Chiral Nonracemic Synthesis and Reactivity of Two New Endocyclic Enamines in the Phenyloxazolopiperidine Series

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As part of our continuing work on bicyclic chiral nonracemic oxazolopiperidines, we became interested in the synthesis of analogues of building block **1**,[1] viz. the α-cyano-1,4-dihydropyridine (**2**) and the simple oxazolopiperidine (**3**) (Figure 1).

On the basis of the versatility of the 1,4-dihydropyridine equivalent **1**, for the asymmetric synthesis of a wide range of substituted piperidines,[2] we sought to elaborate new systems which could afford a larger scope of syntheses targeting additionnal substituents or functions at all the piperidine ring positions.

While compound **3** should react as a simple enamine, compound **2** would in fact combine both the reactivity of an α-cyanoenamine at the C-2, C-3, and C-4 carbon atoms and that of a simple enamine at the C-5 and C-6 centers. This postulate led us to synthesize these two building blocks and to examine their reactivity in a preliminary study.

A large amount of work has been devoted to the chemistry of α-cyanoenamines due to their high reactivity[3] and captodative properties.[4] Cyclic α-cyanoenamines of type **2** were recently investigated. While Meyers[5] obtained compound **4** in a four-step synthesis starting from the corresponding lactam, Grierson and Fowler prepared compounds **5**[6] and the racemic **6**[7] by an intramolecular Diels−Alder reaction (IMDA) of a 2-cyano-*N*-alkylazadiene in a five- or three-step procedure, respectively (Figure 1). Cyclic cyanoenamines similar to **4** and **5** were recently investigated and interestingly led to the introduction of electrophiles at the C-4 carbon atom.[5,7a] However, none of these building blocks permits deprotection of the piperidine nitrogen for further *N*-substitution or heterocyclization. Consequently, we were

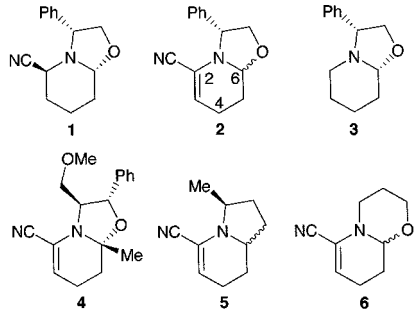
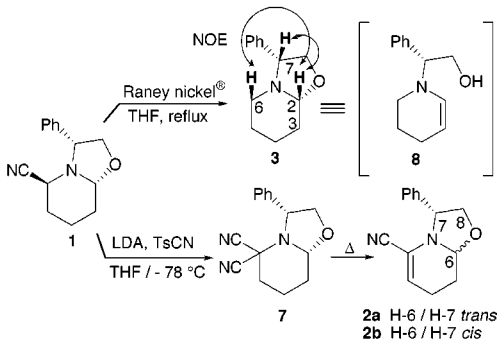


Figure 1.

Scheme 1



interested in the preparation of the analogue in the phenylglycinol series which allows elimination of the chiral appendage.

Taking advantage of synthon **1**, its lithiated anion was reacted with tosyl cyanide to afford dicyano derivative **7** in 67% yield (Scheme 1). Several attempts using conventional methods to remove one of the two cyano groups were unsuccessful. Finally, thermolysis of derivative **7** as described for *N*-methyl-2,2-dicyanopiperidine[8] gave a mixture of two compounds in moderate yield. A careful separation by column chromatography allowed the obtention of pure cyanoenamine **2a** as the major product accompanied by the epimeric oxazolidine **2b**, epimeric at position 6.

The structures of the major (**2a**) and minor (**2b**) compounds were deduced from the ^{1}H NMR spectra. A correlation between H-6 and the axial protons H-7 and H-8 was observed in the NOESY spectrum of **2b**. Moreover, the chemical shift and the signal pattern of H-6 were characteristic of equatorial (**2a**, 4.95, dd, $J = 7$ and 3.5 Hz) or axial (**2b**, 4.81, dd, $J = 10$ and 2.5 Hz) orientation as already described for similar derivatives.[9]

A simple preparation of **3** as a single diastereomer was achieved in good yield (79%) by reductive decyanation of **1**, using a large excess of Raney nickel in refluxing THF (Scheme 1). In comparison with classical methods, such as the use of $NaBH_4$[10] or Na in liquid ammonia,[11] this new process permitted a very mild reductive elimination

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of the cyano group while the oxazolidine ring remained unchanged.

Structure **3** of the new phenyloxazolopiperidine[12] obtained as a single diastereomer was ascertained on the basis of NMR. The correlations of H-2 with the axial protons H-6 and H-7 in the 2D NOESY experiment established the relative configuration of C-2 in respect to H-7.[13] Moreover, the coupling constant $J_{H-2/H-3ax} = 9$ Hz was in agreement with the axial position of H-2.[14] Finally, the chemical shift at 2.85 ppm of the equatorial proton H-6 was characteristic of the thermodynamically more stable structure **3** in which both the nitrogen lone pair and the phenyl ring contribute to the strong deshielding.

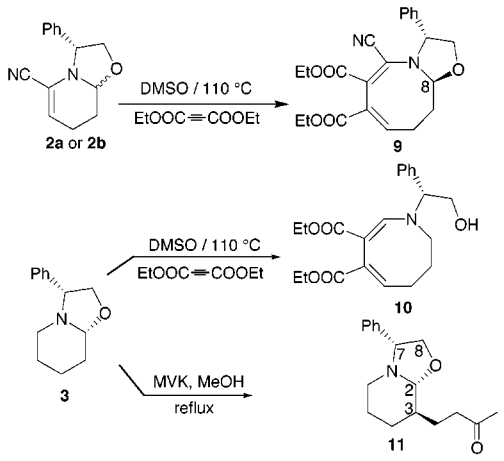
Unsubstituted endocyclic enamines are very unstable compounds. For instance, 1,2,3,4-tetrahydropyridine does not exist as such, while the extremely reactive parent imine is only isolated as a dimeric or trimeric form.[15] Several publications[16] reported attempts to overcome this difficulty since six-membered cyclic enamines in their monomeric form would be of great interest in organic synthesis.[17] In this context, the achiral *N*-(phenylmethylsilyl)-1,2,3,4-tetrahydropyridine was recently prepared.[18]

In all respects, compound **3** constitutes a new stable and chiral synthetic equivalent of 1,2,3,4-tetrahydropyridine. Indeed, the enamine functionality (**8**) could be revealed through equilibration with **3** in protic medium or by heating (Scheme 1). Furthermore, the chiral auxiliary can be easily removed by hydrogenolysis at the end of the synthesis.

The access to these new related enamines **2** and **3** leads us to report in this paper our first results concerning their reactivity. Reaction of an enamine with diethyl acetylenedicarboxylate is a well-known procedure for construction of functionalized 1,2,3,4-tetrahydroazocines according to a [2 + 2] thermal cycloaddition.[19] When heated in a polar aprotic solvent, the electron-rich carbon−carbon double bond of the cyclic enamine reacts with the electron-deficient alkyne to give an intermediate cyclobutene. Spontaneous ring opening of the unstable cyclobutene affords ring-enlarged compounds according to a well-investigated mechanism.[20]

We chose this reaction not only as an efficient method to compare the reactivity of enamines **2a**, **2b**, and **3** with that of compound **1**[21] but also because there has been increasing interest recently in the synthesis of eight-membered ring systems such as azocines. This diverse

Scheme 2



class of compounds often possesses biological activity[22] and has been widely used in synthetic chemistry.[23] It is of note that this type of medium size ring nitrogen heterocycle is not easily accessible and is interesting for the design of conformationally restricted peptides.[24]

α-Cyanoenamine **2a** appeared to be a very reactive compound. Treatment with diethyl acetylenedicarboxylate in DMSO at 110 °C afforded in 30 min (48 h for compound **1**[21]) a mixture of two diastereomeric cyanotetrahydroazocines. The major compound was isolated in 82% yield and characterized as **9** (Scheme 2). The configuration at C-8 was assigned on the basis of the NMR data we reported previously for analogues.[21] This reaction constitutes a very straightforward procedure for the synthesis of chiral nonracemic tetrahydroazocines possessing four different functionalities. α-Cyanoenamine **2b** afforded **9** as the major compound under the same reaction conditions.

Another new tetrahydroazocine, **10**, was obtained in excellent yield simply by heating **3** with diethyl acetylenedicarboxylate in DMSO for 3 h (Scheme 2).

In contrast to the bicyclic azocine **9**, this new compound was shown by NMR in various solvents ($CDCl_3$, CD_3OD, DMSO-d_6) to be a 6:4 mixture of two conformers. Indeed, two singlets for the signal of H-2 at 7.77 and 7.90 ppm were observed while the ^{13}C NMR spectrum showed two signals for each carbon atom. Heating a DMSO-d_6 solution of **10** to 70 °C led to the coalescence of those signals in the ^1H NMR and the ^{13}C NMR spectra.

It is well known[25] that the azocine ring possesses mostly a crown conformation, but there are also boat-chair, chair-chair, and boat-boat conformations. In particular, this was not found in the related bicyclic derivative **9** which combines a tetrahydoazocine core and a fused five-membered oxazolidine ring, assigning a conformationally restricted framework.

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To finalize this preliminary study of the use of building block **3** as a latent enamine, we investigated its reaction with Michael acceptors such as methyl vinyl ketone (MVK) to provide β-alkylated chiral nonracemic piperidines or chiral annelated quinolones according to a previously reported method.[26] Reaction of **3** in MeOH with a stoichiometric amount of MVK gave only piperidine **11** (63% yield). The axial relationship between H-2 and H-3 ($J_{H-2/H-3} = 9$ Hz) (Scheme 2) was in favor of the configuration 2*R*,3*R*. This reaction could constitute a very simple preparation with excellent stereocontrol of β-substituted piperidines. Furthermore, opening of the oxazolidine ring is reported to afford stereocontrolled formation of C-2,C-3 disubstituted piperidines.[9]

In summary, we have described an easy access to compounds **2** and **3** which were found to be powerful enamines by [2 + 2] cycloaddition reactions with diethyl acetylenedicarboxylate. A further example of the enamine reactivity of **3** was furnished by a stereocontrolled β-alkylation.

We are continuing our exploration of the synthetic potential of these two useful building blocks toward asymmetric syntheses.

Experimental Section

General Methods. ^{1}H and ^{13}C NMR spectra of $CDCl_3$ solutions were recorded at 300 and 75 MHz (Bruker, AC-300), respectively. Mass spectra (low resolution) were obtained in the chemical ionization mode with NH_3 on a Nermag/Sidar V 2.3. Fourier transform infrared absorption spectra were recorded on a Perkin-Elmer 1600 spectrophotometer. Optical rotations were determined at room temperature with a Perkin-Elmer 141 MC polarimeter and are referenced to the D-line of sodium. Concentrations were performed under reduced pressure with a Büchi rotary evaporator. Melting points were measured with a Leica Galen III apparatus. Starting materials and solvents were purchased from commercial sources. Tetrahydrofuran was dried via distillation from sodium−benzophenone ketyl. Flash chromatography was carried out on silica gel (20−45 μm).

2,2-Dicyanophenyloxazolopiperidine (7). To a stirred solution of diisopropylamine (4.05 mL, 28.9 mmol) in anhydrous THF (10 mL) at 0 °C was added *n*-butyllithium (2.5 M in hexanes, 11.6 mL, 28.9 mmol) under an argon atmosphere. The mixture was stirred at 0 °C for 30 min and then cooled at −78 °C for 20 min, at which time 2-cyanophenyloxazolopiperidine **1** (2.19 g, 9.6 mmol) in anhydrous THF (40 mL) was added dropwise over 7 min. The solution was stirred at −78 °C for 20 min, and a solution of tosyl cyanide (3.34 g, 18.4 mmol) in anhydrous THF (30 mL) was added dropwise. The mixture was then stirred for 4 h at −78 °C and quenched with a saturated aqueous solution of NH_4Cl. The aqueous phase was extracted (three times) with CH_2Cl_2, and the combined organic phases were dried over anhydrous Na_2SO_4 and concentrated. Flash chromatography of the residue (80:20 cyclohexanes−ether) provided 1.56 g (67%) of dicyano compound **7**. Colorless crystals were obtained from cyclohexanes−ether (80:20): mp = 134−135 °C; $[\alpha]^{20}_D$ = −151 (*c* 1, $CHCl_3$); ^{1}H NMR δ 1.60−1.80 (m, 2H), 2.00−2.30 (m, 3H), 2.33−2.38 (m, 1H), 3.90 (dd, *J* = 7, 8.5 Hz, 1H, H-8), 4.05 (dd, *J* = 7, 8.5 Hz, 1H, H-7), 4.09 (dd, *J* = 3, 10.5 Hz, 1H, H-6), 4.33 (t, *J* = 8.5 Hz, 1H, H-8), 7.40−7.55 (m, 5H); ^{13}C NMR δ 19.1, 28.6, 36.4, 52.1, 64.2, 73.7, 90.4, 111.0, 112.3, 128.4, 128.8, 129.1, 137.4; IR (film) 2362, 2344 cm^{-1}; MS *m*/*z* 254 (M + 1)$^+$. Anal. Calcd for $C_{15}H_{15}N_3O$: C, 71.13; H, 5.97; N, 16.59. Found: C, 70.96; H, 6.11; N, 16.41.

α-Cyanoenamines 2a and 2b. Compound **7** (500 mg, 1.97 mmol) was heated at 170−190 °C under reduced pressure (20 mmHg) for 5 h. The ratio of the different compounds in the crude residue (452 mg) was estimated by ^{1}H NMR: **2a** (48%), **2b** (16%), **7** (36%). Purification by flash chromatography over silica gel (85:15 cyclohexanes−ethyl ether) gave 61 mg (35%) of α-cyanoenamine **2a**, 150 mg (14%) of α-cyanoenamine **2b**, and 80 mg of starting material **7**. **2a:** mp = 100−104 °C (MeOH−ether); $[\alpha]^{20}_D$ = −297 (*c* 1, $CHCl_3$); ^{1}H NMR δ 1.70−1.78 (m, 1H, H-5), 2.26−2.35 (m, 3H), 4.10 (dd, *J* = 1.5, 8.5 Hz, 1H, H-8), 4.30 (dd, *J* = 6, 8.5 Hz, 1H, H-8), 4.72 (d, *J* = 6 Hz, 1H, H-7), 4.81 (dd, *J* = 2.5, 10 Hz, 1H, H-6), 5.32 (brs, 1H, H-3), 7.32−7.41 (m, 5H); ^{13}C NMR δ 21.2, 26.0, 61.6, 73.7, 87.4, 114.0, 115.1, 115.7, 127.7, 128.0, 128.6, 141.0; IR (film) 2223, 1669, 1608 cm^{-1}; MS *m*/*z* 227 (M + 1)$^+$. Anal. Calcd for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.21; H, 6.39; N, 12.21. **2b:** $[\alpha]^{20}_D$ = −245 (*c* 1, $CHCl_3$); ^{1}H NMR δ 1.70−1.80 (m, 1H), 2.05−2.38 (m, 3H), 3.82 (dd, *J* = 6.5, 8.5 Hz, 1H, H-8), 4.35 (dd, *J* = 6.5, 8.5 Hz, 1H, H-8), 4.65 (t, *J* = 6.5 Hz, 1H, H-7), 4.95 (dd, *J* = 3.5, 7 Hz, 1H, H-6), 5.67 (t, *J* = 4.5 Hz, 1H, H-3), 7.28−7.48 (m, 5H); ^{13}C NMR δ 19.0, 24.7, 64.5, 72.2, 87.8, 115.6, 118.9, 119.5, 126.7, 127.9, 128.6, 139.5; IR (film) 2223, 1670, 1610 cm^{-1}; MS *m*/*z* 227 (M + 1)$^+$; HRMS (CI, CH_4) *m*/*z* (M + 1)$^+$ calcd for $C_{14}H_{15}N_2O$ 227.1184, found 227.1177.

Phenyloxazolopiperidine (3). Compound **1** (5 g, 2.19 mmol) was dissolved in THF (100 mL). Raney nickel (25 g, W-2, 50% slurry in water) was added and the suspension refluxed for 20 h. The reaction mixture was then filtered on Celite with MeOH (400 mL). The filtrate was dried over anhydrous Na_2SO_4 and concentrated under vacuum to give an oily residue (4.35 g). Compound **3** was isolated after flash chromatography on silica gel (90:10 cyclohexanes−ether) and crystallized from cyclohexane (colorless crystals, 3.5 g, 79%): mp = 38−41 °C; $[\alpha]^{20}_D$ = −103 (*c* 1, $CHCl_3$); ^{1}H NMR δ 1.30−1.45 (m, 1H, H-4), 1.48−1.61 (m, 3H), 1.85−1.89 (m, 1H), 1.97−2.05 (m, 2H), 2.85 (br d, *J* = 10.5 Hz, 1H, H-6), 3.53 (t, *J* = 8 Hz, 1H, H-7), 3.65 (t, *J* = 8 Hz, 1H, H-8), 3.68 (dt, *J* = 3, 9 Hz, 1H, H-2), 4.17 (t, *J* = 8 Hz, 1H, H-8), 7.26−7.40 (m, 5H); ^{13}C NMR δ 22.5, 24.8, 30.3, 47.8, 67.1, 72.9, 94.6, 127.6, 127.7, 128.4, 138.9; MS *m*/*z* 204 (M + 1)$^+$. Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.75; H, 8.15; N, 6.96.

2-Cyanotetrahydroazocine (9). Diethyl acetylenedicarboxylate (0.1 mL, 106 mg, 0.62 mmol) was added to a solution of α-cyanoenamine **2a** (100 mg, 0.44 mmol) in dry DMSO (2 mL). The reaction mixture was heated at 110 °C under an argon atmosphere for 30 min. After cooling, the reaction mixture was diluted with water (10 mL) and extracted with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4 and evaporated to dryness under reduced pressure. Purification by flash chromatography (1:1 cyclohexanes−ether) of the crude residue furnished the major diastereomer as an oily product (144 mg, 82%): $[\alpha]^{20}_D$ = +21 (*c* 1, $CHCl_3$); ^{1}H NMR δ 1.0−1.5 (m, 6H), 1.7−2.0 (m, 2H), 2.5−2.8 (m, 2H), 3.82 (dd, *J* = 3, 9 Hz, 1H), 3.9−4.4 (m, 5H), 5.22 (dd, *J* = 3, 7 Hz, 1H), 5.92 (dd, *J* = 3, 9 Hz, 1H), 6.82 (dd, *J* = 8, 9 Hz, 1H), 7.1−7.5 (m, 5H); ^{13}C NMR δ 13.7, 13.8, 23.9, 24.8, 61.0, 61.5, 66.4, 71.3, 90.2, 113.4, 113.6, 126.1, 127.9, 128.7, 131.3, 140.8, 140.9, 165.2, 165.5; IR (film) 2200, 1735, 1610, 1247 cm^{-1}; MS *m*/*z* 397 (M + 1)$^+$.

Tetrahydroazocine (10). To a solution of phenyloxazolopiperidine **3** (1 g, 4.9 mmol) in dry DMSO (10 mL) was added diethyl acetylenedicarboxylate (1.02 mL, 1.09 g, 6.4 mmol), and the solution was stirred under an argon atmosphere at 110 °C for 3 h. After cooling, the mixture was diluted with CH_2Cl_2 and washed 10 times with water. After drying over anhydrous Na_2SO_4 and concentration under vacuum, the crude residue (2.6 g) was purified by flash chromatography over silica gel (97:3 CH_2Cl_2−MeOH) to afford compound **10** (1.71 g, 93%), as an orange oil: $[\alpha]^{20}_D$ = −20 (*c* 1, $CHCl_3$); ^{1}H NMR (mixture of isomers) δ 0.8−1.1 (m, 2H), 1.1−1.2 (m, 6H), 1.24−1.33 (m, 8H), 2.0−2.4 (m, 4H), 2.4−2.6 (m, 2H), 2.78 (dd, *J* = 3, 14 Hz, 1H), 2.90 (dd, *J* = 3, 14 Hz, 1H), 3.25 (brs, 1H), 3.83 (dt, *J* = 3, 14 Hz, 1H), 3.9−4.2 (m, 12H), 4.2−4.4 (m, 2H), 6.2−6.3 (m, 2H), 7.26−7.40 (m, 10H), 7.77 (s, 1H), 7.90 (s, 1H); ^{1}H NMR (DMSO-d_6, 70 °C) δ 1.02 (t, *J* = 7 Hz, 3H), 1.11 (t, *J* = 7 Hz, 3H), 1.15 (m, 1H), 2.26 (brm, 2H), 3.2−3.6 (m, 5H), 3.87 (m, 4H), 4.01 (q, *J* = 7 Hz, 2H), 4.25 (t, *J* = 6.5 Hz, 1H), 6.04 (t, *J* = 8.5 Hz, 1H), 7.1−7.3 (m, 5H), 7.59 (s, 1H); ^{13}C NMR (mixture of isomers) δ 14.1, 17.6, 18.6, 24.9, 25.0, 42.7, 45.1, 59.7, 60.4, 60.5, 61.9, 70.9, 71.9, 92.7, 93.1, 127.4, 127.6, 128.2, 128.6, 133.9, 134.4, 134.6, 136.3, 137.1, 149.7, 150.0, 169.5, 169.6; ^{13}C NMR (DMSO-d_6, 70 °C) δ 14.3, 14.5, 18.2, 25.1, 44.9, 59.0, 59.9, 62.2, 71.3, 93.0, 128.0,

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128.1, 128.8, 133.9, 134.9, 138.6, 149.5, 168.3, 168.6; IR (film) 3400, 1674, 1579, 1252 cm^{-1}; MS *m*/*z* 374 $(M + 1)^+$; HRMS (CI, CH_4) *m*/*z* $(M + 1)^+$ calcd for $C_{21}H_{28}NO_5$ 374.1967, found 374.1974.

Piperidine (11). A solution of phenyloxazolopiperidine **3** (225 mg, 1.1 mmol) and MVK (77 mg, 0.09 mL, 1.1 mmol) in methanol was refluxed for 4 h. Then the reaction mixture was concentrated and the crude material submitted to a flash chromatography over silica gel (85:15 cyclohexanes−ether) affording **11** as a colorless oil (191 mg, 63%): $[\alpha]^{20}_D = -80$ (*c* 1, $CHCl_3$); ^1H NMR δ 0.92−1.10 (m, 1H), 1.45−1.65 (m, 4H), 1.70−2.05 (m, 3H), 2.15 (s, 3H), 2.45−2.70 (m, 2H), 2.81 (b d, $J = 11$ Hz, 1H), 3.37 (d, $J = 9$ Hz, 1H), 3.48 (t, $J = 8$ Hz), 3.59 (t, $J = 8$ Hz, 1H), 4.13 (t, $J = 8$ Hz, 1H), 7.25−7.45 (m, 5H); ^{13}C NMR δ 24.8, 26.5, 29.3, 29.8, 40.5, 41.6, 47.5, 66.9, 72.9, 99.2, 127.6, 128.4, 138.9, 209.2; IR (film) 1743 cm^{-1}; MS *m*/*z* 274 $(M + 1)^+$; HRMS (CI, CH_4) *m*/*z* $(M + 1)^+$ calcd for $C_{17}H_{23}NO_2$ 273.1729, found 273.1732.

Supporting Information Available: Supporting Information Available: ^1H NMR and ^{13}C NMR spectra for all compounds, 2D-experiments ($^1H-^1H$ and/or $^{13}C-^1H$) for **2a**, **2b**, **3**, and **7** and (NOESY) for **2b** and **3**, and ^1H and ^{13}C NMR spectra at high temperature for **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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