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A new high-loading water-soluble scavenger for anhydrides, acid chlorides and isocyanates

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Abstract—We demonstrate here that a new quaternary ammonium salt bearing three amino functionalities can be used to remove electrophiles. In most cases, final products were essentially pure after treatment of the crude reaction mixture with this new scavenger reagent. © 2002 Elsevier Science Ltd. All rights reserved.

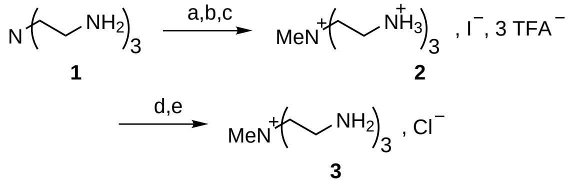
Although the principle of using scavenger reagents for straightforward purification of reaction products is well established, the rate at which novel drug candidates may be prepared today stimulated renewed interest in these systems.[1] Scavenging methods are therefore becoming widespread in chemical libraries preparation, and there are a number of appropriate reagents commercially available. However, there is considerable scope for improvement. Most of these compounds are reticulated polymers and the major drawbacks of these supported scavengers are the high cost and the large amount generally required to clean up a typical reaction product.

To address this issue, several groups have recently developed high-loading scavenger reagents using dendrimer-like structures, essentially to reduce the cost of scavenging (less solvent, less reagent).[2] In fact, a few of these high-loading scavenger resins are now commercially available, and their number will most likely increase in the future. However, the technique of using solid-supported scavenger reagents has drawbacks in automated synthesis, namely difficult automation of resin addition and longer reaction times due to solid–liquid interface. Some aqueous-phase[3] and fluorous-phase[4] scavengers, as well as some polyaromatic,[5] PEG[6] and magnetic beads[7] supported scavenger reagents have been designed to avoid these limitations.

The basic idea here was to replace the polymeric core of scavenger reagents by a functionality of low molecular weight which could make the scavenger water soluble at any time. Such molecule may be seen as an efficient, very high-loading and readily removable scavenger reagent. This report describes the synthesis of a new quaternary ammonium salt bearing three amino functionalities, and demonstrates how it can be used to remove electrophiles.

N-Methyl substituted tris-(2-aminoethyl)-amine **3** was synthesized by standard protection of the primary amines, followed by methylation of the tertiary amine and deprotection (Scheme 1). Filtration through anion exchange resin (Amberlite IRA400) allowed to isolate compound in which TFA counter ions were quantitatively replaced by chloride ions, as indicated by ^{13}C NMR. This salt was deprotonated with sodium hydroxide and separated from sodium chloride by trituration with ethyl alcohol.[8]

After evaporation of the solvent, we noticed that triamine **3** was difficult to manipulate because of its high viscosity. Since we could reasonably expect it to be hygroscopic, we decided to use it in aqueous solution, and therefore dissolved it in water at a concentration of 0.87 M. We considered using water because another



Scheme 1. (a) Boc$_2$O, NaOH, H$_2$O, dioxane (84%); (b) MeI, CH$_3$CN (75%); (c) TFA/CH$_2$Cl$_2$ (quant.); (d) Amberlite IRA400 (90%); (e) NaOH (3 equiv.) (89%).

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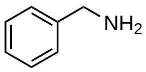
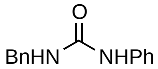
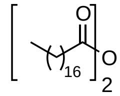
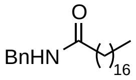
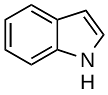
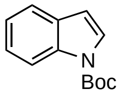
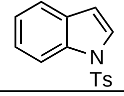
Table 1. Electrophile trapping from crude reaction mixtures

entry	Substrate	Electrophile	Product	Remaining electrophile *before scavenging*	Remaining electrophile *after scavenging*[a]
1		Boc_2O	BnNHBoc	45%	not detected
2		Ac_2O	BnNHAc	48%	"
3		TsCl	BnNHTs	50%	"
4		PhNCO		50%	"
5				40%	"[b]
6		Boc_2O		45%	"
7		TsCl		48%	"

[a] Method A (addition of ethyl acetate and three times washing with water) or method B (dry with sodium sulfate and filter through a short pad of silica (solvent: AcOEt)) gave the same results.[b] Contaminated with a stearic acid derivative.

solvent might have evaporated over time, making solution concentration not reliable. Nevertheless, amines dissolved in water are acknowledged to readily react with electrophiles in organic phase.

To demonstrate the potential of this triamine in a scavenger role, benzylamine and indole were selected as substrates and were treated intentionally with excess of various electrophiles (1.5 equiv.). Upon completion, the aqueous solution of **3** (0.5 equiv.) was added and the reaction mixture was stirred overnight. Two workup procedures were experimented. We tried either to dilute with ethyl acetate and wash three times with water (method A), or to dry with sodium sulfate and filter through a short pad of silica gel (solvent: AcOEt) (method B). Both strategies proved to be equally efficient. The amount of remaining electrophile was evaluated by proton NMR before and after scavenging. The results are reported in Table 1.

In most cases, the final products were electrophile free and essentially pure. Only in one case (Table 1, entry 5) was the resulting amide contaminated with a stearic acid derivative, probably a stearate salt. However, neither stearic anhydride nor derivative of **3** were left, and this rather polar contaminant was easily removed by chromatography. Entry 5 was the only example where further purification was necessary. Since no residual carboxylate was detected for acetic anhydride scavenging (Table 1, entry 2), small chain carboxylic acids may also be trapped by this triamine, even though the use of ion exchange resins may be preferable. Such reagent dissolved in water, should make scavenger addition easier in automated synthesis. Research into the discovery of new high-loading crystalline scavenger reagents is currently being undertaken.

Acknowledgements

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8. (a) Tris-(2-*tert*-butoxycarbonylaminoethyl)-amine: Starting triamine (3 mL, 0.02 mol) was dissolved in dioxane (40 mL), and sodium hydroxide (7.2 g, 0.18 mol) in water (20 mL) was added. The reaction mixture was cooled to 0–5°C, and solid Boc_2O (26.2 g, 0.12 mol) was quickly added by portions. The reaction was left for 30 min at this temperature, and was then allowed to warm up to room temperature overnight. The crude reaction mixture was then partitioned between AcOEt (100 mL) and water (100 mL), and the aqueous layer was extracted twice with AcOEt (50 mL). The combined organic layers were dried, filtered and concentrated under vacuum. The resulting oil crystallized overnight. The white crystal was triturated with hexane, collected by filtration and washed with this solvent. The desired product was obtained in pure form (7.5 g, 84%) as a white crystal (mp = 96°C); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.47 (s, 27H), 2.55 (t, 6H, $J=5.6$ Hz), 3.17 (q, 6H, $J=5.6$ Hz), 5.17 (br s, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 28.8, 38.9, 54.6, 79.5, 156.8.

(b) Tris-(2-*tert*-butoxycarbonylaminoethyl)methylammonium iodide: Boc-protected triamine (3.13 g, 7 mmol) was dissolved in acetonitrile, MeI (0.46 mL, 7.35 mmol) was added and the reaction mixture was sealed and stirred for 2 days at room temperature. Solvent was evaporated, and ^1H NMR indicated that the nitrogen was not entirely quaternized (around 90% of quaternary ammonium). The residue was diluted in AcOEt (20 mL) and ether (20 mL), and the organic layer was extracted with deionized water (6×40 mL). Water was evaporated and the residue was dried under vacuum at 50°C, to give the expected quaternary ammonium in pure form (3.09 g, 75%) (mp = 86°C); ^1H NMR (CD_3OD, 200 MHz): δ 1.50 (s, 27H), 3.26 (s, 3H), 3.57 (br s, 12H); ^{13}C NMR (CD_3OD, 100.6 MHz): δ 27.7, 34.3, 49.2, 61.2, 80.0, 157.1.

(c) Tris-(2-aminoethyl)methylammonium iodide·3TFA (**2**): TFA (20 mL) was added to a solution of tricarbamate (2.2 g, 3.74 mmol) in methylene chloride (20 mL). After 2 h, solvents were evaporated and remaining TFA was removed by two consecutive additions and evaporations of EtOH (20 mL), yielding the expected tetraammonium (2.35 g, quant.) (mp = 173°C (decomp.)); ^1H NMR (CD_3OD, 200 MHz): δ 3.47 (s, 3H), 3.65 (m, 6H), 3.97 (m, 6H); ^{13}C NMR (CD_3OD, 100.6 MHz): δ 32.7, 49.5, 58.6, 117.0 (q, $J=292$ Hz), 162.6 (q, $J=35$ Hz).

(d) Tris-(2-aminoethyl)methylammonium chloride·3HCl: Compound **2** (2.35 g, 3.73 mmol) was dissolved in distilled water and was percolated through Amberlite IRA400 (20 g, 3.8 mequiv. Cl^-/g, 76 mmol). Water was evaporated and the crystal was dried by azeotropic removal of water with ethanol (1.03 g, 90%) (mp = 235°C (decomp.)); ^1H NMR (D_2O, 200 MHz): δ 3.34 (s, 3H), 3.57 (m, 6H), 3.84 (m, 6H); ^{13}C NMR (D_2O, 100.6 MHz): δ 32.7, 50.0, 58.6.

(e) Tris-(2-aminoethyl)methylammonium chloride (**3**): A mixture of **3**·3HCl (0.98 g, 3.2 mmol) and sodium hydroxide (384 mg, 9.6 mmol) was dissolved in distilled water (20 mL). Water was evaporated and the remaining crystal was dried by double azeotropic removal of water with ethanol. The residue was triturated with ethanol and filtered. Evaporation of the solvent gave the desired product (560 mg, 89%) as a viscous colorless oil; ^1H NMR (CD_3OD, 200 MHz): δ 3.08 (m, 6H), 3.19 (s, 3H), 3.40 (m, 6H); ^{13}C NMR (CD_3OD, 100.6 MHz): δ 34.9, 49.3, 63.8