

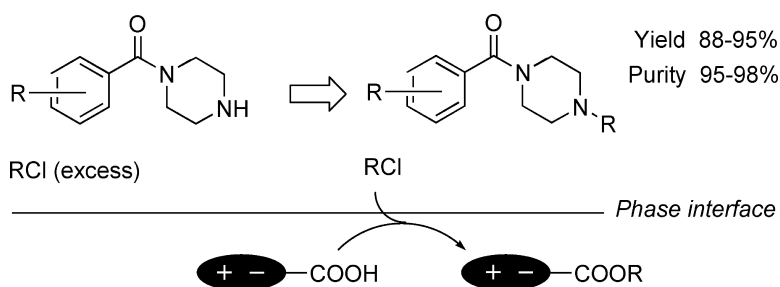
Report

Carboxyl-Functional Ionic Liquids as Scavengers: Case Studies on Benzyl Chloride, Amines, and Methanesulfonyl Chloride

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Reports

Carboxyl-Functional Ionic Liquids as Scavengers: Case Studies on Benzyl Chloride, Amines, and Methanesulfonyl Chloride

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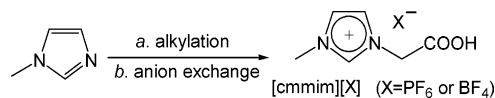
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Over the past decade, the application of polymer-supported scavengers in solution-phase parallel synthesis has become one of the most useful tools for rapid purification or isolation of desired compounds from a reaction mixture in multistep sequences.¹ Polymer-supported scavengers can selectively quench the byproducts of reactions or remove excess starting materials and remove them by filtration. This process has recently been the subject of several reviews containing list of reactants and complementary functionalized sequestrants.² However, polymer-supported scavengers do have limitations because of the nature of solid-phase and related loading issues. To overcome these limitations, some new scavengers, such as fluororous scavengers,³ soluble polymer-supported scavengers,⁴ and scavengers with polyaromatic tags,⁵ have been disclosed in the literature.

In recent years, more attention has been paid to the synthesis of new ionic liquids with functional groups (“task-specific” ionic liquids) and their applications in chemical research.⁶ Recently, we reported the first example in which amino-functionalized ionic liquids were utilized as nucleophilic scavengers for purification in solution-phase parallel synthesis.⁷ Herein, we report a method that utilizes carboxy-functionalized ionic liquids, 1-carboxymethyl-3-methylimidazolium hexafluorophosphate ([cmmim][PF₆]) and 1-carboxymethyl-3-methylimidazolium tetrafluoroborate ([cmmim][BF₄]), as efficient and recyclable scavengers for the sequestration of benzyl chloride, amines, and methanesulfonyl chloride from reaction mixtures. These ionic liquid-based scavengers have advantages such as higher loading, less dosage, and shorter duration in comparison with their polymer-supported counterparts.

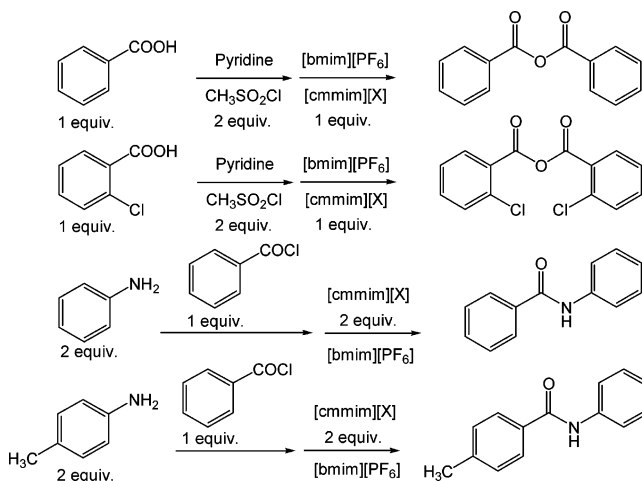
The carboxy-functionalized ionic liquids were prepared using commercially available 1-methylimidazole and 2-chloroacetic acid as starting materials, followed by anion exchange with KPF₆ or NaBF₄ (Scheme 1). After filtration of the salts and removal of solvents in vacuo, the obtained ionic liquids

Scheme 1



Reaction conditions: (a) 1-methylimidazole (1.5 equiv), ClCH₂COOH (1 equiv), 70 °C; (b) KPF₆ (1 equiv) or NaBF₄ (1 equiv), ethanol/H₂O (v/v, 1/1), rt.

Scheme 2



were dried under vacuum to obtain pure products (93–94% yield) as indicated by FTIR, MS (ESI), and ¹H NMR.

The basic idea here was to replace the polymeric core of scavenger reagents with a functionalized ionic liquid. In comparison with the polymer-assisted scavenging, this “beadless” approach has several advantages, such as a high site/material ratio (high loading), time saving, ease in monitoring with GC or HPLC, minimized solvents and waste stream and easier scale-up. Furthermore, it is worth noting that the used ionic liquids could be regenerated and recycled at least three times without significant loss of activity.

Results and Discussion. To examine the utility of [cmmim][PF₆] or [cmmim][BF₄] as a scavenger, methanesulfonyl chloride was used as a model substrate for the initial investigation. Disappointedly, the reaction of [cmmim][PF₆] (2 equiv) and methanesulfonyl chloride in toluene was very slow; it took 10 h (as monitored by TLC) to complete at room temperature. It was surmised that the long reaction time was due to the fact that the ionic liquid became very viscous during the scavenging reaction. It was found that the addition of a conventional ionic liquid, 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF₆]), into the reaction mixture could dramatically enhance the scavenging process. The effect of the molar ratio of [bmim][PF₆] to [cmmim][PF₆] on scavenging efficiency was further investigated. An optimal molar ratio of 2:1 completed the scavenging of methanesulfonyl chloride in 30 min.

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Table 1. Some Excess Reagents Trapping from Reaction Mixtures

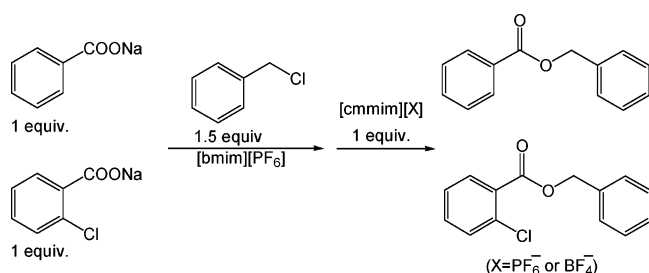
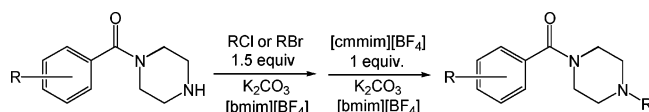
entry	substrate	excess reagent	scavenger	yield ^a (%)	purity ^b (%)
1	benzoic acid	methanesulfonyl chloride	[cmmim][PF ₆]	97	99
2			[cmmim][BF ₄]	98	98
3			[cmmim][PF ₆]	98	99
4	<i>o</i> -chlorobenzoic acid	aniline	[cmmim][BF ₄]	99	99
5			[cmmim][PF ₆]	97	99
6			[cmmim][BF ₄]	98	99
7			[cmmim][PF ₆]	96	99
8	benzoyl chloride	<i>p</i> -toluidine	[cmmim][PF ₆]	96	99
			[cmmim][BF ₄]	97	99

^a Scavenging time: 30 min. ^b Purity was determined by GC.

Table 2. Excess Reagent Trapping from Reaction Mixtures

entry	substrate	excess reagent	scavenger	yield ^a (%)	purity ^b (%)
1	sodium benzoate	benzyl chloride	[cmmim][PF ₆]	98	98
2			[cmmim][BF ₄]	97	98
3	sodium <i>o</i> -chlorobenzoate	benzyl chloride	[cmmim][PF ₆]	98	99
4			[cmmim][BF ₄]	99	99

^a Scavenging conditions: 100 °C, 60 min. ^b Purity was determined by GC.

Scheme 3**Scheme 4**

Next, we examined the effects of the molar ratio of [cmmim][PF₆] or [cmmim][BF₄] to the reagent on scavenging efficiencies. Following an extensive investigation using the model reaction between [cmmim][PF₆] and methanesulfonyl chloride, it was found that even 2 equiv of [cmmim][PF₆] could give shortened sequestration time.

The efficiency of [cmmim][X] (X = PF₆⁻, BF₄⁻) was then demonstrated in several solution-phase syntheses under optimized conditions (Scheme 2). A scavenger was incubated with an excess amount of methanesulfonyl chloride, aniline, and *p*-toluidine at room temperature. In all cases, both the synthesis and purification strategy outlined in Scheme 2 proved successful. The desired products were obtained in high isolated yields (≥96%) and high purity (≥98%) (Table 1). On completion of the reactions, ionic liquid phase was recovered by simple decantation of the organic phase. No ionic liquids were detected in the organic phase (HPLC). For example, benzoyl chloride was treated with 2 equiv of aniline in toluene in the presence of pyridine at room temperature. On completion, 2 equiv of [cmmim][PF₆] was added. The excess aniline was effectively removed from the solution in 30 min. After these manipulations, the toluene layer was decanted, and the ionic liquid phase was extracted with CH₂Cl₂/Et₂O (1:2, v/v). The solvents in the combined organic phase were then removed by evaporation, affording the corresponding amide in excellent yield and purity.

Table 3. Reusability of [cmmim][BF₄] as Scavenger in the Reaction of Sodium Benzoate and Benzyl Chloride

cycles	time (min)	benzyl benzoate		recovery (%)	
		yield (%)	purity (%)	[bmim][PF ₆]	[cmmim][BF ₄]
1	60	98	98	94	91
2	60	96	96	93	90
3	70	96	97	95	92
4	75	96	96	94	90

Table 4. Purification of *N*-Acyl-*N'*-alkyl Piperazines Using [cmmim][BF₄] as Scavenger

entry	<i>N</i> -acyl-piperazines	halides	yield ^a (%)	purity ^b (%)
1			95	98
2			88	96
3			88	98
4			90	98
5			90	95
6			95	96

^a Scavenging conditions: 110 °C, 1.5–2 h. ^b Purity was determined by GC.

To prove the generality of the method, the synthesis of benzyl benzoate from benzyl chloride was also performed using [cmmim][X] as scavenger (Scheme 3). In view of the poor solubility of sodium benzoate in many organic solvents as well as the simplification of the regeneration workup, we employed [bmim][PF₆] as the solvent in these reactions. The sodium benzoate was treated with 1.5 equiv of benzyl chloride in [bmim][PF₆]. When the TLC analysis suggested the complete consumption of sodium benzoate, 1.0 equiv of [cmmim][X] and 1.0 equiv of K₂CO₃ were added. After 60 min of stirring at 100 °C, the residual benzyl chloride disappeared. A mixture of CH₂Cl₂ and Et₂O (1:2, v/v) was

then added to extract the product. Evaporation of combined extracts gave essentially pure product in high yield ($\geq 97\%$ yield, $\geq 98\%$ purity) (Table 2).

Our interest was also focused on the reusability of the ionic liquid-based scavenger from the viewpoints of economy and the environment. In the case of benzyl benzoate synthesis (Table 2, entry 2), after the products were isolated from the ionic phase, the used scavenger was regenerated after hydrolysis. The regenerated [cmmim][BF₄] could be reused without supplement for three consecutive runs with negligible decrease in its activity (Table 3).

Finally, a small library of insecticide-like *N*-acyl-*N'*-alkyl piperazines was constructed using this new strategy (Scheme 4). The starting *N*-acyl-piperazines were treated with halides in toluene in the presence of K₂CO₃ as base. After alkylation (110 °C, 12 h), excess halides were removed by reacting with ionic scavenger [cmmim][BF₄] for 1.5–2 h at 110 °C. The desired products were obtained in good yields (88–95%) in satisfactory purities (95–98%, GC) (Table 4).

Conclusion. In summary, we have introduced the use of ionic liquid-based scavengers in the removal of excess reagents, such as methanesulfonyl chloride, aniline, *p*-toluidine, and benzyl chloride, in solution-phase reactions. Several advantages of this strategy, such as the need for lesser amounts of scavenger as well as a rapid scavenging process (30–120 min), have demonstrated the enormous potential of this new protocol in combinatorial chemistry. Moreover, we are delighted to discover that the ionic liquid-based scavenger can be regenerated and recycled at least three times without apparent loss of activity.

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Supporting Information Available. Experimental procedures for the synthesis of carboxyl-functional ionic liquids, representative scavenging process, and the regeneration of used scavenger. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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