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

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To cite this article: Francisco López-Calahorra , Berta Ballart , Félix Hombrados & Josep Martí (1998) A New High Yield Preparation of Benzyl Phenethyl Ethers by Phase Transfer Catalysis, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 28:5, 795-799, DOI: 10.1080/00032719808006475

To link to this article: <u>http://dx.doi.org/10.1080/00032719808006475</u>

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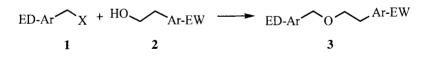
## A NEW HIGH YIELD PREPARATION OF BENZYL PHENETHYL ETHERS BY PHASE TRANSFER CATALYSIS

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**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 electronrich arylmethyl halides and 2-phenylethanols supporting electron withdrawing groups (figure ).



ED: Electron-donor group

EW: Electron-withdrawing group

Figure

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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<sup>1</sup> from benzyl chloride, sodium phenylethoxide in toluene with a yield of only 30 %. Analogously, the reaction<sup>2</sup> between 2-( $\alpha$ -naphthyl)ethanol,  $\alpha$ -chloromethylnaphthalene and NaH in THF produces [2-( $\alpha$ -naphthyl)ethyl] ( $\alpha$ -naphthyl-methyl) ether with 35% yield. Horita *et al*<sup>3</sup> 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  $\beta$ -elimination compound, was the only product isolated<sup>4</sup> 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  $\beta$ -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<sup>5</sup> to the preparation of unsymmetrical ethers. For instance, Fredmann and Dubois described<sup>6</sup> 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 2phenylethanols.

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,  $\beta$ -elimination and erratic yields were observed.

General procedure: preparation of (3d). To a stirred solution of 2-(4nitrophenyl)ethanol (274 mg, 1.64 mmol) in 2 ml of CH<sub>2</sub>Cl<sub>2</sub> was added tetrabutylammonium hydrogen sulphate (32 mg, 0.082 mmol), aqueous NaOH 50% w/v (2 ml) and 4-methoxybenzylchloride (244 $\mu$ l, 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<sub>2</sub>PO4 (2 x 10 ml) and water (2 x 10 ml), dried over MgSO4 and concentrated *in vacuo*. The residue was chromatographed over silica gel. Elution with CHCl<sub>3</sub> gave pure [2-(4-

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 <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	20	96	oil
3c	C <sub>6</sub> H <sub>5</sub>	4-CN C <sub>6</sub> H <sub>4</sub>	20	85	oil
3d	4-MeO C <sub>6</sub> H <sub>4</sub>	$4-CNC_6H_4$	20	90	71 - 73
3e	C <sub>6</sub> H <sub>5</sub>	4-NO2 C <sub>6</sub> H <sub>4</sub>	5	55	52 - 54
3f	4-MeO C <sub>6</sub> H <sub>4</sub>	$4-NO_2 C_6H_4$	5	88	86 - 89
3g	4-MeO C <sub>6</sub> H <sub>4</sub>	4-MeO C <sub>6</sub> H <sub>4</sub>	20	86	69 - 72
3h	4-Cl C <sub>6</sub> H <sub>4</sub>	4-Cl C <sub>6</sub> H <sub>4</sub>	20	95	70 - 71

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

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

20

76

oil

α-naphthyl

 $\alpha$ -naphthyl

3i

nitrophenyl)ethyl] (4-methoxyphenylmethyl) ether (392 mg, 88%) as a light yellow solid, mp 86-89 °C: <sup>1</sup>H-NMR  $\delta$  (200 MHz, CHCl<sub>3</sub>-d<sub>1</sub>) 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); <sup>13</sup>C-NMR  $\delta$  (50.3 MHz, CHCl<sub>3</sub>-d<sub>1</sub>) 36.2 (CH<sub>2</sub>), 55.1 (CH<sub>3</sub>), 69.5 (CH<sub>2</sub>), 72.6 (CH<sub>2</sub>), 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 <sup>1</sup>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  $\beta$ -elimination, forcing us to shorten the reaction times (5 h) and giving as a result a clearly lower yield in **3e**<sup>7</sup>. In the case of **3f**, the 4-MeO group enhances the reaction rate compensating the negative influence of the nitro group.

Acknowledgement. We acknowledge the support of Laboratorios Menarini, S. A.

## **References and notes**

1 Baker, R. H. J. Am. Chem. Soc. 1948, 70, 3857.

2. Todesco, R.; Gelan, J.; Martens, H. and Put, J. Tetrahedron 1983, 39, 1407.

3. Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y. and Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021.

4. Afterwards, we have observed that the 4-cyanostirene is formed from 4cyanophenylethanol and from its benzyl ether in a high amount in both cases when NaH is used as base.

 Starks, C. M. J. Am. Chem. Soc. 1971, 93, 195; 1973, 95, 3613; ACS Symp. Ser., 1987, 326, 1 and references therein cited.

6. Freedman, H. H. and Dubois, R. A. Tetrahedron Lett., 1975, 38, 3251.

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**.

(Received in the UK 1st July 1997)

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