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OXIDATION AND AROMATIZATION OF THE ENANTIOPURE PIPERIDINE DERIVED FROM (*R*)-(-)-2-PHENYLGLYCINOL TO (1'*R*)-(-)-1-(2'-HYDROXY-1'-PHENYLETHYL)-1*H*-PYRIDIN-2-ONE

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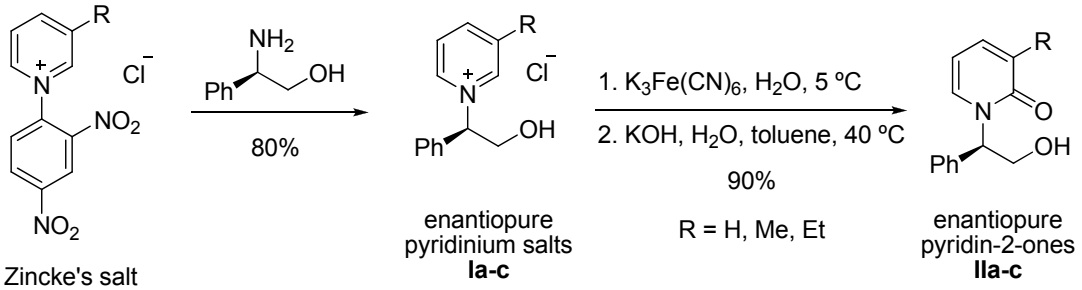
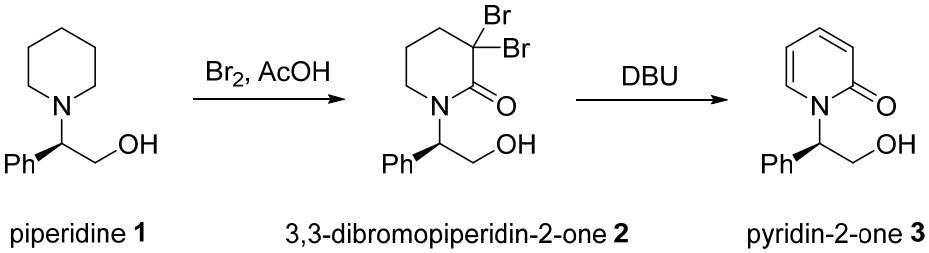
Abstract – An efficient oxidation of enantiopure piperidine **1** with bromine in acetic acid to generate the corresponding enantiopure (*R*)-3,3-dibromo-1-(2'-hydroxy-1'-phenylethyl)piperidin-2-one **2** is described. Then, aromatization of compound **2** to give enantiopure pyridin-2-one **3** in 71% overall yield is presented.

In general, pyridin-2-ones and dihydropyridin-2-ones are versatile synthetic building blocks, which are used as starting materials to carry out the synthesis of interesting and diversely functionalized nitrogen heterocycles.[1] In this context, we previously reported a practical procedure to carry out the oxidation of enantiopure pyridinium salts **Ia-c** to the corresponding pyridin-2-ones **IIa-c**. This procedure involves the treatment of the pyridinium salts **Ia-c** with a mixture of potassium ferricyanide and potassium hydroxide to give the products **IIa-c** with yield of ca. 90%.[2] However, it is remarkable mentioning that the pyridinium salts are obtained from the reaction of Zincke's salts with (*R*)-(-)-2-phenylglycinol with average yields of 85%[3] (Scheme 1).



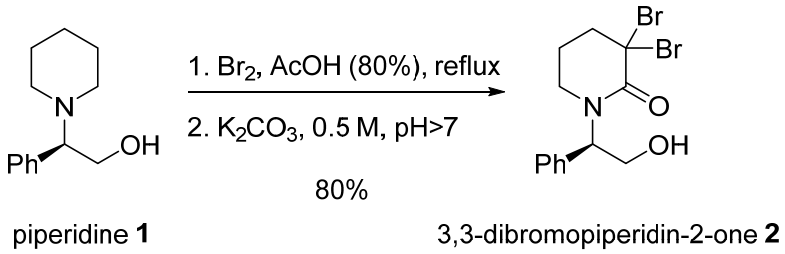
Scheme 1

Herein, we report the oxidation of enantiopure piperidine **1**[4] with bromine in the presence of acetic acid afforded 3,3-dibromopiperidin-2-one **2** in 80% yield.[5] Then, the aromatization of compound **2** under basic conditions gave access quantitatively to the corresponding enantiopure pyridin-2-one **3** (Scheme 2).



Scheme 2

The oxidation of piperidine **1** into 3,3-dibromopiperidin-2-one **2** was achieved using 10.0 eq. of bromine in acetic acid (80%) and refluxing the solution for 1 h. Then, basic aqueous workup allowed to obtain the product **2** in 80% yield, after purification by flash chromatography (Scheme 3).



Scheme 3

Compound **2** was crystallized and submitted to X-ray analysis.[6] The ORTEP view of product **2** is shown in the Figure 1.

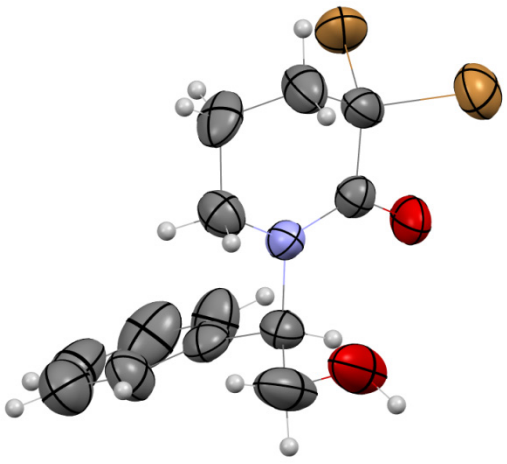
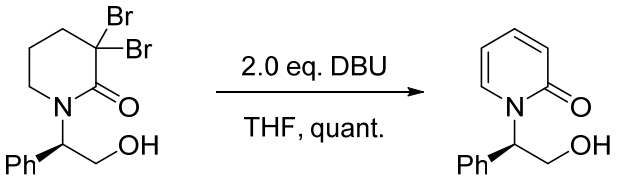


Figure 1. ORTEP of piperidin-2-one **2**

The aromatization of compound **2** was carried out with 2.0 eq. of DBU in refluxing THF for 1 h. Thus, pyridin-2-one **3** was obtained in quantitative yield (Scheme 4).

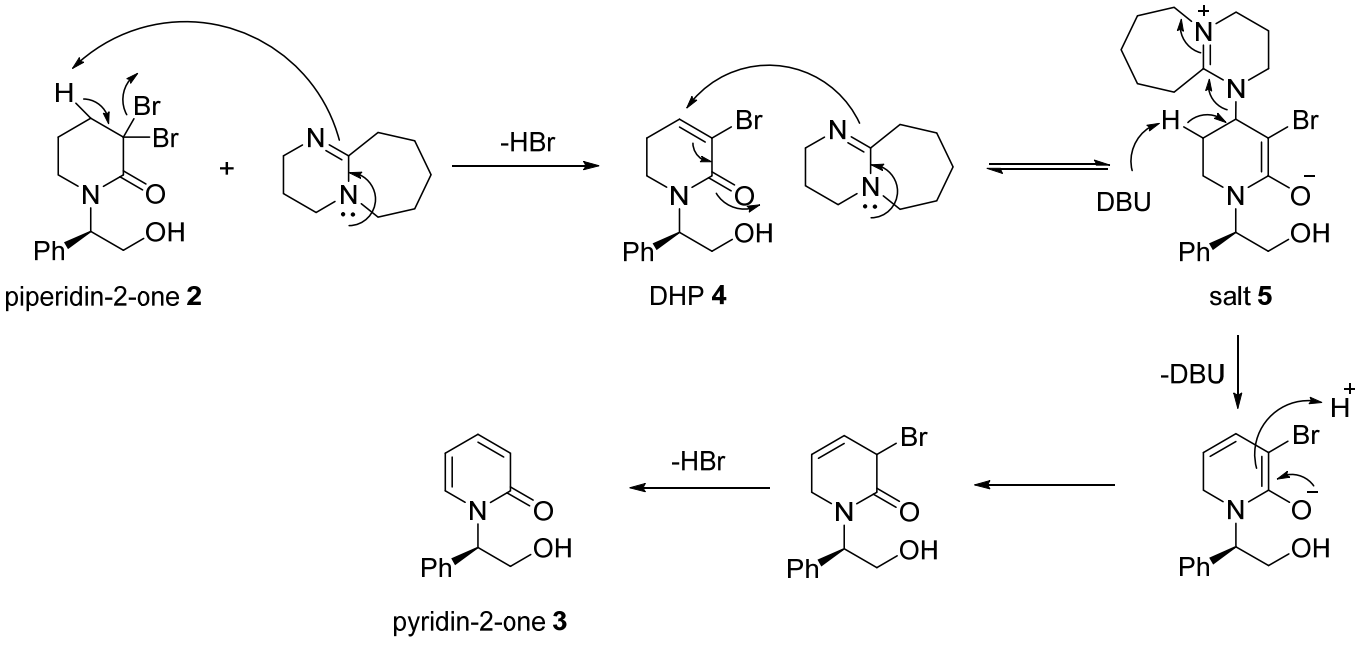


3,3-dibromopiperidin-2-one **2** pyridin-2-one **3**

Scheme 4

The spectroscopic data of compound **3** are in good agreement with the data reported in the literature for the (*R*) enantiomer.[2]

The aromatization process can be explained by a first dehydrobromination to give 5,6-dihydropyridin-2-one **4** which reacts through an aza-Michael reaction with DBU[7] to afford the corresponding salt **5**. Then, elimination of DBU, followed by a secondly dehydrobromination gave access to pyridin-2-one **3** (Scheme 5).

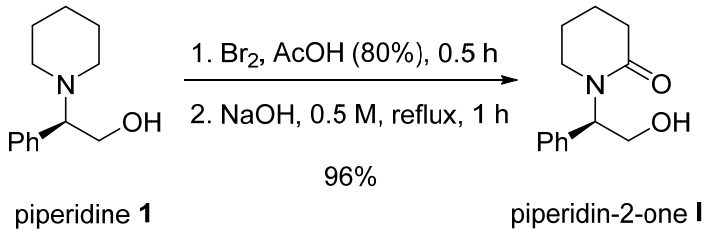


piperidin-2-one **2** DHP **4** salt **5**

pyridin-2-one **3**

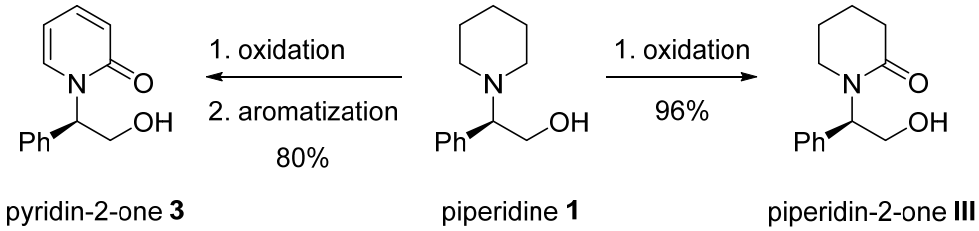
Scheme 5

It is worth mentioning that in a previous work we reported the oxidation of enantiopure piperidine **1** with bromine in acetic acid to achieve the corresponding enantiopure piperidin-2-one **III** in 96% yield[8] (Scheme 6).



Scheme 6

Accordingly, starting from enantiopure piperidine **1**, we can access to both compounds either pyridin-2-one **3** or piperidin-2-one **III** in good yields, through two different oxidation process (Scheme 7).



Scheme 7

An efficient method for the preparation of pyridin-2-one **3** in good yield has been developed. Additionally, two different oxidation processes have been proven, which give access to either piperidin-2-ones or pyridin-2-ones. Further use of these oxidation processes for the oxidation of 2- or 3-alkylpiperidines is currently under investigation.

EXPERIMENTAL

General. The ^{1}H and ^{13}C NMR spectra were determined in $CDCl_3$ using TMS as an internal reference with a Varian VX400 FT NMR spectrometer operating at 400 and 100 MHz respectively. IR spectra were obtained with a Nicolet FTIR Magna 750 spectrometer. Optical rotations were determined at room temperature with a Perkin-Elmer 341 polarimeter, using a 1dm cell with a total volume of 1 mL and are referenced to the D-line of sodium. Mass spectra were recorded with a JEOL JEM-AX505HA instrument at a voltage of 70 eV.

Oxidation of compound 1.

To a solution of **1** (0.205 g, 1.0 mmol) in acetic acid (1.0 mL, 80%) at 0 °C was added dropwise a solution of bromine (10.0 mmol, 0.51 mL) in acetic acid (2.0 mL, 80%) and water (3.0 mL). The resulting solution was stirred at room temperature for 2 h and, then, was heated at reflux for 1 h. After cooling to 0 ºC, the resulting solution was basified by dropwise addition of aqueous K_2CO_3 (0.50 M). The aqueous layer was

extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic extracts were washed with saturated aqueous $Na_2S_2O_3$ (25 mL), dried and concentrated to give a yellow solid. Purification by flash chromatography (SiO_2, gradient from AcOEt to 95:5 AcOEt–MeOH) afforded pure lactam **2** in 80% yield.

Aromatization of compound 2.

To a solution of **2** (0.190 g, 0.50 mmol) in THF (5 mL) was added dropwise DBU (0.170 g, 1.1 mmol) and the mixture was heated at reflux for 1 h. Then, the reaction was quenched with saturated aqueous NH_4Cl (3 mL) and extracted with AcOEt (3 x 10 mL). The combined organic layers were successively washed with 5% aqueous HCl, 5% aqueous $NaHCO_3$, and brine, then dried, filtered, and concentrated to give pyridin-2-one **3** in quantitative yield.

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