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Reductive Cleavage of N–O Bonds Using Samarium(II) Iodide in a Traceless Release Strategy for Solid-Phase Synthesis

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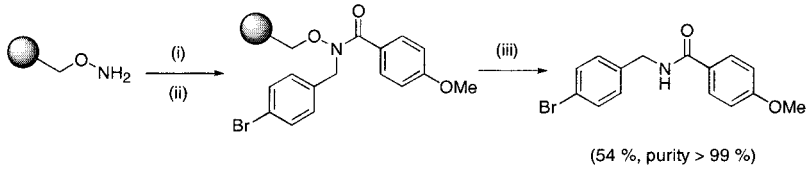
ABSTRACT



(i) *p*-anisoyl chloride, diisopropylethylamine, dichloromethane, 25 °C, 16 h.
(ii) DBU, 4-bromobenzyl bromide, toluene, 25 °C, 48 h.
(iii) SmI_2 / THF, 25 °C, 3 h.

A strategy for making amides and ureas using a polymer-supported hydroxylamine resin as a traceless linker is described. The cleavage of the linker by samarium(II) iodide is reported for the first time.

New methods in solid-phase synthesis of small organic molecules continue to develop rapidly and become more sophisticated.[1] The diversity of synthetic targets maintains the need for new cleavage strategies, with the choice of linker being an essential part of this synthetic design process. Most linkers leave behind tell-tale functional groups on cleavage. Traceless linkers[2] are a subgroup of linkers that have been developed to leave behind, at most, a hydrogen atom at the attachment point between the molecule and the resin.

The objective of the research described herein was to develop a simple traceless linker that could be used for bidirectional elaboration from a central nitrogen atom. To this end we have extended the usefulness of polymer-supported hydroxylamine. This linker has previously been described by others and has been used in the synthesis of tripeptide and sulfonamido hydroxamic acid derivatives,[3] and in the synthesis of a range of carbonyl-containing compounds.[4] An *N*-Fmoc-aminooxy-2-chlorotrityl-polystyrene resin has also been reported. On deprotection it reveals a chlorotrityl hydroxylamine linker and it has been used in the synthesis of peptidyl hydroxamic acids.[5] In these examples, the release strategy either involved C−O bond cleavage with trifluoroacetic acid or C−N bond cleavage with lithium aluminum hydride to give hydroxamic acids and aldehydes,[4b] respectively. To cleave in a traceless

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manner, it is necessary to cleave the N−O bond[6] of the hydroxylamine instead (Figure 1).

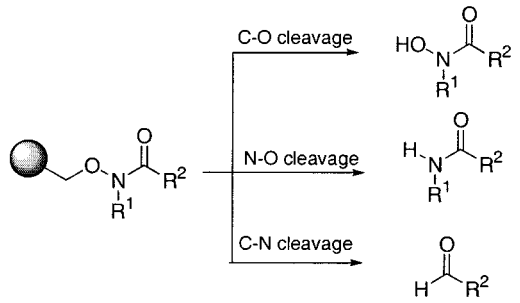
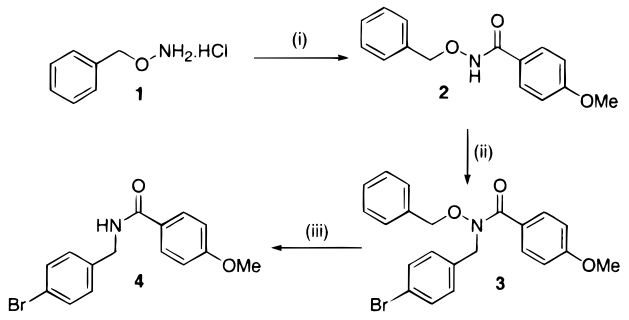


Figure 1. Cleavage options for functionalized hydroxylamine resin.

Samarium(II) iodide[7] has been used for reductive cleavage of N−O bonds in solution,[8] including those in hydroxylamines and hydroxamic acids.[9] This reagent is increasingly being used in a variety of synthetic transformations[10] and can be purchased commercially as a 0.1 M solution in THF (a suitable solvent in terms of resin swelling properties). It can also be prepared in similar concentrations.[11] The use of samarium(II) iodide has the additional benefit that the cleavage reaction does not require acidic conditions. This paper describes our development of a samarium(II) iodide induced reductive cleavage of a hydroxylamine linker for the solid-phase synthesis of amides and ureas.

An initial study was carried out in the solution phase (Scheme 1). Benzylhydroxylamine **1** was used as a model

Scheme 1. Solution-Phase Study[a]

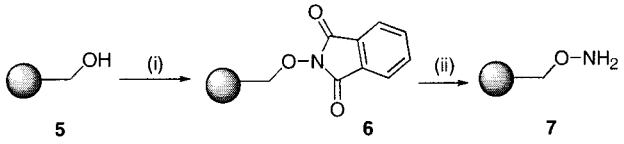


[a] (i) *p*-Anisoyl chloride, DIPEA, DCM, 25 °C, 45 min (72%); (ii) 4-bromobenzyl bromide, DBU, toluene, 0−25 °C, 45 min (40%); (iii) SmI_2 (0.1 M), THF, 25 °C, 5 min (92%).

for the polymer-supported hydroxylamine linker **7**. Rapid acylation of benzylhydroxylamine **1** with *p*-anisoyl chloride gave **2** (72%). Alkylation with 4-bromobenzyl bromide using DBU as the base gave **3** in modest yield (40%). Subsequent reductive cleavage of the N−O bond of **3** was achieved using 0.1 M samarium(II) iodide in THF. The cleavage went to completion at room temperature within 5 min, giving *N*-(4-bromo-benzyl)-4-methoxybenzamide **4** in high yield (92%).

For the solid-phase chemistry the hydroxylamine linker was prepared from Wang resin **5** using an established literature procedure.[4b] This involved coupling *N*-hydroxyphthalimide to the hydroxymethyl group on the resin under Mitsunobu conditions to give **6**. The phthalimido group was removed with a 40% aqueous solution of methylamine and THF (Scheme 2). The loading of **7** was 1.18 mmol g^{-1}, based

Scheme 2. Hydroxylamine Resin Prepared from Wang Resin.[13 a]



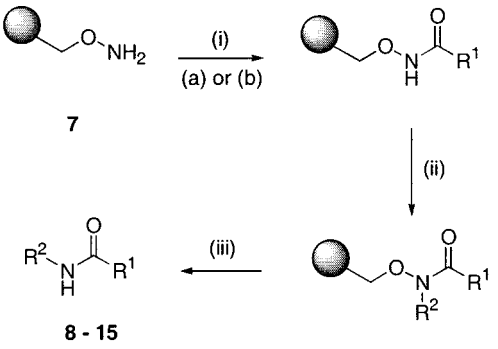
[a] (i) *N*-Hydroxyphthalimide, PPh_3, DIAD, THF, 0 °C − 25 °C, 16 h; (ii) 40% aqueous methylamine, THF, 25 °C, 16 h.

on nitrogen analysis, and corresponded to a yield in excess of 90%. The hydroxylamine linker was also prepared from Merrifield resin (1 mmol g^{-1}) with less success. The *N*-hydroxyphthalimide was loaded onto the resin using sodium hydride and catalytic tetrabutylammonium iodide. Removal of the phthalimido group with hydrazine hydrate gave the hydroxylamine linker with a substantially lower loading of 0.22 mmol/g (by Fmoc analysis[12] at 290 nm).

The utility of this traceless cleavage strategy was demonstrated by the synthesis of a range of amides and ureas, **8**−**15** (Scheme 3).

The procedure involved initial acylation of the Wang-based hydroxylamine resin, which introduced the first level of diversity (step i, Scheme 3). The acylations were carried out using acid chlorides, a benzoic acid derivative, or a carbamyl chloride.

Scheme 3. Solid-Phase Synthesis of Compounds **8**−**15**[13 a]



[a] (a) Acid chloride, DIPEA, DCM or (b) carboxylic acid, DIC, HOBt, DMF, at 25 °C, 16 h; (ii) DBU, alkyl bromide, toluene, 25 °C, 48 h; (iii) 0.1 M SmI_2 in THF, 25 °C, 3 h.

(6) For a discussion of the reduction of N−O bonded groups, see: Gilchrist, T. L. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Vol 8, pp 390−395.

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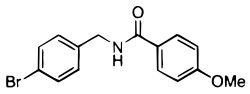
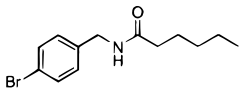
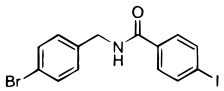
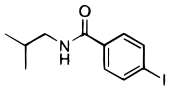
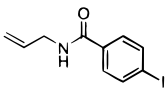
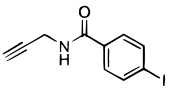
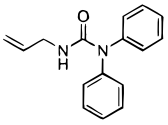
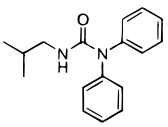
Table 1. Definitions of R^1 and R^2 in Products **8**−**15**

R^1	R^2	product
4-methoxyphenyl	4-bromobenzyl	**8**
n-hexane	4-bromobenzyl	**9**
4-iodophenyl	4-bromobenzyl	**10**
4-iodophenyl	isobutyl	**11**
4-iodophenyl	allyl	**12**
4-iodophenyl	propargyl	**13**
diphenylurea	allyl	**14**
diphenylurea	isobutyl	**15**

Alkylation of the hydroxamic nitrogen in the second step was achieved using the base DBU and the isobutyl, propargyl, allyl, or 4-bromobenzyl bromides in toluene. Reductive cleavages were performed on the resulting dried resins under anhydrous conditions. Products **8**−**15** (Table 1) were obtained by cleavage with samarium(II) iodide over 3 h, although product release could be detected by TLC and HPLC after only a few minutes in most cases. The carbonyl stretches in the FTIR spectra of the cleaved resins had disappeared. The products were obtained in modest yields and in good to excellent purity (Table 2).

Table 2. Products **8**−**15** Obtained Using SmI_2-Induced Reductive Cleavage

Entry	Product	Yield (%)	Purity[14] (%)
8		54	99
9		30	97[15]
10		32	46
11		33	99
12		31	84
13		40	79
14		32	94
15		31	99[16]

The procedure for the preparation of hydroxylamine resin **7**,[17] amide **11**,[18] and urea **15**[19] are given in the references cited.

(8) (a) Natale, N. L. *Tetrahedron Lett*. **1982**, *23*, 5009−5012. (b) Mukaiyama, T.; Yorozu, K.; Kato, K.; Yamada, T. *Chem. Lett*. **1992**, 181−184. (c) Zhang, Y.; Lin, R. *Synth. Commun*. **1987**, *17*, 329−332.

(9) Keck, G. E.; McHardy, S. F.; Wager, T. T. *Tetrahedron Lett*. **1995**, *36*, 7419−7422.

(10) For an early review, see: Soderquist, J. A. *Aldrichimica Acta* **1991**, *24*, 15−23.

(11) Imamoto, T.; Ono, M. *Chem. Lett*. **1987**, 501−502.

(12) A procedure for substitution measurement of Fmoc resins is given in the following: Bennett, W. D.; Christenden, J. W. *Advanced Chemtech Handbook of Combinatorial and Solid-Phase Organic Chemistry*; 1998; p 330.

(13) Abbreviations: dichloromethane (DCM), *N*,*N*-diisopropylethylamine (DIPEA), *N*-hydroxybenzotriazole hydrate (HOBt), diisopropylcarbodiimide (DIC), diisopropyl azodicarboxylate (DIAD), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

(14) HPLC purity at 254 nm unless noted otherwise.

(15) HPLC purity at 220 nm.

(16) Purity determined from the peak area in the LC trace over UV range 215−330 nm.

(17) **Procedure for the preparation of the hydroxylamine linker from Wang resin**.[4b] Wang resin (100−200 mesh, 1.29 mmol/g, 25 g, 32.25 mmol) was suspended in THF (250 mL). The suspension was chilled to 0 °C. Triphenylphosphine (16.92 g, 64.50 mmol, 2 equiv) was added followed by *N*-hydroxyphthalimide (26.13 g, 161.25 mmol, 5 equiv). After stirring at 0 °C for 15 min, diisopropyl azodicarboxylate (12.70 mL, 64.50 mmol, 2 equiv) was added slowly. The suspension was warmed to rt, and stirring was continued for a total of 12 h. The suspension was filtered, and the resin collected in a sintered funnel. The resin was washed with methanol, water, ethyl acetate, and dichloromethane (minimum of 2 × 100 mL of each) until the resin was free from discoloration and was cream in color. ν_{max}/cm^{-1} (gel) 1789 (C═O), 1727 (C═O). The moist resin was transferred to a 1 L conical flask and stirred in a solution of THF (500 mL) and a 40% aqueous methylamine solution (250 mL) for 16 h. The resin was washed as previously described and dried under high vacuum for 4 h (24.9 g). ν_{max}/cm^{-1} (gel) 3323 (ONH_2). Anal. Calcd: N, 1.74. Found: N, 1.95. Loading 1.18 mmol/g (based on N anal.). Yield 91% (based on N analysis).

(18) **4-Iodo-*N*-isobutylbenzamide (11).** Hydroxylamine resin (1.00 g, 1.18 mmol) was suspended in a solution of 4-iodobenzoic acid (0.94 g, 3.78 mmol), diisopropylcarbodiimide (0.58 mL, 3.78 mmol), and *N*-hydroxybenzotriazole hydrate (0.59 g, 3.78 mmol) in DMF (10 mL). The suspension was shaken at 25 °C for 16 h. ν_{max}/cm^{-1} 1668 (C═O). The resin was washed with methanol, ethyl acetate, and dichloromethane (5 × 25 mL of each) and then dried under high vacuum for 16 h. The resin was then suspended in a solution of DBU (0.94 mL, 6.3 mmol) in toluene (15 mL), and isobutyl bromide (1.33 g, 12.2 mmol) was added. The suspension was shaken at 25 °C for 48 h. The resin was washed and dried as described above. The resin (1.21 g, 1.05 mmol) was preswollen with THF (2.1 mL), and samarium(II) iodide (0.1 M in THF, 20.99 mL, 2.10 mmol) was added. The reaction suspension was shaken at 25 °C for 3 h. The resin was filtered off and rinsed with dichloromethane (5 × 10 mL), and the cleavage solution and washings were collected. The filtrate was evaporated to give a dark yellow residue which was redissolved in a solution of diethyl ether (25 mL), 1 M HCl (20 mL), and 10% aqueous sodium thiosulfate (5 mL). The mixture was transferred to a separating funnel and shaken until it became colorless. The organic layer was collected, and the aqueous layer was extracted with diethyl ether (2 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL) and dried over magnesium sulfate. The solid obtained after evaporation was redissolved in the minimum amount of dichloromethane (ca. 0.3−0.5 mL) and filtered through a short pad of silica (ca. 3 cm in a 1.5 cm diameter column, eluting with 20% ethyl acetate in hexanes). The filtrate was collected and evaporated to afford 4-iodo-*N*-isobutylbenzamide **11** (49 mg, 33%): R_f 0.63 [vis UV, ethyl acetate/hexanes (1:1)]; ν_{max}/cm^{-1} 3305 (NH), 1633 (C═O); ^1H NMR (500 MHz, $CDCl_3$) δ 0.96 (6 H, d, J = 6.5, $(CH_3)_2C$), 1.86−1.91 (1 H, m, $(CH_3)_2CH$), 3.27 (2 H, dd, J = 6.5, 6.5, CH_2), 6.06 (1 H, s, br, NH), 7.74 (2 H, d, J = 8.5, Ar−H), 7.77 (2 H, d, J = 8.5, Ar−H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 19.89 (CH_3), 28.34 (CH), 47.15 (CH_2), 128.17 (CH), 137.52 (CH), 163.4 (C═O); MS (ES) m/z = 304.0 ($M + H^+$, 100%), 326.0 ($M + Na^+$, 12%); LCMS t_R 5.0 min; HPLC t_R 14.4 min, 99.2% (254 nm, TSK gel Oligio DNA RP; solvent A acetonitrile + 0.1% TFA, solvent B milliQ water + 0.1% TFA, gradient 5−95% solvent A over 15 min).

Acknowledgment. We thank Peptide Therapeutics for CASE Award funding to R.M.M.

(19) **3-Isobutyl-1,1-diphenylurea (15).** Hydroxylamine resin (1.00 g, 1.18 mmol) was suspended in a solution of diphenylcarbamyl chloride (0.84 g, 3.78 mmol) and *N*,*N*-diisopropylethylamine (0.67 mL, 3.78 mmol) in dichloromethane (10 mL). The suspension was shaken at 25 °C for 16 h. The resin was washed with methanol, ethyl acetate, and dichloromethane (5 × 25 mL of each) and then dried under high vacuum for 16 h. ν_{max}/cm^{-1} (gel) 3372 (NH), 1697 (C═O). The resin was suspended in a solution of DBU (0.94 mL, 6.3 mmol) and toluene (15 mL), isobutyl bromide (1.33 mL, 12.2 mmol) was added, and the suspension was shaken at 25 °C for 48 h. The resin was washed and dried as described above. ν_{max}/cm^{-1} (gel) 1690 (C═O). The resin (0.78 g, 0.97 mmol) was preswollen with THF (1.9 mL), and samarium(II) iodide (0.1 M in THF, 19.34 mL, 1.93 mmol) was added. The reaction suspension was shaken at 25 °C for 3 h. The resin was filtered off and rinsed with dichloromethane (5 × 10 mL), and the cleavage solution and washings were collected. The solution was evaporated to give a dark yellow residue which was redissolved in a solution of diethyl ether (25 mL), 1 M HCl (20 mL), and 10% aqueous sodium thiosulfate (5 mL). The mixture was transferred to a separating funnel and shaken until it became colorless. The organic layer was collected and the aqueous layer extracted with diethyl ether (2 × 10 mL). The combined ethereal layers were washed with brine (2 × 10 mL) and then dried over magnesium sulfate. The solid obtained after evaporation was dissolved in the minimum amount of dichloromethane (ca. 0.3−0.5 mL) and then filtered through a short pad of silica (ca. 3 cm in a 1.5 cm diameter column, eluting with 50% ethyl acetate/hexanes). The filtrate was collected and evaporated to afford *3*-isobutyl-1,1-diphenylurea **15** (58 mg, 31%): R_f 0.55 [vis UV, ethyl acetate/hexanes (1:1)]; ν_{max}/cm^{-1} 3288 (NH), 1643 (C═O); ^{1}H NMR (500 MHz, $CDCl_3$) (two rotamers in a ratio of 0.2:0.3 assigned using HMQC as A and B where possible) δ 0.78 (3 H, d, *J* 7, CH_3), 0.86 (3 H, d, *J* 7, CH_3), 1.70−1.77 (0.4 H, m, CH_3−CH, A), 1.90−1.98 (0.6 H, m, CH_3−CH, B), 3.05 (0.4 H, m, CH_2−N, A), 3.11 (0.6 H, d, J = 7, CH_2−N, B), 4.56 (0.6 H, s, NH, A), 6.52 (0.4 H, s, NH, B), 7.10−7.38 (10 H, m, Ar−H); ^{13}C NMR (500 MHz, $CDCl_3$) (according to the HMQC and APT spectra, all carbon atoms except the aromatic carbons are seen as two rotamers forms and have been assigned as A and B where possible in relation to A and B in the proton spectrum) δ 19.7 (CH_3, A), 19.8 (CH_3, B), 25.9 (CH, B), 28.5 (CH, A), 47.9 (CH_2, A), 58.8 (CH_2, B), 125.4 (Ar), 125.6 (Ar), 125.8 (Ar), 127.1 (Ar), 129.0 (Ar), 142.6 (Ar), 143.7 (Ar), 156.0 (C═O), 161.7 (C═O); MS (ES) m/z = 269.2 ($M + H^+$, 100%); LCMS t_R 5.0 min, purity 99% estimated by LC area (UV 215−330 nm).

Supporting Information Available: Full experimental details and characterization for compounds **2**, **3**, **4**, and **7**−**15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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