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Solution Phase Parallel Synthesis of 4-Aminophenyl Ethers Using a Carboxyl-Functionalized Ionic Liquid as Support

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Summary. A small sortiment of 4-aminophenyl ether derivatives was constructed with good yields and purities *via Williamson* reaction using the carboxyl-functionalized ionic liquid [*cmmim*][BF_4] as soluble support. The recovered ionic liquid could be reused for several times with similar capacity.

Keywords. Parallel synthesis; Functional ionic liquid; Supports; 4-Aminophenyl ethers; Combinatorial chemistry.

Introduction

Combinatorial chemistry is now widely used to generate vast sortiments of molecules for the discovery of new drugs and materials. It generates large numbers of compounds rapidly in parallel fashion, rather than by sequential reiteration of individual syntheses [1]. Solid-phase organic synthesis (SPOS) plays an important role in combinatorial chemistry. Although the insoluble resin offers the advantage of easy purification by filtration, it is often a liability at the reaction stage because of the heterogeneous nature of SPOS [2].

In response to these limitations, several strategies have been developed. Soluble polymer supports (*e.g. PEG*) offer certain advantages over insoluble polymers in terms of ease of analysis and monitoring and, most importantly, the establishment of homogeneous conditions [3]. In addition, owing to the homogeneity of liquid-phase reactions, the reaction conditions can be readily shifted from solution-phase systems without large changes, and the amount of the excess reagents is less than that in solid-phase reactions. More recently, functionalized ionic liquids have been

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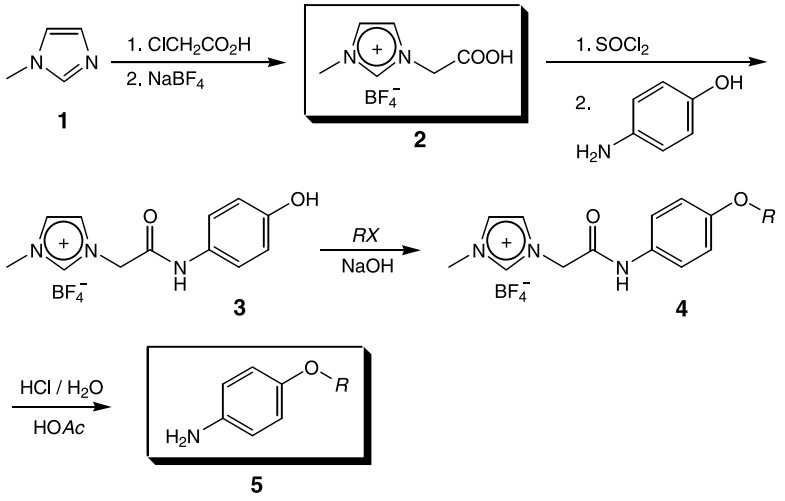

Scheme 1

reported as soluble supports in solution-phase parallel synthesis [4]. Functionalized ionic liquids, instead of resin beads, are employed as the supports to facilitate the separation process. Functionalized ionic liquids are immiscible with weakly polar solvents (*e.g.* hexane, cyclohexane, benzene, toluene, or diethyl ether) but miscible with many polar solvents (*e.g.* water, methanol, ethanol, or acetonitrile). This can be used to separate excess reagents and by-products from the supported products. Moreover, the use of functionalized ionic liquids as soluble supports also has other advantages, such as higher loading capacity and ease in reaction monitoring.

In connection with our research program on solution-phase synthesis and functionalized ionic liquids, we report herein the synthesis of a carboxyl-functionalized ionic liquid and its application as soluble support in parallel synthesis of 4-aminophenyl ethers (Scheme 1). This strategy has advantages including ready product isolation and reusability of the ionic liquid support. To the best of our knowledge, it is the first report on the use of a carboxyl-functionalized ionic liquid as soluble support in solution phase parallel synthesis.

Results and Discussions

Our starting point was to prepare the carboxyl-functionalized ionic liquid, 1-carboxymethyl-3-methylimidazolium tetrafluoroborate (**2**, [*cmmim*][BF_4]), from the commercially available *N*-methylimidazole (**1**). Thus, **1** was reacted with an equimolar amount of chloroacetic acid yielding the corresponding imidazolium cation. The solid [*cmmim*][Cl] was treated through standard anion metathesis, affording [*cmmim*][BF_4] **2** in high yield (93%).

To further evaluate its efficiency in parallel synthesis, **2** was utilized in the construction of a small sortiment of amino ethers. Subsequent transformation of **2** into **3** was performed in one-pot fashion. Thus **2** reacted with an excess thionyl chloride in acetonitrile to yield an acyl chloride-type ionic liquid. This was followed by treatment with 2 equiv. of 4-aminophenol without purification of the intermediate. The isolation procedure for the IL-supported substrate **3** involved

Table 1. Synthesis of 4-aminophenyl ethers **5** using **2** as soluble ionic liquid support

Product	*RX*	Yield/%[a]	Purity/%
5a	2,4-$(Cl)_2$–$C_6H_3CH_2Cl$	79	98
5b	$C_6H_5CH_2Br$	80	99
5c	2,4-$(NO_2)_2$–C_6H_3Cl	75	99
5d	$C_6H_5COCH_2Br$	77	96
5e	$CH_3CH_2CH_2CH_2Br$	78	98

[a] All yields are based on IL-bound aminophenol **3**

neutralization, evaporation, and a simple extraction of the excess reagent with ethyl acetate to afford the immobilized 4-aminophenol in 96% yield.

The step next was the formation of products grafted on ionic liquid **4a**–**4e** *via Williamson* ether synthesis. IL-supported aminophenol **3** was reacted with a 1.5-fold excess of various halides in 95% ethanol in the presence of NaOH. HPLC analysis was used to follow the course of these transformations. After the reaction was complete, the product remained covalently bound to the support, and purification could be accomplished through simple procedure. In all cases, as expected, no excess reagent and by-products were observed by HPLC analysis.

Following solvent washes, immobilized products **4a**–**4e** were subjected to cleavage with concentrated HCl in ethanol to provide the desired compounds in 75–80% overall yield based on the loading of **3** (Table 1). Each crude product was then characterized by GC-MS and ^{1}H NMR and gave 96–99% purity without chromatographic purification.

Finally, for economical and environmental reasons, the regeneration and reuse of **2** was examined by performing the synthesis of **5b**. After the cleavage procedure, the residue after extraction was treated with acetone and concentrated HCl. The precipitates thus formed were filtered off and the filtrate was concentrated to give regenerated **2**. The recovered **2** was then dried for a short time under vacuum to remove traces of water and then recycled. The IL-bound aminophenol **3** was synthesized in the same way using recovered functionalized ionic liquid and was employed in the next run. Thus **2** could be reused for five times without evident loss in efficiency. The recovery of ionic liquid was >95% in each run.

In conclusion, we have developed a novel and efficient liquid-phase method for the parallel synthesis of 4-aminophenyl ether derivatives *via Williamson* reactions using the carboxyl-functionalized ionic liquid **2** as soluble support. The procedure afforded the desired products in good yields and high purities. Furthermore, the recovered ionic liquid could be reused for several times without loss of efficiency.

Experimental

Reagents (A. R. Grade) were purchased and used without further purification.^{1}H NMR spectra were recorded on a Bruker AM 500 (500 MHz) spectrometer with *TMS* as internal standard. The mass spectra were recorded on a Micromass LCT KC317 spectrometer (ESI). Melting points were determined on a BÜCHI B-540 apparatus. All final products **5a**–**5e** are known compounds; their physical and spectroscopic data were compared with those reported in Refs. [5–9] and found to be identical.

1-Carboxymethyl-3-methylimidazolium tetrafluoroborate (**2**, $C_6H_9N_2O_2BF_4$)
A mixture of 9.45 g of chloroacetic acid (100 mmol) and 8.20 g of *N*-methylimidazole (100 mmol) was heated at 70°C for 8 h (monitored by TLC). After washing with $3\times20\,cm^3$ of ethyl ether, the resulting white solid was then added to 10.98 g $NaBF_4$ (100 mmol) and $100\,cm^3$ of acetonitrile. The suspension was stirred rapidly and refluxed for 12 h. After filtration and evaporation, 21.18 g **2** were obtained as a yellowish liquid (93%). ^{1}H NMR (500 MHz, D_2O): $\delta = 3.81$ (s, CH_3), 4.98 (s, CH_2), 7.35–7.36 (d, $J = 5.2$ Hz, H-4, H-5), 8.58 (s, H-2) ppm; FT-IR (KBr): $\bar{\nu} = 3118$, 3088, 3037, 2688, 1732, 1580, 1394, $1090\,cm^{-1}$.

1-[(4-Hydroxylphenylcarbamoyl)methyl]-3-methylimidazolium tetrafluoroborate
(**3**, $C_{12}H_{14}N_3O_2BF_4$)
To a stirred mixture of 4.56 g **2** (20 mmol) and $25\,cm^3$ of anhydrous acetonitrile at 0°C was added 4.76 g $SOCl_2$ (40 mmol). The reaction mixture was heated to reflux until the starting material was completely consumed as judged by TLC (3 h). Excess $SOCl_2$ and solvent were removed on a rotary evaporator, and the residue was diluted with $10\,cm^3$ of anhydrous acetonitrile. The resulting solution was dropped into a mixture of 4.36 g of 4-aminophenol (40 mmol) in $20\,cm^3$ of anhydrous acetonitrile. After refluxing for 2 h, 3 g of powdered anhydrous Na_2CO_3 were added with stirring until no gas was released. The slurry was filtered and the filtrate was concentrated *in vacuo*. The residue was then washed with $4\times15\,cm^3$ of ethyl acetate. Further treatment *in vacuo* gave 5.87 g **3** as a white solid (92%, 98% purity). ^{1}H NMR (500 MHz, D_2O): $\delta = 3.92$ (s, CH_3), 5.18 (s, CH_2), 6.87–7.29 (dd, $J = 8.7$, 8.7 Hz, C_6H_4), 7.48–7.49 (d, $J = 5.9$ Hz, CH=CH), 8.81 (s, CH=N) ppm; FT-IR (KBr): $\bar{\nu} = 3311$, 3162, 3118, 1684, 1602, 1561, 1506, 1443, 1302, 1231, $1064\,cm^{-1}$; MS (ESI): m/z (%) = 231.9 (100, $[M]^+$).

General Procedure for the Preparation of IL-bound Products (***4a–e***)
To a solution of 0.96 g **3** (3.0 mmol) and 4.5 mmol of halide in $10\,cm^3$ of ethanol were added 0.12 g NaOH (3.0 mmol). The mixture was then refluxed for 3 h. After filtration and evaporation, the residue was washed with $4\times15\,cm^3$ CH_2Cl_2 to give **4a**–**4e**.

1-{[4-(2,4-Dichlorobenzyloxy)phenylcarbamoyl]methyl}-3-methylimidazolium tetrafluoroborate (**4a**, $C_{19}H_{18}N_3O_2Cl_2BF_4$)
^{1}H NMR (500 MHz, D_2O): $\delta = 3.91$ (s, CH_3), 5.10 (s, CH_2), 5.16 (s, OCH_2), 7.01–7.02 (d, $J = 8.9$ Hz, CH=CH), 7.46–7.51 (m, C_6H_3), 7.59–7.73 (m, C_6H_4), 9.08 (s, CH=N), 10.39 (s, NH) ppm; FT-IR (KBr): $\bar{\nu} = 3192$, 3184, 3122, 1695, 1608, 1556, 1511, 1461, 1415, 1396, 1300, 1238, 1185, 1106, $1064\,cm^{-1}$; MS (ESI): m/z (%) = 390.1 (100, $[M]^+$).

General Procedure for Product Cleavage
To a solution of **4a**–**4e** in $10\,cm^3$ of ethanol was added $2\,cm^3$ conc. HCl. The mixture was then refluxed for 2 h. Upon completion, ethanol was removed by rotary evaporation and the residue was neutralized with sat. aqu. NaOH. The aqueous phase was extracted with $2\times10\,cm^3$ $CHCl_3$, and the organic layer was dried (Na_2SO_4), filtered, and concentrated under vacuum to afford **5a**–**5e**.

4-(2,4-Dichlorbenzyloxy)anilin (**5a**, $C_{13}H_{11}NOCl_2$)
Mp 69–70°C (Ref. [5] 70–71°C); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 5.04$ (s, CH_2), 6.64–6.82 (m, C_6H_4), 7.25–7.40 (m, C_6H_5), 7.49 (s, NH_2) ppm; MS (EI): m/z (%) = 267 ($[M]^+$), 159, 108 (100), 80, 53.

4-(Benzyloxy)aniline (**5b**, $C_{13}H_{13}NO$)
Mp 54–55°C (Ref. [6] 55–56°C); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 4.99$ (s, CH_2), 6.64–6.83 (dd, $J = 8.7$, 8.7 Hz, C_6H_4), 7.26 (s, NH_2), 7.29–7.43 (m, C_6H_5) ppm; MS (EI): m/z (%) = 199 ($[M]^+$), 108 (100), 91, 80, 65, 53.

4-(2,4-Dinitrophenoxy)aniline (**5c**, $C_{12}H_9N_3O_5$)
Mp 140–141°C (Ref. [7] 143–144°C); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 3.77$ (s, NH_2), 6.74–6.95 (m, C_6H_4), 7.01–8.82 (m, C_6H_3) ppm; MS (EI): m/z (%) = 275 ($[M]^+$), 182, 154, 108 (100), 93, 80, 65, 53.

2-(4-Aminophenoxy)-1-phenylethanone (**5d**, $C_{14}H_{13}NO_2$)
Mp 97–98°C (Ref. [8] 95°C); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 5.19$ (s, CH_2), 6.62–6.82 (m, C_6H_4), 7.27 (s, NH_2), 7.47–8.01 (m, C_6H_5) ppm; MS (EI): m/z (%) = 227 ($[M]^+$), 108 (100), 92, 77, 65.

4-(Butoxy)aniline (**5e**, $C_{10}H_{15}NO$)
Mp 164–165°C (Ref. [9] 168°C); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.95$–0.97 (t, $J = 7.4$ Hz, CH_3), 1.43–1.76 (m, CH_2CH_2), 3.88–3.90 (t, $J = 6.6$ Hz, OCH_2), 6.62–6.86 (m, C_6H_4), 7.26 (s, NH_2) ppm; MS (EI): m/z (%) = 165 ($[M]^+$), 108 (100), 80, 65, 53.

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