ORGANIC LETTERS

2000
Vol. 2, No. 15
2205−2207

Soluble Polymer Bound Cleavage Reagents: A Multipolymer Strategy for the Cleavage of Tertiary Amines from REM Resin

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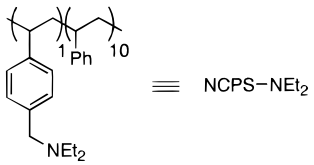
Received April 12, 2000

ABSTRACT



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Soluble polymer bound reagent 1 has been prepared to cleave tertiary amines from REM resin. Normally, amines cleaved from REM resin require extraction or chromatography to remove excess cleavage reagent and its byproducts. The solubility profile of non-crosslinked polystyrene (NCPS) based reagent 1 eliminates the need for such purification and allows for the direct isolation of a library of pure tertiary amines through simple filtration and concentration operations.

The past decade has witnessed a renewal of interest in polymer-supported organic chemistry. Much of the current research has utilized insoluble polymer resins as platforms for organic synthesis.[1] Such resins offer many advantages with regard to compound isolation and handling. However, the insoluble nature of the resins can complicate characterization of compounds attached to them and lead to reagent accessibility problems. Such deficiencies have prompted the evaluation of soluble polymers as supports for organic chemistry,[2] and this field has been a major area of focus for our research group.[2c] Recently our group has begun to examine new solid-phase organic chemistry supports with the goal of identifying materials which maintain the advantages of both types of polymers in an attempt to bridge the gap between solution- and solid-phase organic chemistry.[3]

One successful merging of solid- and solution-phase chemistry is the use of resin-immobilized reagents that selectively remove excess reaction reagents and byproducts.[4] They have found wide application in solution-phase compound library production and allow for isolation of pure compounds after filtration and concentration. A solid-phase analogue of this purification strategy would be to use soluble polymer based reagents to cleave compounds from resins and subsequent removal of the reagents and byproducts through precipitation of the polymers and filtration. Currently, one of the more common methods for cleavage of product compounds from resins is to use volatile reagents such as trifluoroacetic acid in conjunction with linker groups that do not produce byproducts. In situations where such conditions are not possible, a soluble polymer bound cleavage

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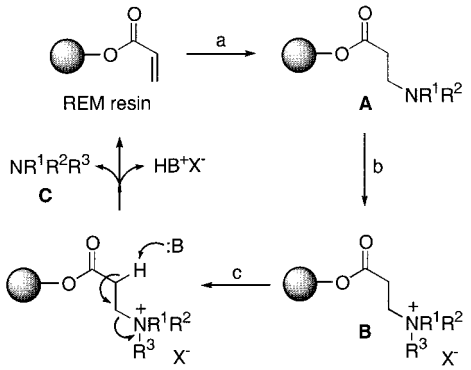
10.1021/ol0059403 CCC: $19.00
Published on Web 06/27/2000

reagent would allow for the isolation of pure compounds through simple liquid transfer and filtration operations. Our experience with soluble polymer assisted organic chemistry prompted us to develop the first such reagent, and its use is described herein. To our knowledge the use of soluble polymers in conjunction with insoluble polymers has only been described in the synthesis of polypeptides[5] and in our Sharpless asymmetric olefin dihydroxylation system.[6]

Rees and co-workers have introduced a recyclable acrylate derivatized solid-phase synthesis support that they named REM (*RE*generated *M*ichael acceptor) resin.[7] It was developed for the preparation of tertiary amines by a sequential process of Michael addition, quaternization, and cleavage (Scheme 1). In addition to the preparation of amines, this

Scheme 1. Synthesis of Tertiary Amines Using REM Resin[a]

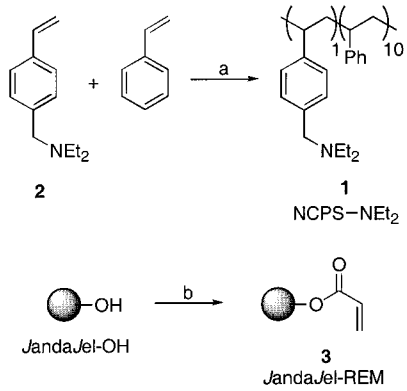


[a] (a) R^1R^2NH, DMF, rt; (b) R^3X (X = Br or I), DMF, rt; (c) *i*Pr_2EtN or **1**, CH_2Cl_2, rt.

resin has been used in the synthesis of 5,6-dihydropyrimidine-2,4-diones [8] and β-peptoids[9] and in Baylis−Hillman[10] and Heck[11] reactions. We chose to use this resin in our study because of the report by Armstrong in which a basic ion-exchange resin was used in the product cleavage step.[7d] Normally, the use of REM resin for amine synthesis requires either extraction or chromatography for product purification. While the use of an insoluble polymer based cleavage reagent eliminated the need for product purification, it complicated the reusability of the REM resin since at the end of the sequence the resins were mixed together. We felt that using non-crosslinked polystyrene (NCPS) based basic reagent **1** would still allow for direct isolation of pure compounds but also have the advantage of easy reuse of the REM resin. The removal of **1** from the other two components of the reaction mixture would be based on its insolubility in methanol (Scheme 1).

Reagent **1** was prepared according to the method outlined in Scheme 2. Amine-containing monomer **2** was prepared

Scheme 2. Synthesis of NCPS-Based Cleavage Reagent **1** and *J*anda*J*el−REM Resin (**3**)[a]



[a] (a) AIBN, PhMe, 85 °C; (b) acryloyl chloride, *i*Pr_2EtN, CH_2Cl_2, rt (two times).

by the procedure of Itsuno from 4-vinylbenzyl chloride and diethylamine.[12] Radical copolymerization of **2** with styrene in a 1:10 ratio was initiated by AIBN to afford **1**.[13]

We have recently introduced a new class of resins (*J*anda*J*els[14]) that contain flexible tetrahydrofuran derived crosslinkers and exhibit superior swelling in common organic solvents.[3b] To use this polymer matrix in the present study, a hydroxymethyl functionalized version of our resin[15] was acylated with acryloyl chloride according to the procedure of Morphy[7c] (Scheme 2) to form **3** (*J*anda*J*el−REM).[16]

(5) (a) Frank, H.; Hagenmaier, H. *Experientia* **1975**, *31*, 131−133. (b) Frank, H.; Meyer, H.; Hagenmaier, H. *Chem. Ztg.* **1977**, *101*, 188−193. (c) Heusel, G.; Bovermann, G.; Gohring, W.; Jung, G. *Angew, Chem., Int. Ed. Engl.* **1977**, *16*, 642−643.

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(11) Kondo, Y.; Inamoto, K.; Sakamoto, T. *J. Comb. Chem.* **2000**, *2*, Articles ASAP.

(12) Itsuno, S.; Sawada, T.; Hayashi, T.; Ito, K. *J. Inorg. Organomet. Polym.* **1994**, *4*, 403−414.

(13) **Preparation of NCPS-NEt_2 (1).** A stirred solution containing 200 g (1.9 mol) of styrene, 36 g (0.19 mol) of diethylaminomethylstyrene (**2**), and 600 mL of toluene was purged with N_2 for 30 min. After addition of 1.5 g of AIBN, the mixture was heated at 90 °C for 24 h. The solution was concentrated, and the residue was taken up in 200 mL of THF. This solution was added dropwise to a cold, stirring solution of methanol (2 L). The white precipitate was filtered and then stirred in methanol at 50 °C for 2 h to remove traces of unreacted monomers. The suspension was filtered, and the white solid was dried under vacuum at 50 °C to afford 150 g (64%) of NCPS-NEt_2 (**1**) as a white powder. A nitrogen loading level of 0.85 mmol/g was determined by ^{1}H NMR spectroscopy: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.00−1.10 (6H), 1.30−1.60 (21H), 1.60−2.00 (11H), 3.40−3.60 (2H), 6.30−6.70 (21H), and 6.90−7.20 (31H). The ratio of monomer incorporation into the product polymer **1** was determined by ^{1}H NMR to be 9.5:1 (styrene:**2**). This corresponds to a loading of 0.85 mmol N/g of **1**. It was found that higher loaded versions of **1** were slightly soluble in methanol and the use of these polymers for amine cleavage afforded impure products.

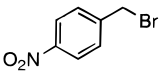
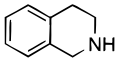
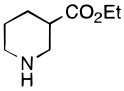
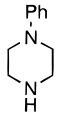
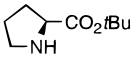
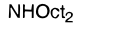
(14) *J*anda*J*el is a registered trademark of the Aldrich Chemical Co.

(15) Reger, T. S.; Janda, K. D. *J. Am. Chem. Soc.* In press.

With the requisite polymeric materials in hand, a library of tertiary amines (Table 1) was prepared in parallel via the reaction sequence described vide supra.[17] Conjugate addition of a set of five secondary amines to **3** afforded resins **A**. These resins were quaternized with three alkylating agents to afford resins **B**. The tertiary amines were cleaved by reaction of **B** with a 3-fold excess of **1**. After completion of the cleavage reaction, the resin was filtered off and the filtrate was concentrated to afford a white paste. This paste (a mixture of **1** and product amines **C**) was washed with cold methanol to separate insoluble **1** from soluble **C**. The methanolic solution was concentrated to afford compounds **C** that were essentially pure as determined by ^{1}H NMR in acceptable yields (Table 1). It should be noted that for unknown reasons a few combinations of the secondary amines and alkylating agents afforded only trace amounts of impure desired product **C**. Perhaps steric hindrance by the bulky ester group prevented alkylation of *tert*-butylproline by allyl bromide and 4-nitrobenzyl bromide.

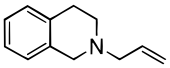
To demonstrate that the use of polymeric reagent **1** did not become entrapped in resin **3** and interfere with the recycling of it, we prepared one library member repeatedly using the same sample of **3** (Table 2). No decrease in yield or purity of **4** was observed even after five synthesis cycles. Attempts to recycle **1** by washing the triturated paste with strong mineral base resulted in material that did not afford pure cleavage products.

Table 1. Tertiary Amine Library

Yield (%)			MeI
	74	70	70
	42	40	42
	73	64	71
	nd[a]	nd	45
	nd	37	48

[a]nd = not determined, only trace amounts of impure product isolated

Table 2. Recycling of REM Resin in the Synthesis of **4**



4

run	yield (%)
1	71
2	79
3	70
4	67
5	68

In summary, we have prepared a soluble polymer bound amine base for use in solid-phase organic chemistry and applied it in a mutipolymer system for the cleavage of tertiary amines from REM resin. The simple liquid handling operations that are required to obtain pure products are amenable to automation, and therefore **1** should find utility in the preparation of large compound arrays.

Acknowledgment. Funding for this research was provided by The Skaggs Institute for Chemical Biology, The Scripps Research Institute, and the National Institutes of Health (GM56154).

Supporting Information Available: Library member structure characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0059403

(16) **Preparation of *J*anda*J*el−REM (3).** To a suspension of 20 g (16.8 mmol) of *J*anda*J*el-OH (loading = 0.84 mmol/g) in 200 mL of CH_2Cl_2 was added 29 mL (168 mmol) of diisopropylethylamine followed by 13.6 mL (168 mmol) of acryloyl chloride. After stirring for 4 h at rt, the suspension was filtered and the resin was washed (CH_2Cl_2, methanol, hexane) and dried under vacuum. This procedure was repeated to ensure complete derivatization of the hydroxyl functional groups.

(17) **Procedure for library synthesis:** To five separate 20 mL vials were added 1 g of *J*anda*J*el−REM (**3**, loading = 0.8 mmol/g) and 15 mL of dimethylformamide. The different secondary amines (10 equiv, 8 mmol) were added to each vial, and the suspensions were shaken for 24 h at rt. The five resins **A** were recovered, washed (CH_2Cl_2, methanol, hexane), and dried. Each resin **A** was divided into three ~300 mg portions which were placed in separate 20 mL vials. Dimethylformamide (10 mL) was added to each vial followed by 10 equiv of the alkylating agent. The suspensions were shaken for 24 h at rt, filtered, washed (CH_2Cl_2, methanol, hexane), and dried to afford resins **B**. Each of the 15 resins **B** were placed in separate 20 mL vials and suspended in 10 mL of CH_2Cl_2, and 3 equiv of NCPS-NEt_2 (**1**) was added. The suspensions were shaken for 24 h at rt, filtered, and washed (CH_2Cl_2, hexane). The filtrate was concentrated to afford a white foam which was dried in vacuo. The foam was triturated with cold methanol, and the resulting slurry was filtered. The filtrate was concentrated to dryness, and a small amount (~5−10 mL) of cold methanol was added. The solution was filtered through a pipet containing a glass wool plug, concentrated, and dried to afford tertiary amines **C** in high purity.