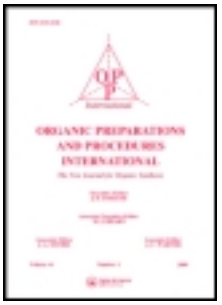

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# WILLIAMSON REACTION IN IONIC LIQUIDS

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# WILLIAMSON REACTION IN IONIC LIQUIDS

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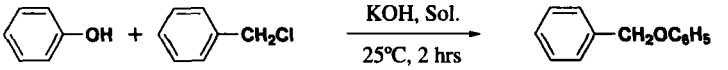
Room temperature ionic liquids (**RTILs**), also called "designer solvents", have been drawing intense scrutiny owing to their properties such as a wide "liquid" range, good ability to dissolve both organic and inorganic compounds, high polarity, good thermal stability and negligible vapor pressure. In some chemical reactions in RTILs as solvents, high selectivity, excellent yields and good catalytic characteristics have been demonstrated. The isolation of products is easy, and the RTILs can usually be recovered and recycled for repeated use.[1] Because of these attributes, RTILs have emerged as a new cleaner alternative to volatile organic solvents.

The Williamson synthesis, an important and widely used reaction, is generally performed in polar aprotic solvents such as acetone, acetonitrile, dimethylformamide (DMF) and dimethyl sulfoxide (DMSO).[2] Sometimes a phase-transfer catalyst (PTC) and elevated temperatures are needed for high yields and short reaction times. Although the reaction usually proceeds smoothly in this type of solvents, the odor, the relatively high toxicity, thermal instability and miscibility of solvents with both aqueous and organic phases, always make product isolation tedious and the recovery of solvents difficult, thus making the process unfriendly to the environment. Hence there is a need to develop not only a facile but also environmentally benign approach to the Williamson etherification. We now disclose herein our study on the feasibility of using RTILs as reaction medium in the Williamson etherification.

We initially evaluated the etherification of phenol with benzyl chloride in 1-*n*-hexyl-3-methylimidazolium chloride (**HMImC**), 1-*n*-butyl-3-methylimidazolium tetrafluoroborate (**BMImBF$_4$**), 1-ethyl-3-methylimidazolium tetrafluoroborate (**EMImBF$_4$**), *N*-(*n*-butyl)pyridinium tetrafluoroborate (**BPyBF$_4$**) and 1-*n*-butyl-3-methylimidazolium hexafluorophosphate (**BMImPF$_6$**), each of which was prepared according to literature procedures.[3] For the sake of comparison, the use of a common conventional solvent, DMF was also explored. Although as shown in *Table 1*, all of the **RTILs** tested here were nearly as effective as DMF, we consider that BMImPF$_6$ may be the solvent of choice because of its insolubility in water and in certain organic solvents such as ethyl ether, ethyl acetate and toluene. Thus isolation of the products can be achieved by simple extraction using common organic solvents and the pure **RTIL** could be recovered easily by washing with water to remove the salts formed in the reaction.

**Table 1.** Etherification of Phenol with Benzyl Chloride in Different Solvents[a]




| Solvent: | DMF | HMImC | $BMImBF_4$ | $BMImPF_6$ | $BPyBF_4$ | $EMImBF_4$ |
|---|---|---|---|---|---|---|
| Yield (%): | 92 | 90 | 91 | 92 | 90 | 90 |

a) All reactions were run with phenol (5 mmol), benzyl chloride (6 mmol), potassium hydroxide (6 mmol) and solvent (4 mL) for 2 hours at room temperature.



While the reaction conditions for the etherification of phenol with benzyl chloride in **$BMImPF_6$** were established (the amount of **$BMImPF_6$**, the ratio of feed stocks, temperature and time), the protocol was extended to the etherification of a series of phenols and alcohols with alkyl halides and the results are summarized in *Table 2*. In the case of phenols, the reaction usually proceeded smoothly at room temperature; however, if the solubility of the starting material is poor in **$BMImPF_6$**, mild heating at 60°C was used to ensure complete reaction (Sr. 8, 9, 13, 14, 17). Phenols bearing very strong electron-withdrawing groups (Sr. 12, 13) as well as reactions with the less reactive epichlorohydrin (Sr. 7, 10) gave somewhat lower yields. Except with the reaction of diphenylcarbinol with methyl iodide (Sr. 18), in the case of aliphatic alcohols, poor yields (less than 30%) were usually obtained even after prolonged reaction times using the above protocol. The reason is that potassium hydroxide is not strong enough to react with most aliphatic alcohols smoothly to form the stronger nucleophilic reagents of aliphatic alkoxides. However, when sodium hydride was used as the base in 1-*n*-butyl-2,3-dimethylimidazolium hexafluorophosphate (**$BDMImPF_6$**) which is particularly suitable for use in strongly basic conditions, good yields could also be obtained. IR, $^1H$ NMR and MS were used to characterize all the products listed in *Table 2*; the spectroscopic data were comparable with those of authentic samples or that reported in the literature.

Our attention was then directed towards to the possibility of recycling the reaction medium. It was found that, using *p*-hydroxyacetophenone as a representative substrate, the ionic liquid **$BMImPF_6$** could be readily recovered and re-used (*Table 3*). After the isolation of the product through extraction with ethyl ether or toluene, the remaining **$BMImPF_6$** layer was washed with water and followed by distillation in vacuum to remove trace of water. The **$BMImPF_6$** can be recycled at least five times with nearly the same efficiency. This feature is of particular significance to develop a greener synthesis through suppressing solvent evaporative loss.

In conclusion, we have demonstrated that the Williamson etherification can be efficiently accomplished in RTILs under mild conditions and high yields. The isolation of products is quite simple and the ionic liquids can be re-used.

**Table 2.** Etherification of Phenols and Alcohols with Alkyl Halides in $BMImPF_6$ or $BDMImPF_6$[a]

$$ROH + R'X \xrightarrow[\text{Base}]{BMImPF_6 \text{ or } BDMImPF_6} ROR'$$

| Sr | Phenol/alcohol (ROH)[b] (mmol) | Alkyl halide (RX)[b] (mmol) | Product Yield (%) | mp (bp) (°C) | *lit.* (°C) |
|---|---|---|---|---|---|
| 1 | $C_6H_5OH$ (5) | $PhCH_2Cl$ (6) | 92 | 38-39 | 39-41[4] |
| 2 | *p*-$MeC_6H_4OH$ (5) | $PhCH_2Cl$ (6) | 95 | 41-42 | 41-42[5] |
| 3 | 4-Me-2,6-$Br_2C_6H_2OH$ (5) | $PhCH_2Cl$ (6) | 92 | 75 | [c] |
| 4 | β-Naphthol (5) | $PhCH_2Cl$ (6) | 93 | 99-101 | 101-102[6] |
| 5 | β-Naphthol (5) | MeI (10) | 92 | 73-74 | 73-74[7] |
| 6 | β-Naphthol (5) | EtBr (10) | 97 | b280-282 | b282[7] |
| 7 | *p*-$MeC_6H_4OH$ (5) | Epichlorohydrin (6) | 77 | $b_5$108-111 | $b_{15}$136-140[8] |
| 8 | β-Naphthol (5) | $PhCOCH_2Br$ (5) | 93 | 119-121 | 120[9] |
| 9 | *p*-$MeC_6H_4OH$ (5) | $PhCOCH_2Br$ (5) | 90 | 55-56 | 56[10] |
| 10 | $C_6H_5OH$ (5) | Epichlorohydrin (6) | 81 | b243-244 | b243-244[7] |
| 11 | $C_6H_5OH$ (5) | iso-PrBr (7) | 91 | b175-178 | b176.8[11] |
| 12 | *p*-$NO_2C_6H_4OH$ (5) | EtBr (10) | 80 | 59-60 | 60[7] |
| 13 | *p*-$NO_2C_6H_4OH$ (6) | 4-$CF_3$-2-$NO_2C_6H_3Cl$ (5) | 82 | 92-93 | 93-94[12] |
| 14 | *p*-$AcC_6H_4OH$ (5) | 4-$CF_3$-2,6 $(NO_2)_2C_6H_2Cl$ (5) | 91 | 104 | [d] |
| 15 | *p*-$AcC_6H_4OH$ (5) | MeI (10) | 94 | 37-38 | 36-38[4] |
| 16 | *p*-$C_6H_4(OH)_2$ (5) | MeI (20) | 95 | 56 | 56[7] |
| 17 | 4-Me-2,6-$Br_2C_6H_2OH$ (5) | $PhCOCH_2Br$ (5) | 93 | 101 | [e] |
| 18 | $(C_6H_5)_2CHOH$ (5) | MeI (10) | 90 | $b_5$134-137 | $b_{0.3}$86-90[13] |
| 19 | $C_6H_5CH_2OH$ (5) | MeI (10) | 75 | b172-174 | b174[14] |
| 20 | $C_6H_5CH_2OH$ (5) | MeI (10) | 91 | b172-174 | b174[14] |
| 21 | PhCH: $CHCH_2OH$ (5) | MeI (10) | 88 | $b_5$85-87 | $b_{27}$125-126[15] |
| 22 | EtCH(Me)$CH_2OH$ (5) | MeI (10) | 85 | b92-95 | $b_{750}$90-93[16] |
| 23 | Cyclohexanol (5) | MeI (10) | 94 | b132-134 | b133.4[11] |
| 24 | $EtC(Me)_2OH$ (5) | MeI (10) | 87 | b85-86 | b85-86[4] |

a) All experiments carried out at 25°C, except Sr. 8, 9, 13, 14 and 17 which were performed at 60°C. b) Sr. 1-18: ROH, R'X, potassium hydroxide (6 mmol) and $BMImPF_6$ (4 mL) for 2 hrs; Sr. 19: ROH, R'X, sodium hydride (6 mmol) and $BMImPF_6$ (4 mL) for 2 hrs; Sr. 20-24: ROH, R'X, sodium hydride (6 mmol) and $BDMImPF_6$ (4 mL) for 2 hrs. c) *Anal.* Calcd for $C_{14}H_{12}Br_2O$: C, 47.23; H, 3.40. Found: C 47.09; H, 3.39. d) *Anal.* Calcd for $C_{15}H_9F_3N_2O_6$: C, 48.66; H, 2.45; N, 7.57. Found: C, 48.54; H, 2.45; N, 7.56. e) *Anal.* Calcd for $C_{15}H_{12}Br_2O_2$: C, 46.91; H, 3.15. Found: C, 46.77; H, 3.15.

**Table 3.** Etherification of *p*-Hydroxyacetophenone with Methyl Iodide in Recovered **BMImPF$_6$**

| Cycle | Fresh | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|
| Yield (%): | 94 | 99 | 99 | 98 | 96 | 96 |

## EXPERIMENTAL SECTION

All starting materials were commercially available from Shanghai Chemical Reagent Company and were used without further purification. Melting points were determined on a microscope melting point detector XT-4 and are uncorrected, $^1$H NMR spectra were obtained on a Bruker Avance 500 ($CDCl_3$, TMS as internal standard), IR spectra were recorded (KBr pellets for solids and films for liquids) on a Bruker Equinox 55 spectrometer, Mass spectra were determined on a Varian CP 3800/Saturn 2000 GC/MS. Elemental analyses were obtained on Carlo Erba EA 1106. HPLC or GC were used to analyze the purity of products.

**Typical Procedure for Preparation of Benzyl Phenyl Ether (Entry 1).**- A mixture of phenol (0.47 g, 5 mmol), benzyl chloride (0.75 g, 6 mmol), KOH (0.41 g, 82%, 6 mmol) and **BMImPF$_6$** (4 mL) in a 20 mL round bottomed flask fitted with mechanical stirrer, was stirred at room temperature and the reaction was monitored by thin layer chromatography (TLC, silica gel 254, eluted hexane-ethyl acetate, 2:1). After all the phenol had been consumed, the reaction mixture was extracted with ethyl ether (3 x 10 mL), the organic extract was washed, dried, and the solvent was distilled off to give 0.86 g (92%) of the desired product (purity 99% by GC); mp. 38-39°C, *lit.*[4] mp 39-41°C.

**Typical Procedure for 4-Trifluoromethyl-2-nitrophenyl 4-Nitrophenyl Ether (Entry 13).**- The same apparatus was used; *p*-nitrophenol (0.84 g, 6 mmol), KOH (0.41 g, 82%, 6 mmol) and **BMImPF$_6$** (4 mL) were charged successively into a 20 mL round bottomed flask, the mixture was heated at 60°C for 15 minutes and then 4-trifluoromethyl-2-nitrochlorobenzene (1.13 g, 5 mmol) was added with vigorous stirring. After an additional 2 hours, the reaction mixture was extracted with toluene (3 x 10 mL), the organic layer separated was washed, dried, and the solvent was distilled off to give 1.48 g (82%) of the desired product (purity 99% by HPLC) as a yellow solid, mp 92-93°C, *lit.*[5] mp 93-94°C

**Typical Procedure for Preparation of p-Methyloxyacetophenone (Entry 15).**- The same apparatus was used; *p*-hydroxyacetophenone (0.68 g, 5 mmol), KOH (0.41 g, 82%, 6 mmol), methyl iodide (1.42 g, 10 mmol) reacted in 4 mL **BMImPF$_6$** at room temperature for 2 hours and then the reaction mixture was extracted with ethyl ether, the separated organic layer was washed, dried, and the solvent was distilled off to give 0.71 g (94%) the desired product (purity 99% by HPLC) as a colorless solid, mp 37-38°C, *lit.*[4] mp 36-38°C. The remaining ionic liquid layer was washed with water (3 x 10 mL), and then distilled under vacuum to remove the trace amount of water; the recovered ionic liquid can be directly used at the next run.

**Typical Procedure for Preparation of Benzyl Methyl Ether (Entry 20).**- The same apparatus was used; benzyl alcohol (0.54 g, 5 mmol), NaH (0.24 g, 60%, 6 mmol), methyl iodide (1.42 g, 10 mmol) reacted in 4 mL $BDMImPF_6$ at room temperature for 2 hours and then the reaction mixture was extracted with ethyl ether, the separated organic layer was washed, dried, and distilled to give 0.56 g (91%) the desired product as a colorless liquid, bp. 172-174°C (purity 99% by GC).

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## IMPROVED SYNTHESIS OF PHENYLSELENOGLYCOLIC ACIDS

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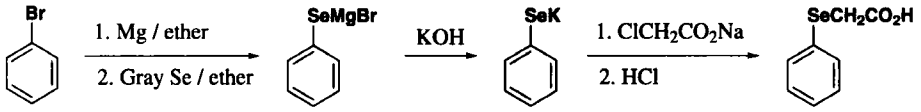
Selenium is a nonmetallic trace element recognized as a nutrient essential to human health.[1,2] Selenium is also an essential constituent of extracellular and cellular glutathione peroxidases, thyroidal and extrathyroidal iodothyronine 5'-deiodinnases, thioredoxin reductase, and other selenoproteins.[2] Various experimental models showed that selenium inhibits tumorigenesis.[3] Low serum selenium levels are associated with an increased risk of developing cancer at several sites, especially cancers of the stomach and lung for men[4]. Thus, many organoselenium compounds have been synthesized.[5,6] Some substituted phenylselenoglycolic acids have been synthesized by using Grignard reagent[7] (*Scheme 1*) (yields 20-25%) and from




**Scheme 1**

diazonium salts.[8,9] In the studies with diazonium salts, substituted anilines were diazotized in aqueous medium, followed by addition of potassium selenocyanide. Although yields were not reported,[8,9] we found them to be lower (25-30%) when the last traces of acids were not removed and reaction performed in aqueous medium. In the presence of acid, potassium selenocyanide decomposes to release poisonous hydrogen cyanide and concurrent decrease in the yields.

In our method (*Scheme 2*), substituted anilinium chlorides are prepared, dried and washed with ether to remove excess acid from the salts. The anilinium chlorides are diazotized with ethyl nitrite in non-aqueous medium, thus avoiding the decomposition of potassium selenocyanide.