Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 46 (2005) 3407–3410
Tetrahedron Letters

A new method for stereoselective oxidation of chiral 2-pyrrolidino-1-ethanol derivatives to oxazolopyrrolidines using trimethylamine-*N*-oxide in the presence of iron carbonyls

Anthony J. Pearson* and Yoonhyun Kwak

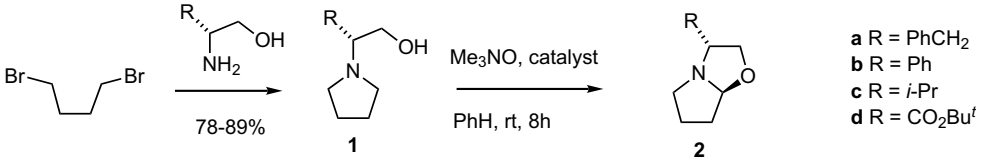
Department of Chemistry, Case Western Reserve University, Cleveland, OH 44106, USA

Received 25 January 2005; revised 28 February 2005; accepted 11 March 2005
Available online 2 April 2005

Abstract—Chiral 2-pyrrolidino-1-ethanol derivatives were oxidatively cyclized to the corresponding oxazolopyrrolidines, with excellent stereoselectivity by treatment with excess Me_3NO in the presence of 20% of an iron carbonyl complex.

Pyrrolidine ring systems are of considerable interest in organic chemistry because they are present in the structures of numerous biologically important compounds and natural products.[1] In addition, this heterocyclic moiety can be used as a structural component of chiral auxiliaries and chiral ligands for asymmetric synthesis.[2] So it is not surprising that various approaches have been developed for the stereoselective functionalization of these heterocycles.[3] Oxazolopyrrolidines occupy an important place as intermediates for the construction of substituted pyrrolidines,[4] since they undergo stereocontrolled ring-opening reactions with organometallic reagents such as Grignard and Reformatsky reagents.[5] Moreover, chiral oxazolidines have themselves been widely exploited as chiral templates in asymmetric synthesis.[6] However, most of the practical syntheses of oxazolidines have been carried out by condensation of amino alcohols with an aldehyde or its equivalent,[4a,c,6a–c] and even though other methods have been reported, they are less practical because of harsh reaction conditions or low yields.[7]

In this letter we report a new method for oxidative cyclization of chiral 2-pyrrolidino-1-ethanol derivatives that promises to be a valuable approach for functionalization of the pyrrolidine ring. The oxidation uses trimethylamine-*N*-oxide in the presence of sub-stoichiometric amounts of an iron carbonyl. Various reaction conditions were examined for this transformation, using compound **1a** as the test system (Eq. 1), and these are summarized in Table 1, along with the results for other pyrrolidines using the optimized conditions. While benzene was used as solvent for the reactions listed here, acetonitrile can also be used. A single diastereomer, thermodynamically more stable according to MM2 calculations, was formed in each case except **1c**, which gave a 7:1 mixture in favor of **2c**, and the structures were confirmed by NMR NOESY experiments and comparison with similar known compounds.[4] As far as we are aware, this is the first reported example of an oxidation reaction promoted by this reagent combination. Trimethylamine-*N*-oxide is generally used to remove CO ligands from metal carbonyls, and to demetallate



(1)

* Corresponding author. Tel.: +1 216 3685920; fax: +1 216 3683006; e-mail: ajp4@po.cwru.edu

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.03.101

Table 1. Reaction conditions for oxidation of chiral 2-pyrrolidino-1-ethanol derivatives to oxazolopyrrolidines

Substrate	Catalyst (mol %)	Me_3NO, equiv	Product (% yield)
1a	$CHDFe(CO)_3$ (20)	6.0	**2a** (91)
1a	$CHDFe(CO)_3$ (20)	2.0	**2a** (40)[a]
1a	$Fe(CO)_4PPh_3$ (20)	6.0	**2a** (90)
1a	$Fe(CO)_5$ (20)	6.0	**2a** (ca. 10)[a]
1b	$CHDFe(CO)_3$ (20)	6.0	**2b** (28)
1c	$CHDFe(CO)_3$ (20)	6.0	**2c** (83)[b]
1d	$CHDFe(CO)_3$ (20)	6.0	**2d** (76)

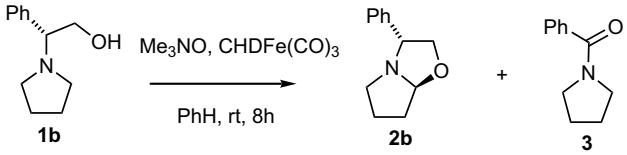
[a] Unreacted starting material was recovered.
[b] Inseparable 7:1 mixture of diastereomers.

diene–$Fe(CO)_3$ complexes,[8] though the mechanisms of these processes are still unclear,[9] and we do not presently have any information on the nature of the actual oxidant.

Both amine oxide and iron carbonyl are essential for this reaction. When either was omitted starting material was recovered quantitatively. An excess of Me_3NO is required for high yield conversion, 2 equiv leading to only 40% yield over a reaction time of 8 h. Generally we have used 6 equiv to ensure complete oxidation in a reasonable time. The reaction uses sub-stoichiometric amount of the iron carbonyl, but since these complexes are slowly destroyed by the amine oxide, 20 mol % was generally used to ensure completion of reaction before the catalyst is lost.

Pentacarbonyliron is more reactive toward Me_3NO, and is completely destroyed before the pyrrolidine oxidation has proceeded to the extent of 10%. The phosphine derivative, $Fe(CO)_4PPh_3$, is a stable and inexpensive solid that has excellent shelf life,[10] but for the present applications it was difficult to separate residual iron complex from the products. The 1,3-cyclohexadiene complex, $CHDFe(CO)_3$, is readily prepared,[11] affords comparable yields to those obtained using $Fe(CO)_4PPh_3$, and is easier to separate from the oxidation product, so we used this material for all subsequent reactions. Iron carbonyls appear to be uniquely suited for this transformation, as attempts to convert **1a** to **2a** under similar conditions by using $FeCl_3$, $FeSO_4$, or $Fe(OAc)_2$ as catalysts were completely unsuccessful, and **1a** was recovered unchanged in each case.

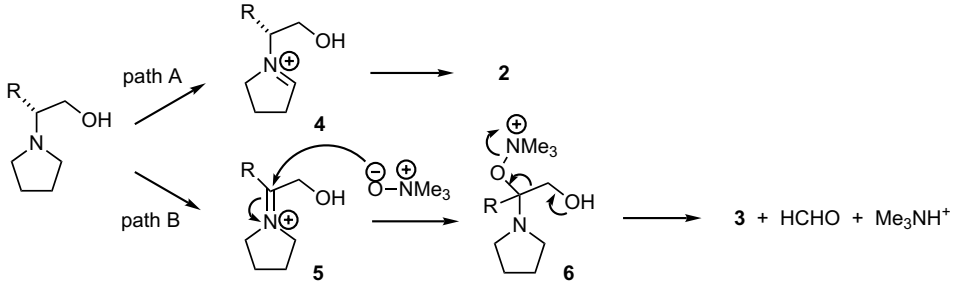
The oxidation requires a neighboring hydroxyl group—treatment of the methyl ether of **1a** with Me_3NO/$CHDFe(CO)_3$, even for prolonged reaction time gave no oxidation products, and starting material was recovered quantitatively. This is not surprising in view of the known role of hydroxyl groups in a variety of transition metal catalyzed oxidation reactions.[12] Presumably the actual oxidant becomes coordinated to the OH group and the amine oxidation reaction occurs intramolecularly. While the exact details of this process are not known, we believe that an iminium intermediate is formed, and the hydroxyl reacts with this moiety to form the oxazolidine ring. This is suggested by the observation that **1b** gave a low yield of **2b**, and the only other product that we observed is *N*-benzoylpyrrolidine (**3**, Eq. 2). A plausible mechanism that accounts for the formation of **3** is outlined in the Scheme 1.



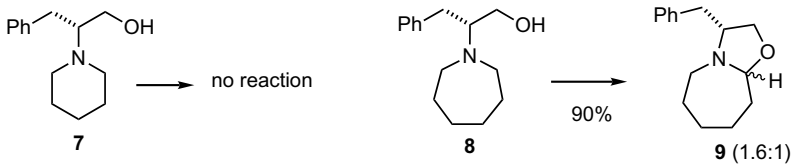
(2)

For most substrates, intermediate **4** is the preferred iminium cation (with an endocyclic double bond), and cyclization of the pendant OH group affords **2**. However, when R = Ph, resonance stabilization of the alternative iminium **5** promotes its formation in addition to **4**. Since the hydroxyl cannot cyclize onto the iminium cation of **5**, this intermediate instead reacts with the amine oxide to generate **6**, fragmentation of which generates **3** in addition to formaldehyde and trimethylamine (as its ammonium salt). This type of reaction of amine oxides is known to account for the conversion of alkyl bromides to carbonyl compounds when treated with Me_3NO,[13] a reaction that is closely related to the Kornblum oxidation.[14]

The mechanism shown here is supported by the observation that **1** (R = 4-methoxyphenyl) gives a poorer yield (12%) of the cyclization product **2**, with a greater amount of the corresponding benzamide, while **1** (R = 2-nitrophenyl) gives a higher yield (35%) of **2** (R = 2-nitrophenyl), with a smaller amount of the benzamide. These results are consistent with the expected



Scheme 1.



(3)

stabilities of the cations **5**, though we were not able to completely suppress the undesired pathway.

Further evidence for the intermediacy of an iminium intermediate comes from studies on the cyclization of related piperidine and azacycloheptane derivatives (Eq. 3). Thus, the six-membered ring derivative **7** was completely resistant to oxidation under the normal conditions, while **8** was converted to **9** in excellent yield (as a 1.6:1 mixture of diastereomers, which are calculated to have similar MM2 energies). Both mechanistic studies and synthetic applications for oxidative functionalization of tertiary amines have been described in the literature,[15] and it is known that the rate constant for oxidation of a five- or seven-membered ring amine is 5 and 13 times greater, respectively, than that of the six-membered ring system.[16] This has been attributed to the energy difference associated with planarization of the nitrogen in these ring systems during conversion of the amine to an iminium cation. Our results are therefore consistent with this mechanism.

In summary, we have discovered a novel oxidizing system that allows the stereoselective conversion of *N*-hydroxyethylpyrrolidines to oxazolopyrrolidines. These products are known to have useful chemistry that allows their applications in synthesis of substituted pyrrolidine derivatives. Future efforts in our laboratory will be focused on exploring the chemistry of these systems, as well as other oxidation reactions promoted by the Me_3NO/iron carbonyl system.[17]

Acknowledgements

We are grateful to the National Science Foundation for financial support of this research.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.03.101. Experimental procedures for the preparation of compounds **1**, as well as the oxidation of **1** to **2**, and spectroscopic data of all new compounds. The supplementary data is available online with the paper in ScienceDirect.

References and notes

1. (a) Elbein, A. D.; Molyneux, R. In *Alkaloids; Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; John Wiley and Sons: New York; (b) Attygalle, A. B.; Morgan, E. D. *Chem. Soc. Rev.* **1984**, *13*, 245; (c) Michael, J. P. *Nat. Prod. Rep.* **2001**, *18*, 520–542; (d) Garraffo, H. M.; Jain, P.; Spande, T. F.; Daly, J. W.; Jones, T. H.; Smith, L. J.; Zottig, V. E. *J. Nat. Prod.* **2001**, *64*, 421–427.
2. (a) Huryn, D. M. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 1, p 64; (b) Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581–1590; (c) Whitesell, J. K. *Acc. Chem. Res.* **1985**, *18*, 280–284; (d) Sprott, K. T.; Corey, E. J. *Org. Lett.* **2003**, *5*, 2465–2467.
3. (a) Lutete, L. M.; Kadota, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 1622–1623; (b) Jahn, U.; Müller, M.; Aussieker, S. *J. Am. Chem. Soc.* **2000**, *122*, 5212–5213; (c) Trost, B. M.; Pinkerton, A. B.; Kremzow, D. *J. Am. Chem. Soc.* **2000**, *122*, 12007–12008; (d) Marks, T. J.; Hong, S. *J. Am. Chem. Soc.* **2002**, *124*, 7886–7887; (e) Burgess, L. E.; Meyers, A. I. *J. Am. Chem. Soc.* **1991**, *113*, 9858–9859.
4. (a) Husson, H.-P.; Royer, J. *Chem. Soc. Rev.* **1999**, *28*, 383–394; (b) Katritzky, A. R.; Cui, X.-L.; Yang, B.; Steel, P. J. *J. Org. Chem.* **1999**, *64*, 1979–1985; (c) Andrés, J. M.; Herráiz-Sierra, I.; Pedrosa, R.; Pérez-Encabo, A. *Eur. J. Org. Chem.* **2000**, 1719–1726.
5. (a) Takahashi, H.; Niwa, H.; Higashiyama, K. *Heterocycles* **1988**, *27*, 2099–2102; (b) Wu, M.-J.; Pridgen, L. N. *J. Org. Chem.* **1991**, *56*, 1340–1344; (c) Alberola, A.; Alvarez, M. A.; Andrés, C.; González, A.; Pedrosa, R. *Synthesis* **1990**, 1057–1058; (d) Andrés, C.; González, A.; Pedrosa, R.; Pérez-Encabo, A. *Tetrahedron Lett.* **1992**, *33*(20), 2895–2898; (e) Muralidharan, K. R.; Mokhallalati, M. K.; Pridgen, L. N. *Tetrahedron Lett.* **1994**, *35*, 7489–7492.
6. (a) Hoppe, I.; Hoppe, D.; Wolff, C.; Egert, E.; Herbst, R. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 67–69; (b) Scolastico, C. *Pure Appl. Chem.* **1988**, *60*(11), 1689–1698; (c) Adam, W.; Peters, K.; Peters, E.-M.; Schambony, S. B. *J. Am. Chem. Soc.* **2000**, *122*, 7610–7611; (d) Adam, W.; Schambony, S. B. *Org. Lett.* **2001**, *3*, 79–82.
7. (a) Möhrle, H.; Kamper, C. *Die Pharm.* **1983**, *38*, 512–520; (b) Leonard, N. J.; Musker, W. K. *J. Am. Chem. Soc.* **1960**, *82*, 5148–5155; (c) Pandey, G.; Kumaraswamy, G. *Tetrahedron Lett.* **1988**, *29*, 4153–4156.
8. Shvo, Y.; Hazum, E. *Chem. Commun.* **1974**, 336–337.
9. (a) Eekhof, J. H.; Hogeveen, H.; Kellogg, R. M. *Chem. Commun.* **1976**, 657; (b) Elzinga, J.; Hogeveen, H. *Chem. Commun.* **1977**, 705–706.
10. Clifford, A. F.; Mukherjee, A. K. *Inorg. Chem.* **1963**, *2*, 151–153.
11. (a) Pearson, A. J. *Iron Compounds in Organic Synthesis*; Academic: San Diego, 1994, Chapter 4; (b) Knölker, H.-J.; Ahrens, B.; Gonser, P.; Heininger, M.; Jones, P. G. *Tetrahedron* **2000**, *56*, 2259–2271.
12. Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976.
13. Franzen, V.; Otto, S. *Chem. Ber.* **1961**, *94*, 1360–1363.

14. Kornblum, N.; Powers, J. W.; Anderson, G. J.; Jones, W. J.; Larson, H. O.; Levand, O.; Weaver, W. M. *J. Am. Chem. Soc.* **1957**, *79*, 6562.
15. (a) North, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4126–4128; (b) Murahashi, S.-I.; Komiya, N.; Terai, H.; Nakae, T. *J. Am. Chem. Soc.* **2003**, *125*, 15312–15313; (c) Ferroud, C.; Rool, P.; Santamaria, J. *Tetrahedron Lett.* **1998**, *39*, 9423–9426; (d) Burka, L. T. *J. Am. Chem. Soc.* **1985**, *107*, 2549–2551.
16. Wang, F.; Sayre, L. M. *J. Am. Chem. Soc.* **1992**, *114*, 248–255.
17. Dasgupta, B.; Donaldson, W. A. *Tetrahedron Lett.* **1998**, *39*, 343–346.