

Nucleophilic Substitution Reactions in Ionic Liquid: Towards a Real Continuous-Flow Process for Synthesis of Alkyl Bromides and Cyanides

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Abstract: A real continuous-flow process for synthesis of alkyl bromides or cyanides was demonstrated by nucleophilic substitution reactions of tosylates with bromide and/or cyanide conducted in ionic liquid 1-ethyl-3-methylimidazolium tosylate. The process provides higher yields and shorter reaction time and is easily upgraded to large scale.

Keywords: Continuous-flow process, ionic liquid, nucleophilic substitution reaction, distillation, alkyl bromide, alkyl cyanide.

INTRODUCTION

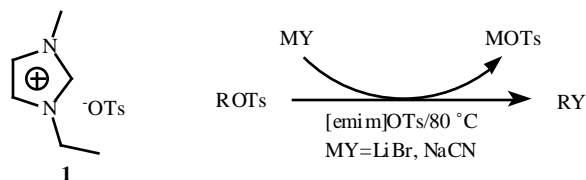
Room temperature ionic liquids (ILs) are novel and promising materials for a variety of chemical applications [1-2]. They have been described as "designer solvents" for their properties such as viscosity, solubility and density can be adjusted to suit various requirements by simply changing the structure of cation or anion [1-3]. Because of their unique physical and chemical properties, ILs have also been widely applied in organic reactions as "green solvents" and they can accelerate reaction rates, improve selectivity, and facilitate catalyst recovery [1-3]. However, the green nature of processes conducted in ILs is seriously limited by the need to utilize hazardous molecular organic solvents such as ether, hexane, acetone and toluene etc. to isolate the products from the reaction system, as well as to recover the ILs themselves [4]. To overcome these limitations, there have been several investigations of novel methods [3]. Among them, the combination of ILs with supercritical carbon dioxide is one of the most attractive approaches, as the separation of the products in solvent-free form can be effective and CO₂ can be recycled by recompressing it back into the reactor. Continuous flow catalytic systems based on the combination of these two solvents have been reported [4, 6-7]. Profited from the low vapor pressure of ILs, another efficient protocol is that the product can be isolated from reaction mixture simply and directly by vacuum distillation if the boiling point of the product is not too high. One example is the catalytic hydroformylation of methyl-3-pentenoate in ILs by a homogeneous Rh-phosphite system and the product isolation was achieved by a vacuum distillation process after the reaction was completed [5].

When the boiling points of starting materials are rightly higher than the products' and the reaction speed is reasonably fast, the product can be separated from reaction system directly by distillation just at the same time of substrate addition and the reaction was conducting. This is another type of real continuous-flow process, and is

technically more attractive to realize the applications of ionic liquids in clean and economically designed chemical engineering. Herein we wish to report a real continuous-flow reaction, in which the substrate is continuously flowed into the reactor and the product is continuously distilled out at the same time (Scheme 1).

RESULTS AND DISCUSSION

Nucleophilic substitution reaction of tosylates with bromide or cyanide was chosen as a model reaction to test the possibility of the idea, because one of the most common reactions in organic synthesis is the nucleophilic substitution. In recent years, some reports have indicated that ILs not only can be used as the excellent reagents [8-11] but also as the efficient reaction promoting solvents in nucleophilic substitution reactions [3, 12-14]. Kim and co-workers investigated the reactivities of various metal fluorides in the presence of [bmim][BF₄] (bmim = 1-butyl-3-methylimidazolium, and BF₄ = tetrafluoroborate) [12]. Eckert *et al.* reported that the rate of the nucleophilic substitution reaction of benzyl chloride by potassium cyanide in [bmim][PF₆] (PF₆ = hexafluorophosphate) was dependent on temperature and the separation of product from the ILs could be achieved by distillation or by extraction with supercritical CO₂ [13]. However, no such a continuous flow-in and -out process was reported.



Scheme 1. Bromide and cyanide displacement on tosylates.

Another reason to choose the reaction is that the boiling points of starting materials are rightly higher than the products'. This facilitates the isolation of products by a real continuous-flow distillation. The ionic liquid used as solvent was [emim][OTs] (1) (emim = 1-ethyl-3-methylimidazolium and OTs = tosylate). The choice of solvent was motivated that the approach has the major advantage of

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Table 1. The Results of Batch Experiments in IL

Entry	R	MY	Time (min)	B.p. (°C /mmHg)	Yield(%)
1	n-C ₄ H ₉	LiBr	60	50-52/50	78
2	n-C ₆ H ₁₃	LiBr	70	48-49/10	85
3	n-C ₈ H ₁₇	LiBr	80	65-66/5	80
4	iso-C ₄ H ₉	LiBr	70	34-36/50	76
5	sec- C ₄ H ₉	LiBr	90	35-36/50	74
6	cyclo-C ₆ H ₁₁	LiBr	80	53-54/10	78
7	n-C ₄ H ₉	NaCN	70	40-41/10	73
8	n-C ₅ H ₉	NaCN	80	52-54/10	75
9	n-C ₆ H ₁₃	NaCN	75	58-59/10	85
10	iso - C ₄ H ₉	NaCN	80	50-51/50	72
11	cyclo-C ₆ H ₁₁	NaCN	65	30-31/50	80 ^a

^a Elimination product was obtained as the main product.

generating the same anion with ionic liquid, [emim][OTs], and ionic liquid can be re-used simply after filtering the by-product (LiOTs, NaOTs) out.

Obviously to realize or to maintain the real "continuous flow" the reaction scale must be upgraded to more than fifty grams or so. We firstly investigated the rates and yields of the reactions in the ionic liquid as batch reactions in 10g scale. To a three-necked flask (50mL) equipped with a magnetic stirrer, dropping funnel and distilling apparatus, the ionic liquid and alkali metal salt (LiBr or NaCN) were stirred at 80°C for 5 minutes. The corresponding tosylate (10g) was added to the mixture by opening the dropping funnel. After the reaction, the products were distilled out of the ionic liquid system under reduced pressure (<50mmHg) at reaction temperature. The products were collected in a cooling trap. The results of batch experiments were summarized in Table 1. To the displacement with LiBr, not only long chain (C₄-C₈) primary bromides were obtained from corresponding tosylates but also 2-methylpropanyl bromide was formed from isobutyl 4-methylbenzenesulfonate. Interestingly, secondary bromides bromocyclohexane and 2-bromobutane were also obtained from cyclohexyl tosylate and sec-butyl tosylate respectively. The by-product cyclohexene was also detected by ¹H-NMR (bromocyclohexane/cyclohexene= 30/1). To the displacement with NaCN, both chain primary cyanides (C₄-C₆) and 3-methylbutanenitrile were obtained from corresponding tosylates, the presence of - methyl on tosylate appears to have little effect on the rate or the yield of the reaction in our IL system (entry 4 and 10). However, when the cyclohexyl 4-methyl- benzenesulfonate as the starting material, elimination reaction took place and cyclohexene was obtained as the main product. This result is similar to Chiappe's. In their substitution reaction of secondary tosylates with KCN using [bmim][PF₆], [bmim][N(Tf)₂] and [hpyr][N(Tf)₂] ionic liquids (N(Tf)₂ = bis(trifluoromethylsulfonyl)imide and hpyr = 1-hexylpyridium) as solvents, they also obtained alkene as a main product [14c].

From the above batch experiments we got the information that all the above reactions were possible to be conducted in a continuous-flow way, that is, the substrate is

continuously flowed into the reactor and the product is continuously distilled out at the same time, if the scales were upgraded to large, because all the reactions were fast (completed in less than 1.5h) and the products were easily distilled out and collected. So we choose a representative substrate hexyl 4-methyl- benzenesulfonate to test the procedure. In the 500mL recycling reactor, the mixture of ionic liquid [emim]OTs (200mL) and LiBr (25g) was stirred (200r/min) at 80°C. The starting material was added at 2g/min (25min, 50g) rate and the vacuum pump started to work (10mmHg) at the same time. After 6 minutes, the product began to appear in the collecting trap and the volume of the flow depended on the adding rate of the starting material. After 45 minutes, the first run of the reaction was finished (30g, 93% yield). The purity of the product got directly from distillation is higher than 96%. The reuse of IL can be achieved by filtrating the LiOTs off. Comparing the result of batch experiment, the yield of product is higher and the reaction time is shorter (Table 1, entry 2). It is obvious that the pressure reducing and product isolation in situ under the reaction conduction is beneficial to reaction process.

CONCLUSION

In summary, several bromide and cyanide compounds have been synthesized from tosylates in IL and the product isolations have been achieved by a distillation process under reduced pressure. The effective product separation has also been resulted to a continuous process in our designed recycling reactor. In perspective, we believe that the real continuous-flow process can significantly contribute towards clean and economically designed chemical engineering.

EXPERIMENTAL

Typical procedure for nucleophilic substitution reaction: To a 50mL, three-necked flask equipped with a magnetic stirrer, dropping funnel and distilling apparatus, ionic liquid [emim]OTs (20 mL) and LiBr (4.1 g) were added and stirred at 80 °C. After 5 minutes, n-C₆H₁₃OTs (10 g, 0.04 mol) was added to the mixture by opening the dropping funnel.

The reaction was followed by TLC. After the reaction, the product was distilled out of the reaction system under reducing pressure (Bp₁₀ mmHg = 48-49 °C) and collected in a cooling trap (5.5 g, 85% yield).

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