Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 2027–2029

TETRAHEDRON: *ASYMMETRY*

Oxidation of chiral non-racemic pyridinium salts to enantiopure 2-pyridone and 3-alkyl-2-pyridones

Dino Gnecco,* Christian Marazano, Raúl G. Enríquez, Joel L. Terán, María del Rayo Sánchez S. and Alberto Galindo

Centro de Química del Instituto de Ciencias, BUAP Cd., Universitaria Puebla, Pue. C.P. 72570, México

Received 11 February 1998; accepted 2 April 1998

Abstract

Oxidation of chiral non-racemic pyridinium salt **1a** and 3-alkyl pyridinium salts **1b** and **1c** with potassium ferricyanide in an alkaline medium provides a short and practical access to enantiomerically pure 2-pyridone (**2a**) and 3-alkyl-2-pyridones (**2b** and **2c**) in high yields and very good regioselectivity from derivatives **1(b–c)**.

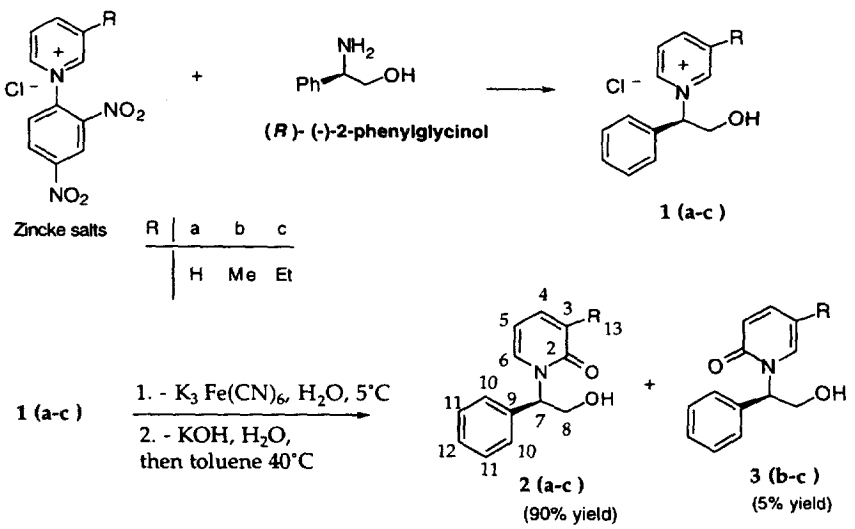
1. Introduction

We have recently reported our contribution to the chemistry of chiral pyridinium salts such as **1(a–c)** (Scheme 1),[1] readily obtained from the reaction of Zincke salts and (R)-(−)-2-phenylglycinol.[2] Considering the ease with which these new derivatives can be obtained, we are now considering further syntheses, from these salts, of new and potentially useful intermediates. Our present strategy aims to make highly substituted enantiomerically pure nitrogen heterocycles readily available, since they are of wide interest in the field of drug and natural product synthesis.

In particular, pyridones and dihydropyridones are a potential source for the synthesis of a variety of alkaloids,[3] although little has been done concerning their use in asymmetric synthesis. This contrasts with the large use of chiral piperidones which have been recently reported.[4] This has stimulated our interest in the preparation of enantiopure pyridones such as **2(a–c)**, whose efficient synthesis from salts **1(a–c)** according to Scheme 1, is now reported.

* Corresponding author.

0957-4166/98/$19.00
PII: S0957-4166(98)00151-7



Scheme 1.

2. Results and discussion

The oxidation of pyridinium salts to 2-pyridones has been reported earlier for the preparation of 1-methyl-2-pyridone from 1-methyl-pyridinium sulfate in 70% yield. This synthetic method, proceeds[5] first through the addition of the hydroxide anion at position 2 of the pyridinium ring[6] giving a pseudobase, which is further oxidized by potassium ferricyanide. When we followed this procedure using salts **1(a–c)**, pyridones **2(a–c)** were obtained in very poor yields (ca. 20%). In contrast, when the same pyridinium salts were stirred for one hour with potassium ferricyanide prior to the addition of potassium hydroxide, we obtained the corresponding pyridones with yields of ca. 90% after chromatography over alumina.[7] The regioselectivity 90:10 in favor of pyridones **2b** and **2c** compared to **3b** and **3c** was observed by integration of signals of the ^{1}H-NMR spectra of the crude reaction mixtures. All reported products gave satisfactory spectroscopic data (see Table 1). The chiral benzylic carbon of **1(a–c)** remains unchanged under these basic conditions as consistently demonstrated in previous work.[1,2]

3. Experimental

3.1. Preparation of chiral pyridones 2(a–c)

A stirred solution of pyridinium salt **1(a–c)** (4.0 mmol) in water (25 mL) was cooled to 5°C and a solution of $K_3Fe(CN)_6$ (11 equiv.) in water (30 mL) was added dropwise over a period of 1 h. Then a solution of KOH (15.8 equiv.) in water (6 mL) was added dropwise over 30 min. Toluene (40 mL) was added and the mixture warmed at 40°C for 30 min. The organic layer was extracted with dichloromethane (4×50 mL). The combined organic layers were dried over Na_2SO_4 and solvent was removed in vacuo. The residue was purified by column chromatography (Al_2O_3), eluting with pentane:dichloromethane 1:5. The average yield of chiral pyridones **2(a–c)** was 90% as oils.

Table 1

Compd 2	R	α_D^{20}	IR,KBr cm-1	^1H ^{13}C NMR: $CDCl_3$ (δ, ppm)
a	H	-162.60	3360 1652 767 700	**^1H NMR:** 4.21-4.25 (m, 2H, H_8); 6.17 (t, 1H, H_5); 6.31 (dd, 1H, H_7); 6.53 (d, 1H, H_3); 7.29-7.32 (m, 2H, H_6, H_4); 7.33-7.35 (m, 5H, Ph). **^{13}C NMR:** 59.9 (C-7); 61.9 (C-8); 106.5(C-5); 120.5 (C-3); 127.3 (2C-10); 128.0 (C-12); 129.5 (2C-11); 136.2 (C-6); 137.3(C-9); 138.2 (C-4); 164.2 (C-2)
b	Me	-193.7	3380 1648 1580 763 699	**^1HNMR**: 2.04 (s, 3H, H_{13}); 3.0 (s,1H, OH); 4.19-4.35 (m, 2H, H_8); 6.13 (t, 1H, H_5); 6.40 (dd, 1H, H_7); 7.14-7.21 (m, 2H, H_6, H_4); 7.30- 7.36(m, 5H, Ph). **^{13}C NMR**: 17.5 (C-13); 60.1 (C-7); 63.6 (C-8); 106.3 (C-5); 128.1 (C-3); 128.6 (2C-10); 128.90 (C-12); 129.6 (2C-11); 132.8 (C-6); 136.8 (C-9); 136.9 (C-4); 163.4 (C-2)
c	Et	-200.0	3375 1645 1582 761 697	**^1H NMR**: 1.00 (t, 3H, CH_2-CH_3); 2.10 (q, 2H, CH_2-CH_3) ; 4.20-4.32 (m, 2H, H_8); 6.10 (t, 1H, H_5); 6.40 (dd, 1H, H_7); 7.20-7.26 (m, 2H, H_6, H_4); 7.30-7.36 (m, 5H, Ph). **^{13}C NMR**: 12.5 (C-13); 17.2 (C-13); 60.0 (C-7); 63.0 (C-8); 106.0 (C-5); 128.1 (C-3); 128.6 (2C-10); 129.4 (C-12); 130.0 (2C-11); 133.0 (C-6); 136.3 (C-9); 136.6 (C-4); 162.5 (C-2)

a (c4.3, $CHCl_3$); b (c1.92, $CHCl_3$); c (c2.00, $CHCl_3$).

Acknowledgements

D.G. and C.M. gratefully acknowledge support from ECOS project #M95E01 (México-France) and to CONACYT-México for financial support to the Lecturing Award to R.G.E., from Instituto de Química, UNAM, México.

References

1. Wong, Y. S.; Marazano, C.; Gnecco, D.; Genisson, Y.; Das, B. C. *J. Org. Chem.* **1997**, 62, 729 and references cited therein.
2. Genisson, Y.; Marazano, C.; Mehmandoust, M.; Gnecco, D.; Das, B. C. *Synlett.* **1992**, 431.
3. Coffen, D. L.; Hengartner, U.; Katonak, A.; Mulligan, M. E.; Burdick, D. C.; Olson, G. L.; Todaro, L. J. *J. Org. Chem.* **1984**, 49, 5109. Amat, M.; Llor, N.; Hidalgo, J.; Hernández, A.; Bosch, J. *Tetrahedron: Asymmetry* **1996**, 7, 977 and references therein. Kuethe, J. T.; Padwa, A. *Tetrahedron Lett.* **1997**, 38, 1505 and references therein. Mabic, S.; Castagnoli Jr., N. *J. Org. Chem.* **1996**, 61, 309. An enantioselective approach has been recently reported in the isoquinolinone series: Munchhof, M. J.; Meyers A. I. *J. Org. Chem.* **1995**, 60, 7086.
4. Munchhof, M. J.; Meyers A. I. *J. Org. Chem.* **1995**, 60, 7084. Micouin, L.; Bonin, M.; Cherrier, M.-P.; Mazurier, A.; Tomas, A.; Quirion, J.-Ch.; Husson, H.-P. *Tetrahedron* **1996**, 52, 7719 and references therein.
5. Prill, E. A.; McElvain *Org. Syn.* **1943**, 2, 419.
6. Becher, I. *Synthesis* **1980**, 589.
7. Fujii, T.; Yoshifuji, S.; Mishishita, K.; Mitsukushi, M.; Yoshida, K. *Chem. Pharm. Bull.* **1973**, 20, 2695 and references cited therein. For a recent example on quinolinium series see Gonzalez-Bello, C.; Abell, C.; Leeper, F. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1017.; Cooksey, C. J.; Johnson, M. D. *J. Chem. Soc.* B, **1968**, 10, 1191; Ruchirawat, S.; Sunkul, S.; Thbtaranonyh, Y. *Tetrahedron Letters* **1977**, 27, 2335 and references therein.