Williamson reaction in [bmim][BF_4]: clean and facile synthesis of aryl benzyl ethers

Xinmin Wen*

Department of Chemistry, Jining Medical College, Jining 272013, China

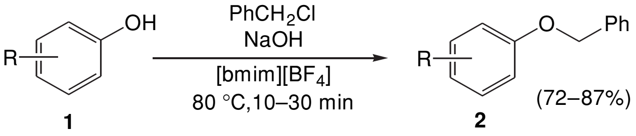
1-Butyl-3-methylimidazolium tetrafluoroborate ([bmin][BF_4]) has been demonstrated to be a suitable reaction medium for the synthesis of aryl benzyl ethers by the Williamson reaction. A variety of phenols react with benzyl chloride in [bmim][BF_4] to afford the desired ethers in satisfactory yields. The reaction proceeds cleanly and the use of the ionic liquid allows for easy product isolation.

Keywords: green chemistry, Williamson reaction, ionic liquids, recycling

Williamson reaction is a very useful transformation in organic synthesis since the products are of value both in industrial and academic applications.[1] The Williamson synthesis usually involves the employment of the alkali salts of hydroxy compounds and halides. These reactions are generally performed by using organic solvents[2] or with phase transfer catalysts,[3] followed by refluxing for several hours.

Over recent years, one of the most imperative issues for chemists is the search for green chemical transformations. Room temperature ionic liquids are molten salts that are comprised of an array of heterocyclic cations and various anions. They are becoming increasingly popular as alternative reaction media for separations[4] and organic transformations.[5] The desirable advantages of ionic liquids such as the lack of vapour pressure, wide liquid range and thermal stability have made them environmentally benign solvents. They are practically nonvolatile and hence do not pose the risks associated with volatile organic compounds. In addition, they are nonflammable and can be recycled easily without any significant loss in activity. Often, unexpected or improved reactivity is seen in ionic liquids. Accordingly, they are emerging as novel replacements for volatile organic compounds (VOCs) that are used as solvents in organic synthesis.

Seddon and co-workers have described the *O*-alkylation of 2-naphthol with four alkyl bromides or iodides in [bmim][PF_6].[6] However, the use of less reactive organic chlorides has not been investigated. More recently, several nucleophilic substitution reactions have been carried out in ionic liquids.[7] In this paper, we report our results concerning the preparation of aryl benzyl ethers from benzyl chloride and phenols in the ionic liquid [bmim][BF_4] (Scheme 1). This method is simple, fast and affords satisfactory yields. Products are easily separated from the reaction mixture by simple extraction with an immiscible solvent.



Scheme 1

The treatment of benzyl chloride with phenol and NaOH in 1-butyl-3-methyl-imidazolium tetrafluoroborate ionic liquid resulted in the formation of the corresponding ether in satisfactory yields. This approach was then applied to the several other phenols to expand the generality of the reaction conditions. Yields ranging from 72 to 87% were obtained. The products were isolated by extraction with diethyl ether several times. After evaporation of the combined ether layers, the residue was purified by recrystallisation or vacuum distillation (**2c**). The results are summarised in Table 1.

Furthermore, to demonstrate the advantages of ionic liquids, reaction has been performed in the aprotic polar solvent, DMF. The reaction proceeds slowly in DMF under similar conditions. A reasonable decrease in reaction time, but no significant improvements regarding yields, was encountered with all reactions carried out in the ionic liquid. For example, 2-naphthol reacted with 1.1 equiv. of benzyl chloride in [bmim][BF_4] (80 °C) to afford 83% yield of phenyl benzyl ether within 15 min. In contrast, with DMF as solvent, 1 h is needed to give 81% yield of the corresponding ether.

Another advantage of the use of ionic liquids as solvent for this transformation is that the ionic liquid was easily recovered. The products were easily separated by extraction with ether. By using the reaction between benzyl chloride and 2-naphthol as a model, recycling of the ionic liquid was investigated to give reproducible yields as shown in Table 2. The ionic liquid could be reused several times without any loss of activity, simply by filtering off the salt formed, extracting with ether and reusing in the subsequent runs. In these cases, NaOH was freshly added for each cycle. The results showed that the ionic liquid could be recycled at least eight times with negligible loss in yields. Purification of [bmim][BF_4] was not required within these cycles. This procedure worked well and the use of aprotic solvents such as DMF or toxic phase transfer catalysts (*e.g.* quaternary ammonium salt) were avoided.

In conclusion, ionic liquid [bmim][BF_4] offers an environmentally benign alternative solvent for the preparation

Table 1 Synthesis of aryl benzyl ethers in [bmim][BF_4]

Entry	Ar	Time[a]/min	Yield[b]/%	M.p./°C[c]	
				Obs.	Lit.
2a	C_6H_5	10	79	38-39	40 [8]
2b	4-$CH_3C_6H_4$	15	81	40	41 [9]
2c	2-$CH_3C_6H_4$	20	79	oil	——
2d	4-$NO_2C_6H_4$	25	87	107-108	106-107 [10]
2e	4-BrC_6H_4	20	72	60-61	64 [11]
2f	4-[$(CH_3)_3C$]C_6H_4	10	86	61-62	63-64 [12]
2g	2-Naphthyl	15	83	102-103	98-100 [13]

[a]monitored by TLC; [b]isolated yields; [c]uncorrected.

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* Correspondent. E-mail: xinmwen@yahoo.com.cn

Table 2 Recycling of [bmim][BF_4] in the synthesis of naphthyl benzyl ether

Cycle	Time/min[a]	Yield/%[b]
1	15	83
2	15	80
3	16	83
4	16	81
5	18	84
6	15	80
7	16	81
8	18	82

[a]Monitored by TLC; [b]isolated yields.

of aryl benzyl ethers by the Williamson reaction. The present protocol has advantages of rapid reaction, simple work-up, satisfactory yields and recoverable solvent, which make it a useful method for the preparation of aryl benzyl ethers without aprotic solvents or PTCs.

Experimental

All reagents were available commercially. Melting points are uncorrected and recorded on a WRS capillary apparatus. IR spectra were obtained on a Nicolet Nexus 470 infrared spectrometer using KBr discs and ^1H NMR spectra were recorded on a Bruker AC 200 spectrometer with TMS as internal standard.

General procedure: A mixture of powdered NaOH (0.44 g, 11 mmol) and phenol (10 mmol) in [bmim][BF_4] (5 ml) was stirred at 80 °C for 5 min before addition of benzyl chloride 1.37 g (11 mmol). The reaction mixture was then stirred at 80 °C for the indicated time (Table 1). On completion of the reaction (monitored by TLC), the mixture was cooled to room temperature, filtered and the filtrate was extracted with ether (4 ml × 4). The ether layer thus obtained was combined and concentrated under ambient pressure. The crude product was purified by vacuum distillation (**2c**) or recrystallisation from aqueous EtOH to afford the pure aryl benzyl ether.

Selected spectral data: Benzyl phenyl ether (**2a**): FTIR (KBr): ν_{max} 3040, 1540, 1500, 1460, 1030 cm^{-1}; ^1H NMR ($CDCl_3$): δ_H 5.12 (s, 2H, CH_2), 7.10–7.32 (m, 5H, Ar–H), 7.35–7.45 (m, 5H, Ar–H) ppm. Benzyl 4-methylphenyl ether (**2b**): FTIR (KBr): ν_{max} 3010, 1580, 1520, 1240, 1020 cm^{-1}; ^1H NMR ($CDCl_3$): δ_H 2.20 (s, 3H, CH_3), 4.82 (s, 2H, CH_2), 6.85–7.10 (m, 4H, Ar–H), 7.30–7.44 (m, 5H, Ar–H) ppm. Benzyl 4-nitrophenyl ether (**2d**): FTIR (KBr): ν_{max} 3050, 1600, 1580, 1500, 1350, 1250, 1010 cm^{-1}; ^1H NMR ($CDCl_3$): δ_H 5.12 (s, 2H, CH_2), 7.00 (d, 2H, Ar–H), 7.33 (s, 5H, Ar–H), 8.15 (d, 2H, Ar–H) ppm. Benzyl 4-*t*-butylphenyl ether (**2f**): FTIR (KBr): ν_{max} 3015, 1605, 1520, 1370, 1250, 1025 cm^{-1}; ^1H NMR ($CDCl_3$): δ_H 1.30 (s, 9H, *t*-Bu), 5.05 (s, 2H, CH_2), 6.85–7.45 (m, 9H, Ar–H) ppm.

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