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SYNTHESIS OF α-CHLOROALKYL ARYL ETHERS FROM PHENOLS

Bernard Loubinoux*, Raphaël Schneider

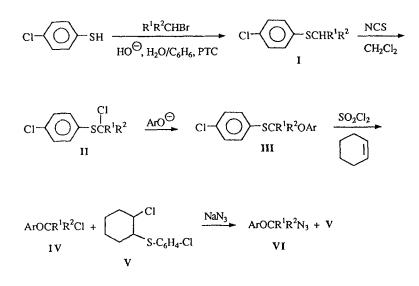
Laboratoire de Chimie Organique 4, Université de Nancy I, Faculté des Sciences, BP 239, 54506 Vandoeuvre-les-Nancy (France)

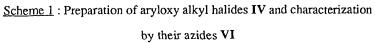
ABSTRACT: α -Chloroalkyl aryl ethers has been obtained in good yields from phenols and aryl α -chloroalkyl sulfides.

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 CH₂Cl₂, 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, H₂SO₄ cat., 25°C) - elimination

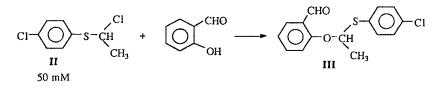
(20 % NaOH, 0°C) sequence.3

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





·	<u> </u>	I (a)		II (b)
R1	R2	Time (h)	Temp. (°C)	¹ H NMR (δ, ppm)
CH3	H	1	25	1.8 (d, 3 H); 5.3 (q, 1 H); 7.1-7.7 (m, 4 H)
C ₂ H ₅	Н	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)
CH3	CH3	6	40	1.9 (s, 6 H); 7.1-7.7 (m, 4 H)
CH(CH ₃) ₂	Н	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-C7H15	Н	2	25	0.7-2.2 (m, 15 H); 5.1 (t, 1 H); 7.2-7.8 (m, 4 H)
n-C11H23	Н	2	25	0.7-2.1 (m, 23 H); 5.1 (t, 1 H); 7.2-7.8 (m, 4 H)



tBuOK (1 cq.), DMF (60 ml), 35 h, 80°C	80 %
tBuOK (1 cq.), DMF (60 mi), NaI (1 cq.), 6 h, 80°C	80 %
50 % NaOH (20 g), C6H6 (60 ml), Bu4NHSO4 (0.1 eq.), 5 h, reflux	87 %

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

Sulfides I⁴ and α -chlorosulfides II⁵ were readily and quantitatively prepared (Table I). It will be noted that N-chlorosuccinimide (NCS) in CCl4 converts sulfides containing β -hydrogen atoms into the α -chlorinated derivatives without elimination.

The reaction in DMF between potassium phenolates and aryl α -chloroalkyl sulfides² 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 (vN3: 2100 cm⁻¹), ¹H NMR (O-CHRN3: 4.9-5.2 ppm).

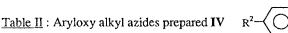
OCHRN₁

85

80

80

R'



CH3 CH3 C2H5 C7H15 CH3 C2H5 C7H15 CH3 C2H5 CH3 C2H5 C7H15 H CH3 CH3 CH3 CH3 C2H5 C7H15 CHO C2H5 Н C2H5 C7H15 Н Н Η Н C2H5 C7H15 C2H5 CHO C2H5 C7H15 CI н

78

69

65

EXPERIMENTAL6

80

70

75

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

76

80

A mixture of H₂O (50 ml), C₆H₆ (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 MgSO4. 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 CH₂Cl₂ 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. NaN3, 0.05 eq. Bu4NBr and 5 ml H2O were stirred at room temperature for 0.5 h.

R R¹

 R^2

%

Yield

80

After extraction with CH₂Cl₂, the organic phase was washed with water, dried over MgSO4 and evaporated. The azides were purified by chromatography on silica gel.

REFERENCES AND NOTES:

1. See for instance

Loubinoux, B.; Viriot-Chauveau, C.; Sinnes, J.L., Tetrahedron Letters, 1992, in press. Loubinoux, B.; Gérardin, P., Tetrahedron, 1991, <u>47</u>, 239-248; Tetrahedron Letters, 1991, <u>32</u>, 351-354. Loubinoux, B.; Colin, J.L.; Antonot-Colin, B., Tetrahedron, 1987, <u>43</u>, 93-100.

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- 4. Herriot, A.W.; Picker, D., Synthesis, 1975, 447-448.
- 5. Tuleen, D.L.; Stephens, T.B., Chemistry and Industry, 1966, 1555-1556.
- ¹H Spectra were recorded at 80 MHz with Bruker AW-80 in CCl4 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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