PREPARATION AND ALKYLATION REACTIONS OF 4-NITROBENZYL AND 5-NITROFURFURYL SULFONES

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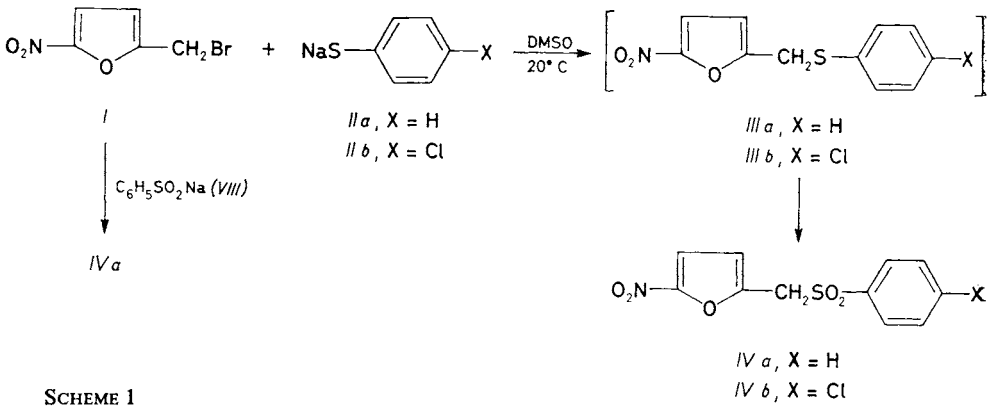
Substitution reaction of 5-nitrofurfuryl bromide (*I*) with sodium thiophenoxide and 4-chlorothiophenoxide in dimethyl sulfoxide at 20°C and oxidation with dimethyl sulfoxide in the reaction medium afforded 5-nitrofurfuryl phenyl sulfone (*IVa*) and 5-nitrofurfuryl 4-chlorophenyl sulfone (*IVb*), respectively. Similarly, 4-nitrobenzyl bromide reacted with sodium 4-chlorothiophenoxide to give 4-nitrobenzyl 4-chlorophenyl sulfone (*VII*) and with sodium phenylsulfinate to afford 4-nitrobenzyl phenyl sulfone (*IX*). The sulfide intermediates were not isolated. The sulfone *IX* was used as substrate in alkylation reactions, catalysed by polyethylene glycols. Derivatives *IVb* and *VII* were identified by IR and mass spectroscopy, alkylation products by ^{1}H NMR spectroscopy.

In our previous communications we studied S_N or S_{RN} reactions in the 5-nitrofurfuryl series[1-5]. The course of reactions proceeding by S_N or S_{RN} mechanism has been discussed in many papers (see e.g. refs[6-10]).

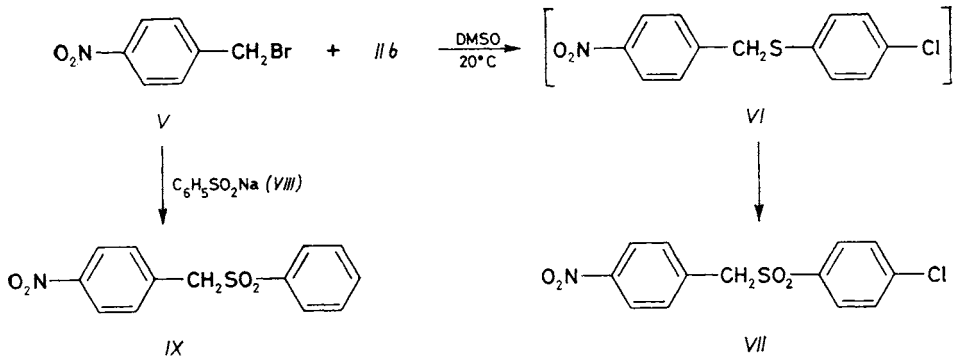
In our present study we treated 5-nitrofurfuryl bromide (*I*) with sodium thiophenoxide (*IIa*) or 4-chlorothiophenoxide (*IIb*) in dimethyl sulfoxide at 20°C and obtained directly the products of oxidation with dimethyl sulfoxide, i.e. 5-nitrofurfuryl phenyl sulfone (*IVa*) and 5-nitrofurfuryl 4-chlorophenyl sulfone (*IVb*), respecti-



SCHEME 1

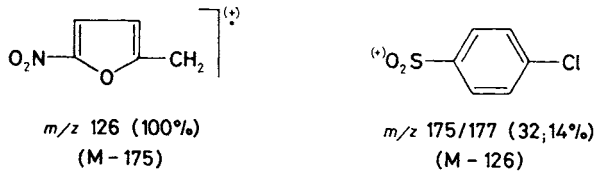
vely (Scheme 1). The sulfone *IVa* was also obtained (in 90–100% yield) by reaction of bromide *I* with sodium phenylsulfinate (*VIII*) in dimethyl sulfoxide at 20°C.

Analogously to the bromide *I*, 4-nitrobenzyl bromide (*V*) reacted with *IIb* under the same conditions to give 4-nitrobenzyl 4-chlorophenyl sulfone (*VII*) (Scheme 2).



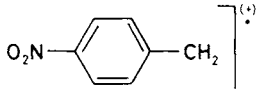
SCHEME 2

Reaction of bromide *V* with sodium phenylsulfinate (*VIII*) in dimethyl sulfoxide or dimethylformamide afforded 4-nitrobenzyl phenyl sulfone (*IX*) in 80–90% yield. The sulfide intermediates *IIIa*, *IIIb*, and *VI* were not isolated. Sulfones *IVa* and *IVb* have been already prepared by S_N reaction of the corresponding sulfinates with bromide *I* in ethanol[11]. Toxicity of sulfone *VII* was tested in ref.[12].

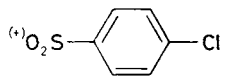


Mass spectrum of the sulfone *IVb* exhibited two principal fragment ions, in addition to the molecular ion $M^{+\cdot}$, *m/z* 301/303 (4; 2%). The fragment *m/z* 126 loses $NO_2^{\cdot}$ to give an ion *m/z* 80 (14%), the fragment *m/z* 175/177 splits off SO_2 under formation of ion *m/z* 111/113 (26; 11%). The mass spectrum further exhibited ions arising from the molecular ion by fragmentation of the NO_2 group[13] (M–16 (*m/z* 285/287), M–30 (*m/z* 271/273), and M–46 (*m/z* 255/257)). Mass spectrum of the sulfone *VII* contained, besides the molecular ion $M^{+\cdot}$ *m/z* 311/313 (15; 7%), fragment ions analogous to those formed from *IVb*. The ion *m/z* 136 loses $-NO_2^{\cdot}$, $-NO^{\cdot}$ or $-O$, affording the respective fragments *m/z* 90 (21%), 106 (46%), and 120

(5%), the fragment ion m/z 175/177 splits off SO_2 to give the ion m/z 111/113 (13; 4%). Fragmentation of the NO_2 group in the $M^{+\cdot}$ ion was not observed.



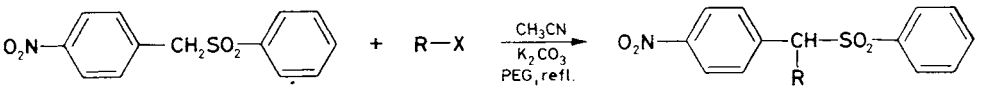
m/z 136 (100%)
(M - 175)



m/z 175/177 (5:2%)
(M - 136)

Because of the typical colouration of the solutions during the preparation of derivatives *IVa*, *IVb*, and *VII* we assume that these reactions are $S_{RN}1$ substitutions, contrary to direct preparations of sulfones *IVa* and *IX* in dimethylformamide or dimethyl sulfoxide, proceeding by S_N reaction without any colour effects.

We investigated 4-nitrobenzyl phenyl sulfone (*IX*) as a substrate for alkylation reactions, catalyzed by polyethylene glycols (PEG) (Scheme 3). Makosza and Tyrala[14]



X, R = $CH_2CH_2CH_3$
XI, R = $(CH_2)_3CH_3$

SCHEME 3

described analogous alkylation reactions, using 18-crown-6 as catalyst. It has been found that complexation properties of crown ethers and PEGs (refs[15-20]), are comparable. Their use as catalysts for S_N reactions has been suggested already in 1965 by Ugelstad[21] who studied alkylations of sodium and potassium phenoxide, using polyethyleneglycol dimethyl ethers as solvents. Substitution reactions of non-activated aryl halides with mercaptides in the presence of various PEGs were studied by Pastor[22]. The new synthesis[23] of PEGs contributes to their extended utilization as catalysts and solvents.

Our investigations have also confirmed that PEGs are good catalysts for alkylation reactions which otherwise do not take place. We obtained good yields of racemic alkylation products *X* and *XI* (Scheme 3). Of the PEGs tested, PEG-400 proved to be the best and gave well reproducible results. Contrary to the published data[14], longer reaction time is necessary to achieve higher yields. Alkylation reaction of 5-nitrofurfuryl phenyl sulfone (*IVa*) under the given conditions led to an undefined mixture of products. The ^1H NMR spectra of derivatives *X* and *XI* exhibited characteristic chemical shifts. As follows from the literature[24,25], the compounds

represent systems with nonequivalent protons in the —CH_2—R group vicinal to the chiral center.

EXPERIMENTAL

The melting points were determined on a Kofler block and are uncorrected. IR spectra were recorded on a UR-20 (Zeiss, Jena) spectrophotometer, mass spectra on an AEI MS 902 S spectrometer. ^{1}H NMR spectra were obtained with a Varian VXR 300 instrument (300 MHz, FT mode) at 28°C in hexadeuterodimethyl sulfoxide with tetramethylsilane as internal standard. 5-Nitrofurfuryl bromide (*I*) was prepared from furfuryl alcohol according to ref.[26], 4-nitrobenzyl bromide and PEG-400 were commercial products.

5-Nitrofurfuryl Phenyl Sulfone (*IVa*)

A) Bromide *I* (1·0 g; 0·005 mol) was added at 20°C to a stirred solution of sodium thiophenoxide (*IIa*; 0·7 g; 0·005 mol) in dimethyl sulfoxide (30 ml). The deep wine-red colour of the solution changed within 3 h to light yellow and after 24 h the reaction mixture was poured into water. The precipitate was filtered and crystallized from acetone to yield colourless crystals of *IVa* (0·6 g; 46·5%), m.p. 195—196°C (reported[27] m.p. 196—197°C).

B) Bromide *I* (1·0 g; 0·005 mol) was added at 20°C under stirring to a solution of *VIII* (1·0 g; 0·005 mol) in dimethyl sulfoxide (30 ml) or dimethylformamide (30 ml). After 2—4 h the reaction mixture was poured into water, the precipitate was collected, washed with water and dried to yield *IVa*, m. p. 195°C (1·33 g; 100%).

5-Nitrofurfuryl 4-Chlorophenyl Sulfone (*IVb*)

A solution of bromide *I* (1·0 g; 0·005 mol) in dimethyl sulfoxide (20 ml) was added under nitrogen in the course of 30 min to a solution of thiophenoxide *IIb* (0·83 g; 0·005 mol) in dimethyl sulfoxide (50 ml). The originally brick-red colour changed to wine-red and after 1 h to yellow. After 24 h the solution was poured into water (200 ml) and the formed precipitate was taken up in ethyl acetate (4 × 30 ml). Crystallization afforded 400 mg (27%) of *IVb*, m.p. 209—210°C (reported[11] m.p. 210—211°C). For $C_{11}H_8ClNO_5S$ (301·6) calculated: 43·80% C, 4·67% N; found: 43·41% C, 4·57% N. IR spectrum (KBr), $\tilde{\nu}_{max}$, cm^{-1}: 1 500 $(NO_2)_{as}$, 1 360 $(NO_2)_s$, 1 315 $(SO_2)_{as}$, 1 157 $(SO_2)_s$, 1 030 (furan C—O—C), 973 (furan C—H). Mass spectrum *m/z* (rel. intensity, %): 303 (2) M + 2, 301 (4) $M^{(+\cdot)}$, 177 (14), 175 (32), 126 (100), 113 (11), 11 (26), 80 (14).

4-Nitrobenzyl 4-Chlorophenyl Sulfone (*VII*)

Bromide *V* (2·16 g; 0·01 mol) and thiophenoxide *IIb* (1·66 g; 0·01 mol) were dissolved under vigorous stirring at 20°C in dimethyl sulfoxide (30 ml). The wine-red solution decolourized during 3 h. After 24 h the reaction mixture was poured into water (150 ml) and the formed precipitate was extracted with ethyl acetate, the solution was dried and treated with charcoal. Crystallization afforded colourless crystals of *VII* (1·58 g; 51%), m.p. 178—179°C (reported[12] m.p. 175—176°C). For $C_{13}H_{10}ClNO_4$ (311·7) calculated: 11·37% Cl, 4·49% N; found: 11·41% Cl, 4·50% N. IR spectrum (KBr), $\tilde{\nu}_{max}$, cm^{-1}: 1 520 $(NO_2)_{as}$, 1 350 $(NO_2)_s$, 1 309 $(SO_2)_{as}$, 1 145 $(SO_2)_s$. Mass spectrum *m/z* (rel. intensity, %): 313 (7) M + 2, 312 (3) M + 1, 311 (15) $M^{(+\cdot)}$, 177 (2), 175 (5), 136 (100), 120 (5), 113 (4), 111 (13), 106 (46), 90 (21).

1-(4-Nitrophenyl)butyl Phenyl Sulfone (*X*)

Potassium carbonate (5·8 g) and PEG-400 (1 g) were added to a stirred solution of sulfone *IX* (1·37 g; 5 mmol) in acetonitrile (50 ml). The reaction mixture turned red. After 10 min, propyl bromide (3 g) was added, the mixture was refluxed for 18 h, the solvent was evaporated in vacuo and the residue was extracted with benzene–acetone (9 : 1). The extract was separated on a column of alumina (Brockmann II) in the same solvent mixture. The combined fractions were further purified by treatment with charcoal, the solvents were evaporated and the product was crystallized from n-hexane, affording 1·32 g (83%) of *X*, m.p. 125–126°C. For $C_{16}H_{17}NO_4S$ (319·4) 5·36% H, 4·38% N; 10·04% S; found: 60·01% C, 5·28% H, 4·30% N, 10·10% S. ^{1}H NMR spectrum (hexadeuterodimethyl sulfoxide: 8·15 d, 2 H (H-3, $J(2, 3) = 8·4$); 7·53 d, 2 H (H-2); 7·72 to 7·57 m, 5 H (H–phenyl); 4·85 m, 1 H (—CH—); 2·09 m, 2 H ($—CH_2—$); 1·10 m, 2 H ($—CH_2—$); 0·79 t, 3 H ($—CH_3$).

1-(4-Nitrophenyl)pentyl Phenyl Sulfone (*XI*)

PEG-400 (1·5 g) was added to a stirred mixture of sulfone *IX* (1·37 g; 5 mmol), potassium carbonate (5·8 g), n-butyl bromide (3·0 g) and acetonitrile (50 ml). The mixture turned deep violet-red. After reflux for 28 h the solvent was evaporated, the residue was extracted with tetrachloromethane and the extract was chromatographed on a column of alumina (Brockman II) in benzene–acetone (9 : 1). The first fractions afforded 1·60 g (96·4%) of white crystalline *XI*, m.p. 124–125°C (reported[14] m.p. 120°C). For $C_{17}H_{19}NO_4S$ (333·4) calculated: 61·24% C, 5·74% H, 4·20% N, 9·62% S; found: 61·18% C, 5·67% H, 4·25% N, 9·72% S. ^{1}H NMR spectrum (hexadeuterodimethyl sulfoxide: 8·15 d, 2 H (H-3, $J(2, 3) = 8·85$); 7·53 d, 2 H (H-2); 7·72 to 7·57 m, 5 H (H–phenyl); 4·84 m, 1 H (—CH—); 2·11 m, 2 H ($—CH_2—$); 1·12 m, 4 H ($—CH_2CH_2—$); 0·72 t, 3 H ($—CH_3$).

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