A New Synthesis of Highly Functionalized Oxazoles

Peter Wipf* and Chris P. Miller

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

Received April 6, 1993

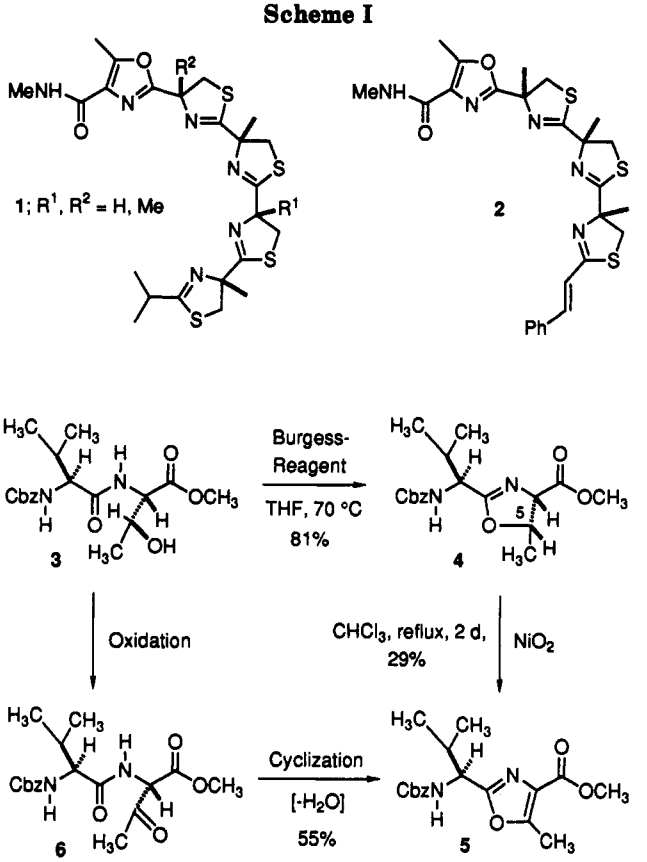
Summary: Functionalized oxazoles and bis-oxazoles are obtained by side-chain oxidation of β-hydroxy amides with the Dess–Martin periodinane, followed by cyclodehydration with triphenylphosphine/iodine in the presence of triethylamine.

Introduction

As a part of our efforts toward the total synthesis of the antiviral natural products tantazoles (1) and thiangazole (2),[1] we have investigated several protocols for the oxidative conversion of α-amino-β-hydroxy acid derivatives into the corresponding oxazoles (Scheme I). Formation of the intermediate oxazoline **4** by cyclization of the model valylthreonine dipeptide **3** with Burgess reagent occurs stereospecifically and in high yield.[2] However, the usual reagent for the oxidative aromatization of oxazolines, nickel peroxide,[3] provides only a low yield of the desired oxazole **5** after a 48-h reflux in $CHCl_3$. Generally, this reagent appears to be quite sensitive toward steric hindrance and therefore unsuitable for the oxidation of C(5)-substituted oxazolines.[3] An alternative pathway for the preparation of oxazole **5**, the Robinson–Gabriel cyclization of β-keto amide **6**,[4-6] requires a mild and selective protocol for the side-chain oxidation and subsequent cyclodehydration of β-hydroxy amide **3**. Especially the oxidation of alcohol **3** to the 1,3-dicarbonyl compound **6** is problematic in this sequence, since significant fragmentation of threonine derivatives has been observed with lead tetraacetate,[7] PCC,[8] as well as the Jones reagent.[9]

In this paper, we report a highly efficient side-chain oxidation of β-hydroxy amides with the Dess–Martin[10,11] reagent, followed by a mild cyclodehydration of the intermediate β-keto amides with triphenylphosphine/iodine. This versatile extension of the Robinson–Gabriel concept allows the rapid synthesis of highly substituted and functionalized oxazoles directly from readily available amino acid derivatives in good (55–81%) overall yields.

Scheme I



Treatment of a solution of the β-hydroxy amide **3** in CH_2Cl_2 with 1.2 equiv of Dess–Martin periodinane resulted in a rapid conversion to the corresponding ketone **6**. After filtration of the reaction mixture through a short column of basic alumina, this compound was directly cyclized without further purification by addition to a dehydrating mixture of 2 equiv of triphenylphosphine and iodine and 4 equiv of triethylamine to give oxazole **5** in 55% overall yield. Importantly, the entire synthetic sequence was completed in less than 90 min, whereas the nickel peroxide route to the same product required more than 2 days and resulted only in a 23% overall yield. The broad scope of this new oxazole synthesis is documented in Table I.

Both oxidation and cyclodehydration with activated triphenylphosphine proceed cleanly with sterically hindered as well as unhindered substrates (entries 1 and 3) and in the presence of multiple enolizable functional groups (entries 2 and 5). No racemization or epimerization of the chiral centers in **5** and **15** was observed under the reaction conditions. Phenylserine derivatives gave the C(5)-arylated oxazoles in 65–73% yield, whereas the monosubstituted oxazole **21** was only obtained in 17% overall yield from the primary alcohol **20**. Several side products were observed in this reaction.[12] Nonetheless, entry 8 represents a useful example of the extension of the

(1) (a) Carmeli, S.; Moore, R. E.; Patterson, G. M. L.; Corbett, T. H.; Valeriote, F. A. *J. Am. Chem. Soc.* **1990**, *112*, 8195. (b) Jansen, R.; Kunze, B.; Reichenbach, H.; Jurkiewicz, E.; Hunsmann, G.; Höfle, G. *Liebigs Ann. Chem.* **1992**, 357.

(2) (a) Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *33*, 907. (b) Wipf, P.; Miller, C. P. *J. Am. Chem. Soc.* **1992**, *114*, 10975. (c) Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 1575.

(3) Evans, D. L.; Minster, D. K.; Jordis, U.; Hecht, S. M.; Mazzu, A. L.; Meyers, A. I. *J. Org. Chem.* **1979**, *44*, 497.

(4) Robinson, R. *J. Chem. Soc.* **1909**, *95*, 2167.

(5) For a review, see: Turchi, I. J. In *The Chemistry of Heterocyclic Compounds*, *45*; Wiley: New York, 1986; pp 1–342.

(6) For a conceptually related cyclization of α-acylamino ketimines, see: (a) Engel, N.; Steglich, W. *Liebigs Ann. Chem.* **1978**, 1916. (b) Evans, D. A.; Lundy, K. M. *J. Am. Chem. Soc.* **1992**, *114*, 1495. (c) Gordon, T. D.; Singh, J.; Hansen, P. E.; Morgan, B. A. *Tetrahedron Lett.* **1993**, *34*, 1901.

(7) Oettmeier, W. *Chem. Ber.* **1970**, *103*, 2314.

(8) Stachulski, A. *Tetrahedron Lett.* **1982**, *23*, 3789.

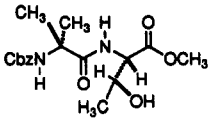
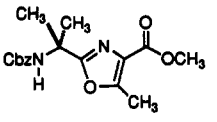
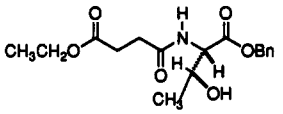
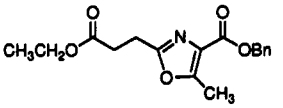
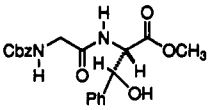
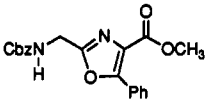
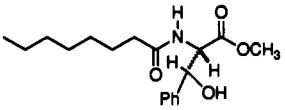
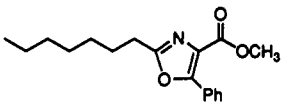
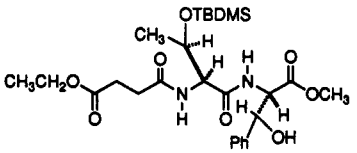
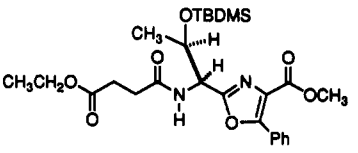
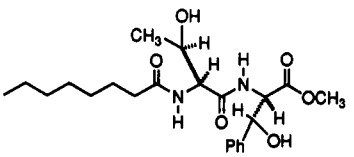
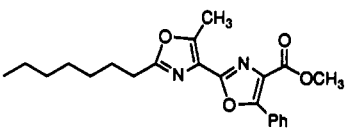
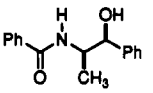
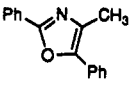
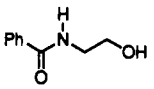
(9) Delacotte, J.-M.; Galons, H.; Schott, D.; Morgat, J.-L. *Synth. Commun.* **1992**, *22*, 3075, and references cited therein.

(10) (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. For an improved procedure for the preparation of this reagent, see: (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

(11) For other protocols for the oxidation of α-amino alcohols to aldehydes, see: (a) Jurczak, J.; Golebiowski, A. *Chem. Ber.* **1989**, *89*, 149. (b) Leanna, M. R.; Sowin, T. J.; Morton, H. E. *Tetrahedron Lett.* **1992**, *33*, 5029.

0022-3263/93/1958-3604$04.00/0

Table I. Synthesis of Oxazoles from β-Hydroxy Amides via Side-Chain Oxidation with Periodinane[10] and Cyclodehydration with $Ph_3P/I_2/Et_3N$[15]

	β-hydroxy amide		oxazole		
entry	structure	no.	structure	no.	yield (%)
1		6		7	58
2		8		9	61
3		10		11	73
4		12		13	65
5		14		15	71
6		16		17	37
7		18		19	81[a]
8		20		21	17

[a] The cyclodehydration was performed for 8 h at 22 °C.

Robinson–Gabriel approach to the difficult cyclodehydration of aldehydo amides.[13] Secondary alcohols, even in the absence of electron-withdrawing carboxyl substituents at C(4), undergo this process in high yield, however. Norephedrine derivative **18**, for example, provided 81% of the desired oxazole **19** (entry 7).

Polyoxazole segments are a common feature of several recently isolated biologically active natural products.[14] Our methodology can be applied for the rapid preparation of these heterocycle chains from oligopeptide segments. Dipeptide **16**, for instance, was directly converted to the bis-oxazole **17** in 37% yield by tandem oxidation and cyclization (entry 6).

Several mechanisms for the conversion of the intermediate β-keto amides into oxazoles can be envisioned.[16] Since the presence of a base (triethylamine) in the reaction mixture with triphenylphosphine and iodine is necessary (no reaction occurs in the absence of base at room temperature), we propose an initial enolization of the

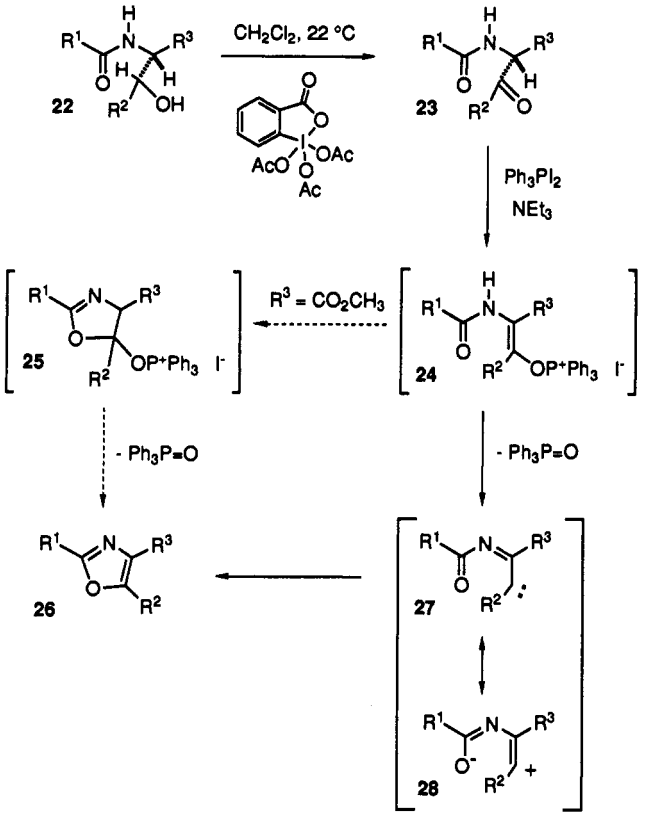
(12) Interestingly, control reactions revealed that the cyclization of the isolated intermediate aldehyde to oxazole **21** occurs in 75% yield. Therefore, the problematic step appears to be the oxidation of amino alcohol **20**, which provides only a 31% yield of the desired aldehyde after chromatographic purification. We thank Mr. Sungtaek Lim for performing these experiments.

(13) To the best of our knowledge, there is only one other example in the literature where the cyclodehydration of an aldehydo amide with $SOCl_2$ results in an 8.5% yield of oxazole: Sen, P. K.; Veal, C. J.; Young, D. W. *J. Chem. Soc., Perkin Trans. 1* **1981**, 3053.

(14) Hennoxazoles: Ichiba, T.; Yoshida, W. Y.; Scheuer, P. J.; Higa, T.; Gravalos, D. G. *J. Am. Chem. Soc.* **1991**, *113*, 3173. Diazonamides: Lindquist, N.; Fenical, W.; Van Duyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1991**, *113*, 2303. Ulapuolides: Roesener, J. A.; Scheuer, P. J. *J. Am. Chem. Soc.* **1986**, *108*, 846. Kabiramides: Matsunaga, S.; Fusetani, N.; Hashimoto, K.; Koseki, K.; Noma, M. *J. Am. Chem. Soc.* **1986**, *108*, 847. Halichondramides: Kernan, M. R.; Molinski, T.; Faulkner, D. J. *J. Org. Chem.* **1988**, *53*, 5014. Matsunaga, S.; Fusetani, N.; Hashimoto, K.; Kosei, K.; Noma, M.; Noguchi, H.; Sankawa, U. *J. Org. Chem.* **1989**, *54*, 1360.

(15) General Procedure: A mixture of 153 mg (0.284 mmol) of ester **14** and 144 mg (0.340 mmol) of Dess–Martin reagent in 3 mL of dry (P_2O_5) CH_2Cl_2 was stirred for 1 h and filtered through a short (1.5-cm) plug of basic alumina (activity I) and sand (0.25 cm) into a flask containing a freshly prepared solution of 150 mg (0.573 mmol) of triphenylphosphine, 144 mg (0.567 mmol) of I_2, and 0.16 mL (1.15 mmol) of triethylamine in 5 mL of CH_2Cl_2. The filter cake was washed with CH_2Cl_2 (2 × 5 mL). After 15 min, the dark reaction mixture was transferred to a separatory funnel, treated with 30 mL of aqueous $Na_2S_2O_3$, and extracted with 100 mL of Et_2O. The organic layer was washed with 20 mL of saturated aqueous $NaHCO_3$ and dried (Na_2SO_4). Chromatography on SiO_2 (25% EtOAc/hexanes) afforded 105 mg (71%) of oxazole **15** as an amber oil: $[\alpha]_D$ −46.2° (*c* 2.15, CH_2Cl_2, 22 °C); IR (neat) 3345, 2932, 2857, 1732, 1688, 1591, 1562, 1510, 1495, 1474, 1462, 1439, 1354, 1208, 1094, 1071, 1018, 883, 835, 810, 777 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.97–7.94 (m, 2 H), 7.43–7.41 (m, 3 H), 6.61 (d, 1 H, *J* = 9 Hz), 5.23 (dd, 1 H, *J* = 9.1, 1.7 Hz), 4.55–4.45 (m, 1 H), 4.11–4.07 (m, 2 H), 3.89 (s, 3 H), 2.69–2.63 (m, 4 H), 1.22–1.17 (m, 6 H), 0.73 (s, 9 H), −0.05 (s, 3 H), −0.24 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 171.7, 162.3, 161.0, 155.6, 130.3, 128.3 (5 C), 126.7, 69.8, 60.6, 53.3, 52.2, 30.9, 29.4, 25.5 (3 C), 20.4, 17.7, 14.1, −4.8, −5.5; HRMS *m/e* calcd for $C_{26}H_{38}N_2O_7Si$ 518.2448, found 518.2441.

Scheme II



ketone **23**, followed by formation of the enol phosphonium salt **24** by trapping with the highly electrophilic Ph_3PI_2[17] (Scheme II). Subsequently, intramolecular addition of the amide onto the vinylphosphonium species is feasible, especially in the presence an additional electron-withdrawing R^3 substituent. However, this represents a disfavored 5-*endo-trig* ring closure,[18] and since the reaction is rapid at room temperature and an increase rather than a drop in yield for $R^3 = CH_3$ is observed, we prefer an alternative mechanism via acylimino carbene **27**. Ring closure of these species to oxazoles **26** has already been observed by Huisgen and Seidel.[19]

The preparation of oxazoles as building blocks for synthetic and natural products is currently the focus of intensive research,[20] and, due to their ready availability, β-hydroxy amides are highly attractive starting materials for the synthesis of these heterocycles. The side-chain oxidation of β-hydroxy amides with the Dess–Martin periodinane, followed by immediate cyclodehydration with triphenylphosphine/iodine, provides an efficient access to substituted oxazoles in good overall yields. The mild reaction conditions permit the use of epimerizable substrantes without loss of stereochemical integrity. A variety of functional groups (amide, carbamate, ester, silyl ether) is compatible with this new process whereas the alternative nickel peroxide oxidation of C(5)-substituted oxazolines proceeds very sluggishly and in extremely low yields.

Acknowledgment. This work was supported by the donors of The Petroleum Research Fund, administered by the American Chemical Society.

Supplementary Material Available: Experimental procedures and compound characterization data (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(16) For a discussion of the mechanism of the acid-catalyzed Robinson–Gabriel synthesis, see: Wasserman, H. H.; Vinick, F. J. *J. Org. Chem.* **1973**, *38*, 2407.

(17) For a review of applications of this reagent, see: Castro, B. R. *Org. React.* **1983**, *29*, 1.

(18) Baldwin, J. E. *J. Chem. Commun.* **1976**, 734.

(19) Huisgen, R.; Seidel, M. *Chem. Ber.* **1961**, *94*, 2509. See also: Williams, E. L. *Tetrahedron Lett.* **1992**, *33*, 1033.

(20) For some recent syntheses of oxazoles, see: (a) Tiecco, M.; Testaferri, L.; Tingoli, M.; Marini, F. *J. Org. Chem.* **1993**, *58*, 1349. (b) Short, K. M.; Ziegler, C. B. *Tetrahedron Lett.* **1993**, *34*, 71. (c) Kawase, M.; Miyamae, H.; Narita, M.; Kurihara, T. *Tetrahedron Lett.* **1993**, *34*, 859. (d) Das, J.; Reid, J. A.; Kronenthal, D. R.; Singh, J.; Pansegrau, P. D.; Mueller, R. H. *Tetrahedron Lett.* **1992**, *33*, 7835. (e) Fukumoto, T.; Aso, Y.; Otsubo, T.; Ogura, F. *J. Chem. Soc., Chem. Commun.* **1992**, 1070. (f) Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434. (g) Gangloff, A. R.; Akermark, B.; Helquist, P. *J. Org. Chem.* **1992**, *57*, 4797. (h) Aken, K. v.; Hoornaert, G. *J. Chem. Soc., Chem. Commun.* **1992**, 895. (i) Doyle, K. J.; Moody, C. J. *Tetrahedron Lett.* **1992**, *33*, 7769. (j) Yoo, S. *Tetrahedron Lett.* **1992**, *33*, 2159. (k) Yokokawa, F.; Hamada, Y.; Shioiri, T. *Synlett* **1992**, 153. (l) Mazurkiewicz, R. *Synthesis* **1992**, 941. (m) Bossio, R.; Marcaccini, S.; Pepino, R. *Liebigs Ann. Chem.* **1991**, 1107. (n) Zhao, Z.; Scarlato, G. R.; Armstrong, R. W. *Tetrahedron Lett.* **1991**, *32*, 1609. (o) Connell, R. D.; Tebbe, M.; Helquist, P.; Akermark, B. *Tetrahedron Lett.* **1991**, *32*, 17. (p) Takeuchi, H.; Yanagida, S.; Ozaki, T.; Hagiwara, S.; Eguchi, S. *J. Org. Chem.* **1989**, *54*, 431. (q) Freeman, F.; Kim, D. S. H. L. *Tetrahedron Lett.* **1989**, *30*, 2631. (r) Alvarez-Ibarra, C.; Mendoza, M.; Orellana, G.; Quiroga, M. L. *Synthesis* **1989**, 560. (s) Ibata, T.; Isogami, Y. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 618.