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New methodology for the synthesis of enantiopure (3*R*,2a*R*)-(−)-3-phenyl-hexahydro-oxazolo[3,2-*a*]-pyridin-5-one: a synthesis of (*S*)-(+)-coniine

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Abstract—A new and efficient methodology for the enantiopure synthesis of (3*R*,2a*R*)-(−)-3-phenyl-hexahydro-oxazolo[3,2-*a*]pyridin-5-one **3** starting from (1′*R*)-(−)-1-(2′-hydroxy-1′-phenyl-ethyl)-(1*H*)-pyridin-2-one **1** is described. In addition, the enantiospecific synthesis of (*S*)-(+)-coniine hydrochloride **6** in good yield from **3** is reported.

1. Introduction

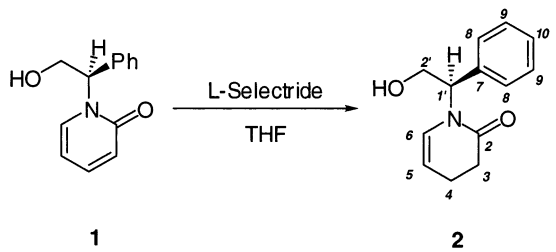
Chiral hexahydro-oxazolo[3,2-*a*]pyridin-5-ones are widely used in the formation of C–C bonds α- to nitrogen. The preparation, reactivity and application of these compounds in the asymmetric synthesis of alkaloids and piperidine derivatives[1–3] have been thoroughly studied. We have previously reported[4] the synthesis of enantiopure (1*H*)-pyridin-2-ones from chiral non-racemic pyridinium salts. Considering the ease with which these compounds are obtained, we decided to explore the utility of (1′*R*)-(−)-1-(2′-hydroxy-1′-phenyl-ethyl)-1*H*-pyridin-2-one **1** in the preparation of 3-phenyl-hexahydro-oxazolo[3,2-*a*]pyridin-5-one. For this purpose, we carried out three different reductions[5] of **1**, using L-selectride™, PtO_2/H_2 and $LiAlH_4$.

The most efficient reduction of (1′*R*)-(−)-1-(2′-hydroxy-1′-phenyl-ethyl)-(1*H*)-pyridin-2-one **1** was seen with L-selectride™ (3 equivalents) in THF solvent (Scheme 1). The reaction took 4 hours at room temperature.[6] Using these conditions and after purification by column chromatography over silica (dichloromethane/ethylacetate) the (1′*R*)-(−)-1-(2′-hydroxy-1′-phenyl-ethyl)-3,4-dihydro-(1*H*)-pyridin-2-one **2** was obtained in 85% yield. Product **2** had satisfactory spectroscopic data.[7]

Unexpectedly, when the ^1H NMR of **2** was recorded after standing for 12 hours in $CDCl_3$, its transformation to the corresponding 3-phenyl-hexahydro-oxazolo[3,2-*a*]pyridin-5-one in a 15% yield was observed. It is well known that $CDCl_3$ normally contain traces of DCl and it was thought that this could explain the observed transformation.

Suitable crystals of **2** were obtained from an ether/*n*-hexane mixture and X-ray diffraction analysis was performed. Atom C-(4) is disordered over two sites (A and B); nevertheless, bond lengths C-(3)–C-(4A) and C-(3)–C-(4B), at 1.446 (16) and 1.380 (15), respectively, were consistent with a single bond, while the C-(5)–C-(6) distance of 1.298 (5) has double bond character. The C-(2)–O-(1) bond length of 1.232 (4) is characteristic of a carbonyl group[8] (Fig. 1).

In order to explore this transformation, we prepared a solution of **2** in $CHCl_3$ containing a catalytic amount of



Scheme 1.

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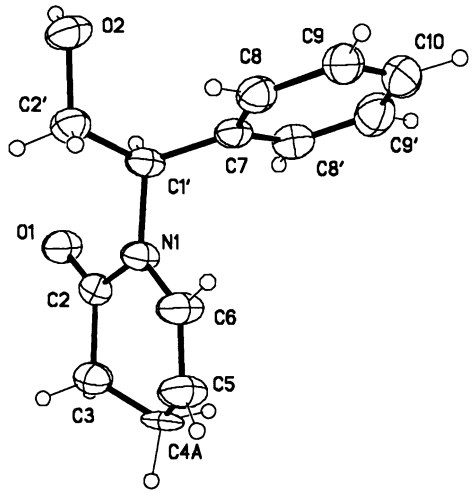
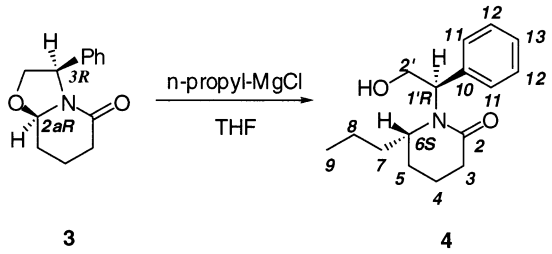


Figure 1. Crystal structure of **2**. Thermal ellipsoids are at 30% probability level. Disordered position for C-(4) was omitted for clarity.

dry HCl gas. This solution was stirred for 6 hours at 25°C and a single product was formed with $R_f = 0.76$ (R_f of **2** was 0.20 on SiO_2 in the same CH_2Cl_2/MeOH, 19:1 eluent). The solution was dried over anhydrous Na_2SO_4, filtered and the solvent removed in vacuo affording **3** in quantitative yield.[9] Both ^1H and ^{13}C NMR data of the crude reaction showed only one compound, in agreement with the single product observed by TLC analysis. Assignments in ^1H NMR were confirmed by extensive use of ^{13}C–^1H shift correlation experiments and the configuration of the new stereogenic centre C-(2a) in **3** was assigned by ^1H NMR 1D NOE and ROESY experiments, which showed that H-(3) and H-(2a) had a *cis* relationship; these results allowed us to assign the stereochemistry of **3** as *cis*-C-(3*R*)/C-(2a*R*) as shown in Fig. 2. However, this compound had identical spectral data with those reported by Husson[2c] for the *trans*-(3*R*,2a*S*)-(−)-3-phenyl-hexahydro-oxazolo[3,2-*a*]pyridin-5-one.[10]

These contradictions stimulated our interest and prompted us to carry out the synthesis of a coniine enantiomer, which is accepted as a standard for the demonstration of chiral methodology. The synthesis



3 4

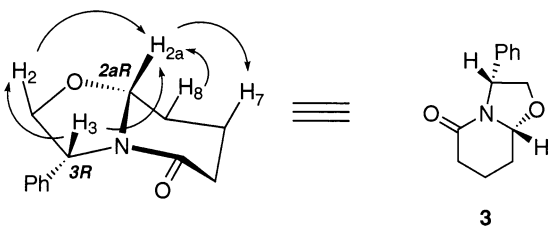
Scheme 2.

was performed in three steps from **3** affording (*S*)-(+)-coniine hydrochloride **6** exclusively in good yield.[1–3] The first step was the reaction of **3** with 3 equivalents of *n*-propylmagnesium chloride in THF;[11] the reaction was carried out at 0°C; and was complete after 6 hours. After purification by column chromatography over silica (dichloromethane/ethylacetate), (1′*R*,6*S*)-(+)-1-(2′-hydroxy-1′-phenyl-ethyl)-6-propyl-piperidin-2-one **4**[12] was afforded in 85% yield. The ^1H and ^{13}C NMR spectra of the crude reaction mixture of **4** showed that only one product had formed. Assignments in ^1H NMR were confirmed by the extensive use of ^{13}C–^1H shift correlation experiments (Scheme 2).

As shown in Scheme 3, the second step of the synthesis was the lithium aluminium hydride reduction of **4** which was completed under reflux in 1 hour, and afforded (2*R*,2′*S*)-(+)-2-phenyl-2-(2′-propyl-piperidin-1′-yl)-ethanol **5**[13] in 90% yield after purification by column chromatography over silica (*n*-hexane/ethylacetate). Assignments from the ^1H NMR spectrum of **5** were again confirmed by use of ^{13}C–^1H shift correlation experiments.

In the third step, **5** was subjected to hydrogenolysis in ethanolic solution, in the presence of 10% Pd-C/HCl, at 30°C over 48 hours, affording (2*S*)-(+)-coniine hydrochloride **6**[14] in a 90% yield.

This reaction sequence described for the synthesis of coniine indicates that in the first step, the oxazolo opening of **3** by *n*-propylmagnesium chloride proceeds with complete inversion[11] at C-(2a*R*) via an S_N2 mechanism. Such an interpretation is in agreement with the enantiomerically pure (*S*)-(+)-coniine **6** obtained.

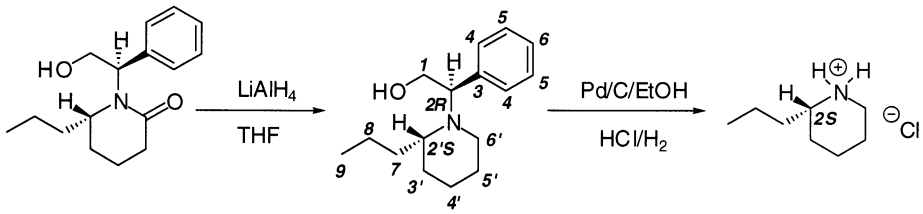


3

$J(H_{2a} - H_2) = 4.40$ Hz $J(H_{2a} - H_3) = 1.33$ Hz $J(H_{2a} - H_7) = 2.93$ Hz

$J(H_{2a} - H_8) = 8.80$ Hz $J(H_2 - H_3) = 8.07$ Hz

Figure 2. Selected NOE and ROESY of **3**.



4 5 6

Scheme 3.

2. Conclusion

A simplified method allowing the preparation of (1′*R*)-(−)-1-(2′-hydroxy-1′-phenyl-ethyl)-3,4-dihydro-(1*H*)pyridin-2-one **2** in 85% yield from enantiopure (1*H*)-pyridin-2-one **1** has been developed. The structure of **2** was confirmed by X-ray crystal study. A new and facile methodology for the synthesis of enantiopure (3*R*,2a*R*)-(−)-3-phenyl-hexahydro-oxazolo[3,2-*a*]pyridin-5-one **3** in quantitative yield from **2** is also presented.

Finally, (*S*)-(+)-coniine was efficiently prepared in five steps and 59% overall yield from **1**. These results have potential use in the total synthesis of this class of alkaloid, and are currently under investigation in our laboratory.

Acknowledgements

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4. Gnecco, D.; Marazano, C.; Enríquez, R. G.; Terán, J. L.; Sánchez, M.; Galindo, A. *Tetrahedron: Asymmetry* **1998**, *9*, 2027–2029.
5. The reduction of **1** with, PtO_2/H_2 afforded quantitatively the 1-(2-hydroxy-1-phenyl-ethyl)-piperidin-2-one, while with $LiAlH_4$ a complex mixture was obtained.
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7. Compound **2**. Crystallised from ether/*n*-hexane. $R_f=0.20$ (SiO_2, CH_2Cl_2/MeOH, 95/5); mp 76–78°C; $[\alpha]_D^{20}$ −49 (*c* 1.0, CH_2Cl_2). IR (KBr, cm^{-1}): 3450–3300, 2960, 1658; ^1H NMR (400 MHz): δ (ppm, $CDCl_3$, *J* Hz): 7.35–7.26 (ϕ-H, 5H, m); 6.02 (H-6, dt, 7.70, 1.47); 5.82 (H-1′, dd, 8.43, 5.13); 5.16 (H-5, dt, 8.08, 4.40); 4.17–3.99 (2H-2′, AB system, 8.43, 5.13); 2.62 (2H-3, td, 8.10, 4.80); 2.32 (2H-4, m). ^{13}C NMR: C-(2), 171.15; C-(7), 137.07; 2C-(8), 128.86; C-(10), 127.96; 2C-(9), 127.65; C-(6), 126.48; C-(5), 107.24; C-(2′), 62.77; C-(1′), 57.38; C-(3), 31.79; C-(4), 19.98.
8. Crystal structure of **2**. Colourless, irregular crystal, 0.34×0.18×0.10 mm^3, $C_{13}H_{15}NO_2$, orthorhombic, $P2_12_12_1$, $a=8.5603(8)$, $b=10.7338(13)$, $c=12.4368(16)$ Å, $Z=4$. Bruker P4 diffractometer using Mo Kα radiation, $T=298(2)$ K, 2827 reflections measured up to $2\theta=50°$, 2013 independent data ($R_{int}=3.56\%$) for 155 refined parameters. The structure was refined on the basis of non-absorption-corrected data, using standard methods[15] without restraints or constraints. Final *R* indices: $R_1=5.61\%$ for 1246 data having $F_0>4\sigma$ (F_0) and $wR_2=14.18\%$ for all data.
9. Compound **3**. Viscous oil (volatile in vacuo); $R_f=0.76$ (SiO_2, CH_2Cl_2/MeOH, 95/5); $[\alpha]_D^{20}$ −92 (*c* 1.0, CH_2Cl_2), [(lit.[2c] $[\alpha]_D^{20}$ −88 (*c* 0.6, CH_2Cl_2)]. IR (KBr, cm^{-1}): 3450–3400, 2954, 1660; ^1H NMR (400 MHz): δ (ppm, $CDCl_3$, *J* Hz): 7.33–7.25 (ϕH, 5H, m); 5.26 (H-3, dd, 8.07, 7.70); 5.00 (H-2a, dd, 4.77, 4.40); 4.48 (H-2, dd, 8.07,7.70); 3.74 (H-2, dd, 8.07, 7.70); 2.52 (H-6, dd, 18.33, 5.87); 2.37 (H-8, m); 2.31 (H-6, dd, 6.60, 5.13); 1.95 (H-8, m); 1.76 (H-7, m); 1.54 (H-7, m). ^{13}C NMR: C-(5), 169.07; C-(9), 139.64; 2C-(11), 128.87; C-(12), 127.67; 2C-(10), 126.18; C-(2a), 88.77; C-(2), 72.54; C-(3), 58.21; C-(6), 31.39; C-(8), 28.53; C-(7), 17.21.
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12. Compound **4**. Viscous oil; $R_f=0.25$ (Al_2O_3, CH_2Cl_2/MeOH, 98/2); $[\alpha]_D^{20}$ +21.0 (*c* 1.0, CH_2Cl_2). IR (KBr, cm^{-1}): 3550–3380, 2925, 1640; ^1H NMR (400 MHz): δ (ppm, $CDCl_3$, *J* Hz): 7.33–7.22 (ϕ-H, 5H, m); 5.24 (H-1′, dd, 7.70, 4.77); 4.21 (2H-2′, AB, 24.56, 4.77); 3.21 (H-6, m); 2.56 (2H-3, dd, 8.43, 5.87); 1.85 (H-4, m); 1.74 (H-4, m); 1.55 (2H-5, m); 1.52 (H-7, m); 1.28 (H-8, m); 1.25 (H-7, m); 1.10 (H-8, m); 0.83 (3H-9, t, 7.33). ^{13}C NMR: C-(2), 172.68; C-(10), 137.38; 2C-(11), 128.58; 2C-(12),

127.80; C-(13), 127.56; C-(2′), 64.0; C-(1′), 63.37; C-(6), 56.42; C-(3), 35.39; C-(4), 31.83; C-(7), 25.73; C-(8), 19.54; C-(5), 16.24; C-(9), 13.91.

13. Compound **5**. Viscous oil; $R_f = 0.63$ (Al_2O_3, CH_2Cl_2/MeOH, 98/2). $[\alpha]_D^{20}$ +17 (*c* 1.0, CH_2Cl_2). IR (KBr, cm^{-1}): 3650–3200, 2930, 1061; ^1H NMR (400 MHz): δ (ppm, $CDCl_3$, *J* Hz): 7.35–7.28 (ϕ-H, 5H, m); 3.88 (H-2, dd, 6.23, 5.87); 3.77 (2H-1, AB, 30.08, 6.60); 2.95 (H-2′, m); 2.62 (2H-6′, AB, 44.76, 10.26); 1.85 (H-7′, m, 3.30); 1.68 (H-3′, m); 1.56–1.48 (H-7′, 2H-5′, 2H-4′, m); 1.42 (H-3′, m); 1.25 (2H-8′, m); 0.86 (3H-9′, t, 7.33). ^{13}C NMR: C-(3), 135.20; C-(4), 128.81; C-(5), 128.50; C-(6), 127.73; C-(2), 67.53; C-(1), 62.09; C-(2′), 57.58; C-(6′), 43.46; C-(5′), 27.28; C-(7′), 25.42; C-(4′), 20.34; C-(8′), 20.33; C-(3′), 19.50; C-(9′), 14.38.
14. (*S*)-(+)-Coniine·6HCl. $[\alpha]_D^{20}$ +6.3 (*c* 1.0, EtOH), [(lit.[11] $[\alpha]_D^{26}$ +6.2 (*c* 0.40 EtOH)]. Mp 212–214°C, [(lit.[11] mp 219–221°C)]. IR (KBr, cm^{-1}): 2950, 2848, 1587, 1454, 1387; ^1H NMR (400 MHz): δ (ppm, $CDCl_3$, *J* Hz): 3.45 (H-6, dd, 12.83, 3.30); 2.94 (H-2, m); 2.83 (H-6, td, 12.83, 3.30); 2.01–1.38 (2H-7, 2H-3, 2H-4, 2H-5, 2H-8, m); 0.95 (3H-9, t, 7.33). ^{13}C NMR: C-(2), 57.18; C-(6), 44.79; C-(7), 35.39; C-(3), 28.16; C-(5), 22.46; C-(4), 22.22; C-(8), 18.61; C-(9), 13.78.
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