Cupric Bromide Mediated Oxidation of 4-Carboxyoxazolines to the Corresponding Oxazoles

Joel C. Barrish,* Janak Singh,* Steven H. Spergel, Wen-Ching Han, Thomas P. Kissick, David R. Kronenthal, and Richard H. Mueller

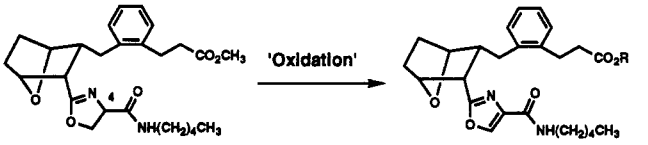
Bristol-Myers Squibb Pharmaceutical Research Institute, PO Box 4000, Princeton, New Jersey 08543

Received January 19, 1993

The 4-carboxyoxazole moiety is a structural feature found in a variety of natural products.[1] Although several methods have been reported for the direct synthesis of 4-carboxyoxazoles from acyclic precursors,[2] oxidation of an intermediate oxazoline can also be a useful approach.[3] However, the use of NiO_2 is the only general method currently available for the conversion of 4-carboxyoxazolines to the corresponding oxazoles.[4] Recently, during the synthesis of the thromboxane receptor antagonist **3**, we discovered a novel procedure using a mixture of $CuBr_2$ and DBU for the oxidation of **1** to **2**.[5] Herein, we describe the scope and limitations of this reaction and provide the details for a significant improvement which has made the oxidation process practical. A tentative mechanism involving an intermediate copper enolate is proposed.

We initially reasoned that introduction of a leaving group (*e.g.*, halogen) at C-4 of **1** could provide access to the desired oxazole after treatment of the intermediate with base. Although halogenation of oxazolines such as **1** is unknown, it occurred to us that a mild procedure using a copper(II) salt for the α-halogenation of ketones, developed over 30 years ago by Kochi, might suit our purpose.[6] Treatment of the simple 4-(carbobenzyloxy)oxazoline **4a** under modified bromination conditions[7] ($CuBr_2$, 1:1 EtOAc/$CHCl_3$, room temperature) gave only recovered starting material. However, pretreatment of a suspension of $CuBr_2$ in $CHCl_3$ with diisopropylethylamine followed by addition of **4a** in EtOAc (Table I) resulted in the formation of ~20% of a new, less polar product. The ^1H NMR of this compound displayed a characteristic singlet at δ 8.1 ppm, thereby confirming direct formation of the 4-carboxyoxazole product **5a**.

Scheme I



1 **2** (R = CH_3) **3** (R = H)

Substitution of DBU for diisopropylethylamine resulted in a dramatic improvement in yield; other bases such as 2,6-di-*tert*-butylpyridine or triethylamine were ineffective or gave less consistent results. Other copper(II) reagents ($CuCl_2$, CuI_2, $Cu(OTf)_2$) were also tried, but only $Cu(OTf)_2$ gave results equivalent to those produced by $CuBr_2$. With regard to the scope of the reaction, oxidation of the 4-carbamyloxazoline **4b** with $CuBr_2$/DBU gave the oxazole **5b** while oxazoline **4c**, which does not contain a 4-carboxy group, did not react under these conditions. Application of this methodology to the more complex 7-oxabicyclo[2.2.1]heptane substrates **1** and **4d** provides ample evidence of the selectivity of the reaction. A major drawback of the $CuBr_2$/DBU procedure is that the reaction is slow (usually 1–2 days). In many cases, the reaction was incomplete and required a second charge of reagents. In some cases, particularly on a larger scale, 10–15% of the substrate survived even after the second charge of reagents, and a third charge was necessary to drive the reaction to completion. It is known that the complexes formed between $CuCl_2$ and amine bases such as triethylamine[8] and pyridine[9] are unstable and undergo internal electron transfer to give copper(I) complexes. We have demonstrated that copper(I) salts, either alone or in combination with DBU, are not capable of carrying out the oxidation of oxazolines to oxazoles. A similar electron transfer process may occur, but to a lesser extent, between copper(II) salts and DBU.[10,11] An alternative mechanism involves hydride transfer from the amine to Cu(II).

In an effort to improve the reaction, we examined the use of other amine bases, particularly those without the ability to act as efficient hydride donors [t-$BuNH_2$, 1,4-diazabicyclo[2.2.2]octane (DABCO) and hexamethylenetetramine (HMTA)]. These bases are less susceptible to oxidation either due to the lack of an α-hydrogen atom or due to the α-CH_2 being part of a rigid cyclic structure with poor overlap between the nitrogen lone pair and adjacent C–H bonds. Oxidation reactions with $CuBr_2$ in the presence of t-$BuNH_2$, DABCO, and HMTA alone were not efficient due to the low solubility of the corresponding $CuBr_2$ complexes. However, the oxidation process became much more efficient by the use of a mixture of a nonhydride donor amine (t-$BuNH_2$, DABCO, or HMTA) and DBU. HMTA gave the best results. The reaction of oxazoline **1** with 4 mol equiv each of $CuBr_2$/DBU/HMTA in CH_2Cl_2 at room temperature for *5 h* produced oxazole **2** in >80% isolated yield with no remaining oxazoline. Second charges of reagents were not necessary, even on a large scale. Ester

(1) Connell, R. D.; Tebbe, M.; Helquist, P.; Akermark, B. *Tetrahedron Lett.* **1991**, *32*, 17 and references cited therein.

(2) *Oxazoles*; Turchi, I. J., Ed.; Wiley: New York, 1986. For new methods for the synthesis of 4-substituted oxazoles by cyclization of vinyl bromides, see: Das, J.; Reid, J. A.; Kronenthal, D. R.; Singh, J.; Pansegrau, P.; Mueller, R. H. *Tetrahedron Lett.* **1992**, *33*, 7835.

(3) Evans, D. L.; Minster, D. K.; Jordis, U.; Hecht, S. D.; Mazzu, A. L., Jr.; Myers, A. I. *J. Org. Chem.* **1979**, *44*, 479. Lakhan, R.; Ternal, B. *Adv. Heterocycl. Chem.* **1974**, *17*, 99. Turchi, I. J.; Dewar, M. J. S. *Chem. Rev.* **1975**, *75*, 389. Kashima, C.; Arao, H. *Synthesis* **1989**, 873.

(4) Recent examples include applications to the synthesis of Calyculin: (a) Vaccaro, H. A.; Levy, D. E.; Sawabe, A.; Jaetsch, T.; Masamune, S. *Tetrahedron Lett.* **1992**, *33*, 1937. (b) Yokokawa, F.; Hamada, Y.; Shioiri, T. *Synlett* **1992**, 149, 151, 153. (c) Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434 and references cited therein. The authors in ref 4c also describe an alternative procedure for the conversion of a 4-carboxyoxazoline to the oxazole via oxidative elimination of an intermediate phenyl selenide.

(5) Misra, R. N.; Brown, B. R.; Sher, P. M.; Patel, M. M.; Hall, S. E.; Han, W.-C.; Barrish, J. C.; Floyd, D. M.; Sprague, P. W.; Morrison, R. A. Ridgewell, R. E.; White, R. E.; DiDanato, G. C.; Harris, D. N.; Hedberg, A.; Schumacher, W. A.; Webb, M.; Ogletree, M. L. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 73.

(6) Kochi, J. K. *J. Am. Chem. Soc.* **1955**, *77*, 5274. See also: Glazier, E. R. *J. Org. Chem.* **1962**, *27*, 2937. Glazier, E. R. *J. Org. Chem.* **1962**, *27*, 4397.

(7) King, L. C.; Ostrum, G. K. *J. Org. Chem.* **1964**, *29*, 3459.

(8) Yoke, J. T.; Weiss, J. F.; Tollin, G. *Inorg. Chem.* **1963**, *2*, 1210. Weiss, J. F.; Tollin, G.; Yoke, J. T. *Inorg. Chem.* **1964**, *3*, 1344. Clifton, J. R.; Yoke, J. T. *Inorg. Chem.* **1968**, *7*, 39.

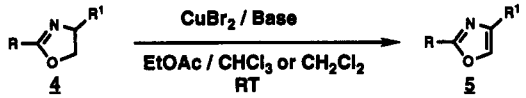
(9) Gupta, A. K. *J. Chem. Soc.* **1952**, 3473.

(10) The combination of $CuBr_2$(catalytic)/DBU has been reported to effect the cyclopropanation of olefins with bromomalonic esters: Kawabata, N.; Yanao, S.; Yoshida, J.-I. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2687.

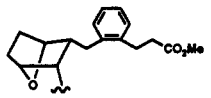
(11) A 4-day old solution of $CuBr_2$/2 equiv of DBU in chloroform is totally ineffective for the oxidation of oxazolines.

0022-3263/93/1958-4494$04.00/0

Table I. Oxidation of Oxazolines to Oxazoles with $CuBr_2$/Base

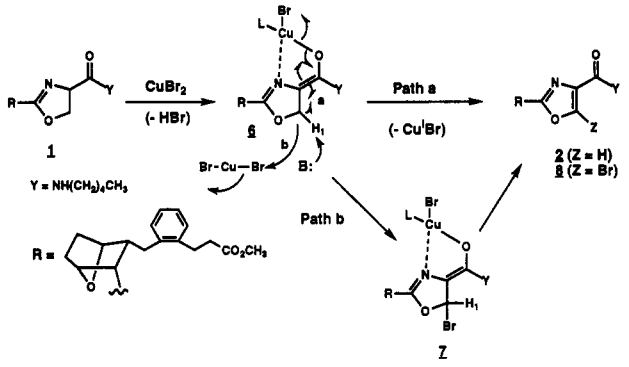


4 5

oxazoline	R	R^1	base	time	oxazole	yield[a] (%)
4a	*i*-Pr	CO_2Bn	*i*-Pr_2NEt	2 d	5a	20[b]
4a	*i*-Pr	CO_2Bn	DBU	1 d	5a	55[b]
4b	*i*-Pr	$CONEt_2$	DBU	2 d	5b	65[b]
4c	Et	H	DBU	>2 d	5c	NR[b]
4d		CO_2Bn	DBU	1->2 d	5d	60–78[c]
4d		CO_2Bn	DBU/HMTA	2 h	5d	81[e]
4e		$CONEt_2$	DBU/HMTA	4 h	5e	80[e]
1			DBU	≥2 d	2	55–80[c,d]
1			DBU/HMTA	5 h	2	82[e]

[a] Reactions 1–5 were run in a 1:1 mixture of $CHCl_3$/EtOAc; reactions 6–9 were done in CH_2Cl_2. [b] The reaction was run with 2 equiv each of $CuBr_2$ and base and was stopped after 1 day. [c] The reaction was started with 2 equiv of $CuBr_2$ and 2–4 equiv of DBU and recharged with 2 equiv of each reagent after approximately 1 day. On scale-up (>10 g oxazoline), a second recharge of reagents was required. [d] In large scale runs, starting oxazoline (up to 30%) remained after 2 days. [e] The reaction was run with 4 equiv each of $CuBr_2$, DBU, and hexamethylenetetramine.[16] No starting oxazoline remains in these reactions independent of scale.

Scheme II



4d and tertiary amide 4e are also readily converted into the oxazoles 5d and 5e under these improved reaction conditions. Reactions could be easily scaled up to produce several hundred grams of the oxazole 2. All oxidation reactions in the presence of HMTA were fast, efficient, and reproducible.

A possible mechanism for the oxidation of 4-carboxyoxazolines is shown in Scheme II. The inability of the unsubstituted oxazoline 4c to undergo oxidation under these conditions suggests the intermediacy of the copper(II) enolate 6 (L = DBU).[12] Intermediate 6 undergoes oxidation–reduction, probably via an internal electron-transfer process, to furnish oxazole 2. Although we are unable at this time to completely rule out a mechanism which involves the intermediacy of a C-4 bromide followed by elimination to give 2, the equivalence of $Cu(OTf)_2$ and $CuBr_2$ in the reaction strongly supports the above mechanism. Under the basic reaction conditions, formation of the 5-bromooxazole 8[13] as a minor byproduct in the oxidation of 1 may be explained by bromination at C-5 (path b) by a second molecule of $CuBr_2$ to give 7 followed by an oxidation–reduction process.[14] A complex shown to be HMTA·HBr·0.5CuBr by ^1H NMR, ^{13}C NMR, and combustion analysis crystallized out in ~95% yield during the oxidation reactions. A possible rationale for the effectiveness of the $CuBr_2$/DBU/HMTA procedure is that the HMTA/CuBr complex efficiently scavenges the HBr thereby preventing reversal of the Cu enolate to starting material and facilitating the subsequent oxidation–reduction step.[15]

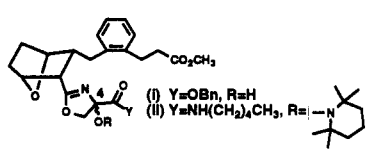
In conclusion, we have discovered a novel method for the oxidation of 4-carboxyoxazolines to oxazoles which we believe will prove useful in the preparation of this important heterocyclic moiety.

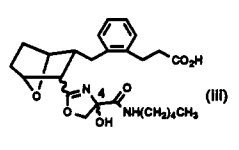
Experimental Section

1,8-Diazabicyclo[5.4.0]undec-7-ene was dried over molecular sieves. Hexamethylenetetramine was purchased from Aldrich. Cupric bromide was handled under nitrogen atmosphere. Dichloromethane was dried over molecular sieves and deoxygenated by bubbling argon for 0.5 h. All reactions were performed under an argon atmosphere.

General Procedure for the Oxidation of Oxazolines to Oxazoles Using $CuBr_2$/DBU/HMTA.[17] Hexamethylenetetramine (4 equiv) was added to a suspension of $CuBr_2$ (4 equiv) in deoxygenated, dry CH_2Cl_2 (0.16 M). 1,8-Diazabicyclo[5.4.0]-undec-7-ene (4 equiv) was added, and the resulting warm, dark brown solution was cooled in a water bath for 5 min. The oxazoline was added neat, and the mixture was stirred at room temperature under argon. After the starting oxazoline was consumed, the solvent was removed *in vacuo* and the residue was taken up in equivolume amounts of EtOAc and saturated aqueous NH_4Cl/concd NH_4OH (1:1). The aqueous layer was extracted with EtOAc

(12) When oxygen is bubbled through the reaction mixture, the 4-hydroxyoxazoline 1 can be isolated as the major product (we thank Joy Jannotti for this result). Reaction in the presence of tetramethylpiperidine oxide radical produced, in addition to ~10% oxazole, the corresponding oxyamines 11 as a mixture of diastereomers in 50% chromatographed yield. Alternatively, oxidation with potassium superoxide [O_2/Cu(OAc)$_2$/DMSO] gave the hydroxy acid 111 as a complex mixture of diastereomers in addition to 5–10% of the oxazole. For α-hydroxylation of lactones with Cu(II) refer to: Tang, C. S. F.; Morrow, C. J.; Rapoport, H. *J. Am. Chem. Soc.* **1975**, *97*, 159.





(13) Bromooxazole 8 was isolated (~1%) as a less polar byproduct from this reaction.

(14) Control experiments demonstrated that 8 is not produced by bromination of 2 under the reaction conditions.

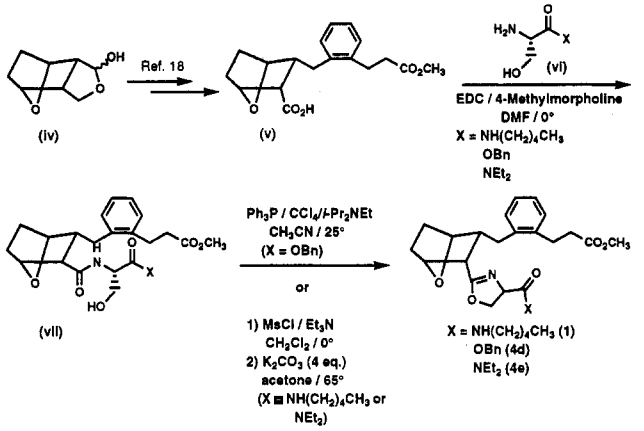
(15) It is also possible that a novel Cu(II)·HMTA·DBU complex is the true oxidizing agent.

(16) Reactions using 4 equiv of all reagents were complete in less than 5 h. The same reactions with 3 equiv of each reagent took approximately 18 h to go to completion.

(3×), and the combined extracts were washed successively with saturated NH_4Cl/concd NH_4OH (1:1, 3×), 10% citric acid, aqueous $NaHCO_3$, and brine. The solution was dried ($MgSO_4$) and evaporated to give the crude oxazole which was purified as described in the examples below.

[1*S*-(1α,2α,3α,4α)]-2-[[3-[4-[(Pentylamino)carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl]methyl]benzenepropanoic Acid, Methyl Ester (2). Oxazoline 1 (2.28 g, 5 mmol) was reacted (5 h) as described in the general procedure above to give, after purification by column chromatography on 200 mL of K-60 silica gel eluted with EtOAc/hexane (1:2), 1.86 g (82% yield) of the oxazole 2: $[\alpha]_D$ = +14.3° (*c* = 1, $CHCl_3$); mp 138–39 °C; IR (KBr) 3387, 2955, 1738, 1651, 1607, 1514, 1194, 1173, 1109, 1003, 762 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 8.1 (1 H, s), 7.12 (5 H, m), 7.03 (1 H, m), 4.97 (1 H, d, *J* = 4.5 Hz), 4.38 (1 H, d *J* = 4.5 Hz), 3.66 (3 H, s), 3.4 (3 H, m), 2.92 (2 H, m), 2.5 (3 H, m), 2.34 (2 H, m), 1.78 (2 H, m), 1.61 (3 H, m), 1.35 (4 H, m), 0.91 (3 H, m); ^{13}C NMR (68 MHz, $CDCl_3$), δ 173.0, 163.7, 160.5, 140.4, 138.5, 137.8, 136.2, 129.6, 128.9, 126.6, 126.4, 79.6, 78.6, 51.5, 50.0, 46.9, 39.0, 34.8, 32.3, 29.9, 29.3, 29.0, 28.8, 27.6, 22.2, 13.8; MS (CI) M + H = 455, M − H = 453. Anal. Calcd for $C_{28}H_{34}N_2O_5$: C, 68.70; H, 7.54; N, 6.16. Found: C, 68.61; H, 7.46; N, 6.36.

(17) The oxazolines 1, 4d, and 4e were prepared from the oxabicyclo acid v and the required serine derivative vi by the general procedure shown below[18] where EDC = *N*-ethyl-*N'*-[3-(dimethylamino)propyl]-carbodiimide hydrochloride:



(18) For experimental details, see: Misra, R. N.; Brown, B. R.; Sher, P. M.; Patel, M. M.; Hall, S. E.; Han, W.-C.; Barrish, J. C.; Kocy, O.; Harris, D. N.; Goldenberg, H. J.; Michel, I. M.; Schumacher, W. A.; Webb, M.; Monshizadegan, H.; Ogletree, M. L. *J. Med. Chem.* **1993**, *36*, 1401.

[1*S*-(1α,2α,3α,4α)]-2-[[3-[4-[(Phenylmethoxy)carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl]methyl]benzenepropanoic Acid, Methyl Ester (5d). Oxazoline 4d (1.0 g, 2.1 mmol) was reacted (2 h) as described in the general procedure above to give, after purification by column chromatography on 200 mL of K-60 silica gel eluted with EtOAc/hexane (2:3), 0.80 g (81% yield) of the oxazole 5d: $[\alpha]_D$ = +29.9° (*c* = 1.4, $CHCl_3$); mp 88–90 °C; IR (KBr) 3435, 2953, 1736, 1636, 1580, 1148, 1101, 1005, 766 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 8.2 (1 H, s), 7.4 (4 H, m), 7.12 (5 H, br s), 5.36 (2H, s), 4.91 (1 H, d, *J* = 5 Hz), 4.35 (1 H, d, *J* = 5 Hz), 3.63 (3 H, s), 3.51 (2 H, d, *J* = 9 Hz), 2.88 (2 H, m), 2.52 (3 H, m), 2.35 (1 H, t, *J* = 14 Hz), 2.19 (1 H, dd, *J* = 4, 14 Hz), 1.74 (2 H, m), 1.60 (1 H, m), 1.45 (1 H, m); ^{13}C NMR (68 MHz, $CDCl_3$) δ 173.0, 164.9, 161.0, 144.1, 138.6, 137.8, 135.5, 132.9, 129.8, 128.8, 128.6, 128.5, 128.4, 126.6, 126.5, 79.5, 78.3, 66.7, 51.6, 50.3, 47.3, 34.8, 32.4, 29.9, 28.9, 27.5; MS (FAB) M + H = 476. Anal. Calcd for $C_{28}H_{29}NO_6$: C, 70.72; H, 6.1; N, 2.95. Found: C, 70.66; H, 6.20; N, 3.29.

[1*S*-(1α,2α,3α,4α)]-2-[[3-[4-(Diethylamino)carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl]methyl]benzenepropanoic Acid, Methyl Ester (5e). Oxazoline 4e (1.1 g, 2.5 mmol) was reacted (4 h) as described in the general procedure above to give, after purification by column chromatography on 200 mL of K-60 silica gel eluted with EtOAc/hexane (1:1), 0.87 g (80% yield) of the oxazole 5e as an oil: $[\alpha]_D$ = +23.8° (*c* = 1.28, $CHCl_3$); IR (KBr) 2978, 1738, 1622, 1576, 1437, 1103, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (1 H, s), 7.13 (5 H, br s), 4.96 (1 H, d, *J* = 5 Hz), 4.36 (1 H, d, *J* = 5 Hz), 3.77 (2 H, m), 3.64 (3 H, s), 3.48 (1 H, m), 3.43 (2 H, d, *J* = 8.5 Hz), 2.91 (2 H, m), 2.53 (3 H, m), 2.34 (1 H, dd, *J* = 12, 14 Hz), 2.21 (1 H, dd, *J* = 4, 14 Hz), 1.78 (2 H, m), 1.60 (1 H, m), 1.44 (1 H, m), 1.22 (6 H, m); ^{13}C NMR (68 MHz, $CDCl_3$), δ 173.1, 163.0, 161.5, 142.5, 138.5, 138.0, 137.1, 129.9, 128.9, 126.6, 126.5, 79.7, 78.4, 51.6, 50.1, 47.1, 42.7, 41.0, 34.3, 32.5, 29.9, 28.9, 27.5, 14.7, 12.8; HR MS (FAB) calcd (M + H) = 441.2389, obsd (M + H) = 441.2398, Δ = 2 ppm.

Acknowledgment. We would like to thank Drs. Steven Hall and David Floyd for helpful discussions. Appreciation is extended to our colleagues in Analytical Research and Development for their help.

Supplementary Material Available: ^1H NMR and ^{13}C NMR spectra for compound 5e (2 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.