Reactions of Organic Anions; XCIV[1]. Catalytic Two-Phase Alkylation of Benzyl Sulfones and Sulfonamides

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We had previously reported that halo- and dihalomethyl sulfones[2] and sulfonamides[3] can be efficiently alkylated with mono- and dihaloalkanes in the presence of 50 % aqueous sodium hydroxide and tetraalkylammonium salts catalyst, refered to as a CTP system (catalytic two-phase system[4]). The CTP system was also recently used for the condensation of dimethyl sulfone[5] and alkyl aryl sulfones[6] with aldehydes. However, to our knowledge, alkylation of aryl alkyl sulfones in the presence of concentrated aqueous sodium hydroxide and tetraalkylammonium salt have not been reported.

The acidity of benzyl sulfones and *N*,*N*-dialkylsulfonamides should be similar to that of the halomethyl analogues, since the phenyl group stabilizes carbanions efficiently. One could therefore reasonable expect that benzyl sulfones and sulfonamides should be alkylated in the CTP system.

Known methods of alkylation of benzyl sulfones via the corresponding carbanions involves the use of alkali metal amides[7,8] or butyllithium[9]. The alkylation of benzylsulfonamides has not been reported to our knowledge.

We have indeed found that benzyl *p*-tolyl sulfone (**1a**) reacts with alkyl halides under CTP conditions. However, the reaction is rather sluggish. For example, when the sulfone and butyl bromide were stirred with 50 % aqueous sodium hydroxide and the catalyst tetrabutylammonium bromide at 60° for 3 h about one third of the starting sulfone remained unchanged. On the other hand, the process is accelerated considerably by the addition of small amounts of hexamethylphosphoric triamide. Therefore, further experiments were carried out with this additive. Under these conditions the alkylation of benzyl sulfones **1a**, **d–g**, and *N*,*N*-dialkylbenzylsulfonamides **1b**, **c**, **h**, proceeded smothly, yielding the expected alkylation products **3** as summarized in Table.

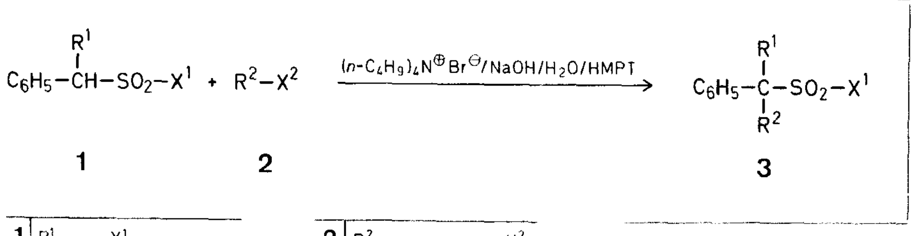
The starting compounds **1a–c** contain two acidic hydrogen atoms in the active methylene group. Thus they could be dialkylated. In fact dialkylation often interfers with preparation of monoalkylated derivatives from C—H acids containing methylene groups; for example as in the cases of phenylacetonitrile[10,11] or cyanoacetate[11]. However, dialkylation of **1a–c** was neglegible and the monoalkylated products were obtained selectively even with such reactive alkylating agents as benzyl chloride (**2d**) or allyl bromide (**2c**).

Nevertheless, it was possible to introduce the second alkyl substituent (Table). Obviously, there is a considerably difference in the rates of mono- and dialkylation processes.

Alkylation of **1a** with 1,4-dibromobutane (**2e**) resulted in the formation of the corresponding cyclopentane derivative **3ae**; while with ethylene dibromide the only observed process was elimination of hydrogen bromide to give vinyl bromide.

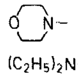
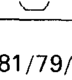
When the benzyl sulfone or sulfonamide contain an activating substituent, such as phenyl or halogen as in the cases of **1e–h**, the alkylation proceeded very easy.

The structures of products were established on the basis of standard analytical data; ^{1}H-N.M.R. spectra and microanalyses and by correlation to properties previously reported in the literature.



$$C_6H_5-\overset{R^1}{CH}-SO_2-X^1 + R^2-X^2 \xrightarrow{(n\text{-}C_4H_9)_4N^{\oplus}Br^{\ominus}/NaOH/H_2O/HMPT} C_6H_5-\underset{R^2}{\overset{R^1}{C}}-SO_2-X^1$$

1 **2** **3**

1	R¹	X¹
a	H	4-$H_3C-C_6H_4$–
b	H	
c	H	$(C_2H_5)_2N$–
d	CH_3	4-$H_3C-C_6H_4$–
e	C_6H_5	H_3C–
f	F	C_6H_5–
g	Cl	C_6H_5–
h	Cl	

2	R²	X²
a	C_2H_5	Br
b	*n*-C_4H_9	Br
c	$H_2C=CH-CH_2$	Br
d	$C_6H_5-CH_2$	Cl
e	Br–$(CH_2)_4$–	Br
f	*n*-C_3H_7	Br
g	CH_3	Br

Our results illustrate that a slightly modificated CTP system can be efficiently employed for alkylation of benzyl sulfones and sulfonamides.

The following starting sulfones and sulfonamides were prepared by literature methods **1a**[12], **1b**[13], **1c**[14], **1e**[15], **1f**[16], **1g**[17]; **1d** was prepared by the reaction of 1-phenylethyl bromide with sodium *p*-toluenesulfinate; synthesis of **1h** had not been previously reported.

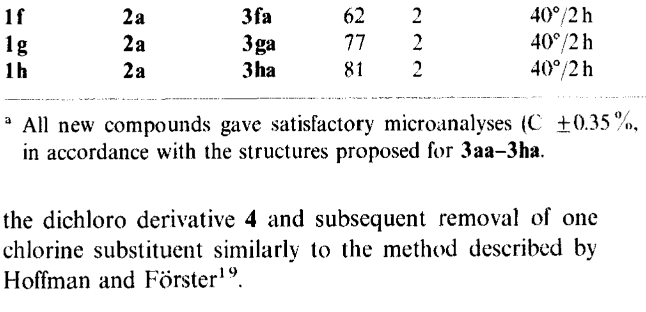
We demonstrated that **1h** can be prepared by dichlorination of **1b** with tetrachloromethane[18] under CTP conditions to

Table. α-Alkylated Benzyl Sulfones and Sulfonamides **3**

Substrate **1**	Alkylating agent **2**	Product **3**	Yield [%]	Ratio of R^2—X^2 : **1**	Reaction conditions temperature/time	m.p. (solvent)	Molecular formula[a] or Lit. m.p.
1a	**2a**	**3aa**	80	2	35°/5 h	139.5–141.5° (CH_3OH)	$C_{16}H_{18}O_2S$ (274.4)
1a	**2b**	**3ab**	84	1.2	60°/3.5 h	132–133.5° (CH_3OH)	$C_{18}H_{22}O_2S$ (302.4)
1a	**2c**	**3ac**	63	1.1	60°/2.5 h	126–127° (CH_3OH)	$C_{17}H_{18}O_2S$ (286.3)
1a	**2d**	**3ad**	90	1.4	60°/2.5 h	183–184° (C_2H_5OH)	180–181°[8]
1a	**2e**	**3ae**	56	1.2	60°/5 h	103–105° (CH_3OH)	$C_{18}H_{20}O_2S$ (300.4)
1b	**2a**	**3ba**	61	2	40°/5 h	84–85° (C_2H_5OH)	$C_{13}H_{19}NO_3S$ (269.4)
1b	**2f**	**3bf**	64	2	50°/5 h	88–89° (C_2H_5OH)	$C_{14}H_{21}NO_3S$ (283.4)
1b	**2c**	**3bc**	71	1.5	50°/3 h	87–88° (C_2H_5OH)	$C_{14}H_{19}NO_3S$ (281.4)
1c	**2d**	**3cd**	66	1.1	50°/4 h	69–70° (CH_3OH)	$C_{18}H_{23}NO_2S$ (317.4)
1d	**2g**	**3dg**	66	8	60°/5 h	144–146° (CH_3OH)	144–145°[21]
1d	**2d**	**3dd**	63	1.2	60°/2 h	116–118° (CH_3OH)	$C_{22}H_{22}O_2S$ (350.5)
1e	**2d**	**3ed**	62	1.1	50°/2 h	108–110° (AcOH)	$C_{21}H_{20}O_2S$ (337.5)
1f	**2a**	**3fa**	62	2	40°/2 h	68–69° (CH_3OH)	$C_{15}H_{15}FO_2S$ (278.4)
1g	**2a**	**3ga**	77	2	40°/2 h	84–85.5° (C_2H_5OH)	$C_{15}H_{15}ClO_2S$ (294.8)
1h	**2a**	**3ha**	81	2	40°/2 h	93–94° (C_2H_5OH)	$C_{13}H_{18}ClNO_3S$ (303.8)

[a] All new compounds gave satisfactory microanalyses (C ±0.35%, H ±0.15%, N ±0.25%, S ±0.30%); ^{1}H-N.M.R. spectra were in accordance with the structures proposed for **3aa–3ha**.

the dichloro derivative **4** and subsequent removal of one chlorine substituent similarly to the method described by Hoffman and Förster[19].



α,α-Dichloro-α-toluenesulfomorpholide (4):

A solution of **1b** (4.8 g, 0.02 mol) in tetrachloromethane (50 ml), 50% sodium hydroxide (20 ml), and triethylbenzylammonium chloride (0.2 g) are stirred at 30–35° for 3 h. The mixture is poured into water (100 ml) and the organic phase is separated. The aqueous phase is extracted with trichloromethane (50 ml) and the combined organic extracts are washed with water, then dried with magnesium sulfate. The solvent is evaporated and the residue recrystallized from ethanol to give **4**; yield: 5.8 g (94%); m.p. 92–94°.

$C_{11}H_{13}Cl_2NO_3S$	calc.	C 42.59	H 4.22	Cl 22.86	N 4.52	S 10.34
(310.2)	found	42.8	4.30	22.7	4.50	10.57

α-Chloro-α-toluenesulfomorpholide (1h):

Compound **4** (3.1 g, 0.01 mol), hexamethylphosphorous triamide (1.65 g, 0.01 mol), methanol (1 ml), and dimethylformamide (10 ml) are heated at 40° for 1.5 h. The mixture is poured into water (100 ml) and extracted with benzene (3 × 30 ml). The organic extracts are washed with 5% hydrochloric acid (3 × 50 ml), water, and then dried with magnesium sulfate. The solvent is evaporated and the residue recrystallized from ethanol to give **1h**; yield: 1.6 g (58%); m.p. 74–75°.

$C_{11}H_{14}ClNO_3S$	calc.	C 47.91	H 5.12	Cl 12.86	N 5.08	S 11.63
(275.8)	found	50.0	5.11	12.8	5.00	11.6

^{1}H-N.M.R. ($CDCl_3$): $\delta = 8.0$–7.4 (m, 5H_{arom}); 5.67 (s, 1H_{C-H}); 3.65–3.55 (m, 4H_{morph}); 3.30–3.15 ppm (m, 4H_{morph}).

1-Phenylethyl *p*-Tolyl Sulfone (1d):

To sodium *p*-toluenesulfinate (37.4 g, 0.21 mol) in dimethyl sulfoxide (100 ml), 1-phenylethyl bromide (37.0 g, 0.20 mol) is added dropwise at 45–50°. The reaction mixture is heated at 70–80° for 5 h, cooled, poured into water (800 ml), and the solid is filtered. The product is washed with water and recrystallized from methanol to give **1d**; yield: 30.2 g (58%); m.p. 133–135° (Lit. [20] m.p. 133–134°).

Alkylation of Benzyl Sulfones and Sulfonamides (1a–h) with Alkyl Halides 2; General Procedure:

The sulfone or sulfonamide **1a–h** (0.01 mol), alkyl halide **2** (0.011–0.02 mol), tetrabutylammonium bromide (0.2 g), hexamethylphosphoric triamide (1 ml), and 50% aqueous sodium hydroxide (15 ml) are stirred at 35–60° for 2–5 h (Table). The mixture is diluted with water (50 ml), and the products are filtered or extracted with benzene (3 × 25 ml). The solids or organic extracts are washed with water, the solvent evaporated, and the residues recrystallized (Table).

Modifications: Methyl bromide (**2g**; 7.8 g, 0.08 m) is bubbled through the mixture at 35° for 1 h and at 60° for 4 h. In the case of 1,4-dibromobutane (**2e**), 30 ml of 50% aqueous sodium hydroxide is used.

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Chlorination of sulfones with CCl_4 in the presence of KOH in *t*-butyl alcohol was reported by C. Y. Meyers, W. S. Matthews, L. L. Ho, V. M. Kolb, T. E. Parady, *Catalysis in Organic Syntheses 1977*, G. V. Smith, Ed., Academic Press, New York, 1978, p. 197.

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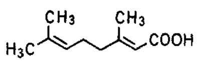
Errata and Addenda 1979

M. Contento, D. Savoia, C. Trombini, A. Umani-Ronchi, *Synthesis* **1979** (1), 30-32;
The structure for compound **3c** (p. 31, Table 1) should be:

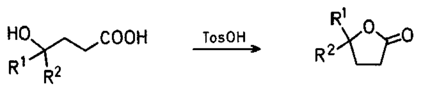


A. Mignot, H. Moskowitz, M. Miocque, *Synthesis* **1979** (1), 52-53;
The correct name for Tetramisole® should be 6-phenyl-2,3,5,6-tetrahydroimidazolo[2,1-*b*]thiazole.

A. N. Pudovik, I. N. Konovalova, *Synthesis* **1979** (2), 81-96;
The first sentence of the experimental procedure on p. 96 should read as follows:
Dialkyl phosphite or phosphorothioate (0.01 mol) is added to the azo compound (0.01 mol) in ether (10 ml).

In Table 13 (p. 96) the entries R^2 for compounds **63b** and **63c** should be $4\text{-}H_3C{-}C_6H_4$ and $4\text{-}O_2N{-}C_6H_4$, respectively.

Abstract 5422, *Synthesis* **1979** (2), 160;
The formula scheme for the conversion **3**→**4** should be:



3 **4**

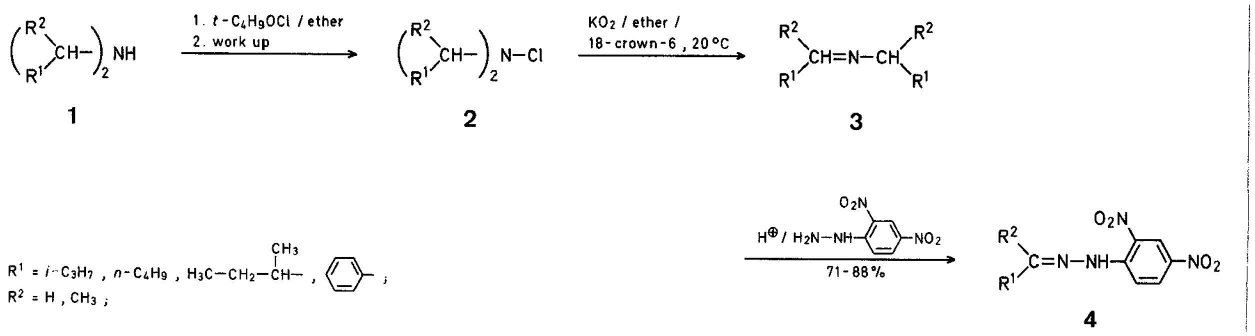
N. Blažević, D. Kolbah, B. Belin, V. Šunjić, F. Kajfež, *Synthesis* **1979** (3), 161-176;
Compounds **78a-e** (p. 173) should be named:
9-chloro-10b-phenyl-2,3,5,6-tetrahydro-10b*H*-[1,3]oxazolo[3,2-*c*]-quinazolines.

K. Herrmann, G. Simchen, *Synthesis* **1979** (3), 204-205
The lines 10 to 17 of the text (p. 204) should read as follows:

sche Acrylcyanide zugänglich[1,5,6]. Aliphatische Carbonsäure-halogenide hingegen setzen sich mit Tetraethylammoniumcyanid zu Acyloxymalodinitrilen („dimere Acrylcyanide") um, wofür auch die hohe Cyanidionen-Konzentration verantwortlich ist[1]. Die Reaktion aliphatischer Säurechloride (**2**) mit Cyanotrimethylsilan (**1**)[7-10] sollte deshalb eine geeignete Synthesenmethode für 2-Oxo-alkannitrile (aliphatische Acrylcyanide, **3**) darstellen. Bisher konnte allerdings nur

L. Caglioti, F. Gasparrini, D. Misiti, G. Palmieri, *Synthesis* **1979** (3), 207-208;
The italic sub-headings in the Table (p. 208) should be *From tosylhydrazones, From* N*-methyl-*N*-tosylhydrazones,* and *From 2,4-dinitrophenylhydrazones.*

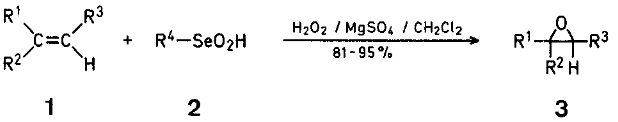
Abstract 5440, *Synthesis* **1979** (3), 238;
The formula scheme for the conversion **1**→**4** should be as follows:



C. Venturello, R. D'Aloisio, *Synthesis* **1979** (4), 283-287;
Entries 3 and 4 of the Mass spectrum column of Table 1 (p. 284) should be 284 (^{35}Cl) and 318 (^{35}Cl), respectively.

J. S. Davidson, *Synthesis* **1979** (5); 359-361;
Compounds **6** (p. 360) should be named:
3,4-diaryl-5-oxo-3,4-dihydro-1*H*-1,2,4-triazoles.

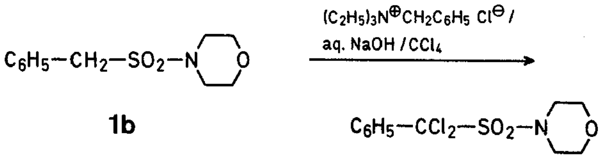
Abstracts 5494, *Synthesis* **1979** (5), 399;
The formula scheme for the conversion **1**→**3** should be as follows:



1 **2** **3**

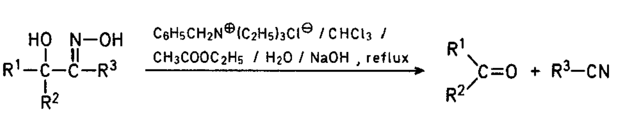
C. Skötsch, I. Kohlmeyer, E. Breitmaier, *Synthesis* **1979** (6), 449-452;
The name for compound **10a** should be:
3-Methyl-5,6,7,8-tetrahydroisoxazolo[5,4-*b*]chinolin.

J. Goliński, A. Jończyk, M. Mąkosza, *Synthesis* **1979** (6), 461-463;
The formula scheme for the conversion **1b**→**4** (p. 462) should be as follows:



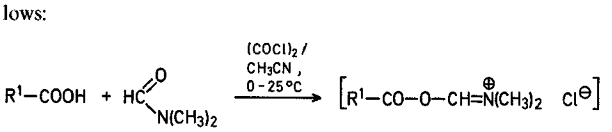
1b **4**

Abstract 5520, *Synthesis* **1979** (6), 479;
The formula scheme should be as follows:



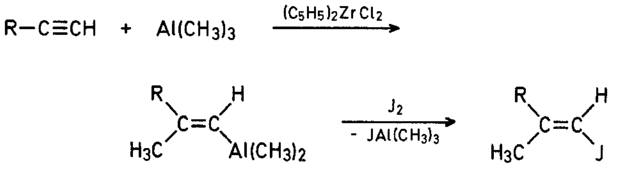
1 **2** **3**

Abstract 5521, *Synthesis* **1979** (6), 479;
The formula scheme for the conversion **1**→**2** should be as follows:



1 **2**

E. Negishi, D. E. Van Horn, A. O. King, N. Okukado, *Synthesis* **1979** (7), 501-502;
For clarity, the following formula scheme should be added:



A. McKillop, D. W. Young, *Synthesis* **1979** (7), 481-500;
The heading for Table 24 (p. 496) should be:

Table 24. Oxidation of Alcohols to Aldehydes and Ketones using Potassium Permanganate/Molecular Sieves[172].