ORGANIC LETTERS

2000
Vol. 2, No. 18
2777−2779

Convenient Preparation of *O*-Linked Polymer-Bound *N*-Substituted Hydroxylamines, Intermediates for Synthesis of *N*-Substituted Hydroxamic Acids

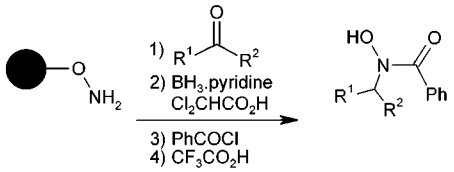
Dale E. Robinson and Mark W. Holladay*

SIDDCO, Inc., 9040 S. Rita Road, Suite 2338, Tucson, Arizona 85747

holladay@siddco.com

Received June 2, 2000

ABSTRACT



An efficient procedure for preparation of *O*-linked polymer-bound *N*-substituted hydroxylamines by reduction of resin-bound oximes with borane·pyridine complex in the presence of dichloroacetic acid is reported. Other reducing systems commonly used for imine or oxime reduction were ineffective, including borane·pyridine in the presence of acetic acid. Oximes derived from a variety of aromatic and aliphatic aldehydes and ketones were successfully reduced. The *N*-substituted products were acylated and cleaved from resin to afford *N*-substituted hydroxamic acids.

Hydroxamic acids are of interest as inhibitors of metalloproteases,[1] and solid-phase methods offer an attractive general approach to this class of compounds.[2] *N*-Substituted hydroxamic acids also are of interest in the same context, and combinatorial solid-phase synthesis of such compounds has recently been reported.[3] In addition, polymer-bound *N*-benzylic hydroxamic acids have been utilized as key intermediates for convenient preparation of aldehydes.[4] The route shown in Scheme 1, whereby an *O*-linked polymer-bound alkoxylamine **1**[2a−c,e,i] is treated with an aldehyde or ketone to form the corresponding oxime, followed by oxime reduction and acylation, would appear to be a straightforward approach to solid-phase synthesis of *N*-substituted hydroxamic acids. However, reported attempts to reduce this strategy to practice have been unsuccessful owing to an inability to cleanly reduce *O*-linked resin-bound oximes **2** to the corresponding *N*-substituted hydroxylamine derivatives **3** using a variety of conditions ($NaBH_3CN$ in HOAc/MeOH/THF; $NaBH(OAc)_3$; $NaBH_4$; $LiBHEt_3$).[3,4] Accordingly, previous workers have resorted to *N*-alkylation of *N*-urethane-protected alkoxylamine derivatives using primary or activated alkyl halides, either prior to or after attachment to the solid phase. In this report, we describe our successful efforts to achieve clean reduction of **2** to **3**, which can be followed by acylation and cleavage from the resin to provide *N*-substituted

(1) Hagmann, W. K.; Lark, M. W.; Becker, J. W. *Ann. Rep. Med. Chem.* **1996**, *32*, 231−240.

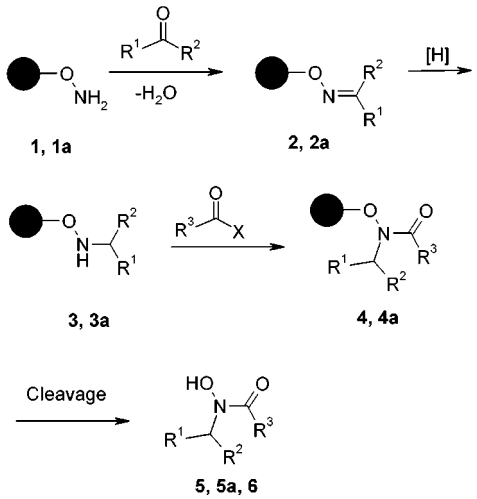
(2) (a) Floyd, C. D.; Lewis, C. N.; Patel, S. R.; Whittaker, M. *Tetrahedron Lett.* **1996**, *37*, 8045−8048. (b) Richter, L. S.; Desai, M. C. *Tetrahedron Lett.***1997**, *38*, 321−322. (c) Mellor, S. L.; McGuire, C.; Chan, W. C. *Tetrahedron Lett.* **1997**, *38*, 3311−3314. (d) Ngu, K.; Patel, D. V. *J. Org. Chem.* **1997**, *62*, 7088−7089. (e) Bauer, U.; Ho, W.-B.; Koskinen, A. M. P. *Tetrahedron Lett.* **1997**, *38*, 7233−7236. (f) Khan, S. I.; Grinstaff, M. W. *Tetrahedron Lett.* **1998**, *39*, 8031−8034. (g) Dankwardt, S. M. *Synth. Lett.* **1998**, 761. (h) Zhang, Y.; Li, D.; Houtman, J. C.; Witiak, D. T.; Seltzer, J.; Bertics, P. J.; Lauhon, C. T. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2823−2826. (i) Barlaam, B.; Koza, P.; Berriot, J. *Tetrahedron* **1999**, *55*, 7221−7232.

(3) Mellor, S. L.; Chan, W. C. *J. Chem. Soc., Chem. Commun.* **1997**, 2005−2006.

(4) Salvino, J. M.; Mervic, M.; Mason, H. J.; Kiesow, T.; Teager, D.; Airey, J.; Labaudiniere, R. *J. Org. Chem.* **1999**, *64*, 1823−1830.

10.1021/ol006152g CCC: $19.00
Published on Web 08/10/2000

Scheme 1. Solid-Phase Synthesis of *N*-Substituted Hydroxamic Acids



hydroxamic acids. This approach offers access to hydroxamic acids having a broad range of nitrogen substituents and complements existing methods that utilize alkyl halides as synthons for substituents at this position.

We chose Wang resin as the solid support for these studies, owing primarily to its commercial availability with high loading levels.[5] Initial efforts were focused on investigating conditions for reduction of oxime **2a**, which was formed by treatment of the known[2a] Wang resin bound hydroxylamine **1a** with excess benzaldehyde in the presence of trimethyl orthoformate (TMOF) in THF. The results from treatment of **2a** under a variety of reducing conditions are shown in Table 1 and support and complement previous observations that many of the common conditions for imine or oxime reduction work poorly in this system. Conditions reported by Kawase and Kikugawa[6] utilizing BH_3·pyridine in the presence of HCl appeared promising for the reduction of *O*-alkyloximes, but the solvents used (water, ethanol) are poorly compatible with polystyrene resin, and acid lability of the resin linkage must be considered. Therefore, BH_3·pyridine in the presence of weaker acids using dichloromethane as the solvent was investigated. Although BH_3·pyridine in the presence of acetic acid[7] failed to effect reduction (entry 1), BH_3·pyridine in the presence of trichloroacetic acid (TCA) resulted in partial (entry 7) or essentially complete (entry 8) conversion to the desired product, depending on the number of equivalents of reducing agent used. In the experiments represented by entries 8−14, it proved beneficial for analytical purposes to subject the product mixture to benzoylation conditions (~10 equiv PhCOCl, $NEtiPr_2$, CH_2Cl_2, 4-DMAP) prior to cleavage (1:1 TFA/CH_2Cl_2). Under these conditions, the desired product is converted to hydroxamate **5a**, which contains a better chromophore than the unbenzoylated product for detection by HPLC/UV. Moreover, reductive cleavage of the N−O bond is potentially a side reaction in the reduction of oximes to hydroxylamine derivatives, and benzoylation permits detection of the extent of this side reaction by ultimately producing benzoic acid. Entries 9 and 13 demonstrate that over-reduction can indeed be an issue in the present system, i.e., BH_3·pyridine in the presence of trifluoroacetic acid[8] caused some over-reduction, and BH_3·THF, even when used in only slight excess, resulted both in over-reduction and unreacted oxime.

Table 1. Results for Attempted Reductions of Oxime **2a**

entry	conditions[a]	results[b,c]
1	$NaCNBH_3$ (10), 1:1 HOAc/DMF	min oxime reduction
2	$NaBH(OAc)_3$ (10), HOAc (10), DMF/CH_2Cl_2	min oxime reduction
3	$Me_4NBH(OAc)_3$ (5), 1:1:1 HOAc/CH_3CN/CH_2Cl_2	min oxime reduction
4	Ph_2SiH_2 (3), $Ti(OiPr)_4$ (3), H_2Cl_2	min oxime reduction
5	Me_2PhSiH (3), TCA (3), CH_2Cl_2	min oxime reduction
6	BH_3·pyridine (10), HOAc (10), CH_2Cl_2	min oxime reduction
7	BH_3·pyridine (3), TCA (18), CH_2Cl_2	partial oxime reduction
8	BH_3·pyridine (10), TCA (15), CH_2Cl_2	**5a** (93%), no N−O cleavage
9	BH_3·pyridine (10), TFA (15), CH_2Cl_2	**5a** (89%), N−O cleavage (8%)
10	BH_3·pyridine (10), DCA (15), CH_2Cl_2	**5a** (97%), no N−O cleavage
11	BH_3·pyridine (5), DCA (7.5), CH_2Cl_2	**5a** (97%), no N−O cleavage
12	BH_3·pyridine (10), CA (15), CH_2Cl_2	unreacted oxime (97%)
13	BH_3·THF (1.1), THF	**2a** (61%), **5a** (24%), N−O cleavage (15%)
14	$NaCNBH_3$ (10), 1:1 DCA/DMF	**5a** (87%), no N−O cleavage

[a] Reactions were conducted at room temperature for 16−18 h. Numbers in parentheses indicate number of equivalents of reagent relative to oxime substrate. Abbreviations: CA, DCA, TCA: mono-, di-, and trichloroacetic acids, respectively; TFA, trifluoroacetic acid. [b] Entries 8−14 represent experiments that were carried through the entire sequence in Scheme 1 (**a** series). Extent of N−O cleavage was inferred from the amount of benzoic acid produced. [c] Values expressed as percentages refer to relative peak area in the HPLC of the crude reaction mixture, monitored at 215 nm. Peak identities were supported by LC/MS.

The results of experiments designed to investigate the effect of small changes in the successful BH_3·pyridine/TCA/CH_2Cl_2 system described above also are included in Table 1. Dichloroacetic acid (DCA) in place of TCA also gave

(5) Wang resin with nominal loading of 1.4 mmol/g was purchased from Chem Impex Internation, Inc., Wood Dale, IL.

(6) Kawase, M.; Kikugawa, Y. *J. Chem. Soc., Perkin Trans. 1* **1979**, 643−645.

(7) Pelter, A.; Rosser, R. M. *J. Chem. Soc., Perkin Trans. 1* **1984**, 717−720.

(8) Satoh, Y.; Stanton, J. L.; Hutchison, A. J.; Libby, A. H.; Kowalski, T. J.; Lee, W. H.; White, D. H.; Kimble, E. F. *J. Med. Chem.* **1993**, *36*, 3580−3594.

excellent results (entry 10), whereas chloroacetic acid (CA) was an ineffective promoter under the same conditions (entry 12). Smaller excesses of BH_3·pyridine and DCA gave comparable results in the case of substrate **2a** (entry 11), but larger excesses often proved helpful on some of the more demanding substrates described below. On the basis of the results in Table 1, BH_3·pyridine in the presence of DCA was adopted as the reducing system of choice, as described in more detail below. The results with BH_3·pyridine and various carboxylic acids suggest that a minimum acid strength is necessary to promote oxime reduction by BH_3·pyridine. This effect is consistent with findings reported by Kikugawa,[9] whereby aldehydes were transformed to symmetrical ethers with BH_3·pyridine in trifluoroacetic acid but not in acetic acid. Interestingly, dichloroacetic acid also was found to be a better promoter than acetic acid of sodium cyanoborohydride mediated reduction (Table 1, entry 1 vs entry 14), although conditions for application of this reducing system were not optimized.

The scope of the BH_3·pyridine/DCA system with respect to aldehydes and ketones was examined. First, the conditions for oxime formation using a variety of ketones and aldehydes were reexamined, and it was observed that for several ketones, use of HOAc in TMOF/1,2-dichloroethane (DCE) gave somewhat better results compared to the conditions previously used for benzaldehyde (TMOF/THF without HOAc). Thus, double treatment of **1a** with 10 equiv of aldehyde or ketone (0.5 M) and 3.5 equiv of HOAc (0.2 M) in 1.3:1 DCE/TMOF for 16−18 h at room temperature was adopted as a standard protocol for oxime formation. Table 2 summarizes the results from application of this procedure

Table 2. Results for Conversion of **1a** to Oximes Using the Standard Protocol (see text) with Aldehydes and Ketones $R^1(C{=}O)R^2$

aldehyde or ketone (R^1/R^2)	extent of oxime formation[a]
Ph/H; *p*-MeO-Ph/H; *p*-CF_3-Ph/H; Ph-$(CH_2)_2$/H; *p*-NO_2−Ph/Me; Et/Et; ketone = *N*-benzyl-4-piperidinone	>90%
Ph/Me; Ph/Ph (as imine)	70−90%
Ph/*i*-Pr; Ph/*t*-Bu; Ph/*c*-Pr; Ph/Ph; *i*-Pr/*i*-Pr	<20%

[a] Data estimated from HPLC peak areas monitored at 215 nm.

to various aldehydes and ketones, including a number of sterically or electronically demanding examples. Following attempted oxime formation, resin samples were washed and then subjected to benzoylation and cleavage conditions, as described above, permitting detection of unreacted **1a** as benzohydroxamic acid (in some cases, accompanying hydrolysis to benzoic acid, presumably during cleavage, also was observed). The results show that aliphatic and aromatic aldehydes, unbranched acetophenones, and unbranched cyclic and acyclic ketones are good or excellent substrates, whereas benzophenones and α-branched acetophenones will likely require more forcing conditions to induce oxime formation.

The oximes that formed successfully were then subjected to one or two cycles of reduction with BH_3·pyridine (15 equiv)/DCA (22 equiv) in CH_2Cl_2 at room temperature for 16−18 h, with the product mixture subjected to benzoylation followed by cleavage as described above. The results (Table 3) indicate that the majority of cases produce the desired

Table 3. Results for Conversion of **1a** to Hydroxamates **5** According to Scheme 1 Using the Standard Protocols (see text) and Aldehydes or Ketones $R^1(C{=}O)R^2$ [a]

aldehyde or ketone	% unreacted oxime (**2**)	% hydroxamic acid (**5**)
benzaldehyde	<5	>95
p-methoxybenzaldehyde	<5	>95
p-trifluoromethylbenzaldehyde	21	79
3-phenylpropionaldehyde[b]	<5	>95
acetophenone	<5	80
p-nitroacetophenone[b]	55	24
N-benzyl-4-piperidinone	<5	90
benzophenone imine	40	15
3-pentanone[b]	ND	83 (compd **6**)

[a] Data estimated from relative HPLC peak areas monitored at 215 nm. [b] Subjected to double reduction (see text).

N-substituted benzohydroxamic acid in good to excellent purities. However, electron-withdrawing substituents on the aromatic ring of a starting benzaldehyde or acetophenone appear to inhibit oxime reduction, and reduction also is quite sluggish for the benzophenone-derived oxime.

To demonstrate the sequence on a preparative scale, **1a** (1.0 g, 1.4 mmol) was reductively alkylated with 3-pentanone (two cycles of oxime reduction), followed by acylation with benzoyl chloride and acidolytic cleavage under the conditions described above. After evaporation of the volatile components, the residue (83% pure by HPLC at 215 nm; unacylated precursor not detected by ^{1}H NMR) was chromatographed over silica gel to afford **6** (Scheme 1) in 60% yield and >95% purity by HPLC monitored at 215 nm. ^{1}H NMR (500 MHz) and high resolution mass spectral data were fully consistent with the structure.[10]

Acknowledgment. We thank Dr. R. M. Scarborough (COR Therapeutics, S. San Francisco, CA) for valuable input into this work.

Supporting Information Available: Experimental procedure for preparation of **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL006152G

(9) Kikugawa, Y. *Chem. Lett.* **1979**, 415−418.

(10) ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89 (t, 6H), 1.53 (m, 2H), 1.87 (m, 2H), 3.65 (m, 1H), 7.43−7.51 (m, 5H). High-resolution MS (FAB+): calcd for $C_{12}H_{18}NO_2$ (M + H) 208.1338; found 208.1337.