2% silicon OV-1 Chromosorb W on SiO_2 (80–100 mesh) column]. Silica gel used in column chromatography was Merck Kieselgel 60. Mass spectra were taken with a Hitachi RMU-6MG mass spectrometer. Elemental analyses were carried out in the Chemical Analysis Center in this University.

Materials.—All reagents were obtained from Wako Pure Chemical Industries Ltd., Tokyo Kasei Co. Ltd., or Aldrich Chemical Co. The reagents used as reaction solvents were further purified by general methods.

Preparation of the Sulphoxides (1a–e) and (2), and the Sulphone (3).—The title compounds were prepared from the

Table 1. Characteristic data of several sulphoxides

Compd.	Yield %	M.p. (lit.) °C	$\nu_{\max.}$ (KBr) (cm ⁻¹)	δ (CDCl ₃)	Formula	Found (Calc.) (%)	
						C	H
(1a)	62	205—215 (205) ⁸	1 420, 1 050, 1 010	2.72 (12 H, s, MeSO), 3.47 (8 H, m, CH ₂ SO)	C ₉ H ₂₀ O ₄ S ₄	33.1 (33.7)	6.3 (6.3)
(1b)	61	150—153 (159) ⁸	1 050	0.90 (12 H, t, Me), 1.30 [32 H, m, (CH ₂) ₄], 2.80 (8 H, m, CH ₂ SO), 3.42 (8 H, m, CCH ₂ SO)	C ₂₉ H ₆₀ O ₄ S ₄	57.6 (57.95)	10.0 (10.1)
(1c)	50	66—72	2 900, 1 420, 1 040	0.96 (12 H, t, Me), 1.15—1.75 [80 H, m, (CH ₂) ₁₀], 2.83 (8 H, m, CH ₂ SO), 3.41 (8 H, m, CCH ₂ SO)	C ₅₃ H ₁₀₈ O ₄ S ₄	67.8 (67.95)	11.5 (11.5)
(1d)	78	92—103	2 900, 1 460, 1 410, 1 020	0.90 (12 H, t, Me), 1.13—1.70 [64 H, m, (CH ₂) ₁₆], 2.76 (8 H, m, CH ₂ SO), 3.39 (8 H, m, CCH ₂ SO)	C ₇₇ H ₁₅₆ O ₄ S ₄	72.3 (72.6)	12.2 (12.3)
(1e)	30	180—190	3 040, 2 900, 1 570, 1 470, 1 440, 1 400, 1 040, 740	3.18—3.93 (8 H, m, CCH ₂ SO), 7.19—8.01 (20 H, m, Ph)	C ₂₉ H ₂₈ O ₄ S ₄	61.5 (61.2)	4.8 (5.0)
(2)	55	liquid	1 270, 1 050	0.91 (9 H, t, Me), 1.05—1.62 [60 H, m, (CH ₂) ₁₀], 2.76 (6 H, m, CH ₂ SO), 3.31 (6 H, m, CCH ₂ SO), 4.03 (2 H, br s, CH ₂ Br)	C ₄₁ H ₈₃ BrO ₃ S ₃	58.9 (59.2)	9.9 (10.05)
(3)	63	76—78 (78.3) ⁹	2 910, 1 310, 1 140		C ₅₃ H ₁₀₈ O ₈ S ₄	63.4 (63.6)	10.7 (10.8)

Table 2. Solid-liquid two-phase reactions catalysed by tetrakis-sulphoxide (1b)
$$\text{C}_8\text{H}_{17}\text{Br} + \text{MNu} \xrightarrow[\text{Xylene}]{(1b)} \text{C}_8\text{H}_{17}\text{Nu} + \text{MBr}$$

MNu	Oct. Br: Nu:(1b) ^a	Xylene (ml)	Temp. (°C)	Time (h)	Yield ^b (%)	Product
KSCN	1:5:0.2	2	100	35	90	C ₈ H ₁₇ SCN ^c
KSCN	1:1:0.1	0.5	100	5	100	C ₈ H ₁₇ SCN ^c
KSCN	1:1:0.1	c	100	0.5	100	C ₈ H ₁₇ SCN ^c
KCN	1:5:0.1	2	100	40	5	C ₈ H ₁₇ CN
PhOK	1:5:0.2	2	70	40	25	C ₈ H ₁₇ O ^f Ph
PhSK	1:1:0.1	1	20	3	95	C ₈ H ₁₇ SPh ^f
PhSK	4:4:0.04	1	20	5	85	C ₈ H ₁₇ SPh ^f
PhSK	4:4:0.04	c	20	4	95	C ₈ H ₁₇ SPh ^f
PhSK	4:4:0.04	d	20	4	55	C ₈ H ₁₇ SPh ^f

^a mmol. ^b By g.l.c. analysis. ^c No solvent. ^d Added H₂O (0.5 ml), no solvent. ^e Octyl thiocyanate was obtained in 91% yield when dicyclohexyl-18-crown-6 was used (solid-liquid system): D. Landini, A. M. Maia, F. Montanari, and F. Pirisi, *Gazz. Chim. Ital.*, 1975, **105**, 863. ^f Octyl phenyl sulphide was obtained in 88% yield when dicyclohexyl-18-crown-6 was used (solid-liquid system): A. W. Herriott and D. Picker, *J. Am. Chem. Soc.*, 1975, **97**, 2345.

corresponding sulphides with hydrogen peroxide as oxidant, according to the general method. The characteristics of these compounds are summarized in Table 1.

Synthesis of Substituted Tetrakis-sulphides (4a), (4b), (4c), (4d), and (4e).—A typical procedure was as follows. A solution of 1,3-dibromo-2,2-bis(bromomethyl)propane (0.78 g, 2 mmol) and sodium methanethiolate (ca. 15% aqueous solution; 4.5 g, 9.6 mmol) in methanol was refluxed for 5 h under N₂. After concentration of the solution, the residue was diluted with water and extracted with dichloromethane. The organic layer was dried (MgSO₄) and concentrated and the resulting residue purified by silica gel column chromatography with hexane-benzene (1:3) as eluant to afford a colourless liquid.

(4a) (0.42 g, 81%), δ (CDCl₃) 2.12 (12 H, s, MeS) and 2.66 (8 H, s, CH₂S) (Found: C, 42.1; H, 7.8. C₉H₂₀S₄ requires C, 42.2; H, 7.8%).

(4b) (60%), b.p. 206—208 °C at 0.1 mmHg; $\nu_{\max.}$ (neat) 2 900 and 1 420 cm⁻¹; δ (CDCl₃) 0.87 (12 H, t, Me), 1.06—1.68 [32 H, m, (CH₂)₄], 2.65 (8 H, t, *J* 6 Hz, CH₂S), and 2.80 (8 H, s, CCH₂S) (Found: C, 64.5; H, 11.2. C₂₉H₆₀S₄ requires C, 64.9; H, 11.3%).

(4c) (63%), m.p. 32—33 °C (lit.,⁷ 35—36 °C); $\nu_{\max.}$ (neat) 2 900 and 1 420 cm⁻¹; δ (CDCl₃) 0.96 (12 H, t, Me), 1.17—1.75 [80 H, m, (CH₂)₁₀], 2.64 (8 H, t, *J* 6.6 Hz, CH₂S), and 2.78 (8 H, s, CCH₂S).

(4d) (40%), m.p. 59—60 °C; $\nu_{\max.}$ 2 900 and 1 420 cm⁻¹; δ (CDCl₃) 0.87 (12 H, t, Me), 1.11—1.62 [64 H, m, (CH₂)₁₆], 2.53 (8 H, t, *J* 6.6 Hz, CH₂S), and 2.67 (8 H, s, CCH₂S) (Found: C, 76.4; H, 13.0. C₇₇H₁₅₆S₄ requires C, 76.4; H, 13.0%).

(4e) (65%), m.p. 85—86 °C; $\nu_{\max.}$ (neat) 1 580, 1 480, 1 440, 1 400, and 730 cm⁻¹; δ (CDCl₃) 3.27 (8 H, s, CCH₂S) and 7.09—7.42 (20 H, m, Ph) (Found: C, 68.8; H, 5.6. C₂₉H₂₈S₄ requires C, 69.0; H, 5.6%).

Table 3. Comparison of the catalytic activity of these sulfoxides and sulphone on two-phase displacement^a

$$\text{C}_8\text{H}_{17}\text{Br} + \text{KSCN} \xrightarrow[\text{Xylene}]{\text{Catalyst}} \text{C}_8\text{H}_{17}\text{SCN} + \text{KBr}$$

Catalyst	Time (h)	Yield (%) ^b
(1a)	40	0
(1b)	35	90
(1c)	31	95
(1d)	28	91
(1e)	40	0
(2)	40	76
(3)	40	20

^a C₈H₁₇Br (1 mmol), KSCN (5 mmol), catalyst (0.2 mmol), xylene (2 ml), at 100 °C. ^b By g.l.c. analysis.

2,6-Dithiaspiro[3.3]heptane (5).—To a solution of 1,3-dibromo-2,2-bis(bromomethyl)methane (31 g, 80 mmol) in ethanol (600 ml) was added Na₂S·9H₂O (48 g, 200 mmol) in water (100 ml), and the mixture was refluxed for 10 h. The solvent was removed under reduced pressure, the residue extracted with chloroform, and the extracts dried (MgSO₄). After removal of the solvent, the residue was purified by silica-gel column chromatography using hexane–benzene (1:1) as eluant or by distillation to give compound (5) (6.5 g, 61%), m.p. 31–32 °C (lit.,¹⁰ 31.5 °C); b.p. 70–72 °C at 1 mmHg; δ(CDCl₃) 3.28 (8 H, s, CH₂S).

3-(Bromomethyl)-3-(dodecylthiomethyl)thietane (6).—A solution of 2,6-dithiaspiro[3.3]heptane (5) (2.64 g, 20 mmol) and benzyl bromide (5.48 g, 22 mmol) in benzene–ethanol (1:1; 120 ml) was heated in a sealed tube at 160 °C for 24 h. After removal of the solvent, the residue was purified by silica-gel column chromatography using benzene–hexane (1:1) as eluant. A colourless liquid was obtained (3.8 g, 50%); ν_{max}(neat) 2920, 1610, 1420, and 1240 cm⁻¹; δ(CDCl₃) 0.88 (3 H, t, Me), 1.12–1.75 [20 H, m, (CH₂)₁₀], 2.63 (2 H, t, J 7 Hz, CH₂S), 3.00 (2 H, s, CCH₂S), 3.04 (4 H, s, CH₂S), and 3.80 (2 H, s, CH₂Br) (Found: C, 53.5; H, 8.8. C₁₇H₃₃BrS₂ requires C, 55.5; H, 8.7%).

3,3-Bis(dodecylthiomethyl)thietane (7).—A solution of compound (6) (2.7 g, 7 mmol), dodecanethiol (1.7 g, 8.4 mmol), and sodium metal (0.23 g, 10 mmol) in benzene–ethanol (1:1; 80 ml) was refluxed for 10 h. The mixture was concentrated, diluted with water, extracted with dichloromethane, and the extract dried (MgSO₄). After removal of the solvent, the title compound was purified to afford a colourless liquid (2.8 g, 80%) by silica-gel column chromatography using hexane–benzene (1:1) as eluant; ν_{max}(neat) 2900, 1620, and 1420 cm⁻¹; δ(CDCl₃) 0.88 (6 H, t, Me), 1.13–1.65 [20 H, m, (CH₂)₁₀], 2.55 (4 H, t, J 6.6 Hz, CH₂S), 2.91 (4 H, s, CH₂S), and 3.00 (4 H, s, CCH₂S) (Found: C, 69.2; H, 11.6. C₂₉H₅₈S₃ requires C, 69.25; H, 11.6%).

Tris(dodecylthiomethyl)(bromomethyl)methane (8).—A solution of the thietane (7) (1 g, 2 mmol) and dodecyl bromide (0.55 g, 2.2 mmol) in benzene–ethanol (20 ml, 1:1) was heated in a sealed tube at 130 °C for 8 h. The solvent was removed under reduced pressure and the residue purified to afford a colourless liquid (0.32 g, 32%) by silica-gel column chromatography using hexane–benzene (1:3) as eluant; ν_{max}(neat) 2900, 1450, 1410, 1270, and 830 cm⁻¹; δ(CDCl₃) 0.85 (9 H, t, Me), 1.07–1.62 [60 H, m, (CH₂)₁₀], 2.57 (6 H, t, J 7 Hz, CH₂S), 2.69 (6 H, s, CCH₂S), and 3.57 (2 H, s, CH₂Br) (Found: C, 65.2; H, 11.0. C₄₁H₈₃BrS₃ requires C, 65.5; H, 11.1%).

Table 4. Liquid–liquid two-phase alkylations catalysed by tetrakis-sulphoxide (1b)
$$\text{PhCH}_2\text{CN} + \text{RX} \xrightarrow[50\% \text{ aq. NaOH, r.t.}]{(1b)} \text{PhCH(R)CN} + \text{NaX}$$

Halide	Catalyst (mol %)	Time (h)	Product yield (%) ^a	
			mono	di
MeI	none	24	12	
MeI	2.0	20	87	3
MeI	2.0	28	92	5
MeI	1.0	24	60	4
EtBr	5.0	17	91	1
EtI	5.0	13	92	
Pr ⁱ	5.0	28	29	
Bu	5.0	28	84	

^a By g.l.c. analysis.

General Procedure for PTC Reactions.—Nucleophilic substitution reactions. The reactions were carried out in a two-necked reactor equipped with a condenser. A mixture of octyl bromide (1–4 mmol), nucleophile (e.g., KCN, KSCN, PhOK, or PhSK; 1–5 mmol), and sulphoxide [e.g., (1a), (1b), (1d), (1e), or (2); 0.04–0.2 mmol] or sulphone (3) in xylene (0.5–2 ml) was vigorously stirred at constant temperature. Small samples of the reaction mixture were withdrawn with a microsyringe at intervals and monitored by gas chromatography. When the reaction was complete, the yield of product was determined by g.l.c. analysis.

Alkylation. The reactions were carried out in a two-necked reactor. To a mixture of phenylacetonitrile (2 mmol), alkyl halide (e.g., methyl iodide, ethyl iodide, ethyl bromide, isopropyl bromide, or butyl bromide; 2.4 mmol), and the sulphoxide (1b) (0.02–0.1 mmol) was added 50% aqueous sodium hydroxide (5.0 mmol). The mixture was stirred vigorously at room temperature. Small samples of the reaction mixture were withdrawn with a microsyringe at intervals, quenched with dilute HCl, and extracted with dichloromethane; the extract was monitored by gas chromatography. When the reaction was complete, the yield of alkylated product was determined by g.l.c. analysis.

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