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Parallel Synthesis of Tertiary Amines using Polystyrene Sulfonylchloride (PS-TsCl) Resin

Yonghan (Fred) Hu *, Owen W. Gooding, Jeff W. Labadie, Wendy Miller, and John A. Porco, Jr.*
Argonaut Technologies, 887 Industrial Road, Suite G, San Carlos, CA 94070
Tel. (650) 598-1350, Fax (650) 598-1359

Abstract

A focused library of tertiary amines was synthesized by reacting alcohols with polystyrene sulfonyl chloride resin to give polystyrene sulfonates, which were then reacted with secondary amines to give tertiary amines.

Keywords

polystyrene sulfonylchloride resin, tertiary amine synthesis.

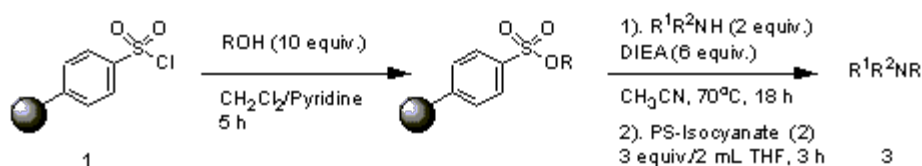
Introduction

The use of polymer-supported reagents and scavengers continues to receive much attention as evidenced by the growing number of parallel solution phase synthesis applications.^{1,2,3,4,5} Polymers with sulfonyl chloride functionality may react with a variety of nucleophiles to produce a number of functional derivatives.⁶ Polymeric sulfonyl chlorides have been employed in the synthesis of 6-deoxyoligosaccharides⁷, tertiary amines, thioethers, and imidazoles^{7,8}, aldehydes¹⁰, arginine-containing peptides¹¹, and a guanidinium-based "tweezer" receptor.¹²

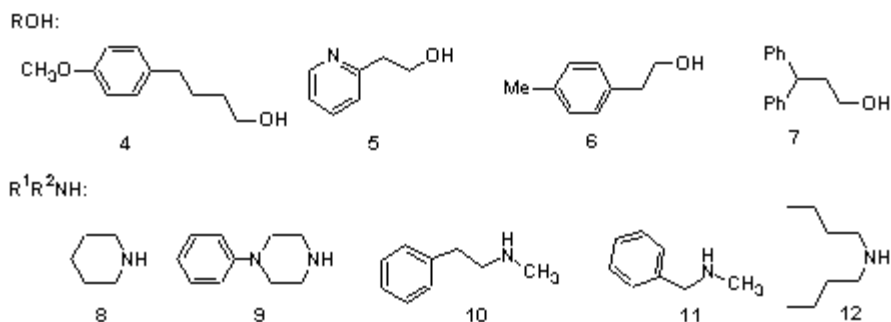
We recently developed a polymer-supported tosyl chloride equivalent, PS-TsCl (**1**)¹³. This resin may be used to "catch" alcohols as polymer-bound sulfonates. After a simple workup involving resin washing, the resin-bound sulfonates can be reacted with secondary amines to "release" tertiary amine products (**Scheme 1**). After nucleophilic displacement of the polymer-bound sulfonates to form the tertiary amines, excess secondary amines may be scavenged using PS-Isocyanate resin (**2**)¹⁴. The latter resin may be used to scavenge excess nucleophiles from solution, which are often used to drive reactions to completion, thereby facilitating work-up and purification.¹⁵ By performing parallel synthesis on the Quest 210 organic

synthesizer (Argonaut Technologies), which facilitates both parallel synthesis and purification, a focused library of tertiary amines (**3**) was generated.

Scheme 1. Tertiary Amine Synthesis using PS-TsCl resin



Scheme 1. Tertiary Amine Synthesis using PS-TsCl resin



Results and Discussion

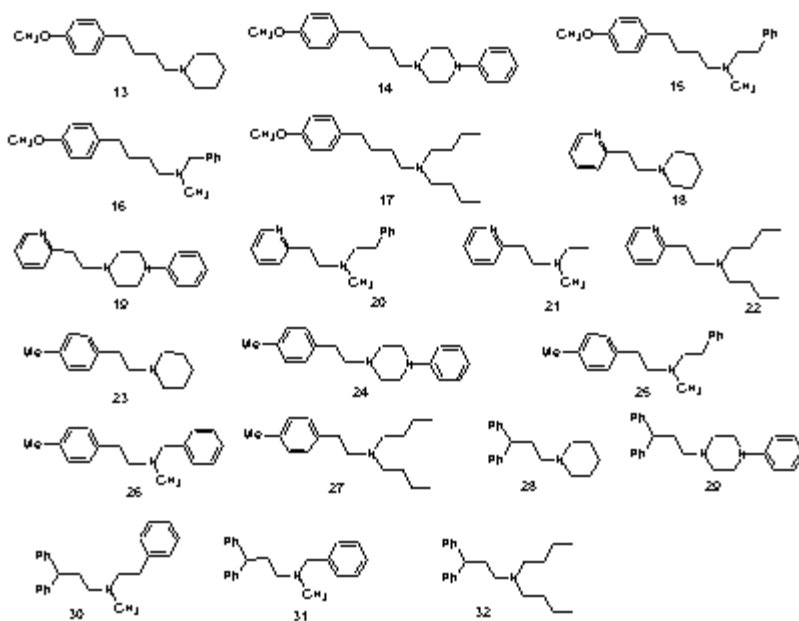
Loading of alcohols to PS-TsCl resin was complete in 5 h at room temperature using a 1:1 mixture of CH₂Cl₂ and pyridine.¹⁶ Extensive washing (including washing with protic solvents to fully extract pyridine salts) was required for complete removal of reagent-based impurities. Nucleophilic substitution of sulfonate resins was accomplished using 2 equiv. of secondary amine and six equiv. of DIEA in acetonitrile. Excess secondary amine was scavenged by excess PS-Isocyanate resin. **Table 1** provides chemical yields for the tertiary amine products. All products were characterized by GC (GC method: 175°C (3 min), ramp up to 300°C (20 °C/min), 300 °C for 5 min.) and were found in high purity (100 % GC area) and free of secondary amine starting materials. The twenty tertiary amines (**Figure 1**) were isolated with chemical yields ranging from 66-100%. Representative experimental procedure (entry 2): To a reaction vessel containing 75 mg of PS-TsCl resin (1.47 mmol/g, 0.11 mmol) under argon was added 3 mL of a 4-(methoxyphenyl)-1-butanol (0.178 mL, 1.05 mmol) in DCM/pyridine (1:1). The mixture was stirred for 5 h. The resin was then washed with DCM (3 x), DMF (5 x), DMF/H₂O (3:1, 5 x), THF (3 x), DCM (3 x) and dried under vacuum. A solution of 1-phenylpiperazine (0.31 mL, 0.21 mmol) and N,N-diisopropylethylamine (0.107 mL, 0.63 mmol) in 3 mL acetonitrile was then added and the mixture was heated at 70°C for 18 h. Finally 255 mg of PS-Isocyanate resin (1.21 mmol/g, 0.31 mmol) was added with 2 mL of THF. After 3 h at room temperature, the solution was filtered into a pre-weighed vial (three THF washes to rinse product from the resin). The solvent was then concentrated to give 1-phenyl-4-(4-methoxyphenyl)butyl-piperazine in 98% yield (GC purity 100%). ¹H NMR (CDCl₃, 300 MHz): 7.33-6.81 (m, 9 H, Ar-H), 3.79 (s, 3 H, CH₃O-), 3.27 (m, 4 H), 2.72-2.41 (m, 8 H), 1.63 (m, 4 H) ppm; ¹³C NMR (CDCl₃, 75 MHz): 157.69, 150.88, 134.12, 129.12, 129.02, 119.90, 116.11, 113.61, 58.05, 55.00, 52.66, 48.37, 34.45, 29.11, 25.39 ppm.

Table 1. Tertiary Amine Synthesis using PS-TsCl resin

RV	ROH	R ¹ R ² NH	R ¹ R ² NR	Yield (%)	RV	ROH	R ¹ R ² NH	R ¹ R ² NR	Yield (%)
1	4	8	13	100	11	6	8	23	90
2	4	9	14	98	12	6	9	24	92
3	4	10	15	99	13	6	10	25	97

4	4	11	16	99	14	6	11	26	95
5	4	12	17	78	15	6	12	27	68
6	5	8	18	98	16	7	8	28	87
7	5	9	19	99	17	7	9	29	96
8	5	10	20	89	18	7	10	30	89
9	5	11	21	88	19	7	11	31	84
10	5	12	22	76	20	7	12	32	66

Figure 1. Focused Library of Tertiary Amines



In summary, a library of twenty tertiary amines was synthesized in high yield and chemical purity on the Quest 210 using PS-TsCl resin. The synthesizer provided an inert environment for "catching" alcohols onto PS-TsCl resin. The ability to perform parallel washing greatly facilitated the removal of reagent-based impurities. The Quest 210 synthesizer provided a closed system for "releasing" tertiary amines at elevated temperature. Excess secondary amines from the cleavage of sulfonates were scavenged using PS-Isocyanate resin preloaded into SPE cartridges on the SPE rack accessory. The use of SPE cartridges in conjunction with the Quest SPE rack expedited parallel product purification.

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- [16] We have recently found that sulfonate formation may be accomplished by use of 2.5 equiv. alcohol (0.45 M, 1:1 CH₂Cl₂ / pyridine, 5 h). The sulfonate formation may also be monitored using a simple bead staining test. To check for residual sulfonyl chloride groups on the resin, a few beads may be sampled from the alcohol loading reaction, and the beads washed with DCM (3 x), DMF (3 x), DMF/H₂O (3:1, 3 x), and THF (3 x). The resin is then treated with 5% ethylenediamine in DMF for 5 mins to convert remaining sulfonyl chloride groups into a sulfonamide-linked primary amine. The beads are washed with DMF (3 x), DCM (3 x), THF (3 x), then stained with a few drops of bromophenol blue (1% in dimethylacetamide). The beads are further washed with DMF (5 x). If the final color of the beads is white or off-white, the reaction is complete.

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Comments

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