A Practical, Water-Soluble, Ionic Scavenger for the Solution-Phase Syntheses of Amides

by **Ming Lei**, **Xiao-Le Tao**, and **Yan-Guang Wang***

Department of Chemistry, Zhejiang University, Hangzhou 310027, P.R. China
(e-mail: orgwyg@zju.edu.cn)

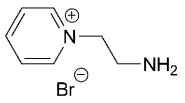
A new ionic, water-soluble scavenger for acyl chlorides, 1-(2-aminoethyl)pyridinium bromide (**1**), has been investigated. Compound **1** was used for the rapid and simple purification of a series of benzamides and sulfonamides (*Table*) obtained by solution-phase synthesis from the corresponding amines (*Scheme*). The inexpensive scavenger, which can be prepared on large scale, was shown to readily 'eliminate' excess acyl chlorides (reagent) by simple aqueous extraction. The amides purified in this way were obtained in excellent yields and purities (*Table*), which makes **1** a versatile new reagent, especially for the combinatorial solution-phase synthesis of amide libraries.

Introduction. – Solution-phase combinatorial chemistry for library generation has been receiving increased attention as a powerful tool for lead discovery and optimization in drug development [1]. Solution-phase synthetic techniques offer many advantages over solid-phase approaches such as unlimited scale, simple manipulation, and cost effectiveness. However, with solution-phase syntheses, the rapid purification or isolation of desired compound from a reaction mixture is difficult, and represents the 'bottleneck' in the synthetic process.

Recently, polymer-supported scavengers have been developed for compound purification in solution-phase combinatorial chemistry [2]. These scavengers allow the removal of excess reagents and side products by simple filtration, but low loading capacity and high costs have, so far, limited their application for large-scale library preparation. Although several high-loading solid scavenger reagents have been developed, they suffer from slow exchange at the solid–liquid interface [3]. An efficient solution to these problems is replacement of the polymer-supported scavenger with small-molecule reagents such as *Girard*'s reagent T [4], *N*-methyltris(2-aminoethyl)amine [5], *N*-Boc-iminodiacetic anhydride [6], and potassium sarcosinate [7] to generate water-soluble byproducts, which can be separated, together with the excess scavengers, from the products by liquid–liquid extraction.

Recently, *Song* and co-workers [8] reported an amino-functionalized ionic liquid, *i.e.*, 1-aminoethyl-3-methylimidazolium hexafluorophosphate ([2-aemim][PF_6]), as an electrophile scavenger for solution-phase synthesis; the scavenging products were separated by extraction with the ionic liquid [bmim][PF_6].

Herein, we describe the application of the practical, ionic, water-soluble scavenger 1-(2-aminoethyl)pyridinium bromide (**1**) for the solution-phase synthesis of libraries of amides and sulfonamides.



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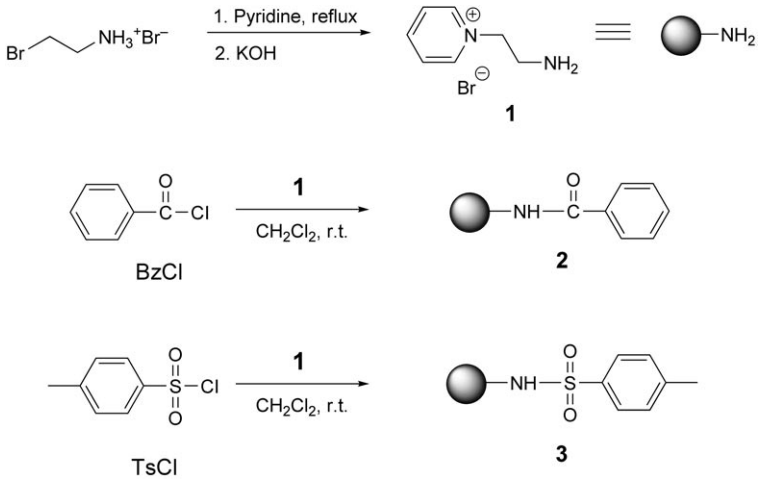
Results and Discussion. – We chose the pyridinium salt **1** as a model of an ionic scavenger since it is highly water-soluble, inexpensive, and can be readily prepared and purified, even on large scale, from pyridine and 2-bromoethylamine hydrobromide (*Scheme 1*). Next, **1** was reacted with benzoyl chloride (BzCl) and toluene-4-sulfonyl chloride (TsCl) to afford the corresponding benzamide **2** and sulfonamide **3**, respectively. As expected, both compounds are water soluble, which ensured that the scavenger **1** is capable of trapping excess reagent (acid chloride) to generate water-soluble byproducts (such as **2** and **3**), which, in turn, can be removed by washing.

Scheme 1



The ionic scavenger **1** was evaluated in the purification of various amides prepared by benzoylation of the corresponding amines **4** (*Scheme 2*). Typically, an amine (1 mmol) was reacted with excess BzCl (2 mmol) in CH_2Cl_2 (5 ml) in the presence of excess base (Et_3N or pyridine) at room temperature. After completion of the reaction, compound **1** (1.2 mmol) was added, the mixture was stirred for 6 h, diluted with AcOEt, and washed with brine. The organic layers were passed through a short pad of anhydrous Na_2SO_4, and, finally, evaporated to afford the desired benzamides **5** in good-to-excellent yields (86–92%) and high purities (95–99%; *Table*).

Next, we tested the reaction of different amines with TsCl instead of BzCl. When the same procedure was applied, with **1** acting as a scavenger of excess TsCl, and using pyridine instead of Et_3N as base, similarly high yields and purities were achieved (*Table*).

In summary, we have developed a practical, water-soluble, ionic scavenger for the purification of amide or sulfonamide libraries prepared by solution-phase synthesis. The scavenger **1** can be easily prepared on large scale, and efficiently removes excess

Scheme 2

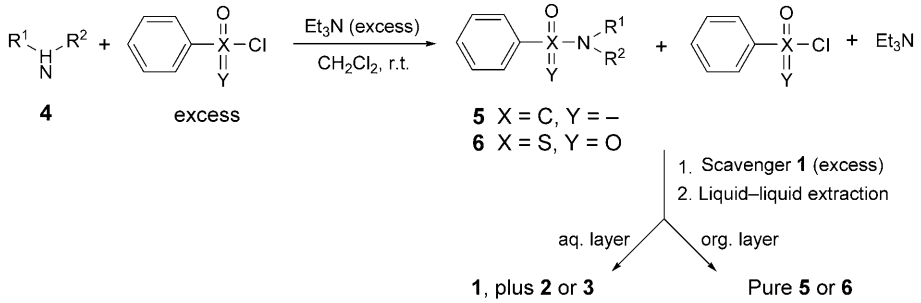


Table. *Amines for the Synthesis of the Corresponding Amides* **5** *and* **6** *Purified with the Aid of the Ionic Scavenger* **1**. All products were identified by GC/MS and ^{1}H-NMR (data not shown). For synthetic details, see *Exper. Part.*

Amine	Benzamide **5**		Sulfonamide **6**	
	Yield [%]	Purity [%][a])	Yield [%]	Purity [%][a])
Aniline	87	97	89	95
N-Ethylaniline	89	99	88	97
4-Methoxyaniline	92	99	93	96
4-Nitroaniline	86	95	85	95
Benzylamine	86	95	85	98
Cyclohexylamine	86	99	87	99
Dodecylamine	88	97	90	96
Morpholine	88	98	88	99
Piperidine	87	99	87	95
Toluidine[b])	90	97	90	95

[a]) Determined by GC/MS. [b]) 2-Toluidine for **5**, 3-toluidine for **6**.

reagents (acid chlorides) by generating water-soluble byproducts that can be removed by simple extraction. Since compound **1** is high loading and cost effective, it should prove useful in solution-phase combinatorial chemistry.

Experimental Part

General. All chemicals were reagent grade, and used as purchased. M.p.: *WRS-1B* digital melting-point apparatus; uncorrected. ^{1}H- and ^{13}C-NMR Spectra: *Bruker Avance-500* or *Avance-400* spectrometers; at 500 (^{1}H) and 125 MHz (^{13}C), or at 400 MHz (^{1}H); δ in ppm, J in Hz. GC/MS: *Hewlett-Packard HP-6890* gas chromatograph coupled to a mass spectrometer; in m/z.

1-(2-Aminoethyl)pyridinium Bromide (**1**). A soln. of 2-bromoethylamine hydrobromide (20.49 g, 0.1 mol) in freshly dist. pyridine (50 ml) was heated at reflux for 24 h. Excess pyridine was removed *in vacuo*, the solid residue was dissolved in a minimal amount of H_2O, and the pH was adjusted to *ca.* 8 by adding solid KOH in small portions. The aq. soln. was extracted with AcOEt (2 × 30 ml), and evaporated to dryness. The resulting solid residue was extracted with MeCN. The combined MeCN extracts were concentrated to afford **1** (18.3 g, 90%) as a solid. M.p. 227.9–229.6°. IR (KBr): 3555, 3481, 3418, 1637, 1618, 1079,

1036. ^{1}H-NMR (500 MHz, D_2O): 3.43 (t, J = 6.0, 2 H); 4.80 (t, J = 6.0, 2 H); 8.09–8.12 (m, 2 H); 8.56–8.59 (m, 1 H); 8.89–8.90 (m, 2 H). ^{13}C-NMR (125 MHz, D_2O): 40.89; 61.43; 128.98; 145.00; 146.76. ESI-MS: 123 ($[M-Br]^+$).

1-[2-(Benzoylamino)ethyl]pyridinium Bromide (**2**). To a soln. of BzCl (211 mg, 2 mmol) in CH_2Cl_2 (5 ml) was added **1** (203 mg, 1 mmol) and Et_3N (2 mmol). The mixture was stirred at r.t. for 2 h, and then diluted with H_2O (5 ml). The aq. layer was extracted with CH_2Cl_2 (2×5 ml), and concentrated. The resulting residue was purified by column chromatography (SiO_2; CH_2Cl_2/MeOH 5:2) to afford **2** (252 mg, 82% based on **1**) as a yellow solid. M.p. 241.1–242.7°. IR (KBr): 3424, 3018, 2999, 2820, 1637, 1492, 1328, 1158, 1095. ^{1}H-NMR (500 MHz, D_2O): 3.76 (t, J = 5.2, 2 H); 4.62 (t, J = 5.2, 2 H); 7.19–7.22 (m, 2 H); 7.28–7.32 (m, 1 H); 7.37–7.39 (m, 2 H); 7.78–7.81 (m, 2 H); 8.29–8.33 (m, 1 H); 8.66–8.68 (m, 2 H). ^{13}C-NMR (125 MHz, D_2O): 40.35; 61.30; 127.29; 128.55; 129.16; 132.65; 132.83; 144.91; 146.48; 170.61. ESI-MS: 227 ($[M-Br]^+$).

1-(2-{[(4-Methylphenyl)sulfonyl]amino}ethyl)pyridinium Bromide (**3**). Prepared in analogy to **2** (see above), but from TsCl and pyridine. Yield of **3**: 85% (based on **1**). Yellow solid. M.p. 234.3–235.6°. IR (KBr): 3448, 3029, 2972, 1633, 1489, 1316, 1159, 1092. ^{1}H-NMR (500 MHz, D_2O): 2.33 (s, 1 H); 3.47 (t, J = 5.2, 2 H); 4.61 (t, J = 5.2, 2 H); 7.29–7.31 (m, 2 H); 7.51–7.53 (m, 2 H); 7.94–7.98 (m, 2 H); 8.45–8.47 (m, 1 H); 8.70–8.72 (m, 2 H). ^{13}C-NMR (125 MHz, D_2O): 20.85; 42.93; 61.18; 126.70; 128.40; 135.11; 144.92; 145.47; 146.43. ESI-MS: 277 ($[M-Br]^+$).

General Procedure for the Synthesis of Benzamides **5**. To a soln. of the appropriate amine **4** (1 mmol) in CH_2Cl_2 (3 ml) was added BzCl (2 mmol), and Et_3N or pyridine (3 mmol), and the mixture was stirred at r.t. The progress of the reaction was monitored by GC analysis. After completion of the reaction, the scavenger **1** (1.2 mmol) was added, the mixture was stirred at r.t. for 6 h, diluted with AcOEt (10 ml), and washed with brine (2×10 ml). The org. layers were passed through a short pad of anh. Na_2SO_4, and evaporated to afford the benzamides **5**. Their purities were determined by GC/MS analysis and ^{1}H-NMR spectroscopy.

General Procedure for the Synthesis of Sulfonamides **6**. To a soln. of the amine **4** (1 mmol) in CH_2Cl_2 (3 ml) was added TsCl (2 mmol) and pyridine (3 mmol), and the mixture was stirred at r.t. The progress of the reaction was monitored by GC analysis. After completion of the reaction, the scavenger **1** (1.2 mmol) was added at r.t., the mixture was stirred for 6 h, diluted with AcOEt (10 ml), and washed with brine (2×10 ml). The org. layers were passed through a short pad of anh. Na_2SO_4, and evaporated to afford the sulfonamides **6**. Their purities were determined by GC/MS analysis and ^{1}H-NMR spectroscopy.

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