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# A MIXED RESIN BED FOR THE QUENCHING AND PURIFICATION OF TETRABUTYLAMMONIUM FLUORIDE MEDIATED DESILYLATING REACTIONS

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**Abstract**: A polymer-bound calcium sulfonate resin is prepared and used to sequester tetrabutylammonium fluoride. The simultaneous use of the calcium sulfonate resin with a sulfonic acid resin is used for the quenching and purification of desilylating reactions involving tetrabutylammonium fluoride as the reagent. Employment of this resin workup technique eliminates the need for a liquid-phase extractive protocol allowing the procedure to be easily automated. © 1998 Elsevier Science Ltd. All rights reserved.

The use of combinatorial chemistry for the generation of small molecule libraries has become an area of intense research.[1-3] While early disclosures focused on solid-phase organic chemistry methodologies, more recently solution-phase chemical library synthesis methods have been described.[4-10] We have recently reported a solution-phase chemical library synthesis/purification strategy based on principles of functional group molecular recognition and chemoselective sequestration.[6] Included in this general strategy is the use of functionalized resins to chemoselectively sequester excess reagents from solution phase and the use of functionalized resins to perform reaction-quenching operations, allowing purified products to be obtained by simple filtration away from sequestered contaminants and byproducts. Herein we report a mixed-bed resin system that is conveniently used to sequester excess tetrabutylammonium fluoride reagent from solution-phase and to quench desilylation reaction products by efficient proton/tetrabutylammonium exchange.

Silyl protecting groups are commonly used in the protection of many functional groups including alcohols and phenols (as their silyl ethers), carboxylic acids (as their 2-(trimethylsilyl)ethyl esters or trimethylsilyloxy esters), aromatic carbons (trialkylsilyl substituents), and amine functionality (as their 2-(trimethylsilyl)ethyl carbamates).[11] One of the more commonly used reagents for the deprotection of silyl protecting groups is tetrabutylammonium fluoride (TBAF). However, silyl deprotection reactions using TBAF as the reagent often require excess reagents and usually involve liquid-phase extraction protocols for reaction quench and workup. In preparing libraries of compounds in a parallel format, the need to pace all reactions through a liquid-phase extractive protocol can be a very time consuming process to automate. Adaptation of our general solution-phase synthesis/purification strategy to this reaction has led to the identification and use of a mixed bed of Amberlyst A-15 calcium sulfonate resin (to sequester excess TBAF reagent) and Amberlyst A-15 sulfonic acid resin (to perform efficient proton/tetrabutylammonium exchange). Utilization of this purification method allows for the high throughput purification and workup of parallel reaction chambers and is highly amenable to automation.

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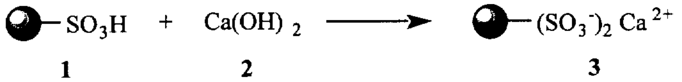
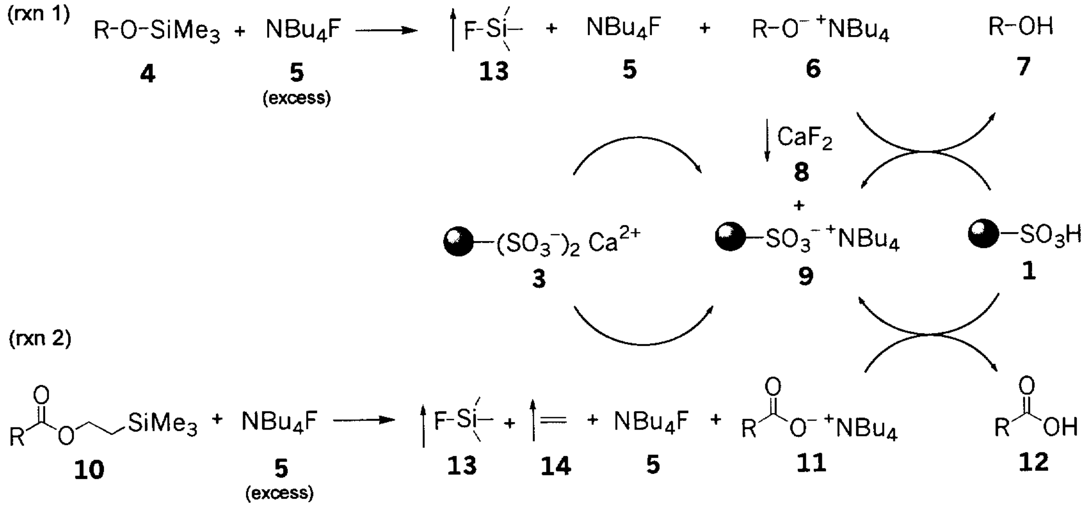
The polymer-bound calcium sulfonate resin **3** was prepared as shown in Scheme 1. Amberlyst® A-15 (hydrogen form) **1** was converted to **3** by treating with a saturated solution of aqueous calcium hydroxide. This proceeded in a quantitative manner as elemental analysis indicated a calcium to sulfur ratio of 1:2, respectively. It was found that reacting an excess of the calcium sulfonate resin **3** with tetrabutylammonium fluoride (TBAF) in tetrahydrofuran resulted in complete sequestration of the TBAF, involving counter ion exchange and precipitation of insoluble calcium fluoride. Filtration and evaporation left a residue-free vial.



**Scheme 1.** Amberlyst® A-15 (H) **1** is packed in a column and flushed with deionized water. A saturated solution of calcium hydroxide in deionized water is passed through the column until the eluent is basic (the resin displays a distinct lightening in color as it exchanges with the calcium cation). Upon completion, the resin is rinsed with deionized water until the eluent is neutral. The resin is then removed from the column and rinsed three times with DCM, three times with THF, three times with ether, and dried in vacuo. Anal. Obsd: Ca, 7.06%, 1.76 mmol/g; S, 11.71%, 3.65 mmol/g.

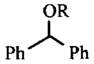
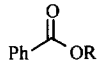
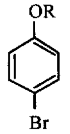
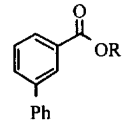
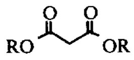
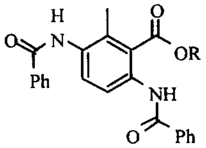
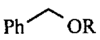
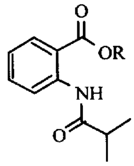
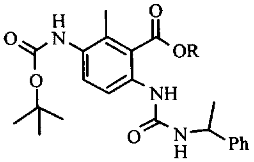
Scheme 2 illustrates two TBAF-mediated silyl deprotection reactions. In reaction 1, a silyl protected alcohol **4** is reacted with excess TBAF **5** to afford a product mixture containing tetrabutylammonium alkoxide **6**, remaining excess TBAF **5**, and volatile fluorotrimethylsilane **13**.[12] Upon completion of the reaction, the mixed resin bed containing **1** and **3** are added simultaneously. Resin **3** reacts with the excess TBAF **5**, forming insoluble calcium fluoride **8** and polymeric tetrabutylammonium sulfonate **9**. Resin **1** quenches the tetrabutylammonium alkoxide **6**, affording polymer-bound tetrabutylammonium sulfonate **9** and the desired protonated product **7**. Filtration (removal of **8** and **9**) and evaporation (removal of **13**) affords the purified product **7**. Reaction 2 shows the deprotection of a 2-(trimethylsilyl)ethyl ester **10** which proceeds as mentioned above (with the additional release of volatile ethylene **14**) to afford the desired carboxylic acid **12**.



**Scheme 2.**

A set of silyl protected substrates was selected to demonstrate this purification method as shown in Table 1. The substrates were chosen to represent a variety of oxygen-silylated compounds including phenols, alcohols, and esters. Compounds **4a–e** are examples of trimethylsilyl ethers or esters and compounds **10aa–ee** are examples of 2-(trimethylsilyl)ethyl protected esters. The silyl protected substrates (**4a–e**, **10aa–ee**) were treated with an excess of TBAF in tetrahydrofuran. Upon completion of the reactions, a mixed-bed of resins **1** and **3** was added and allowed to incubate with the reaction mixtures. Filtration of the reaction slurries, rinsing of the resins, and evaporation of the solvents afforded the desired products **7a–e** and **12aa–ee**. Excellent purities were achieved as determined by HPLC and proton NMR, with the absence of any signals in the proton NMR that would arise from a tetrabutylammonium salt. The only exception was **7a** wherein the $^1$H NMR indicated a small amount (<5%) of a tetrabutylammonium salt. This sample was incubated a second time with resins **1** and **3** to afford purified product **7a**. The silyl protected substrate **10ee** underwent this purification protocol without loss of the *t*-butyl carbamate group, permitting the orthogonal deprotection of either protecting group.[13,14]

**Table 1.** A 1 M solution of TBAF in THF (150 uL, 0.15 mmol) is added to a solution of silyl protected substrate (**4** or **10**) (0.10 mmol) in 3 mL of anhydrous THF (BHT free) and the solution is agitated at room temperature on an orbital shaker for 21 h. Sulfonic acid resin **1** (300 mg, 14.1 mmol ~4.7 meq/g) and calcium sulfonate resin **3** (300 mg, 1.05 mmol ~1.76 meq/g of $Ca^{2+}$) are added and the slurry is agitated at room temperature on an orbital shaker for 3.5 h. The slurry is filtered and the resin is rinsed with dichloromethane. The combined filtrate and washings are evaporated to afford pure products **7** and **12**. Compound **7a** required a second incubation with resins **1** and **3** for complete removal of tetrabutylammonium salt.

| | **(4) R = $SiMe_3$<br>(7) R = H** | **HPLC[a] (%)** | **Yld[b] (%)** | | **(10) R = $(CH_2)_2SiMe_3$<br>(12) R = H** | **HPLC[a] (%)** | **Yld[b] (%)** |
|---|---|---|---|---|---|---|---|
| **a** |  | 98 | 94 | **aa** |  | 96 | 93 |
| **b** |  | 98 | 94 | **bb** |  | 82 | 90 |
| **c** |  | -- | 86 | **cc** |  | 94 | 86 |
| **d** |  | >99 | 85 | **dd** |  | >99 | 96 |
| **e** | PhOR | 97 | 78 | **ee** |  | 96 | 94 |

[a]HPLC conditions: ODS Hypersil 5 um 125 × 4 mm C18 column, 5–95% acetonitrile/1.0% TEA, 0.5% $H_3PO_4$, 30 min.
[b]Yields are based on mass recovery.

Other methods of deprotecting silyl groups have been reported including the use of ion-exchange resins.[11,14,15] However, the use of a fluoride source for deprotection is the most universal and selective method. Attempts at deprotection of the 2-(trimethylsilyl)ethyl ester group of compounds **10cc–ee** were unsuccessful using poly[4-vinylpyridinium poly(hydrogen fluoride)] or Amberlyst® A-26 (fluoride form), in sharp contrast with the successful use of TBAF in combination with the mixed scavenging/quenching resins **1** and **3**. In summary, a polymer-bound calcium sulfonate resin **3** has been prepared and used to sequester tetrabutylammonium fluoride from solution-phase. The simultaneous use of resin **3** with sulfonic acid resin **1** allows for the quenching and purification of reactions involving tetrabutylammonium fluoride as the reagent. This resin workup technique eliminates the need for a liquid-phase extraction workup, allowing for the automated or manual preparation of libraries of compounds in a parallel format.

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12. Fluorotrimethylsilane has a boiling point of 16 °C and is easily evaporated, whereas other higher molecular weight trialkylsilyl fluoride by-products would be difficult to remove by evaporation such as fluorotriphenylsilane with a boiling point of 165–169 °C/1 mm.
13. Selective deprotection of the *t*-butyl carbamate over the 2-(trimethylsilyl)ethyl ester was achieved with compound **14ee** using a 25 mmol solution of 2 N HCl in dioxane at room temperature.
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