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Oxidation–Cope elimination: a REM-resin cleavage protocol for the solid-phase synthesis of hydroxylamines

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Abstract—We have established that using an oxidation-Cope elimination cleavage protocol allows for the synthesis of *N*,*N*-disubstituted hydroxylamines from REM resin (polymer-bound benzyl acrylate). Michael addition of a secondary amine or addition of a primary amine followed by reductive alkylation provides polymer-bound tertiary amines. Oxidation of these resin-bound tertiary amines with MCPBA is followed by concomitant Cope elimination to regenerate the polymer-bound acrylate and provide the cleaved hydroxylamines. © 2001 Elsevier Science Ltd. All rights reserved.

Solid-phase organic synthesis[1] (SPOS) is, at this time, a well respected tool for the production of combinatorial libraries.[2] Linkers, which connect resin and synthetic scaffold, together with cleavage protocols for removing synthetic compounds from the resin are important factors in solid-phase synthesis.[3] Traceless linkers have emerged as useful tools in SPOS; one such traceless linker is polymer-supported benzyl acrylate **A** (Fig. 1), commonly known as REM resin as coined by Morphy et al. (since it's regenerated upon cleavage of the substrate and the first reaction is a Michael addition to the acrylate).[4] To date, Wang and JANDAJEL™ resin-bound acrylates **B** and **C**,[5] polystyrene-bound benzyl and phenyl vinyl sulfones **D** and **E**,[6] and polystyrene-bound acrylamides **F**[7] have all been developed for SPOS.

Some of these resins have been applied to the synthesis of tertiary amines libraries[8] and, to our knowledge, Hofmann elimination[9] (quaternization followed by elimination to give tertiary amines) is the only reported cleavage protocol for REM resins. We now demonstrate that employing the Cope elimination[10] efficiently produces *N*,*N*-disubstituted hydroxylamines. It is important to note both that many hydroxylamines exhibit biological activity[11] and that many hydroxylamine derivatives possess biological activities similar to their corresponding amines (indeed, amine→hydroxylamines conversion can increase potency).[12] *N*,*N*-Disubstituted hydroxylamines have previously been prepared in solution-phase by either direct oxidation of the secondary amine using dimethyldioxirane or dibenzoyl peroxide,[13] addition of Grignard reagents to nitroalka-

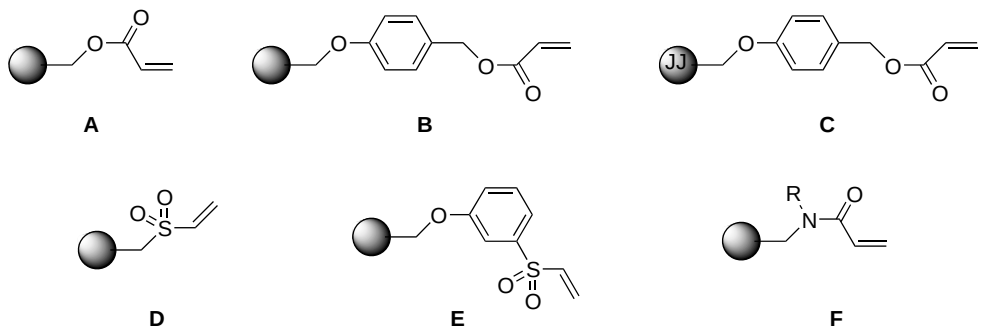

Figure 1. REM resins.

Keywords: solid-phase synthesis; hydroxylamines; Cope elimination; *N*-oxide.

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nes,[14] or reduction of oximes with sodium borohydride in the presence of carboxylic acids.[15]

Our solid-phase route to hydroxylamines began by attachment of acryloyl chloride to hydroxymethyl polystyrene to deliver the REM resin (Scheme 1).[16] Michael addition of secondary amines produced the corresponding tertiary β-amino ester. After washing the resin, this tertiary amine was reacted with MCPBA in chloroform for 1–2 h to deliver the *N*-oxide. Normally, the Cope elimination of the amine oxide is carried out at high temperatures (pyrolysis).[17] It has also been reported that solution-phase Cope eliminations can be effected by passing a chloroform solution of the *N*-oxide through a column of basic alumina.[18] For solid-phase organic synthesis with combinatorial potential, where numerous functional groups would be represented, we required milder conditions. Cram et al. reported that the solution-phase Cope elimination can be carried out at room temperature in either THF or DMSO.[19] In light of their work, we attempted several trial oxidations in chloroform followed by filtration. An additional volume of chloroform was added and the swollen resin was shaken briefly and filtered. THF was added to the resin, mixed briefly, and again filtered. A second volume of THF was added and the resin was shaken overnight to complete the elimination. In our hands, we found that premature elimination occurred prior to addition of THF which lead to MCPBA and MCBA contamination of the cleaved hydroxylamine.[20] In light of this, the organic layers were combined and concentrated to give a white solid. Extraction or chromatography of this residue provided pure hydroxylamine.[21] Using chloroform for the entire process proved more effective.[21b]

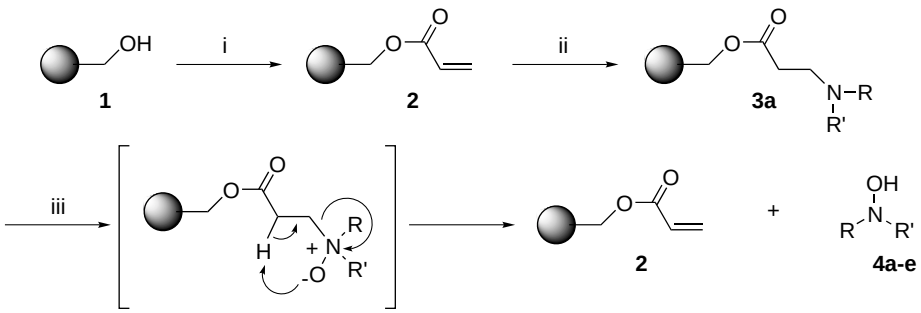
Following literature protocols,[4] Michael addition of a primary amine to the REM resin followed by reductive amination with a pyridine–borane complex[22] in DMF/EtOH gave tertiary amines (Scheme 2). This allows for a more effective combinatorial approach where several amines and aldehydes can be utilized in library production and thus increase the advantages of SPOS. FT-IR shows the typical shift for the acrylate and the unconjugated ester (1721 and 1732 cm^{-1}, respectively) and these were used to monitor Michael addition and Cope elimination reactions. The REM resin was also recycled up to three times without noticeable change in the IR spectrum or dramatic decrease in hydroxylamine yield.

We have also examined other oxidation protocols (hydrogen peroxide in THF, peracetic acid in various solvents, and dimethyldioxirane in acetone/CH_2Cl_2). Unfortunately, these procedures were not as effective as MCPBA/$CHCl_3$.

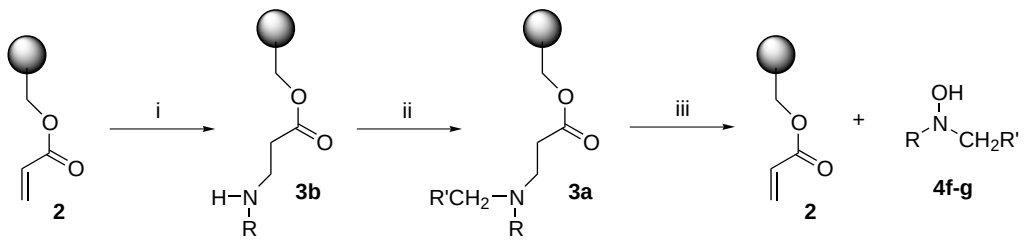
A solid-phase Cope elimination method to prepare *N*,*N*-disubstituted hydroxylamines from tertiary β-amino esters has been developed. Thus, both Cope and Hofmann elimination strategies can be used to deliver product from REM resin.

Experimental

Melting points were determined using an Electrothermal 9100 apparatus and are uncorrected. Infrared spectra were taken on the neat samples or dried beads with the use of a refractive spectrophotometer. ^1H and ^{13}C NMR were measured in $CDCl_3$ at 300 and 75 MHz, with tetramethylsilane and $CDCl_3$ as internal standards,



Scheme 1. (i) Acryloyl chloride, DIPEA, DCM, rt; (ii) RR′NH, DMF, rt; (iii) MCPBA, $CHCl_3$, rt. Product, yield; piperidinol **4a**, 67%; morphin-4-ol **4b**, 70%; 1,2,3,4-tetrahydroisoquinolin-2-ol **4c**, 61%; methylbenzylhydroxylamine **4d**, 47%; 2,6-dimethylmorpholin-4-ol **4e**, 64%.



Scheme 2. (i) RNH_2, DMF, rt; (ii) R′CHO, borane–pyridine complex, DMF/EtOH (4:1), rt; (iii) MCPBA, $CHCl_3$, rt. Product, yield; hexylpropylhydroxylamine **4f**, 60%; (4-nitrobenzyl)propylhydroxylamine **4g**, 56%.

respectively. Elemental analyses were preformed by Midwest Microlabs, Indianapolis, IN. MCPBA (80–90%) had been purchased from Aldrich; hydroxymethyl polystyrene (100–200 mesh), 1% DVB, substitution: 1.10 mmol g^{-1} was purchased from Novabiochem; solvents were purchased from either Fischer Scientific or EM Science and used as received. All reactions and work-ups were carried out using the Eyela CCS-600 V Personal Organic Synthesizer.

Preparation of the REM resin 2

Hydroxymethyl polystyrene resin **1** (0.750 g, 0.825 mmol) was added to the reaction vessel and suspended in DCM. Diisopropylethylamine (1.00 mL, 5.7 mmol) followed by acryloyl chloride (0.50 mL, 5.9 mmol) were added. The reaction was shook for 10 h at rt followed by filtering, washing (2×5 mL DCM, 2×5 mL MeOH, 2×5 mL DCM, 2×5 mL MeOH), and drying in vacuo.

General procedure for the Michael addition

REM resin **2** was swollen in DMF and primary or secondary amine (6.6 mmol, 8 equiv.) was added. The resin was agitated for 20 h at rt, then washed (2×5 mL DMF, 2×5 mL MeOH, 2×5 mL DCM, 2×5 mL MeOH) and dried.

General procedure for the reductive alkylation

Resin containing secondary amine was swollen in DMF:EtOH (4:1) and followed by addition of aldehyde (6.6 mmol, 8 equiv.) and borane–pyridine complex (6.6 mmol, 8 equiv.). After the reaction was shook for 4 days at rt, it was filtered, washed (5 mL DMF: EtOH (4:1), 5 mL MeOH, 2×5 mL DCM, 3×5 mL MeOH), and dried.

General procedure for the oxidation and Cope elimination

Polymer-supported tertiary amine (**3a**) was swollen in chloroform and treated with MCPBA (0.40 g, ~2.0 mmol) and the reaction was agitated at rt for 12 h. The resin was filtered and washed (5 mL DCM, 5 mL ether, 2×5 mL DCM, 2×5 mL MeOH). The combined washings were evaporated to afford a white solid. Method A: this solid was dissolved in ether and extracted three to four times with 5% HCl, the combined aqueous layers were basified with sodium bicarbonate and extracted with DCM three to four times. Method B: the crude white solid was dissolved in ether and extracted three times with saturated sodium bicarbonate. In both cases the final organic extracts were dried with sodium sulfate, filtered, and evaporated to give the desired *N*, *N*-dialkylhydroxylamines.

Compound **4a**[13b] IR 3195, 2936, 2831, 1443 cm^{-1}; ^1H NMR: δ 1.15 (m, 1H), 1.58 (m, 3H), 1.76 (dd, $J=11.7$, 3.3 Hz, 2H), 2.47 (td, $J=11.3$, 2.4 Hz, 2H), 3.28 (d, $J=9.3$ Hz, 2H), 7.25 (br s, 1H); ^{13}C NMR: δ 23.0, 25.3, 58.9.

Compound **4b**[13b] IR 3193, 2937, 2830, 1455 cm^{-1}; ^1H NMR: δ 2.76 (td, $J=11.1$, 2.9 Hz, 2H), 3.14 (dd, $J=10.3$, 1.5 Hz, 2H), 3.59 (td, $J=11.7$, 1.7 Hz, 2H), 3.93 (dd, $J=10.0$, 1.8 Hz, 2H), 7.20 (br s, 1H); ^{13}C NMR: δ 58.2, 65.9.

Compound **4c**[23] mp 76–78°C, IR 3196, 3022, 2899, 2830, 1476, 751 cm^{-1}; ^1H NMR: δ 3.00 (br, 3H), 3.43 (br, 1H), 3.92 (br, 1H), 4.26 (br, 1H), 8.41 (br s, 1H); ^{13}C NMR: δ 28.2, 55.5, 60.0, 126.0, 126.6, 126.8, 128.2, 132.9, 133.1.

Compound **4d**[15] IR 3298, 3027, 2936, 2790,1495, 1447 cm^{-1}; ^1H NMR: δ 3.95 (s, 3H), 5.43 (s, 2H), 7.39 (m, 3H), 7.49 (m, 2H); ^{13}C NMR: δ 47.7, 62.6,127.0, 128.8, 129.2, 129.8.

Compound **4e** mp 78–79.5°C, IR 3207, 2970, 2893, 2839,1461, 1381,1078 cm^{-1}; ^1H NMR: δ 1.21 (d, 6.6 Hz, 6H), 2.28 (t, 10.3 Hz, 2H), 3.14 (d, 10.1 Hz, 2H), 3.63 (m, 2H), 8.02 (br s, 1H); ^{13}C NMR: δ 19.0, 63.9, 71.0. Anal. calcd for $C_6H_{13}NO_2$: C, 54.93; H, 9.99; N, 10.68. Found: C, 54.61; H, 9.60; N, 10.35.

Compound **4f**[14] IR 3250, 2956, 2928, 2857,1495, 1465 cm^{-1}; ^1H NMR: δ 0.91 (m, 6H), 1.30 (br, 6H), 1.59 (m, 4H), 2.62 (m, 4H); ^{13}C NMR: δ 11.8, 14.1, 20.5, 22.6, 27.0, 27.2, 31.8, 60.8, 62.6.

Compound **4g** mp 60–61°C, IR 3219, 3094, 2963, 2870, 1605, 1513, 1346 cm^{-1}; ^1H NMR: δ 0.88 (t, 7.3 Hz, 3H), 1.53 (sx, 7.5 Hz, 2H), 2.62 (t, 7.6 Hz, 2H), 3.83 (s, 2H), 6.75 (br s, 1H), 7.49 (d, 8.8 Hz, 2H), 8.15 (d, 8.8 Hz, 2H); ^{13}C NMR: δ 11.5, 20.1, 62.0, 63.6, 123.3, 130.4, 144.7, 147.1. Anal. calcd for $C_6H_{13}NO_2$: C, 57.13; H, 6.71; N, 13.33. Found: C, 56.99; H, 6.69; N, 13.19.

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21. (a) Trace amounts of 2,6-di-*tert*-butyl-4-methylphenol [BHT; ^{1}H NMR ($CDCl_3$): δ 6.98 (s, 2H), 5.01 (br. s, 1H), 2.26 (s, 3H), 1.43 (s, 18H)] were found; presumably arising from resin contamination, but this BHT could not be removed by resin washing; (b) No BHT contaminate is observed in the crude product when only chloroform is used.
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