Pergamon

Tetrahedron Letters, Vol. 37, No. 47, pp. 8497-8500, 1996
Copyright © 1996 Elsevier Science Ltd
Printed in Great Britain. All rights reserved
0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01976-4

Copper-Catalyzed Olefin Epoxidation by Dioxygen or Amine *N*-Oxide

Guilhem Rousselet, Claude Chassagnard, Patrice Capdevielle* and Michel Maumy

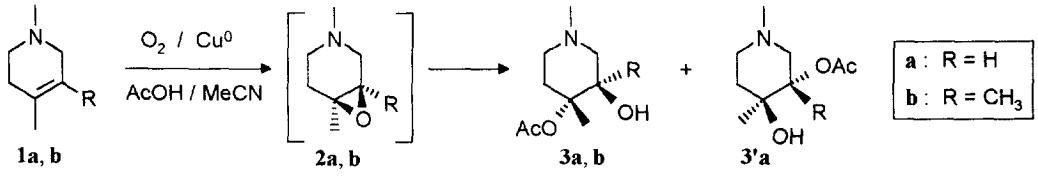
Laboratoire de Recherches Organiques de l' ESPCI, associé au CNRS,
10 rue Vauquelin, F - 75231 Paris Cedex 05, France.

Abstract *:The O_2 / $Cu^{I}OAc$ system oxidizes initially tetrahydropyridines **1a, b** into the corresponding epoxides **2a,b**. Epoxide **2b** is also formed by reaction of tetrahydropyridine N-oxide **4b** with $Cu^{II}(OAc)_2$, providing evidence for active copper-oxygen species as common intermediates in these epoxidizing systems. Subsequent Cu^{II} - promoted regioselective opening of epoxides **2a,b** is studied.*
Copyright © 1996 Elsevier Science Ltd

A number of Cu complexes have been reported in the last decade to catalyze olefin epoxidations. These systems involve oxidants like PhIO,[1] *t*-BuOOH[2] or acylperoxy species[3] resulting from O_2 + RCHO reaction (Mukaiyama's conditions)[4], and Cu can be replaced by other transition metals.[5] On the other hand, some transition metals, Cu excepted, catalyze olefin epoxidations by O_2[6] or amine *N*-oxides.[7] Recently, catalysis of norbornene epoxidation by Cu^{II} or Ni^{II} complexes under O_2 was described as occurring exclusively in THF at 70°C.[8] No mechanistic intermediates were suggested to account for this requirement of a peroxidizable solvent.

We report here: **i)** the epoxidation of the double bonds of tetrahydropyridines **1a,b** by an O_2 /Cu^{I} system, and **ii)** the epoxidation of the double bond of the *N*-oxide **4b** (derived from amine **1b**) in the presence of $Cu^{II}(OAc)_2$, with concomitant reduction of the N^{+}-O^{-} group, acting as an oxygen donor.

i) *O_2 as oxidant:* Tetrahydropyridines **1a,b** [9] are oxidized under O_2 during corrosion of 1 eq. metallic Cu^0 turnings with 2 eq. AcOH in MeCN at 60°C for 15h.[10] Epoxide **2a** is detected in small amount (2 %), and **2b** not at all. In fact, in these conditions, the major part of **2a** is opened into acetoxy-hydroxypiperidines **3a** (5%) and **3'a** (15%), and the whole of **2b** into **3b** (30%) (unreacted **1a,b**: 78 %, 70 %). All products have been identified by comparison with authentic samples, obtained by an independent synthesis (see below).

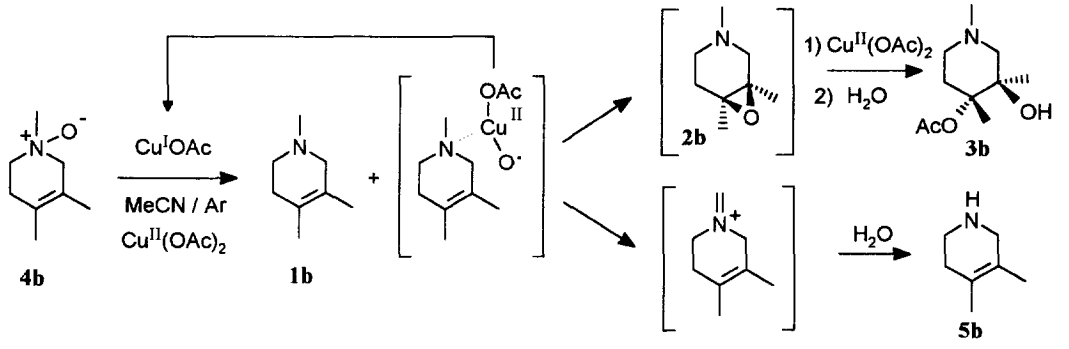


1a, b **2a, b** **3a, b** **3'a**

This system {O_2 / Cu^0 / AcOH / MeCN} was previously described in oxidation of primary amines,[11] carboxylic acids[12] and trimethylamine.[13] Thus, $Cu^{II}(OAc)_2$ finally produced by Cu^0 corrosion is inactive towards **1a, b**, and oxidations have to be attributed to the more reactive intermediate species [Cu^{II}-$O^{\bullet}$]. These intermediates result from O_2 + 2 Cu^{I} → 2 [Cu^{II}-$O^{\bullet}$] reaction,[14] Cu^{I} being continuously produced during the

corrosion, according to $Cu^{II} + Cu^0 \rightarrow 2\ Cu^I$. Hence the active system is in fact $\{O_2 / Cu^I\}$, with a very low instant Cu^I concentration limiting the side-reaction redox trapping of $[Cu^{II}\text{-}O^\bullet]$ by Cu^I.

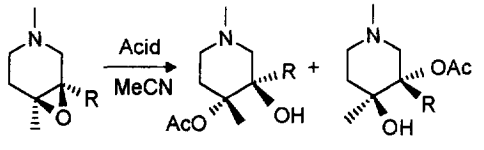
ii) *N-oxide as oxidant.* A further indication that $[Cu^{II}\text{-}O^\bullet]$ may be responsible for the epoxidation is brought by the reaction of the *N*-oxide **4b**[9] in the initial presence of $Cu^{II}(OAc)_2$ without O_2 to yield *inter alia* the same acetoxy-hydroxypiperidine **3b**[15] than does the amine **1b** in the $\{O_2 / Cu^I\}$ system:



1b (30%) is the product of deoxygenation of **4b**, according to a classical side-reaction of *N*-oxides with Cu salts.[16] We reported previously that $\{N^+\text{-}O^- / Cu^I$ or $Cu^{II}\}$ was an alternative system to $\{O_2 / Cu^I\}$ in order to generate active species $[Cu^{II}\text{-}O^\bullet]$, able in particular to hydroxylate aromatics.[17] In the present case, **4b** would globally transfer its oxygen to one Cu^I or two Cu^{II} (intimate mechanism remains unestablished) and the so-formed $[Cu^{II}\text{-}O^\bullet]$ species react either with intracyclic double bond to yield (catalytic) Cu^I and epoxide **2b** then **3b** (30%), or with exocyclic *N*-methyl group, giving an iminium ion. We reported recently this last reaction, in particular with *N*-methylpiperidine *N*-oxide.[13] The iminium yields finally demethylation product **5b** (15%) on hydrolysis. Double bonds of **1a** and its *N*-oxide **4a** [9] are less reactive, and so **4a** does not give rise to epoxide **2a** in the presence of $Cu^{II}(OAc)_2$. Oxidative demethylation yields then **5a** (20%) along with deoxygenation product **1a**.

As none peroxidic compound can be reasonably generated during **4b** / Cu^{II} reaction, one can assume that H_2O_2 or peracetic acid are not either involved in the { **1b** / O_2 / Cu^0 / AcOH } corrosion system, which yields the same epoxide **2b**. Reactive intermediate $[Cu^{II}\text{-}O^\bullet]$ arising from O_2 or $N^+\text{-}O^-$ group would then be involved in these two original epoxidizing systems.

The opening of authentic epoxides **2a, b** (prepared from **1a, b**)[18] by $Cu^{II}(OAc)_2$ + AcOH, representing the average composition of Cu^0 corrosion system, yields **3a** + **3'a** in a 22:78 ratio, or only **3b**.[19] These results are therefore consistent with the formation of **2a, b** during copper-catalyzed oxidation of **1a,b**.

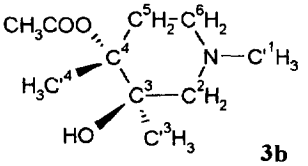


Acid	2a → 3a % + 3'a %		2b → 3b % + 3'b %		
$Cu^{II}(OAc)_2$ + 10 AcOH 60 °C	22	78	100		
$Cu^{II}(OAc)_2$ 65 °C	85	15	100		
AcOH r. t.		100	70 °C	10	5
TFA / AcOH r. t.	100		100		

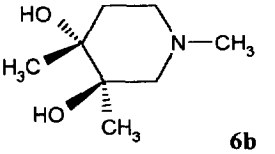
Epoxide **2b** and $Cu^{II}(OAc)_2$ lead also to pure **3b**, as it was supposed in the reaction of *N*-oxide **4a**.

Further experiments can explain these openings: while strong acid TFA gives rise to S_N1 type reaction at the more substituted site of epoxide **2a** to yield **3a**, the (same) regioselectivity observed in **2b** → **3b** opening has to be attributed to intramolecular hydrogen bonding OH···N, known to predominate in 3-hydroxy-*N*-methylpiperidines like **3b** (chair conformation),[20] whereas it is not observed (requiring less stable boat conformation) in 4-hydroxy-*N*-methylpiperidines like **3'b**.[21] $Cu^{II}(OAc)_2$ acts himself as a strong acid, leading to **3a** (85%) from **2a**, and exclusively to **3b** from **2b**. Minor amount of **3'a** (15%) obtained in the reaction of **2a** with $Cu^{II}(OAc)_2$ results from S_N2 type attack on the less hindered site by AcO^- (absent in TFA / AcOH); finally, AcOH yields readily the sole **3'a** from **2a** but hardly reacts with tetrasubstituted epoxide **2b**.

3b structural determination by NMR. Conformational exchange at 20°C gives largely broadened lines for both ^1H and ^{13}C spectra. Hence, data are collected at 50°C, on a 300 MHz Bruker AC spectrometer. COSY and heteronuclear correlations provide non ambiguous assignments for all ^1H and ^{13}C resonances except for quaternary carbons C^3 and C^4 and their substituents. A 2D-inadequate ^{13}C-^{13}C correlation (1.1 mmol **3b** in 0.5 ml $CDCl_3$ at 50°C, 72 h) gives C^3, C'^3, C^4 and C'^4 assignments. Chemical shifts of C^3 (70.7 ppm) and C^4 (82.8 ppm) provide position of OH and OAc substituents by comparison with δ's of $C^{3,4}$ in the corresponding diol **6b** (71.3 and 71.4 ppm),[22] and with literature data.[23]



3b



6b

3b	**C'1**	**C2**	**C3**	**C'3**	**C4**	**C'4**	**C5**	**C6**	**CH_3CO**	**CO**	**OH**
^1H (δ, ppm)	2.25	2.39, d, 1H	--	1.13	--	1.50	2.55	2.50	1.99	--	3.50
	s, 3H	J = 11.4		s, 3H		s, 3H	m, 1H	m, 1H	s, 3H		s broad
J (Hz)		2.30, dd, 1H					1.81	2.03			1H
		J = 11.4; 1.5					m, 1H	m, 1H			
^{13}C (δ, ppm)	45.5	62.9	70.7	19.7	82.8	18.6	30.3	51.3	22.2	169.8	--

Acknowledgement : G. Rousselet thanks the "Institut de Formation Supérieure Biomédicale" (IFSBM), Institut Gustave Roussy (Villejuif, France), for a grant.

REFERENCES AND NOTES

1 Nam, W.; Baek, S. J.; Liao, K. I., Valentine, J. S. *Bull. Korean Chem. Soc.* **1994**, *15*, 1112-1118.

2 Tanase, T.; Mano, K.; Yamamoto, Y. *Inorg. Chem.* **1993**, *32*, 3995- 4003.

3 Murahashi, S.-I.; Oda, Y.; Naota, T.; Komiya, N. *J. Chem. Soc., Chem. Commun.* **1993**, 139-140.

4 Yamada, T., Takai, T., Rhode, O., Mukaiyama, T. *Bull. Chem. Soc. Japn.* **1991**, *64*, 2109-2117.

5 Nam., W.; Kim, H. J.; Kim, S. H.; Ho, R. Y. N.; Valentine, J. S. *Inorg. Chem.* **1996**, *35*, 1045-1049.

6 Simandi, L. I., Ed. *Catalytic Activation of Dioxygen by Metal Complexes*; Kluwer Academic Publishers; Dordrecht, The Netherlands, 1992; pp. 109-132, and references cited therein.

7 Caroling, G.; Rajaram, J.; Kuriacose, J.C. *Ind. J. Chem.* **1988**, *27A*, 873-875 and references cited therein.

8 Gerbeleu, N.V.; Palanciuc, S. S., Simonov, Y. A.; Dvorkin, A. A.; Bourosh, P. N.; Reetz, M. T.; Arion, V. B.; Töllner, K. *Polyhedron* **1995**, *14*, 521-527.

9 Previously described products: **1a**: Gottlieb, H. E.; Cheung, H. T. A. *J. Chem. Res. (M)* **1979**, 4055-4063. **1b** and **4b**: Grierson, D. S.; Harris, M.; Husson, H.-P. *J. Am. Chem. Soc.* **1980**, *102*, 1064-1082. **4a** was synthesized from **1a** according to the same procedure than **4b** from **1b**.

1,4-dimethyl-1,2,5,6-tetrahydropyridine N-oxide **4a**: amorphous solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.8 (s, 3H), 2.25 (m, 1H), 2.55 (m, 1H), 3.2 (s, 3H), 3.4 (m, 2H), 3.9 (m, 2H), 5.35 (s, 1H). ^{13}C NMR (75MHz, $CDCl_3$) δ (ppm): 22.4 (CH_3), 28.6 (CH_2), 56.6 (CH_3), 64.2 (CH_2), 67.7 (CH_2), 115.4(=CH),132.3 (Cq).

10 *Oxidation of* ***1a, b***. A solution of **1a, b** (4 mmol) and AcOH (8 mmol) in MeCN (20 ml) is stirred over copper turnings (4 mmol) at 60 °C for 15h under 1 atm. O_2. Et_2O (30 ml) is added at 0 °C and the mixture stirred for 1 min with 30% aq. NaOH (5 ml). Organic compounds are extracted and identified by GC/MS. **3a, b** and **3'a** are purified by preparative TLC (silica gel, eluent: MeOH / AcOEt, 1/1).
4-acetoxy-3-hydroxy-1,4-dimethylpiperidine **3a**: mp 98 °C, ^{1}H NMR: 1.5 (s, 3H), 1.9 (m, 1H), 2.0 (s, 3H), 2.1 (m, 1H), 2.25 (s, 3H), 2.26 (m, 1H), 2.4 (m, 2H), 2.6 (m, 1H), 3.5 (s broad, 1H), 3.8 (m, 1H). ^{13}C NMR: 19.9 (CH_3), 22.1 (CH_3), 32.3 (CH_2), 45.6 (CH_3), 51.4 (CH_2), 57.6 (CH_2), 70.2 (CH), 82.1 (Cq), 170.5 (Cq). MS: 187 ($M^{+\bullet}$), 158, 128, 110, 86, 57.
3-acetoxy-4-hydroxy-1,4-dimethylpiperidine **3'a**: mp 123 °C, ^{1}H NMR: 1.1 (s, 3H), 1.6 (m, 1H), 1.85 (m, 1H), 2.05 (s, 3H), 2.20 (s, 3H), 2.35 (m, 2H), 2.4 (m, 1H), 2.65 (m, 1H), 3.5 (s broad, 1H), 4.7 (m, 1H). ^{13}C NMR: 21.0 (CH_3), 23.6 (CH_3), 36.3 (CH_2), 45.5 (CH_3), 51.4 (CH_2), 55.2 (CH_2), 68.9 (Cq), 75.0 (CH), 170.7 (Cq). MS: 187 ($M^{+\bullet}$), 144, 127, 112, 84, 57.
4-acetoxy-3-hydroxy-1,3,4-trimethylpiperidine **3b**: mp 50 °C, NMR in text, MS: 201($M^{+\bullet}$), 158, 142, 126, 100, 98, 57.

11 Capdevielle, P.; Lavigne, A.; Maumy, M. *Tetrahedron* **1990**, *46*, 2835-2844.

12 Toussaint, O.; Capdevielle, P.; Maumy, M. *Tetrahedron Lett.* **1984**, *25*, 3819-3822.

13 Rousselet, G.; Capdevielle, P.; Maumy, M. *Tetrahedron Lett.* **1995**, *36*, 4999-5002.

14 Réglier, M.; Amadeï, E.; Tadayoni, R.; Waegell, B. *J. Chem. Soc., Chem. Commun.* **1989**, 447- 450.

15 ***3b from 4b and*** $Cu^{II}(OAc)_2$: A solution of **4b** (1 mmol) and $Cu^{II}(OAc)_2$ (1 mmol) in MeCN (8 ml) is heated for 15h at 65 °C under argon. Products are identified and purified as above.

16 Kametani, T.; Ihara, M. *J. C. S. Perkin Trans I* **1980**, 629-632.

17 Reinaud, O.; Capdevielle, P.; Maumy, M. *J. Chem. Soc., Chem. Commun.*, **1990**, 566-568.

18 ***2a, b from 1a, b***: **1a, b** (16 mmol) are reacted with H_2O_2 30% aq. (70 mmol) in AcOH (10 ml) for 2 weeks at 4 °C. The solution is cooled to 0°C, H_2O (10 ml) then K_2CO_3 are added until pH = 11. **2a, b** are extracted with Et_2O and purified by chromatography on alumina (AcOEt/cyclohexane : 90/10).
3,4-epoxy-1,4-dimethylpiperidine **2a**: liquid, ^{1}H NMR: 1.3 (s, 3H), 1.9 (m, 2H), 2.15 (s, 3H), 2.2 (m, 2H), 2.5 (m, 1H), 3.0 (m, 2H). ^{13}C NMR: 22.9 (CH_3), 30.5 (CH_2), 45.3 (CH_3), 48.9 (CH_2), 54.3 (CH_2), 55.8 (Cq), 58.3 (CH). MS: 127 ($M^{+\bullet}$), 110, 84, 57.
3,4-epoxy-1,3,4-trimethylpiperidine **2b**: liquid, ^{1}H NMR: 1.25 (s, 3H), 1.3 (s, 3H), 1.9 (m, 2H), 2.1 (m, 1H), 2.2 (s, 3H), 2.2 (m, 1H), 2.25 (m, 2H). ^{13}C NMR: 18.9 (CH_3), 19.5 (CH_3), 31.8 (CH_2), 45.5 (CH_3), 52.6 (CH_2), 59.7 (CH_2), 60.4 (Cq), 61.4 (Cq). MS: 141 ($M^{+\bullet}$), 126, 124, 98, 84, 57.

19 *H^+ opening*: **2a, b** (1 mmol) are reacted in AcOH (2 ml) or TFA (0.2 ml) / AcOH (2 ml) for 3 h at r. t. or 4 h at 70 °C (see text). H_2O is added at 0 °C, then K_2CO_3 until pH 11. **3a, b**, **3'a** are extracted in Et_2O.
$Cu^{II}(OAc)_2$ and $Cu^{II}(OAc)_2$ + AcOH opening: **2a, b** (1 mmol) are reacted for 3 h in MeCN (5 ml) either with 1 eq. $Cu^{II}(OAc)_2$ at 65 °C or 1 eq. $Cu^{II}(OAc)_2$ + 10 eq. AcOH at 60 °C. **3a, b** and **3'a** are extracted in Et_2O (30 ml) at 0 °C while stirring (1 min) with 30% aq. NaOH (1 ml).

20 Aaron, H. S.; Ferguson, C. P. *J. Am. Chem. Soc.* **1976**, *98*, 7013-7017.

21 Lyle, R. E. *J. Org. Chem.* **1957**, *22*, 1280-1281.

22 ***6b from 2b***: **2b** (1 mmol) is heated with 50% aq. HCO_2H (2 ml) at 80 °C for 30 min. NaOH 30% aq. is added at 0 °C until pH = 11. The solution is extracted with Et_2O, the solvent evaporated and NaOH 30% aq. (4 ml) added to the residue. The solution is heated at 60 °C for 1 hr, then extracted (Et_2O) to yield 0.4 mmol of *3,4-dihydroxy-1,3,4-trimethylpiperidine* **6b** (amorphous): ^{1}H NMR: 1.15 (s, 3H), 1.25 (s, 3H), 1.4 (m, 2H), 2.0 (m, 1H), 2.3 (s, 3H), 2.35 (m, 1H), 2.45 (m, 1H), 2.55 (m, 1H), 3.5 (s broad, 2H). ^{13}C NMR: 19.0 (CH_3), 23.6 (CH_3), 35.7 (CH_2), 45.6 (CH_3), 51.0 (CH_2), 62.6 (CH_2), 71.3 (Cq), 71.4 (Cq). MS: 159 ($M^{+\bullet}$), 142, 116, 71, 58. The same **6b** is also obtained by hydrolysis (NaOH) of **3b**.

23 Christl, M.; Reich, H. J.; Roberts, J. D. *J. Am. Chem. Soc.* **1971**, *93*, 3463-3468.

* Fax : 33 1 40 79 44 25

(*Received in France* 5 *June* 1996; *revised* 5 *July* 1996; *accepted* 25 *September* 1996)