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

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Abstract

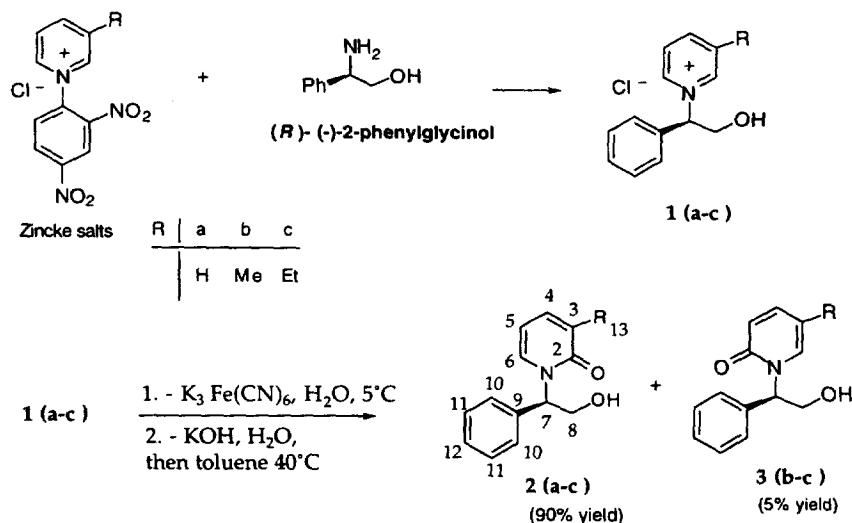
Oxidation of chiral non-racemic pyridinium salt **1a** and 3-alkyl pyridinium salts **1b** and **1c** with potassium ferricyanide in an alkaline medium provides a short and practical access to enantiomerically pure 2-pyridone (**2a**) and 3-alkyl-2-pyridones (**2b** and **2c**) in high yields and very good regioselectivity from derivatives **1(b–c)**. © 1998 Elsevier Science Ltd. All rights reserved.

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.

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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, proceeds⁵ first through the addition of the hydroxide anion at position 2 of the pyridinium ring⁶ 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 ¹H-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 $\text{K}_3\text{Fe}(\text{CN})_6$ (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	¹ H ¹³ C NMR: CDCl ₃ (δ , ppm)
a	H	-162.60	3360 1652 767 700	¹ H 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	¹ H NMR: 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	¹ H 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, CHCl₃); b (c1.92, CHCl₃); c (c2.00, CHCl₃).

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