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

Alejandro Castro, 2 Oscar Romero, 2 Joel L. Terán, 1 Dino Gnecco, 1 Laura Orea, 1 Angel Mendoza, 1 and Jorge R. Juárez 1*

1Centro de Química, Instituto de Ciencias, Benemérita Universidad Autónoma de Puebla, Edif. 103H, Complejo de Ciencias, C.U., 72570 Puebla, Pue., México. 2Universidad Politécnica de Tlaxcala, Av. Universidad Politécnica 1, San Pedro Xalcatzinco, 90180 Tepeyanco, Tlax., México; E-mail: jorge.juarez@correo.buap.mx

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](attachment://Scheme1.png)
Herein, we report the oxidation of enantiopure piperidine 1 with bromine in the presence of acetic acid afforded 3,3-dibromopiperidin-2-one 2 in 80% yield. Then, the aromatization of compound 2 under basic conditions gave access quantitatively to the corresponding enantiopure pyridin-2-one 3 (Scheme 2).

![Scheme 2](image)

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](image)

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

![Figure 1](image)
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).

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 DBU7 to afford the corresponding salt 5. Then, elimination of DBU, followed by a secondly dehydrobromination gave access to pyridin-2-one 3 (Scheme 5).

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% yield8 (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).

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 °C, the resulting solution was basified by dropwise addition of aqueous K$_2$CO$_3$ (0.50 M). The aqueous layer was
extracted with CH₂Cl₂ (3 × 50 mL), and the combined organic extracts were washed with saturated aqueous Na₂S₂O₃ (25 mL), dried and concentrated to give a yellow solid. Purification by flash chromatography (SiO₂, 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 NH₄Cl (3 mL) and extracted with AcOEt (3 x 10 mL). The combined organic layers were successively washed with 5% aqueous HCl, 5% aqueous NaHCO₃, and brine, then dried, filtered, and concentrated to give pyridin-2-one 3 in quantitative yield.

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**REFERENCES**


6. Deposition number CCDC-973161 for compound No. 2. Free copies of the data can be obtained via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK; Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).
