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A Tandem Three-Phase Reaction for Preparing Secondary Amines with Minimal Side Products

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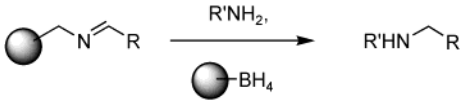
ABSTRACT



A new method for the preparation of secondary amines has been reported. Complementary solution-phase and solid-phase synthesis highlight the process. Amines are obtained in good yields free from the usual byproducts of reductive amination. Secondary amines are unreactive, so overalkylation does not occur. The procedure can be used interchangeably for traditional or parallel synthesis settings.

The genesis of combinatorial chemistry is linked to the discovery of solid-phase peptide synthesis[1] and its modification to more elaborate solid-phase organic synthesis.[2] This eventually led to resin-bound reagents and scavengers as aids for solution-phase synthetic processes. Both solid-phase synthesis and solution-phase synthesis with resin-bound scavengers/reagents are performed in two-phase systems where filtration is used to isolate products and spent reagents/byproducts, respectively.[3] These approaches to the preparation of discrete compounds (individual and parallel) are now commonplace in many labs.

Reports of synthetic methods involving more than two phases are less common. Early accounts of three-phase reaction mixtures dealt with mechanistic studies where reactive intermediates were released into solution from a resin-bound starting material and subsequently trapped by a substrate bound to a second resin.[4] The technique of three (or more) phases working in tandem to provide a resin bound product from a resin-bound starting material, or "resin to resin transfer" (RRTR), requires a transfer agent or chaperone to mobilize resin-bound starting material and hence catalyze the reaction[5] (Figure 1). Normally, soluble substrates A and B could react under little control to provide desired as well as undesired products. Polymer-bound substrates, however, are physically separated from each other even though they are within the same reaction vessel; therefore, little if any interaction occurs between them. This is sometimes referred to as the "Wolf and Lamb" effect.[6]

Solution-phase preparations of target compounds with two or more reagent resins present in a single flask have also been reported. Deuterium labeling of primary alcohols via oxidation−reduction[7] and a 2-aminothiazole synthesis[8] have used reagents bound to inorganic resins, while the preparation of alkoxypyrrazoles has been achieved using three resin-bound reagents in a single-pot operation.[9] Also notable are the "fluorous" methods in which aqueous, organic, and highly

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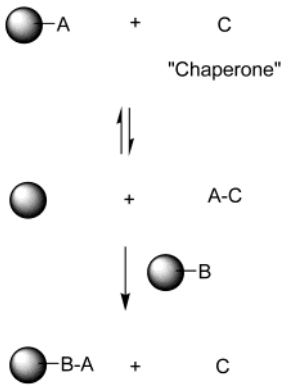

Figure 1. Resin to resin transfer reaction.

fluorinated solvents are used in a three-phase solvent system for compound purification.[10]

We report here a multiphase reaction that combines solid-phase and solution-phase methodologies to produce secondary amines that are free of the usual side products (carbonyl starting materials, alcohols from reduction of the carbonyl group, and products from overalkylation). A resin-bound aldehyde (in the imine form) can undergo a transimination/cleavage equilibrium with a solution-phase primary amine to produce a solution-phase imine. This imine in turn serves as a substrate for a resin bound reducing agent leaving the secondary amine product in solution.[11]

A graphic example is shown in Scheme 1. 3-Fluorobenzaldehyde was reacted with aminomethyl resin (AM resin) under known conditions[12] to provide the resin bound imine (**1**). This resin was treated with *n*-butylamine (**2**, 0.5 equiv) and resin-bound borohydride (**5**, 2 equiv).[13] After 14 h of shaking, the resins were separated by filtration and the filtrate was treated with concentrated HCl and then evaporated.[14] Analysis of the product mixture indicated *N*-(3-fluorobenzyl)-butylamine (**6**) as the sole compound present in 78% yield (Figure 2a). A similar reaction was run under typical solution-phase conditions (1.0 equiv of butylamine and 3-fluorobenzaldehyde and 1.3 equiv of sodium triacetoxyborohydride in dichloromethane at room temperature). The product mixture yielded the desired secondary amine (expected product) heavily contaminated with the tertiary amine (overalkylated product) and starting aldehyde (Figure 2b).

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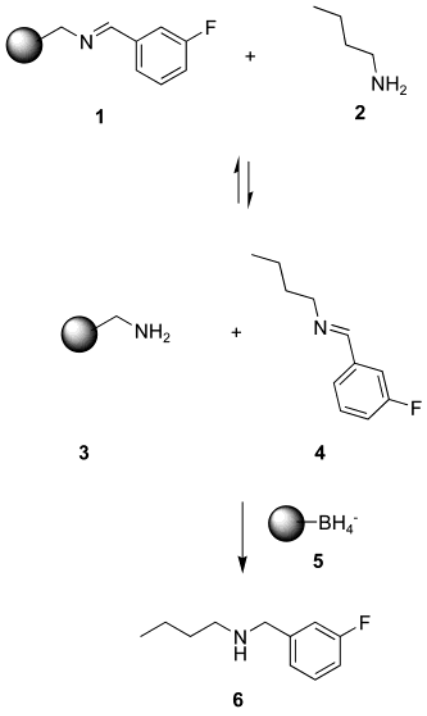
(13) Aminomethylpolystyrene resin (2% DVB, 200−400 mesh, 1.13 mmol/g loading) purchased from Novabiochem (product no. 01-64-0100). Resin-bound borohydride (Amberlite IRA 400, 2.5 mmol/g loading) was purchased from Aldrich Chemical Co. (product no. 32,864-2).

(14) Treatment with a small excess of concentrated HCl ensured hydrochloride formation of products as well as any starting amine that remained, thus preventing evaporation and allowing for accurate product analysis.

Scheme 1. Tandem Three-Phase Preparation of a Secondary Amine



The process, which takes place in a single reaction vessel, can be considered a tandem three-phase reaction. The original starting materials on resin (phase 1) and in solution (phase

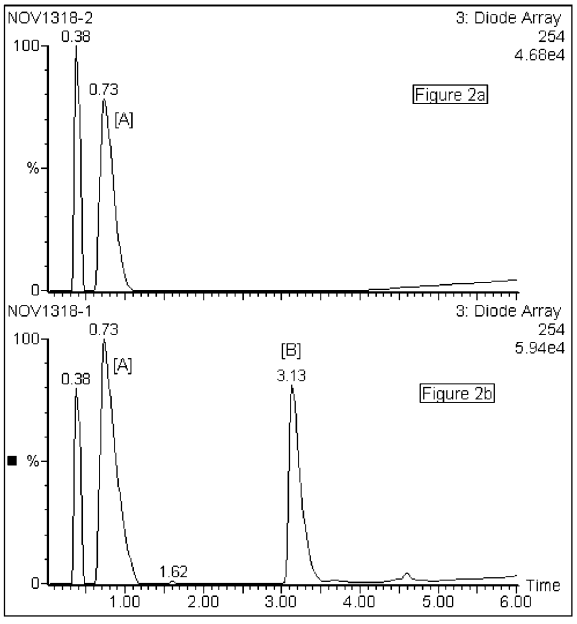


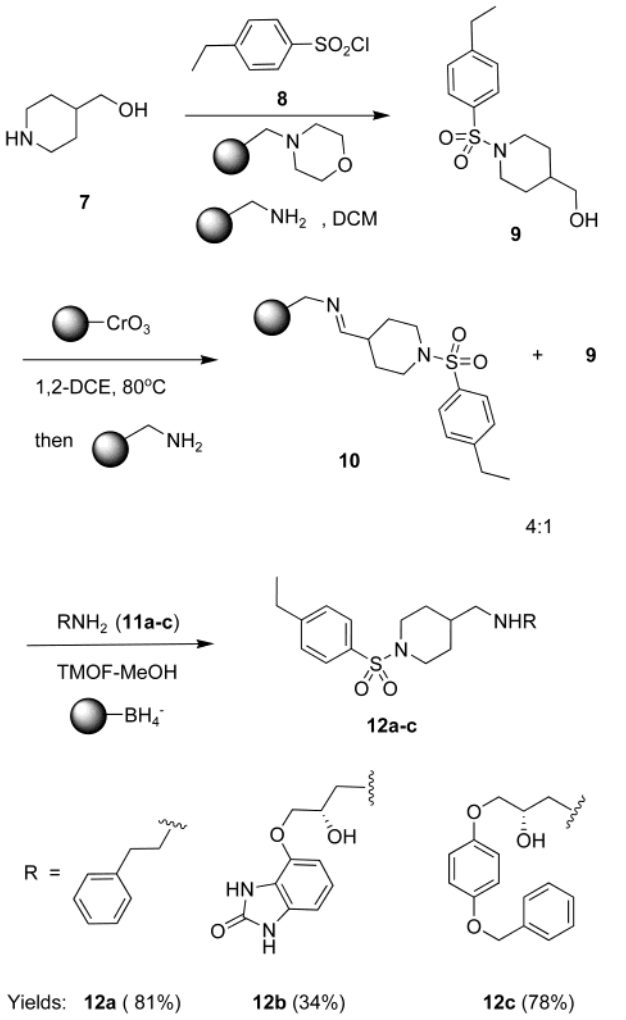
Figure 2. HPLC trace comparison of product mixtures from the tandem three-phase preparation of **6** (Figure 2a) and a typical solution-phase preparation of **6** (Figure 2b, see text for a description of experiment). Peak A: butyl-(3-fluorobenzyl)amine. Peak B: mixture of 3-fluorobenzaldehyde and bis(3-fluorobenzyl)butylamine.

2) react to form an intermediate in solution that is transformed by a reagent resin (phase 3) to form a soluble product. Ideally, filtration and evaporation are all that is needed for product isolation. Imine resin (phase 1) and borohydride resin (phase 3) are physically separate and therefore do not react. Typical side products such as alcohol (aldehyde reduction product), overalkylated amine, and starting aldehyde were not detected. Under these conditions the amount of secondary amine in the reaction mixture determines how much aldehyde reacts. Throughout the progress of the reaction, the excess aldehyde remained in a "prescavenged" state, so no steps were necessary to remove the excess after completion of the reaction.

An in-house program designed to discover novel, selective β-3 agonists required the preparation of secondary amines (**12a**−**c**) to fulfill structure−activity relationship (SAR) requirements. The β-3 adrenergic receptor is selectively located on the surface of adipose cells and serves to regulate lipid metabolism upon stimulation with the endogenous ligand.[15] A selective agonist of the receptor may find indication in obesity treatment. The method described herein appeared to be suitable for their preparation. Furthermore, it could potentially be used to produce focused libraries of similar analogues. As outlined in Scheme 2, 4-(2-hydroxymethyl)piperidine (**7**) was treated with excess 4-ethylbenzenesulfonyl chloride (**8**) as well as polymer-supported scavengers[3] to give the product sulfonamide (**9**) in 93% yield. The alcohol was selectively oxidized to the corresponding aldehyde with chromic acid on resin[16] (8 equiv). Although no overoxidation to the acid took place, the product mixture was always accompanied by approximately 20% starting alcohol (**9**). More oxidizing agent, longer reaction times, and different solvents led to inferior results. Aldehyde purification suitable for library work occurred when the mixture was treated with aminomethyl resin under the normal conditions for scavenging electrophiles.[3] The phase switch allowed the alcohol contaminant to be washed away, and conveniently provided the resin-bound imine (**10**) required for the next step. Hence, resin **10** was treated with primary amines (**11a**−**c**, 0.80 equiv)[17] under the conditions described above for secondary amine formation. Two of the products were isolated in good yields (**12a** and **12c**), while the yield for the remaining product (**12b**) was lower due to the insolubility of the starting amine, which was recovered from the product mixture. As in the case above, byproducts were not detected.

In conclusion, a new tandem three-phase method for the preparation of secondary amines has been described that involves a mixture of solid-phase (resin-bound starting material, cleavage) and solution-phase (resin-bound borohydride reduction) methodology in a single vessel. The procedure uses readily available reagents, provides pure products, and can be run in parallel format. In addition, this technique has been successfully applied to the generation of proprietary secondary amine libraries, and the results will be reported in due course.

Scheme 2. Preparation of β-3 Agonists from the Tandem Three-Phase Reaction for Secondary Amines



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Supporting Information Available: Experimental details and characterization data for compounds **12a**−**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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