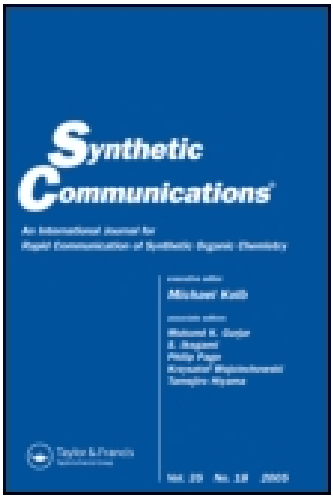

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A New High Yield Preparation of Benzyl Phenethyl Ethers by Phase Transfer Catalysis

Francisco López-Calahorra [a], Berta Ballart [a], Félix Hombrados [a] & Josep Martí [a]
[a] Departament de Química Orgànica, Universitat de Barcelona, Martí i Franquès, 1-11, E-08028, Barcelona, Spain
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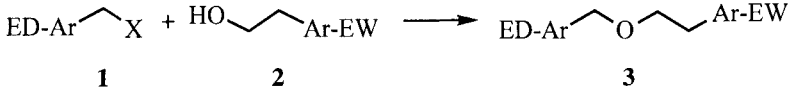
A NEW HIGH YIELD PREPARATION OF BENZYL PHENETHYL ETHERS BY PHASE TRANSFER CATALYSIS

Francisco López-Calahorra*, Berta Ballart, Félix Hombrados and Josep Martí*

Departament de Química Orgànica, Universitat de Barcelona,
Martí i Franquès, 1-11, E-08028 Barcelona, Spain.

Abstract: A phase transfer method to prepare benzyl phenethyl ethers from electron-rich benzyl halides and 2-phenylethanols supporting electron-withdrawing groups is described. The yields are excellent, in contrast to the very low ones previously reported for the same kind of compounds prepared by other ways.

In connection with research developed in our group on the synthesis of certain complex molecules we needed to prepare benzyl phenethyl ethers from electron-rich arylmethyl halides and 2-phenylethanols supporting electron withdrawing groups (figure).



1 **2** **3**

ED : Electron-donor group EW : Electron-withdrawing group

Figure

*To whom correspondence should be addressed.

Surprisingly, in the literature there are few examples of such an apparently easy reaction and the yields are, in general, low or very low. The synthesis of benzyl 2-phenylethyl ether by the classical Williamson method is described[1] from benzyl chloride, sodium phenylethoxide in toluene with a yield of only 30 % . Analogously, the reaction[2] between 2-(α-naphthyl)ethanol, α-chloromethylnaphthalene and NaH in THF produces [2-(α-naphthyl)ethyl] (α-naphthylmethyl) ether with 35% yield. Horita *et al*[3] prepared 4-methoxybenzyl 2-phenethyl ether from 4-methoxybenzyl chloride, 2-phenylethanol and NaH in DMF or DMSO with 85 % yield, but this product does not fulfil our requirements. When we applied Horita's method to the reaction between (4-cyanophenyl)ethanol and benzyl chloride, 4-cyanostyrene, the β-elimination compound, was the only product isolated[4] from the reaction mixture.

The previous data show that the presence of an electron-withdrawing group greatly enhances the acidity of the benzylic proton in β-position of the hydroxyl group, giving rise to an elimination process, in spite of the low leaving group character of the OH.

To solve this problem we have tried the phase transfer catalysis (PTC) method, previously successfully applied[5] to the preparation of unsymmetrical ethers. For instance, Fredmann and Dubois described[6] the preparation of benzyl butyl ether and benzyl allyl ether using tetrabutylammonium hydrogen sulfate as catalyst,

with 50 % (w/w) aqueous sodium hydroxide as base and an excess of benzyl bromide as reagent and solvent.

We report here that the title compounds - benzyl phenethyl ethers - can be obtained in very high yield from electron-rich benzyl halides and 2-phenylethanols supporting electron-withdrawing groups by means of the PTC method, with a small or non formation of the phenylstyrene derived from the substituted 2-phenylethanols.

The optimum conditions have been shown to be equimolar amounts of starting reagents, a two phase system formed by 1:1 methylene chloride and aqueous 50 % (w/v, 12.5 M) sodium hydroxide, and tetrabutylammonium hydrogen sulfate in a 5 % molar relation. The concentration of sodium hydroxide turned out to be critical. Using only slightly more concentrated base (50 % w/w) precipitation of reagents, β-elimination and erratic yields were observed.

General procedure: preparation of (3d). To a stirred solution of 2-(4-nitrophenyl)ethanol (274 mg, 1.64 mmol) in 2 ml of CH_2Cl_2 was added tetrabutylammonium hydrogen sulphate (32 mg, 0.082 mmol), aqueous NaOH 50% w/v (2 ml) and 4-methoxybenzylchloride (244μl, 1.80 mmol). After 5 h at 25°C, the mixture was poured over 15 ml of water and extracted with diethyl ether (3 x 30 ml). The extract was washed with saturated aqueous NaH_2PO_4 (2 x 10 ml) and water (2 x 10 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed over silica gel. Elution with $CHCl_3$ gave pure [2-(4-

Table

Preparation of aryl arylthyl ethers from electron-rich arylmethyl halides and 2-arylethanols supporting electron-withdrawing groups by phase transfer catalysis

(a)	Ar	Ar'	time (h)	yield (%)(b)	mp (°C)
3a	C_6H_5	C_6H_5	20	94	oil
3b	4-$MeOC_6H_4$	C_6H_5	20	96	oil
3c	C_6H_5	4-CN C_6H_4	20	85	oil
3d	4-MeO C_6H_4	4-CNC_6H_4	20	90	71 - 73
3e	C_6H_5	4-NO_2 C_6H_4	5	55	52 - 54
3f	4-MeO C_6H_4	4-NO_2 C_6H_4	5	88	86 - 89
3g	4-MeO C_6H_4	4-MeO C_6H_4	20	86	69 - 72
3h	4-Cl C_6H_4	4-Cl C_6H_4	20	95	70 - 71
3i	α-naphthyl	α-naphthyl	20	76	oil

(a) Correct microanalysis, ir and nmr spectra have been obtained in all cases. (b) After chromatographic purification.

nitrophenyl)ethyl] (4-methoxyphenylmethyl) ether (392 mg, 88%) as a light yellow solid, mp 86-89 °C: ^{1}H-NMR δ (200 MHz, $CHCl_3$-d_1) 2.99 (2H, t, J = 6.6 Hz), 3.69 (2H, t, J = 6.6 Hz), 3.79 (3H, s), 4.43 (2H, s), 6.85 (2H, d, J = 8.8 Hz), 7.19 (2H, d, J = 8.8 Hz), 7.37 (2H, d, J = 8.8 Hz), 8.13 (2H, d, J = 8.8 Hz); ^{13}C-NMR δ (50.3 MHz, $CHCl_3$-d_1) 36.2 (CH_2), 55.1 (CH_3), 69.5 (CH_2), 72.6 (CH_2), 113.6 (CH), 123.3 (CH), 129.1 (CH), 129.2 (C), 129.6 (CH), 129.9 (C), 147.2 (C), 159.1 (C).

The results are summarised in the Table. The ^{1}H-nmr spectra of the crude reaction mixtures showed in all cases, except **3e**, practically quantitative conversions into ether.

The presence of a 4-nitro group on the benzylic moiety (**3e and 3f**) provokes a much faster β-elimination, forcing us to shorten the reaction times (5 h) and giving as a result a clearly lower yield in **3e**[7]. In the case of **3f**, the 4-MeO group enhances the reaction rate compensating the negative influence of the nitro group.

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7. Saunders, D.G. describes (*Synthesis*, **1988**, 377) the reaction between benzyl chloride, (*tert*-butyldimethylsilyl) [2-(4-nitrophenyl)ethyl] ether and tetrabutylammonium fluoride to give only traces of **3e**.

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