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SYNTHESIS OF α-CHLOROALKYL ARYL ETHERS FROM PHENOLS

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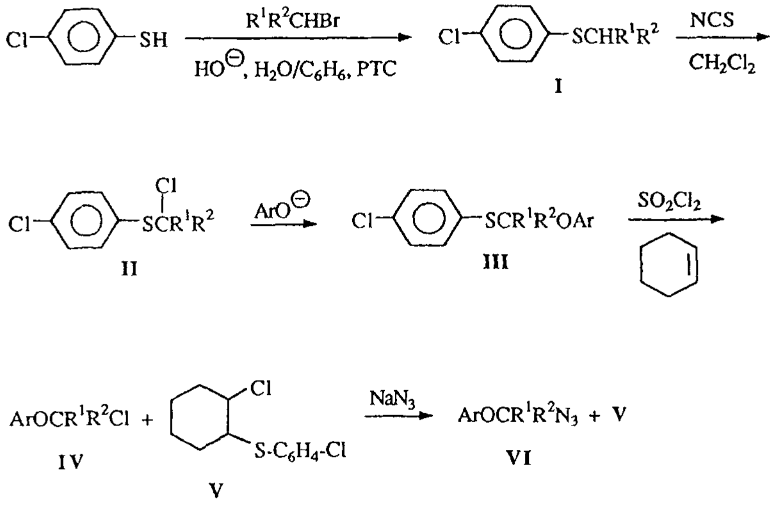
ABSTRACT: α-Chloroalkyl aryl ethers has been obtained in good yields from phenols and aryl α-chloroalkyl sulfides.

Aryloxymethyl halides are interesting intermediates in organic synthesis,[1] which can be obtained according to Benneche and Undheim's procedure.[2] On treatment with bromine or sulfuryl chloride in CH_2Cl_2, O,S-acetals are selectively cleaved at room temperature to give halomethyl aryl ethers and sulfenyl halides. Only one α-alkylated compound, α-chloroethyl phenyl ether, has been described using this method. It was prepared with some difficulties and 33 % yield based on phenol. The same compound was also obtained (no yield mentioned) from phenol and vinyl acetate through an addition ($Hg(OAc)_2$, H_2SO_4 cat., 25°C) - elimination (20 % NaOH, 0°C) sequence.[3]

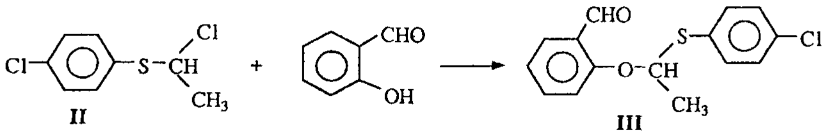
We needed various aryloxy alkyl halides and examined the efficiency of their synthesis with the O,S-acetals method.



Scheme 1 : Preparation of aryloxy alkyl halides **IV** and characterization by their azides **VI**

Table I : Aryl alkyl sulfides (**I**) and aryl α-chloroalkyl sulfides (**II**)

		I (a)		**II** (b)
R1	R2	Time (h)	Temp. (°C)	^{1}H NMR (δ, ppm)
CH_3	H	1	25	1.8 (d, 3 H); 5.3 (q, 1 H); 7.1-7.7 (m, 4 H)
C_2H_5	H	1	25	1.2 (t, 3 H); 1.7-2.3 (m, 2 H); 5.1 (t, 1 H); 7.1-7.7 (m, 4 H)
CH_3	CH_3	6	40	1.9 (s, 6 H); 7.1-7.7 (m, 4 H)
$CH(CH_3)_2$	H	5	40	1.1 (d, 6 H); 1.9-2.6 (m, 1 H); 5.1 (d, 1 H); 7.1-7.6 (m, 4 H)
n-C_7H_{15}	H	2	25	0.7-2.2 (m, 15 H); 5.1 (t, 1 H); 7.2-7.8 (m, 4 H)
n-$C_{11}H_{23}$	H	2	25	0.7-2.1 (m, 23 H); 5.1 (t, 1 H); 7.2-7.8 (m, 4 H)



50 mM

tBuOK (1 eq.), DMF (60 ml), 35 h, 80°C	80 %
tBuOK (1 eq.), DMF (60 ml), NaI (1 eq.), 6 h, 80°C	80 %
50 % NaOH (20 g), C_6H_6 (60 ml), Bu_4NHSO_4 (0.1 eq.), 5 h, reflux	87 %

Scheme 2 : Representative yields and conditions for O,S-acetals synthesis

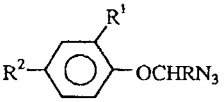
Sulfides I[4] and α-chlorosulfides II[5] were readily and quantitatively prepared (Table I). It will be noted that N-chlorosuccinimide (NCS) in CCl_4 converts sulfides containing β-hydrogen atoms into the α-chlorinated derivatives without elimination.

The reaction in DMF between potassium phenolates and aryl α-chloroalkyl sulfides[2] proved difficult. Long reaction times at 80°C (20-40 h) were required. The reactivity was enhanced by addition of 1 eq. NaI or by using phase transfer catalysis which presented a more convenient procedure (Scheme 2).

Except from **II** ($R^1 = R^2 = CH_3$) where elimination occured, pure O,S-acetals were obtained in 70-90 % yields after washing the organic phase with water, evaporation, and silica gel column chromatography. The ^1H NMR spectra of compounds **III** showed a characteristic signal at 5.3 ppm.

Since the aryloxy alkyl chlorides **IV** were quite unstable (elimination of HCl), we converted them into azides **VI** immediately after their preparation. The azides (table II) were characterized by microanalyses, IR (νN_3: 2100 cm^{-1}), ^1H NMR ($O\text{-}CHRN_3$: 4.9-5.2 ppm).

Table II : Aryloxy alkyl azides prepared **IV**



R	CH_3	CH_3	C_2H_5	C_7H_{15}	CH_3	C_2H_5	C_7H_{15}	CH_3	C_2H_5	CH_3	C_2H_5	C_7H_{15}
R^1	H	CH_3	CH_3	CH_3	CH_3	C_2H_5	C_7H_{15}	CHO	C_2H_5	H	C_2H_5	C_7H_{15}
R^2	H	H	H	H	Cl	C_2H_5	C_7H_{15}	H	C_2H_5	CHO	C_2H_5	C_7H_{15}
Yield %	80	80	70	75	76	80	78	69	65	85	80	80

EXPERIMENTAL[6]

General procedure for the preparation of aryl alkyl sulfides (I)

A mixture of H_2O (50 ml), C_6H_6 (50 ml), NaOH (75 mM), 4-chlorothiophenol (45 mM), the alkylbromide (45 mM) and tricaprylmethylammonium chloride (0.1 g) was vigourously stirred. (The times and temperatures are indicated in Table I). The organic phase was separated, washed with water and dried over $MgSO_4$. The solvent was evaporated and the residual compound used without further purification.

General procedure for the preparation of α-chloroalkyl sulfides (II)

A solution of 45 mM of N-chlorosuccinimide and 45 mM of **I** in 50 ml of CH_2Cl_2 was stirred at room temperature for 40 hours. The mixture was then filtered over celite and the solvent evaporated.

General procedure for the conversion of aryloxy alkyl chlorides IV into azides VI

10 mM of the crude chloride containing the sulfurated by-product, 1.5 eq. NaN_3, 0.05 eq. Bu_4NBr and 5 ml H_2O were stirred at room temperature for 0.5 h.

After extraction with CH_2Cl_2, the organic phase was washed with water, dried over $MgSO_4$ and evaporated. The azides were purified by chromatography on silica gel.

REFERENCES AND NOTES:

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6. ^1H Spectra were recorded at 80 MHz with Bruker AW-80 in CCl_4 using TMS as internal standard. IR Spectra were recorded with a Perkin Elmer 580 spectrometer.

7. We would like to thank Dr. A. O'Sullivan (Ciba Geigy) for his help.

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