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Synthesis of Functionalized Oxazolines and Oxazoles with DAST and Deoxo-Fluor

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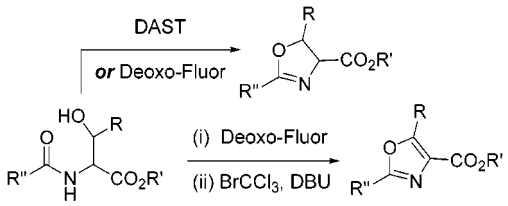
ABSTRACT



A mild and highly efficient cyclization of β-hydroxy amides to oxazolines is described using DAST and Deoxo-Fluor reagents. A one-pot protocol for the synthesis of oxazoles from β-hydroxy amides is also presented.

The discovery of marine natural products containing oxazolines[1] and oxazoles[2] has stimulated substantial contemporary interest in the chemistry of these heterocycles.[3] As part of our programs directed toward the synthesis and study of compounds such as trunkamide A,[4] hennoxazole A,[5] and diazonamide A,[6] we have investigated a number of methods for the conversion of β-hydroxy amides to oxazolines[7] and their further oxidation to oxazoles.[8] In this paper we present the combined results of studies into the use of diethylaminosulfur trifluoride (DAST) or bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor) for the cyclodehydrative conversion of β-hydroxy amides to oxazolines at low temperature, along with a one-pot procedure for the synthesis of oxazoles from β-hydroxy amides.

The dehydrative cyclization of β-hydroxy amides is a conceptually simple and synthetically versatile approach for the synthesis of oxazolines (Figure 1). A number of reagents have been reported to effect this transformation, both directly and indirectly.[7,9] It is worth noting that many of these reagents give only modest yields and are not always compatible with highly functionalized substrates.

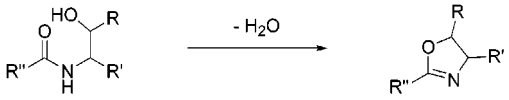


Figure 1. Cyclodehydration of β-hydroxy amides to oxazolines.

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(1) For a review of some of the chemistry of naturally occurring oxazoline cyclopeptides from *Lissoclinum* sp., see: Wipf, P. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon: New York, 1998; pp 187−228.

(2) For examples, see: (a) Faulkner, D. J. *Nat. Prod. Rep.* **2000**, *17*, 7. (b) Lewis, J. R. *Nat. Prod. Rep.* **2000**, *17*, 57 and the earlier reviews in these series.

(3) For representative examples, see: (a) Matsunaga, S.: Liu, P.; Celatka, C. A.; Panek, J. S.; Fusetani, N. *J. Am. Chem. Soc.* **1999**, *121*, 5605. (b) Uckun, F. M.; Narla, R. K.; Navara, C.; Forsyth, C. *Clin. Cancer Res.* **1999**, *5*, 316, Suppl. S. (c) Evans D. A.; Cee, V. J.; Smith, T. E.; Santiago, K. J. *Org. Lett.* **1999**, *1*, 87. (d) Mulder, R. J.; Shafer, C. M.; Molinski, T. F. *J. Org. Chem.* **1999**, *64*, 4995.

(4) Wipf, P.; Uto, Y. *Tetrahedron Lett.* **1999**, *40*, 5165. (b) Wipf, P.; Uto, Y. *J. Org. Chem.* **2000**, *65*, 1037.

(5) (a) Williams, D. R.; Brooks, D. A.; Berliner, M. A. *J. Am. Chem. Soc.* **1999**, *121*, 4924. (b) Wipf, P.; Lim, S. *J. Am. Chem. Soc.* **1995**, *117*, 558. (c) Wipf, P.; Lim, S. *Chimia* **1996**, *50*, 157.

(6) Wipf, P.; Yokokawa, F. *Tetrahedron Lett.* **1998**, *39*, 2223.

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Studies by Jones and co-workers, and later Lellouche and co-workers, have demonstrated that diethylaminosulfur trifluoride (DAST) is able to convert β-hydroxy amides to oxazolines under mild reaction conditions.[10] Encouraged by our recent successful application of this reagent in total syntheses of hennoxazole A[5a] and trunkamide A,[4] we sought to further delineate the utility and functional group compatibility of DAST for the synthesis of oxazolines.

Treatment of a variety of highly functionalized β-hydroxy amides with a slight excess (1.1 equiv) of DAST at −78 °C, followed by addition of K_2CO_3 and warming to room temperature, results in smooth cyclization to oxazolines (Table 1). Good to excellent yields are obtained for a diverse

Table 1. DAST-Mediated Cyclizations of β-Hydroxy Amides to Oxazolines[14]

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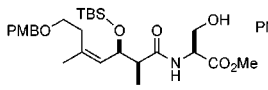
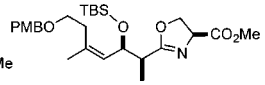
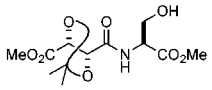
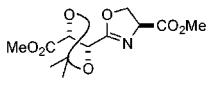
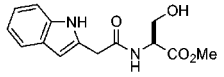
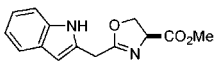
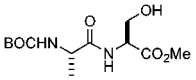
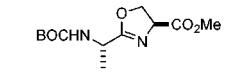
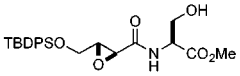
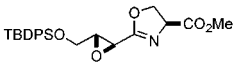
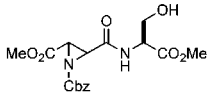
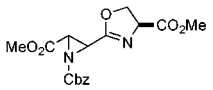
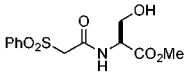
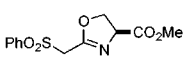
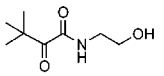
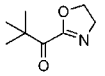
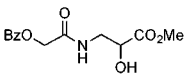
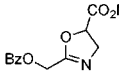
1			80
2			53
3			86
4			71
5			73
6			90
7			60
8			87
9			36

range of β-hydroxy amides.[11] It is noteworthy that silyl ether protecting groups are tolerated[12] (entries 1 and 5) and that the procedure is compatible with epoxides (entry 5), carbamate-protected aziridines (entry 6), and α-keto amides (entry 8). Double cyclizations to generate potentially useful tridentate ligands are also possible (Figure 2).[13]

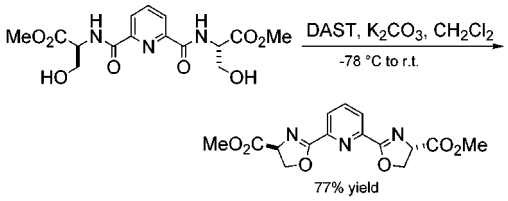


Figure 2. Double cyclization of a pyridine-2,6-dicarboxamide.

These investigations provided no evidence for competing formation of the corresponding primary fluorides via the well-characterized hydroxyl replacement. Moreover, the low yield of entry 9 is probably indicative of the unfavorable electronic contributions of the adjacent methyl ester and is suggestive of some limitations for this strategy. Sensitive stereochemical features are well tolerated as examination of crude reaction products failed to show evidence of epimerizations. For example, reactions of the homochiral substrates in entries 1, 2, 4, and 5, as well as the double cyclization in Figure 2, resulted in formation of a single diastereomer.

Recently, bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor) has been reported as an alternative to DAST.[15] Preliminary studies have indicated that the reactivity profiles of these two reagents are similar, although Deoxo-Fluor displays increased thermal stability. In the context of our studies, we felt that a comparison of these two reagents for the synthesis of oxazolines would be informative (Table 2).

It was possible to achieve smooth cyclization by treating peptidyl β-hydroxy amides with Deoxo-Fluor (1.1 equiv) at −20 °C in the absence of an added base. In general, the yields obtained with Deoxo-Fluor are comparable to those obtained with DAST. Despite this generalization, it is apparent that DAST gives slightly higher yields for serine-

(7) (a) Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *33*, 907. (b) Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 1575. (c) Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, 6267. (d) Wipf, P.; Hayes, G. B. *Tetrahedron* **1998**, *54*, 6987. (e) Wipf, P.; Venkatraman, S. *Tetrahedron Lett.* **1996**, *37*, 4659.

(8) (a) Williams, D. R.; Lowder, P. D.; Gu, Y.-G.; Brooks, D. A. *Tetrahedron Lett.* **1997**, *38*, 331. (b) Chen, H. M.Sc. Thesis, University of Pittsburgh, 1999.

(9) (a) For a recent review, see: Gant, T. G.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 2297. (b) Kamata, K.; Agata, I.; Meyers, A. I. *J. Org. Chem.* **1998**, *63*, 3113. (c) Yokokawa, F.; Hamada, Y.; Shioiri, T. *Synlett* **1992**, 149. (d) Miller, M. J.; Mattingly, P. G.; Morrison, M. A.; Kerwin, J. F. *J. Am. Chem. Soc.* **1980**, *102*, 7026. (e) Vorbrüggen, H.; Krolikiewicz, K. *Tetrahedron* **1993**, *49*, 9353. (f) Galéotti, N.; Montagne, C.; Poncet, J.; Jouin, P. *Tetrahedron Lett.* **1992**, *33*, 2807.

(10) (a) Burrell, G.; Evans, J. M.; Jones, G. E.; Stemp, G. *Tetrahedron Lett.* **1990**, *31*, 3649. (b) Lafargue, P.; Guenot, P.; Lellouche, J.-P. *Heterocycles* **1995**, *41*, 947.

(11) Yields are for purified compounds. All new compounds were fully characterized by ^{1}H NMR, ^{13}C NMR, IR, and HRMS.

(12) Although mechanistic details for reactions of alcohols with DAST are scarce, it is likely that the formation of an intermediate alkoxy-*N*,*N*-diethylaminodifluorosulfane would generate fluoride species which conceivably could be deleterious to silyl protecting groups.

(13) For a related example, see: Harm, A. M.; Knight, J. G.; Stemp, G. *Synlett* **1996**, 677.

(14) **Representative procedure:** Diethylaminosulfur trifluoride (1.1 equiv) was added dropwise to a cold (−78 °C) solution of the β-hydroxy amide in CH_2Cl_2. After stirring for 1 h at −78 °C, anhydrous K_2CO_3 (1.5 equiv) was added in one portion and the mixture was allowed to warm to ambient temperature. The reaction was poured into saturated aqueous $NaHCO_3$, and the biphasic mixture was extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (SiO_2, hexane: ethyl acetate mixtures) led to the desired oxazolines.

(15) Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Prozonic, F. M.; Cheng, H. *J. Org. Chem.* **1999**, *64*, 7048. Deoxo-Fluor is commercially available from both Aldrich Chemical Co., Milwaukee, WI 53201, and Air Products and Chemicals, Allentown, PA 18195-1501.

Table 2. Comparative Data for the Cyclization of Peptide β-Hydroxy Amides to Oxazolines with Deoxo-Fluor or DAST[16]

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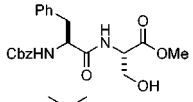
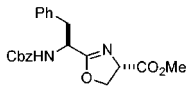
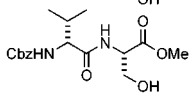
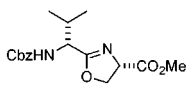
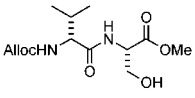
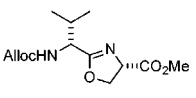
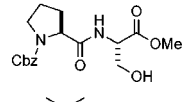
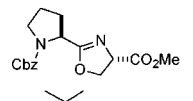
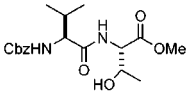
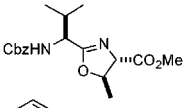
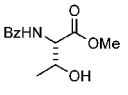
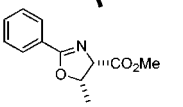
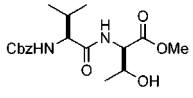
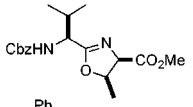
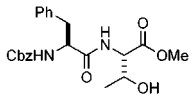
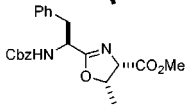
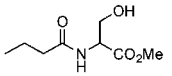
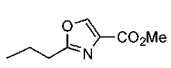
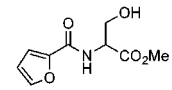
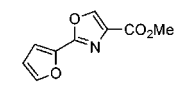
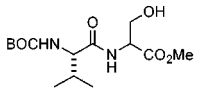
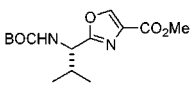
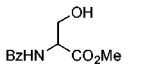
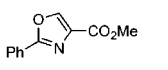
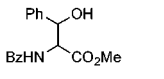
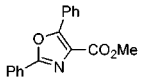
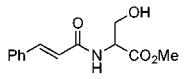
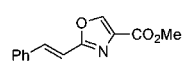
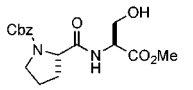
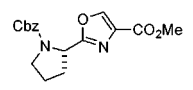
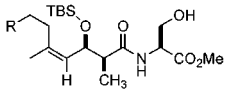
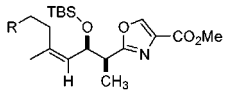
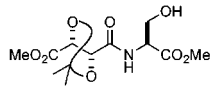
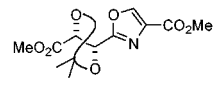
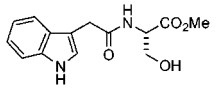
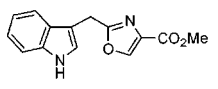
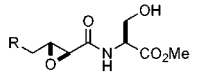
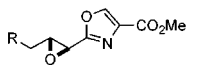
1			72 / 86
2			83 / 92
3			80 / 90
4			73 / 92
5			72 / 72
6			91 / 86
7			72 / 27
8			61 / 43

Table 3. One-Pot Cyclizations of β-Hydroxy Amides to Oxazoles[21,a]

entry	substrate	product	yield [%] (method)
1			49 (A)
2			67 (A)
3			62 (A)
4			82 (A)
5			70 (A)
6			88 (A)
7			65 (A)
8	 R = OPMB	 R = OPMB	71 (B)
9			50 (B)
10			68 (B)
11	 R = OTBDPS	 R = OTBDPS	54 (B)

[a] Method A: Deoxo-Fluor, −20 °C; then $BrCCl_3$, DBU, 2−3 °C, 8 h. Method B: DAST, −78 °C; then DBU at −40 °C and $BrCCl_3$ at 0 °C, 0 °C → 22 °C.

derived β-hydroxy amides than Deoxo-Fluor (entries 1−4), whereas the reverse is true for threonine-derived β-hydroxy amides (entries 5−8). It is noteworthy that it had been previously reported that attempted cyclization of BOC-Phe-Thr-OMe resulted only in elimination to give dehydroamino acid esters.[10b] Under our reaction conditions, oxazolines from threonine-derived β-hydroxy amides can be obtained in modest yields with DAST (entries 7 and 8). Further, Deoxo-Fluor provides a clear improvement over DAST for these substrates, allowing the desired oxazolines to be obtained in >60% yield.

The observation that cyclization occurred rapidly and cleanly (by TLC) at −20 °C led us to speculate that a one-pot process for the synthesis of oxazoles should be possible. After a modicum of experimentation, it was established that oxazoles could be readily obtained by treatment of β-hydroxy amides with a slight excess of Deoxo-Fluor (1.1 equiv) at −20 °C for 30 min, followed by bromotrichloromethane and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[8a] (Table 3). A significant feature of this cyclization is that it allows for a facile synthesis of C5-unsubstituted oxazoles. This is complementary to our previously reported Dess−Martin periodinane−I_2/PPh_3 protocol for the synthesis of oxazoles,[17] which is optimal for the synthesis of C5-substituted oxazoles.[18]

This general protocol can also be extended to the use of

(16) **Representative procedure** (Table 2, entry 2): Deoxo-Fluor (24.0 mL, 0.130 mmol) was added dropwise to a suspension of Cbz-D-Val-Ser-OMe (40.6 mg, 0.115 mmol) in CH_2Cl_2 (1 mL) cooled to −20 °C (bath temperature). After 30 min, the reaction mixture was quenched with saturated aqueous sodium bicarbonate at −20 °C. After warming to room temperature, the mixture was further diluted with saturated aqueous sodium bicarbonate and extracted with $CHCl_3$. The combined organic layer was dried (Na_2SO_4), filtered, and concentrated. Purification of the residue by flash chromatography (SiO_2, 1:1 hexane:ethyl acetate) gave the desired oxazoline as a colorless solid (31.8 mg, 83%): mp 78.0−80.0 °C; $[\alpha]_D$ +85.8 (*c* 1.1, $CHCl_3$, 22 °C); IR (film) 3312, 1720, 1660, 1526 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36−7.30 (m, 5 H), 5.33 (d, 1 H, J = 9.1 Hz), 5.14, 5.09 (AB, 2 H, J = 12.9 Hz), 4.76 (dd, 1 H, J = 10.4, 7.8 Hz), 4.57 (t, 1 H, J = 8.2 Hz), 4.65−4.40 (m, 2 H), 3.78 (s, 3 H), 2.15−2.08 (m, 1 H), 1.00−0.92 (m, 6 H); ^{13}C NMR δ 171.3, 169.2, 156.1, 136.5, 128.6, 128.3, 70.0, 67.9, 67.1, 54.7, 52.8, 31.9, 18.9, 17.8; HRMS *m*/*z* calcd for $C_{17}H_{22}N_2O_5$ 334.1529, found 334.1523.

DAST as illustrated by our limited number of examples (Table 3, entries 8−11). Thus, the dehydration reaction with DAST was initiated at −78 °C as previously described. Sequential introduction of DBU at −40 °C and $BrCCl_3$ at 0 °C followed by warming to room temperature for 2.5 h resulted in dehydrogenation. The oxidations in entries 8 and 10 proceeded more slowly and required stirring at 22 °C over 20 h.

The issue of potential racemization of the benzylic center under the dehydrogenation conditions was addressed by HPLC analysis of the oxazole derived from Cbz-Val-Ser-OMe (Figure 3). Comparison of the chiral HPLC trace for

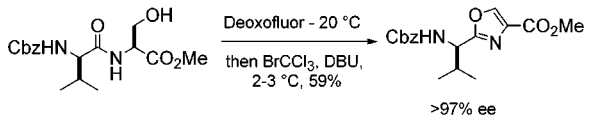


Figure 3. Cyclization of Cbz-D-Val-L-Ser-OMe.

the racemic oxazole[19] with that for the oxazole derived from cyclodehydration of Cbz-D-Val-L-Ser-OMe indicated <1.5% racemization (ee >97%).[20]

In summary, we have demonstrated that DAST and Deoxo-Fluor are useful reagents for the synthesis of highly functionalized oxazolines and oxazoles. Our results indicate that DAST and Deoxo-Fluor are compatible with a wide range of functional groups and that these reagents perform comparably in terms of yields for the cyclization of serine-derived peptidyl β-hydroxy amides. Our results indicate that Deoxo-Fluor is the reagent of choice for the cyclization of threonine-derived β-hydroxy amides. The mild conditions of the DAST- or Deoxo-Fluor-mediated cyclization also allow for a novel one-pot synthesis of oxazoles.

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OL005777B

(17) Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 3604.

(18) For a modification that allows the synthesis of some C(5)-unsubstituted oxazoles, see refs 5b and 5c.

(19) Synthesized in 57% yield by the same one-pot cyclodehydration−dehydrogenation procedure from the dipeptide derived from coupling of D/L-Cbz-Val-OH and D/L-Ser-OMe·HCl.

(20) Chiralcel OD column; λ = 245 nm; 17% 2-propanol:hexane; 0.5 mL min^{-1}; t_R = 24.8 min. The enantiomer had t_R = 16.8 min.

(21) **Representative procedure** (Table 3, entry 4): Deoxo-Fluor (45.0 mL, 0.246 mmol) was added dropwise to a solution of Bz-Ser-OMe (50.0 mg, 0.224 mmol) in CH_2Cl_2 (2 mL) cooled to −20 °C (bath temperature). After 30 min, bromotrichloromethane (80.0 mL, 0.812 mmol) was added dropwise to the reaction mixture, followed by DBU (121 mL, 0.812 mmol). The reaction was stirred at 2−3 °C for 8 h and then quenched with saturated aqueous sodium bicarbonate. The mixture was extracted with EtOAc, and the combined organic layer was dried ($MgSO_4$), filtered, and concentrated. Purification of the residue by flash chromatography (SiO_2, 2:1 hexane:ethyl acetate) gave the desired oxazole as a colorless solid (37 mg, 82%): mp 83 °C (lit. mp 86 °C); ^1H NMR ($CDCl_3$) δ 8.29 (s, 1 H), 8.12−8.10 (m, 2 H), 7.49−7.47 (m, 3 H), 3.96 (s, 3 H). Full data: Connell, R. D.; Tebbe, M.; Gangloff, A. R.; Helquist, P.; Akermark, B. *Tetrahedron* **1993**, *49*, 5445.