Report

Vapor-Phase Hofmann Elimination: A Rapid One-Pot Method for the Cleavage of Tertiary Amines from Radio Frequency Encoded Solid-Phase Synthesis

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Reports

Vapor-Phase Hofmann Elimination: A Rapid One-Pot Method for the Cleavage of Tertiary Amines from Radio Frequency Encoded Solid-Phase Synthesis

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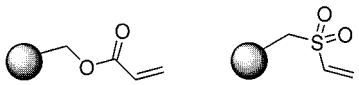
The efficiency of split-pool techniques[2] is a major reason for utilizing this solid-phase synthesis methodology to produce lead finding libraries during the drug discovery process. More recently, the advent of commercially available technology allowing the radio frequency encoding of split-pool libraries and directed sorting prior to cleavage has combined the advantages of parallel and split-pool synthesis.[3] However, although this encoded split-pool strategy minimizes the number of individual reaction steps prior to cleavage, the subsequent cleavage of large numbers of single compounds can prove to be the rate-determining step for production of large libraries. We have therefore been investigating methodologies which should alleviate this "bottleneck".

We are currently utilizing solid-phase techniques to generate libraries of tertiary amine containing small molecule lead finding libraries. The general methodology for these libraries involves functionalization of resins **1**[4] or **2**[5] by



1 **2**

Michael addition. Bifunctional amines can then be further

Scheme 1

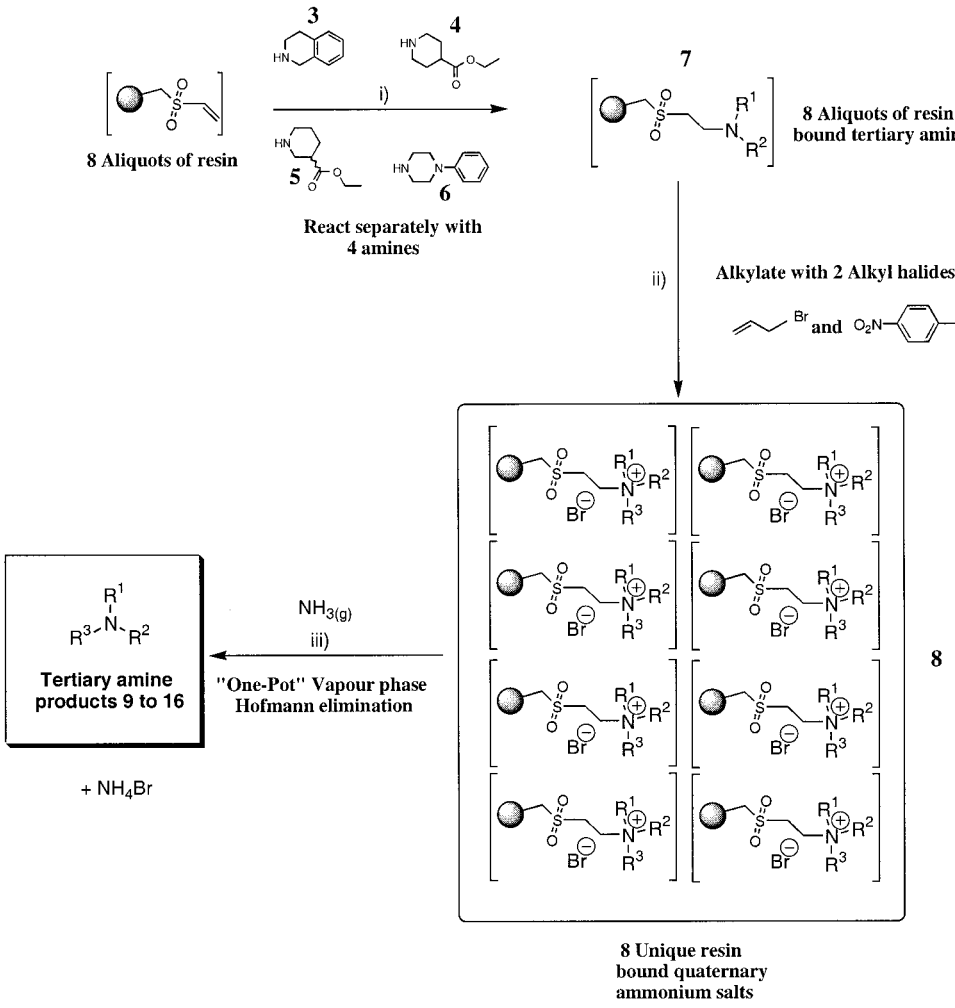


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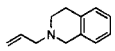
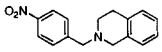
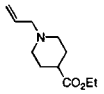
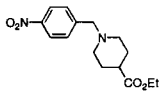
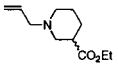
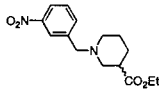
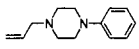
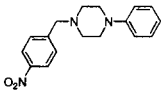
Table 1

Tertiary Amine[8]	Yield (mg)	Yield (%)[9]	Expected M.Wt.	Found M+H	HPLC Purity[10] 214nm
 **9**	22	37	173.2	174.4	>95%
 **10**	58.1	64	268.3	269.3	>95%
 **11**	24.6	37	197.3	198.0	>95%
 **12**	32.9	33	292.3	292.8	75.9%
 **13**	6.8	10	197.3	198.0	64.5%
 **14**	16.2	16	292.3	293.2	83.4%
 **15**	22.5	33	202.3	203.2	>95%
 **16**	12.7	12.6	297.4	298.2	>95%

elaborated using a range of solid-phase reactions, and finally the desired tertiary amine products (Scheme 1) are released from the resin by quaternization with alkyl halide and base induced Hofmann elimination.[4]

Typical cleavage procedures[4−6] require overnight treatment with excess diisopropylethylamine or triethylamine. Hence the time to cleave a large library can be far longer than the time taken to construct the library on the solid support. Additionally, the use of excess organic base to facilitate the Hofmann elimination contaminates the final products with amine and amine salt unless this is removed by solid-phase extraction, aqueous workup, or utilization of the two-resin system reported by Ouyang et al.[6] We were interested in finding a rapid method of parallel processing which would not only reduce the time taken to cleave the library products from the solid support but also minimize the residues due to the cleavage reagent. Hence, gaseous ammonia seemed to be the ideal reagent for vapor-phase Hofmann elimination.[7]

This methodology (Scheme 1) was tested by constructing a small library of eight tertiary amines from four secondary amines **3, 4**, **5**, and **6** which were loaded onto vinyl sulfone resin **2**. The resulting resin-bound tertiary amines **7** were then quaternized with both allyl bromide and 4-nitrobenzyl bromide to give eight resin-bound quaternary ammonium salts **8** which were then transferred to porous polypropylene containers (IRORI MacroKans).

These MacroKans were placed in a glass peptide vessel which was then sealed under a slight positive pressure of ammonia gas and stored overnight at room temperature. After being dried under vacuum, the individual encoded resins were sorted into test tubes. Acetonitrile was added to each tube to dissolve the tertiary amine products from the resin and, after the tubes were shaken for 2 h, the solvent was concentrated (GeneVac) and the resin-containing kan removed to leave the pure tertiary amine products **9**−**16**. All products[8] were obtained in useful yield[9] and the majority of examples in high purity[10] (Table 1 and Figure 1). No

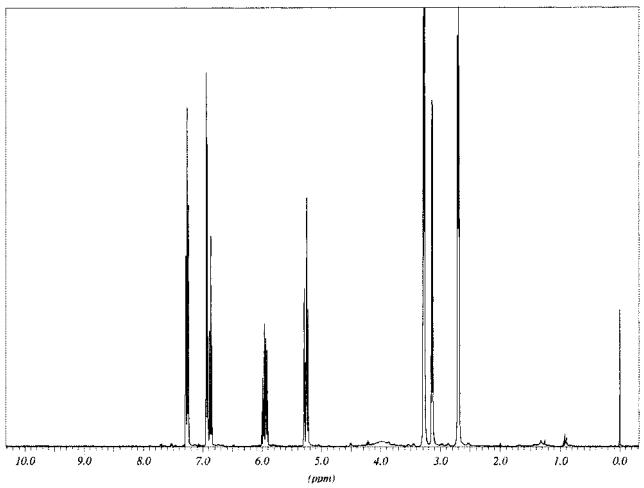


Figure 1. ^{1}H NMR spectum of crude cleaved product **15**.

evidence of cross-contamination due to mixing of solid products during mechanical sorting has been observed.

This methodology[11] has also successfully been applied to larger lead finding libraries where a full range of amines (e.g., primary, secondary, and bifunctional amines) and activated alkyl halides (e.g., methyl iodide, allyl bromide, and various substituted benzyl bromides) have successfully been incorporated. Both resins **1** and **2** give comparable results in terms of yield and purity, and no evidence of nucleophilic cleavage of the ester−resin linkage has been observed when using acrylate resin **1**. However, for larger libraries containing a diverse range of functional groups, the products are more reliably eluted from the resin matrix by incubation with dimethyl sulfoxide (DMSO). This can easily be carried out in parallel by immersing the kans in DMSO within a deep well microtiter plate followed by centrifugal evaporation, with the kans being held in place at the top of the wells. The average isolated yield of product is typically much improved when using DMSO, presumably due to improved solubility of tertiary amine containing products in this polar aprotic solvent.

Supporting Information Available. Experimental procedure for the synthesis of vinyl sulfone resin as well as HPLC and ^{1}H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

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(6) Ouyang, X.; Armstrong, R. W.; Murphy, M. M. *J. Org. Chem.* **1998**, *63*, 1027−1032.
(7) The vapor-phase cleavage of a silyl linker with TFA vapor has previously been reported. Newlander, K. A.; Chenera, B.; Veber, D. F.; Yim, N. C. F.; Moore M. L. *J. Org. Chem.* **1997**, *62*, 6726.
(8) All compounds gave satisfactory 400 MHz ^{1}H NMR spectra and the expected molecular ion by flow injection ES-MS.
(9) Percentage yields are based on the weight of isolated product obtained. Calculations are based on the initial resin substitution level of the chloromethyl polystyrene resin used to make vinyl sulfone resin **2**.[5]
(10) Reverse-phase HPLC was carried out using rapid water/acetonitrile (0.1% TFA) linear gradients from 5% organic to 100% organic component over 6 min. Flow: 2 mL/min. Column: Phenominex LUNA 3 mM C18 (2) 30 × 4.60 mm.
(11) Solid-phase synthesis was carried out on loose sulfone resin **2**[5] using a SyRo synthesis robot. (i) The resin (200 mg, 0.34 mmol, 1.7 mmol/g) was treated with the corresponding amine (10 equiv in DMF) at 50 °C for 4 h. The resins were then drained and washed with DMF (×5). (ii) The resin-bound tertiary amines **7** were treated at 50 °C with the corresponding alkyl halide (10 equiv in DMF). The resins were then drained, washed with DMF (×5), MeOH (×5), and DCM (×5), and dried. The dry resins **8** were transferred to polypropylene MacroKans for gas-phase cleavage. (iii) The eight resin-containing MacroKans were placed into a glass peptide vessel and treated with a stream of anhydrous ammonia gas for a few minutes. The vessel was then sealed under a slight positive pressure of ammonia gas and allowed to stand overnight. The vessel was then evacuated and the MacroKans dried in a vacuum oven. The individual MacroKans were then placed into tared test tubes containing acetonitrile (5 mL). After the tubes were shaken for 2 h, the solvent was concentrated (GeneVac), and the MacroKan was removed to leave the crude cleaved products.

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