

Regioselective Oxidation of 3-Substituted Pyridinium Salts

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Abstract: (1'R)-(+)-3-Hydroxymethyl-1-(1'-phenyl-ethyl)-pyridinium chloride (**1**), 1-benzyl-3-[1', 3']-dioxolan-2'-yl-pyridinium chloride (**2**) and (2'S, 4'S, 5'R)-(-)-1-benzyl-3-(3',4'-dimethyl-5'-phenyl-oxazolidin-2'-yl)-pyridinium bromide (**3**), were transformed by oxidation with potassium ferricyanide into the corresponding 1*H*-pyridin-2-ones in excellent yields with high regioselectivity.

Keywords: pyridinium salts, regioselective oxidation and chirality.

Introduction

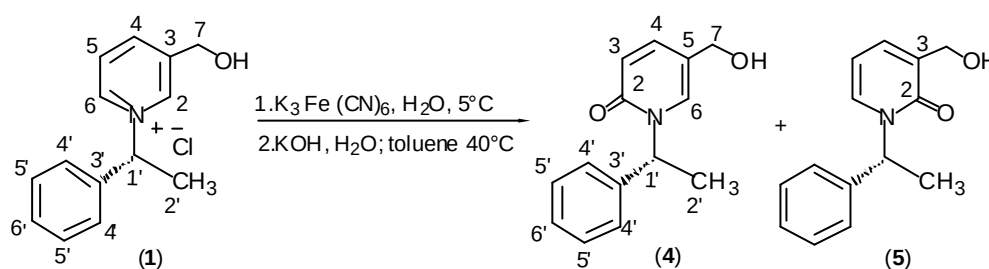
The oxidation of chiral pyridinium salts is an area of research with wide interest because enantiopure 1*H*-pyridin-2-ones obtained can be used in the asymmetric synthesis of alkaloids. The synthesis of chiral 1*H*-pyridin-2-ones is useful, because the starting material is easily obtained and the regioselectivities of the reactions can attain high values depending on the substituent at position 3. [1, 2, 3, 4, 5, 6, 7, 8]. In a preliminary communication [9], we reported the oxidation of 3-(methyl and ethyl) pyridinium salts, where in all cases, the oxidation at the 2-position in the starting material was favored. Now, we report three different examples of pyridinium salts differently substituted at position 3, incorporating chiral substituents in the quaternary nitrogen or at position 3, which were oxidized with potassium ferricyanide.

We observe an increasing percentage of oxidation at position 6 when the bulkiness of the substituent was increased. The products obtained were characterized by NMR and in one case, by X-ray diffraction.

Results and Discussion

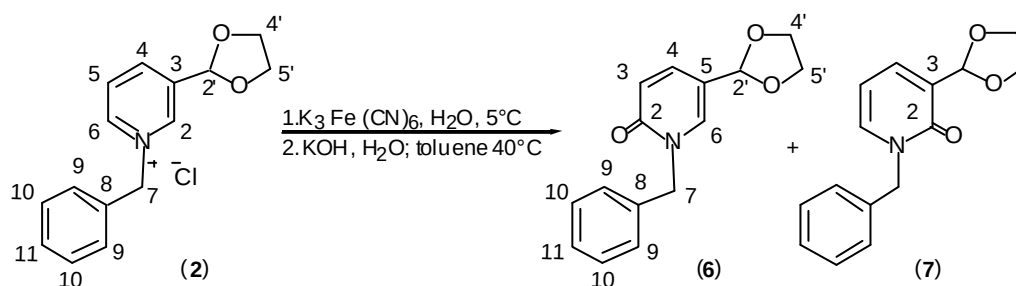
For this purpose, we prepared pyridinium salt (**1**) from the corresponding 1-(2,4-dinitro-phenyl)-3-hydroxymethyl-pyridinium chloride and (R)-(+)-1-phenyl-ethylamine [10]. The salts (**2**) and (**3**) were obtained from pyridin-3-carbaldehyde with ethane-1, 2-diol or (1R, 2S)-(-)-2-methylamino-1-phenyl-propan-1-ol followed of quaternisation with benzyl bromide [11]. See Experimental.

The oxidation of chiral non-racemic pyridinium salt (**1**) with potassium ferricyanide produced a mixture of (1'R)-(+)-5-hydroxymethyl-1-(1'-phenyl-ethyl)-1*H*-pyridin-2-one (**4**) and (1'R)-(+)-3-hydroxymethyl-1-(1'-phenyl-ethyl)-1*H*-pyridin-2-one (**5**) (Scheme 1); the overall yield was 90% with a ratio of (**4**):(**5**) = 70:30 after column chromatography (SiO₂, gradient dichloromethane-methanol). The products all gave satisfactory spectroscopic data.



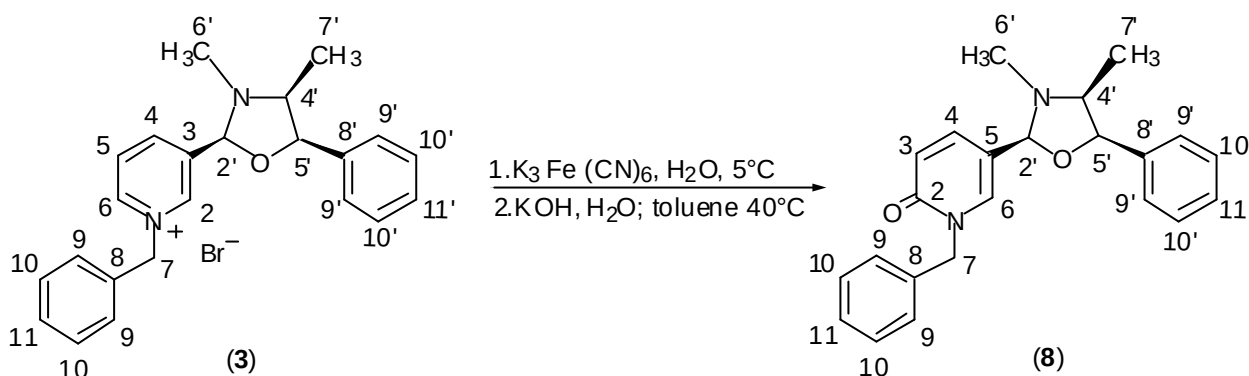
Scheme 1.

Similarly, the oxidation of (**2**) afforded a mixture of 1-benzyl-5-[1',3']-dioxolane-2'-yl-1*H*-pyridin-2-one (**6**) and 1-benzyl-3-[1',3']-dioxolane-2'-yl-1*H*-pyridin-2-one (**7**) (Scheme 2); overall yield 92% with a ratio of (**6**):(**7**) = 80:20 after column chromatography (SiO₂, gradient dichloromethane-methanol). The products all gave satisfactory spectroscopic data.



Scheme 2.

Finally, the oxidation of chiral non-racemic pyridinium salt (**3**) exclusively afforded the (2'S, 4'S, 5'R)-(-)-1-benzyl-5-(3',4'-dimethyl-5'-phenyl-oxazolidin-2'-yl)-1*H*-pyridin-2-one (**8**) (Scheme 3) in a yield of 97% after column chromatography (SiO₂, gradient dichloromethane-methanol). The product gave satisfactory spectroscopic data. This compound was crystallized from Et₂O/CHCl₃ and submitted to X-ray studies. The ORTEP [12] view of (**8**) is shown in Fig 1.



Scheme 3.

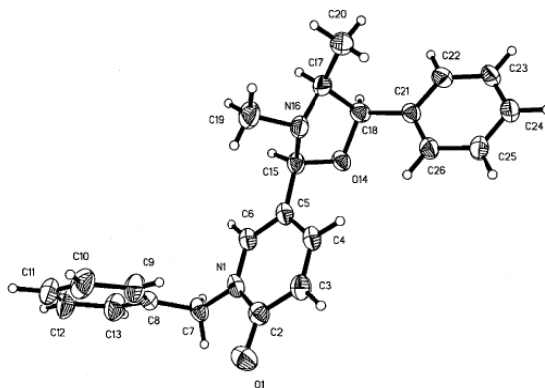


Fig. 1. ORTEP view of the crystal structure of compound (**8**).

Conclusions

These results show that the steric hindrance exerted by the substituent at position 3 plays a key role in the extent of 6-oxidation in the starting material. In particular, we found that the size of the substituent in (2'S, 4'S, 5'R)-(-)-1-benzyl-3-(3',4'-dimethyl-5'-phenyl-oxazolidin-2'-yl)-pyridinium bromide (**3**) results in the exclusive generation of the chiral, non-racemic (2'S, 4'S, 5'R)-(-)-1-benzyl-5-(3',4'-dimethyl-5'-phenyl-oxazolidin-2'-yl)-1*H*-pyridin-2-one (**8**).

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Experimental

General.

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded in KBr on a Nicolet Magna-750 spectrophotometer. NMR spectra were measured on a Jeol 400 MHz. spectrometer, using TMS as the internal standard. ^1H -NMR assignments were confirmed by extensive use of ^{13}C - ^1H correlation techniques. Optical rotation was measured on a Perkin-Elmer Polarimeter M241. X-ray diffractions were measured on a Siemens P4/PC diffractometer.

Preparation of Chiral Pyridinium Salt (1).

To a solution of 1-(2,4-dinitro-phenyl)-3-hydroxymethyl-pyridinium chloride at 70°C (3.0 g, 9.64 mmol) in vigorously stirred *n*-butanol (150 mL), a solution of (R)-(+)-1-phenyl-ethylamine (1.16 g, 9.64 mmol) in *n*-butanol (50 mL) was added dropwise over a period of 15 min and the mixture was then refluxed for 12 h. Thereafter, the solvent was removed *in vacuo*, affording a viscous residue, which was dissolved in water (50 mL), filtered and the water solution washed with dichloromethane (5x20 mL). To the 2,4-dinitroaniline-free water solution, toluene (75 mL) was added. The toluene-water azeotrope was removed under reduced pressure, affording **1** (2.40g, 80% yield), after column chromatography (SiO_2 , $\text{CH}_2\text{Cl}_2/\text{MeOH}$, 100:0; 99:1; 98:2; 97:3 and 95:5 v/v).

Spectral Data.

Chiral Pyridinium Salt (**1**). Oil; $[\alpha]_D^{25} +12.3$ ($c=2$, MeOH); IR: (KBr, cm^{-1}) 3345-3300, 2923, 1636, 1058. ^1H NMR: δ (ppm, CD_3OD , JHz): 8.97 (H-2, s); 8.91 (H-6, d, 6.05); 8.56 (H-4, d, 7.97); 8.08 (H-5, t, 7.97, 6.05); 7.55-7.40 (5H, ϕ -H); 6.20 (H-1', q, 7.03); 4.85 (2H-7, s); 2.02 (3H-2', d, 7.03). ^{13}C NMR: δ (ppm, CD_3OD): C-2, 145.98; C-6, 145.23; C-3, 143.21; C-4, 142.48; C-3', 138.79; C-6', 131.78; 2C-4', 130.90; C-5, 129.50; 2C-5', 128.78; C-1', 72.50; C-7, 61.38; C-2', 21.03.

General Procedure for Synthesis of Pyridinium Salts (2) and (3).

A solution of pyridine-3-carbaldehyde protected with ethane-1,2-diol or (1R, 2S)-(-)-2-methylamino-1-phenyl-propan-1-ol (1.0 eq) in anhydrous CH_2Cl_2 , was cooled to 0°C and a solution of

benzyl bromide (1.1 eq) in anhydrous CH_2Cl_2 was added dropwise over a period of 30 min with stirring. After maintaining the temperature at 35°C for 12h the reaction was complete, as evidenced by by TLC monitoring (Al_2O_3 , $\text{CH}_2\text{Cl}_2/\text{MeOH}$, 97:3 v/v). Average yields of pyridinium salts (**2**) and (**3**) were 85% and 90% respectively after column chromatography (SiO_2 , $\text{CH}_2\text{Cl}_2/\text{MeOH}$, 100:0; 99:1 and 98:2 v/v).

Spectral Data.

Pyridinium Salt (2). Oil. IR: (KBr, cm^{-1}) 3422-3400, 2897, 1636, 1105; ^1H NMR: δ (ppm, CD_3OD , JHz): 9.91 (H-6, d, 5.1); 9.57 (H-2, s); 8.42 (H-4, d, 7.7); 8.08 (H-5, t, 6.0); 7.72 (2H-9, m); 7.34 (2H-10 and H-11, m); 6.36 (2H-7, m); 6.02 (H-2', s); 4.08 (2H-4', 2H-5', td, 11.2, 8.0). ^{13}C NMR: δ (ppm, CD_3OD): C-2, 146.20; C-6, 143.80; C-3, 140.10; C-8, 132.80; C-11, 129.87; 2C-10, 129.71; 2C-9, 129.50; C-4; C-5, 128.34; C-2', 99.80; C-4'; C-5', 66.00; C-7, 64.20.

Chiral Pyridinium Salt (3). Crystallized from $\text{Et}_2\text{O}/\text{CHCl}_3$, mp. $153\text{--}155^\circ\text{C}$; $[\alpha]_D = -58.4$ ($c = 2$, MeOH); IR: (KBr, cm^{-1}) 3445-3400, 2977, 2937, 1457; ^1H NMR: δ (ppm, CDCl_3 , JHz): 10.04 (H-6, d, 5.60); 9.69 (H-2, s); 8.63 (H-4, d, 7.60); 8.12 (H-5, dd, 6.40, 1.30); 7.75 (2H-9, m); 7.39 (2H-10 and H-11, m); 7.30 (2H-9', H-11', m); 7.18 (2H-10', m); 6.38 (2H-7, AB, 22.4, 13.2); 5.14 (H-5', d, 8.0); 5.07 (H-2', s); 3.11 (H-4', m); 2.32 (3H-6', s); 0.71 (3H-7', d, 6.24). ^{13}C NMR: δ (ppm, CDCl_3): C-2, 145.93; C-6, 144.80; C-3, 144.18; C-4, 140.80; C-8, 138.23; C-8', 132.94; C-5, 130.10; 2C-9, 2C-10, C-11, 2C-9', 2C-10', C-11', 129.79 to 127.59; C-2', 93.82; C-5', 83.22; C-7, 64.44; C-4', 63.88; C-6', 36.59; C-7', 15.28.

General Procedure for Synthesis of 1H-pyridin-2-ones (4+5), (6+7) and (8).

A stirred solution of the corresponding pyridinium salt (4.0 mmol) in water (25 mL) was cooled to 5°C and a solution of $\text{K}_3\text{Fe}(\text{CN})_6$ (11.0 eq) in water (30 mL) was added dropwise over a period of 1h. Then, a solution of KOH (15.8 eq) in water (10 mL) was added dropwise over 30 min. Toluene (40 mL) was added and the mixture warmed at 40°C for 30 min. After maintaining the temperature at 40°C for 2h the reaction was complete, as indicated by TLC (Al_2O_3 , $\text{CH}_2\text{Cl}_2/\text{MeOH}$, 99:1 v/v). The organic layer was separated and the aqueous solution extracted with dichloromethane (4x50 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The mixture was purified and separated by column chromatography (SiO_2 , $\text{CH}_2\text{Cl}_2/\text{MeOH}$, 100:0; 99:1 and 98:2 v/v). Overall yields: (**4+5**), 90% (**4**, 63% / **5**, 27%); (**6+7**), 92% (**6**, 73.6% / **7**, 18.4%) and 97% (**8**).

Spectral Data.

Chiral 1H-pyridin-2-one (4): Oil. $[\alpha]_D = +15.82$ ($c = 1$, CH_2Cl_2). IR (KBr, cm^{-1}): 3550-3200, 2926, 1662, 1580, 1539. ^1H NMR: δ (ppm, CDCl_3 , JHz): 7.35-7.28 ($\phi\text{-H}$, 5H, m); 7.23 (H-4, d, 9.52); 7.10

(H-6, d, 1.80); 6.51 (H-3, d, 9.12); 6.36 (H-1', q, 7.32); 4.26 (2H-7, s); 1.66 (3H-2', d, 7.32). ^{13}C NMR: δ (ppm, CDCl_3): C-2, 162.00; 2C-4', 140.03; C-4, 139.51; C-6, 132.25; 2C-4', 128.93; C-6', 128.12; 2C-5', 127.47; C-3, 120.55; C-5, 119.88; C-7, 61.90; C-1', 52.65 and C-2', 19.13.

Chiral 1H-pyridin-2-one (5): Oil. $[\alpha]_D = +27.61$ ($c = 1$, CH_2Cl_2). IR (KBr, cm^{-1}): 3500-3200, 3062, 2979, 1645, 1581, 1555. ^1H NMR: δ (ppm, CDCl_3 , J Hz): 7.36-7.28 (ϕ -H, 5H, m); 7.25 (H-4, d, 6.24); 7.08 (H-6, d, 6.96); 6.42 (H-1', q, 7.32); 6.14 (H-5, t, 6.96); 4.58 (2H-7, s); 1.70 (3H-2', d, 7.32). ^{13}C NMR: δ (ppm, CDCl_3): C-2, 162.39; C-3', 140.02; C-4, 135.46; C-6, 133.14; C-3, 131.23; 2C-4', 128.96; C-6', 128.15; 2C-5', 127.46; C-5, 106.54; C-7, 62.97; C-1', 52.68 and C-2', 19.21.

1H-Pyridin-2-one (6): Oil. IR (KBr, cm^{-1}): 3450-3400, 2925, 2880, 1669, 1607, 1544. ^1H NMR: δ (ppm, CDCl_3 , J Hz): 7.41 (H-4, dd, 9.16, 2.56); 7.31 (H-6, s); 7.30 (2H-9, m); 7.29 (2H-10, m); 7.28 (H-11, m); 6.63 (H-3, d, 9.16); 5.49 (H-2', s); 5.12 (2H-7, s); 3.97 (2H-4', 2H-5', A_2X_2 , 8.8). ^{13}C NMR: δ (ppm, CDCl_3): C-2, 162.51; C-4, 137.82; C-6, 136.29; C-8, 136.20; 2C-10, 129.0; 2C-9; C-11, 128.19; C-3 121.39; C-5, 115.55; C-2', 101.54; C-4'; C-5', 65.35; C-7, 53.52.

1H-Pyridin-2-one (7): Oil. IR (KBr, cm^{-1}): 3450-3400, 2925, 2880, 1650, 1591, 1559. ^1H NMR: δ (ppm, CDCl_3 , J Hz): 7.59 (H-4, dd, 6.76, 2.2); 7.31 (H-11, m); 7.30 (2H-9 and 2H-10, m); 7.28 (H-6, dd, 6.76, 1.84); 6.16 (H-5, t, 6.76); 6.00 (H-2', s); 5.14 (2H-7, s); 4.05 (2H-4' and 2H-5', dt, 15.4, 4.03, 1.84). ^{13}C NMR: δ (ppm, CDCl_3): C-2, 161.51; C-4, 137.74; C-3, C-6, 136.41; 2C-10, 128.97; 2C-9, C-11, 128.51; C-8, 128.16; C-5, 105.56; C-2', 99.51; C-4'; C-5', 65.37 and C-7, 51.93.

Chiral 1H-pyridin-2-one (8): Crystallized from $\text{Et}_2\text{O}/\text{CHCl}_3$, mp = 144°C. $[\alpha]_D = -6.1$ ($c = 1$, CH_2Cl_2). IR (KBr, cm^{-1}): 3450-3400, 2947, 2892, 1667, 1610, 1541. ^1H NMR: δ (ppm, CDCl_3 , J Hz): 7.67 (H-4, dd, 9.32, 2.2); 7.45 (H-6, d, 2.2); 7.33- 7.30 (2 ϕ -H, 10H, m); 6.69 (H-3, d, 9.52); 5.16 (2H-7, AB, 23.98, 14.28); 5.06 (H-5', d, 8.04); 4.41 (H-2', s); 2.90 (H-4', qd, 8.4, 6.6); 2.13 (3H-6', s); 0.73 (3H-7', d, 6.6). ^{13}C NMR: δ (ppm, CDCl_3): C-2, 163.03; C-4, 139.33; C-6, 137.65; C-8, C-8', 136.25; C-11, C-11', 129.02; 2C-10, 2C-10', 128.18; 2C-9, 2C-9', 128.10; C-3, 121.47; C-5, 116.79; C-2', 95.96; C-5', 82.28; C-4', 63.67; C-7, 52.13; C-6', 35.74; C-7', 15.14.

X-ray structure of (8) Crystal data: $\text{C}_{23}\text{H}_{24}\text{N}_2\text{O}_2$, $M_w = 360.44$, monoclinic, space group $P2_1$, $Z = 2$, $a = 5.443$ (1) Å, $b = 8.634$ (1) Å, $c = 21.073$ (2) Å, $\beta = 96.23$ (1)°, $V = 984.4$ (2) Å³, $D_{\text{calc}} = 1.216$ g cm⁻³, $T = 293$ K, $R_1 = 0.041$, $wR_2 = 0.101$ for 2608 reflections with $I > 2\sigma(I)$. [$R_1 = 0.043$, $wR_2 = 0.104$ for all 3120 independent reflections].

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Sample Availability: Available from the authors.