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In Situ Chemical Tagging: Tetrafluorophthalic Anhydride as a "Sequestration Enabling Reagent" (SER) in the Purification of Solution-Phase Combinatorial Libraries

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Abstract: *A specific example of a Sequestration Enabling Reagent (SER), tetrafluorophthalic anhydride, is used in the purification of solution-phase reactions involving amines with electrophiles. The SER is added to an incomplete reaction mixture containing product, amine, and electrophile. The SER covalently reacts with remaining amine, affording a derivatized amine with an artificially-imparted acid tag. This "tagged" amine is now sequesterable by the same CMR/R polyamine resin used to sequester the electrophile and both are easily removed from the reaction mixture affording pure product.*
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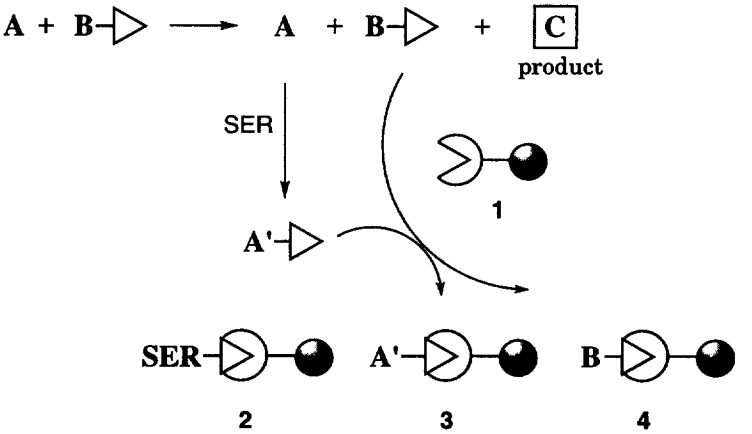
The use of cominatorial chemistry in the generation of small molecule libraries has become a rapidly evolving area of research. While both solid[1] and solution-phase[2,3] synthetic techniques have been employed to generate libraries, the majority of the compound libraries have been synthesized on a solid support. More recently, purification strategies for solution-phase chemical library synthesis have been described.[4,5,6,7] We have recently reported a purification strategy based on principles of complementary molecular reactivity and molecular recognition (CMR/R) using resins containing molecular recognition or molecular reactivity functionalities complementary to those of solution-phase reactants, reagents, and byproducts.[4] The various CMR/R resins are used in sequential or simultaneous combinations to remove excess reactants, reagents and byproducts from solution-phase reaction products, which are isolated in purified form by filtration.

Many transformations are performed involving the reaction of primary amines, secondary amines, heterocyclic amines, and anilines with electrophiles such as sulfonyl halides, acid halides, isocyanates, and chloroformates. In many cases these reactions fail to go to completion, despite the use of excess electrophile or prolonged reaction times, leaving the product and both reactants as a reaction mixture. Moreover, in most cases, the unreacted amine is only modestly reactive, rendering direct sequestrative removal from solution-phase problematic. An extension of our CMR/R methodology utilizes "Sequestration Enabling Reagents" (SER) to transform these types of poorly-sequestrable or undesirably-functionalized solution-phase reactants into chemically tagged species capable of sequestration.[8,9,10,11] Scheme 1 illustrates the use of an SER for product purification and isolation. Reactants **A** are reacted with excess reactants **B** to afford the products **C**.

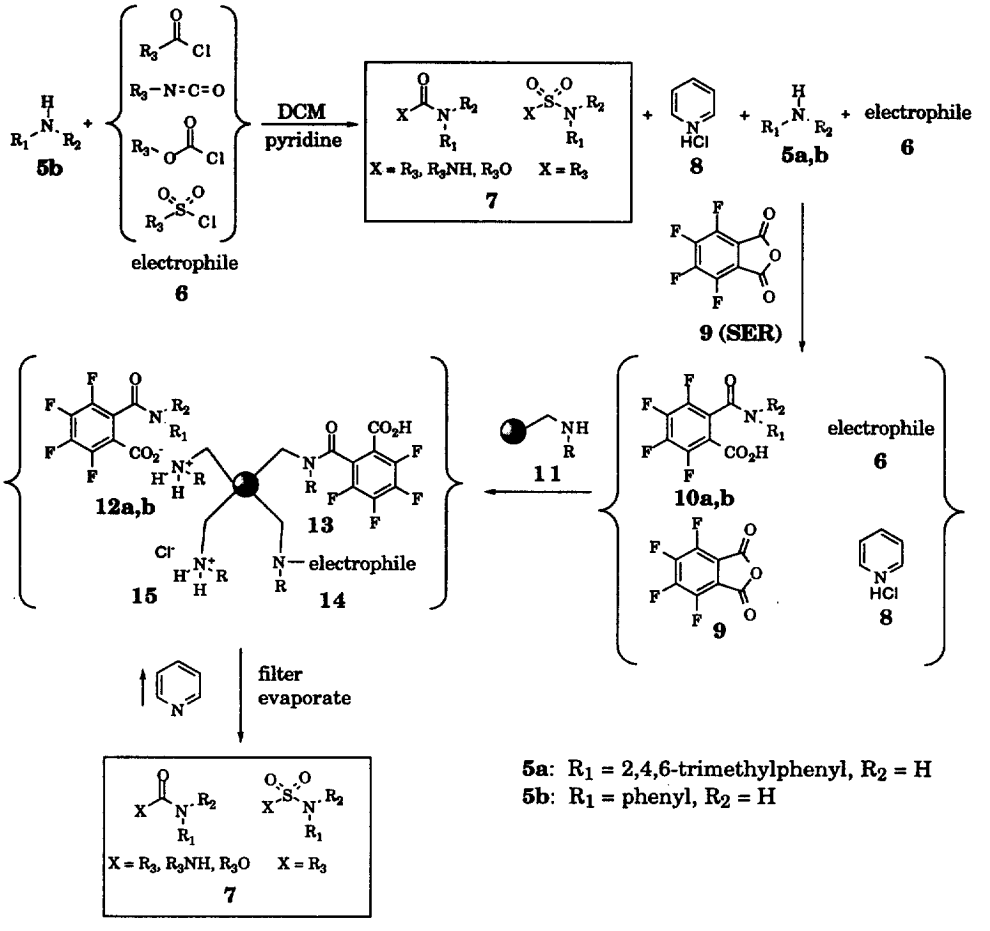
At the end of the reaction, the incomplete reaction mixtures contain the products **C** and both reactants **A** and **B**. An excess of an SER is added to the product mixture quantitatively transforming reactants **A** into a sequesterable species **A'**. The CMR/R resin **1** is added to the product mixture to sequester excess SER, the derivatized reactants **A'**, and reactants **B** as polymer-bound adducts **2**, **3**, and **4** respectively. Filtration and evaporation afford the purified products **C**. A specific example of this *in situ* tagging method is illustrated with the SER tetrafluorophthalic anhydride which quantitatively reacts with amines (including sterically hindered and electron-deficient amines) to yield carboxy-tagged derivatives sequesterable by a complementary amine-functionalized CMR/R resin. This same complementary amine-functionalized CMR/R resin is also used to efficiently sequester any excess electrophiles from solution-phase library reactions. A model study was performed using 2,4,6-trimethylaniline (**5a**, see amine Scheme 2) as a sterically hindered aniline and tetrafluorophthalic anhydride **9** as the SER agent. Reaction between **5a** and **9** was conducted in deuterated DMF and followed by ^{19}F NMR and GC/MS. After a 15 minute incubation, the carboxy-tagged aniline derivative **10a** was formed as evidenced by ^{19}F NMR, and 2,4,6-trimethylaniline **5a** was completely consumed as evidenced by GC/MS. Subsequent incubation with CMR/R polyamine-functionalized resin[4] **11** led to complete sequestration of both carboxy-tagged aniline **10a** and excess SER **9** as polymer-bound adducts **12a** and **13** respectively.[12] Filtration and evaporation left a residue-free vial.

Scheme 1



To demonstrate this purification strategy in an experimental setting, aniline **5b** (excess) was reacted with the following electrophiles **6**: benzyl chloroformate, benzoyl chloride, benzenesulfonyl chloride, and phenylisocyanate. After 24 h, tetrafluorophthalic anhydride **9** (excess relative to aniline) was added to each product mixture. To mimic incomplete reactions containing residual nucleophile **5b** and electrophiles **6**, an additional 0.02 mmoles of **6** were then added to each vial. CMR/R polyamine resin **11** was added to each vessel and the mixtures stirred an additional 1 h at RT. The singular CMR/R resin **11** sequestered the carboxy-tagged aniline derivative **10b**, excess SER **9**, excess electrophiles **6**, and byproduct HCl as polymer-bound adducts **12b**, **13**, **14**, and **15**, respectively. Filtration, rinsing with dichloromethane, and concentration afforded highly purified products **7** in each case (Scheme 3).[13]

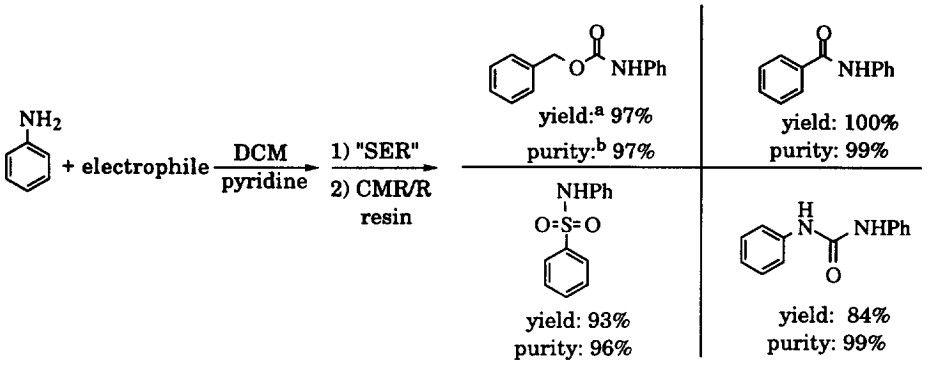
Scheme 2



Scheme 2. The electrophile (0.10 mmoles) is added to a solution of nucleophile (0.12 mmoles) and pyridine (0.12 mmoles) in dichloromethane and the solution is stirred at room temperature for 24 hours. Tetrafluorophthalic anhydride (0.05 mmoles) is added and the solution is stirred at room temperature for 1.5 hours followed by addition of electrophile (0.02 mmoles). The CMR/R polyamine resin (200 mg, 0.60 mmoles, ~2.98 meq/g) is added and the slurry stirred at room temperature for 1 hour. The slurry is filtered and the resin is rinsed with dichloromethane. Evaporation of the solvents affords a pure product.

Tetrafluorophthalic anhydride has been successfully utilized with a variety of amines and is presently used in the purification of our proprietary small molecule libraries. The limitation experienced with tetrafluorophthalic anhydride is the slow reactivity with extremely electron-deficient anilines and the instability of carboxy-tagged derivatives **10** if heating is attempted during the *in situ* tagging process (decarboxylation, leading to loss of carboxy-tag). Scoping of the steric limitations demonstrated satisfactory tagging and sequestration of 2,6-di-*iso*-propylaniline, but not 2,6-di-*tertiary*-butylaniline.

Scheme 3



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

In summary, the use of tetrafluorophthalic anhydride as a sequestration enabling reagent (SER) has been described. Utilization of this SER to derivatize modestly reactive amines allows for sequestration by basic containing CMR/R resins. This strategy allows for easy purification of incomplete reactions that would otherwise require tedious, time consuming purification processes. Other sequestration enabling reagents have been utilized and will be reported in due course.

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12. Other CMR/R resins containing 1° and 2° amines have been successfully used. It was found that some resins containing 3° amines and A-26(CO_3^{2-}) also sequester the tetrafluorophthalic anhydride.
13. ^{19}F NMR were performed on each product and all lacked any fluorine signal indicating the disappearance of any the tetrafluorophthalic anhydride **9** and artifically-tagged **10**.

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