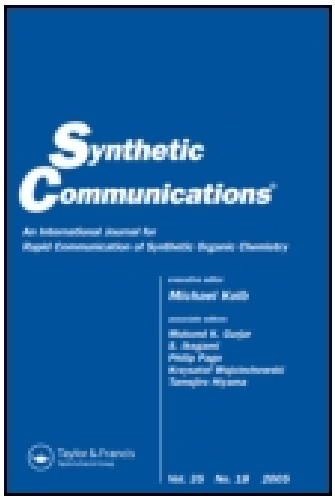

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SYNTHESIS AND REACTIVITY OF ENDOCYCLIC α-CYANOENAMINES IN THE PHENYLOXAZOLOPIPERIDINE SERIES

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SYNTHESIS AND REACTIVITY OF ENDOCYCLIC α-CYANOENAMINES IN THE PHENYLOXAZOLOPIPERIDINE SERIES

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ABSTRACT

Using the capto-dative character of piperidine building block **1**, the diastereomeric α-cyanoenamines **2a** and **2b** accompanied by dimer **5** were prepared through a SET pathway in a one-step procedure. Adjustment of the reaction conditions afforded either **2a** or **2b** as the major constituent. γ-Alkylation of **2b** with benzyl bromide proceeded smoothly.

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The development of general synthetic methods involving chiral building units have attracted increasing attention in the recent years. In connection with our methodology directed towards the asymmetric syntheses of piperidine alkaloids, we have been engaged in the preparation of chiral non-racemic building blocks related to **1**. As a result various molecules have been elaborated through the introduction of several substituents at the $\alpha,\alpha',\beta,\beta'$ positions relative to the tertiary nitrogen atom of **1**,[1] which may clearly evidence the chemical potential of this compound.

To explore a new aspect of the versatile building block **1**, we were interested in the substitution at the γ-position relative to the nitrogen atom. This novel approach may involve a derivatization into an α-cyanoenamine **2a** or **2b** (Figure 1). Indeed, compounds **2a** and **2b** can be considered as precursors of homoenolates, a series of synthetic intermediates that have attracted much attention in virtue of their useful activities.[2] In this context, endocyclic enamines have recently been the subject of synthetic approaches.[3] The chiral non-racemic endocyclic enamines **2a** (7,8-dihydro-3-phenyl-3*R*-[3α,8aβ]-5*H*-oxazolo[3,2a]pyridine-5-carbonitrile) and **2b** (7,8-dihydro-3-phenyl-3*R*-[3α,8aα]-5*H*-oxazolo[3,2a]pyridine-5-carbonitrile) have already been synthesized[4] in our hands with modest yields through cyanation of **1** followed by thermic HCN elimination. The high enamine reactivity of both compounds **2a** and **2b** was revealed by the [2 + 2] cycloaddition reaction with diethyl acetylendicarboxylate.[4]

In this paper we wish to describe a new access to α-cyanoenamines **2a** and **2b** as well as their reactivity in γ-alkylation reactions.

We reasoned that α-cyanoenamine **2a** or **2b** could be obtained in a one-pot oxidation procedure through the lithiated anion **3**. Since O_2 oxidation[5] of **3** afforded lactam **4** in 46% yield, we thought to perform the preparation of **2a** by submitting a 2-substituted selenium derivative of **1** to an oxidative elimination. In fact, treatment of **3** with phenylselenium bromide in oxygen-free conditions yielded directly α-cyanoenamine **2a** and a new compound (**5**), in addition to the recovered starting material **1** (Scheme 1).

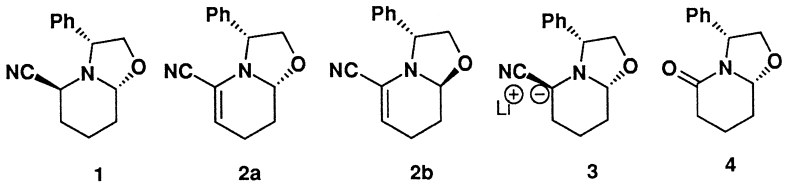

Figure 1.

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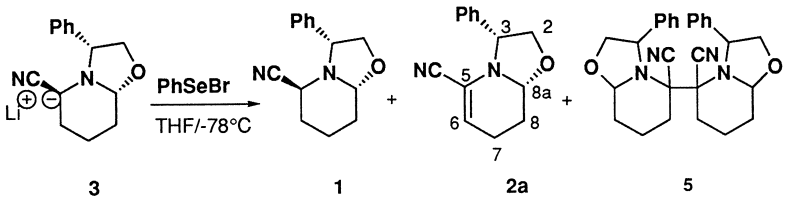

3 1 2a 5

Scheme 1.

The dimeric structure of **5** was established by mass- and NMR-spectroscopies. Indeed, the mass spectrum obtained by chemical ionization revealed the molecular peak at m/z 455 $(M+1)^+$ accompanied by a major fragment at m/z 401 $(M+1-54)^+$, due to the elimination of two molecules of HCN. The ^{13}C-NMR spectrum which differs mostly from the spectrum of **1** by the presence of a quaternary carbon at 64.1 ppm and by the deshielded resonance of the CN group (119.5 ppm versus 116.0 ppm), confirmed the symmetrical feature of **5** and the newly created carbon-carbon bond at C-5.

The oxidative dimerization reaction leading to the obtention of **5** was reminiscent of the well known dimerization of carbanions through a radical process.[6] The radical formation involves a single electron transfer (SET)[7] and is particularly well documented for the treatment of carbanions with polyhaloalkanes or other donors of positive halogen.[8] Very recently, Gawley[9] examined the reactions of unstabilized α-aminoorganolithiums derived from pyrrolidines and piperidines with electrophiles and reported a competition between electrophilic substitution reactions and single electron transfer reactions. It was suggested that SET is operative when the lithiated anion is easily oxidized by the electrophile, depending on the difference in redox potentials. This led us to take into account for the first time in our study the capto-dative character of **1**. The capto-dative concept was formulated by Viehe[10] as the result of electron-donating (dative) and electron-withdrawing (capto) substituents giving easily access to stabilized radicals.[11] The cyano/dialkylamino pair appears to be the most effective combination.[12] It is now well established that capto-dative anions are destabilized by electron-donating substituents such as amino groups and consequently oxidize rapidly into the more stable capto-dative radical.[10] The relative stability of capto-dative radicals was shown to favor radical reaction at low energy activation such as dimerization.[13] Thus, anion **3** would generate a capto-dative radical **6** leading to the dihydrodimer **5** while **2a** could result of a disproportionation of the radical (Scheme 2). Many such dimerization and disproportionation reactions of α-amino nitrile

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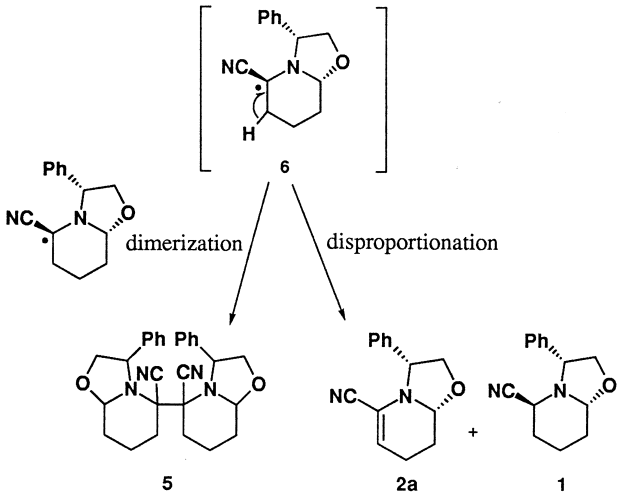


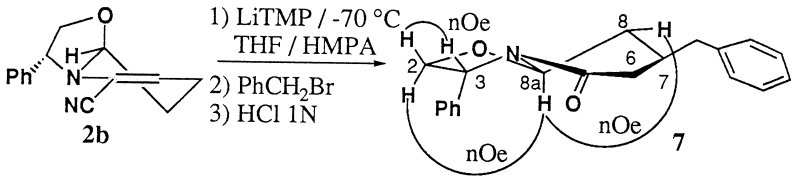
Scheme 2.

radicals have already been reported.[14] A recent study of the kinetics of thermolysis concerning capto-dative trimethylsilyl cyanohydrin radicals demonstrated a simultaneous disproportionation and dimerization.[15] Although the dimerization occurs mostly 10–50 times faster than disproportionation, this latter process is favored by steric effects and by the presence of vicinal hydrogens leading to β-elimination.[16] In our case, the three compounds of the reaction, **1**, **2a**, and **5** can be considered as the result of a simultaneous disproportionation and dimerization mechanism of radical **6** (Scheme 2). Since the reversible dimerization does not proceed with stereospecificity,[17] the relative stereochemistry of the carbon centers in dimer **5** is not ascertained.

In the light of the mechanism we repeated the reaction with iodine, a classical reagent for the oxidation of capto-dative anions.[6,10] In the presence of an equivalent of iodine compound **3** afforded in 5 min a mixture of **1** (25%), **2a** (25%), and **5** (25%). Other agents (tosyl chloride, ICN, NBS, NIS, benzoylperoxide) led to the same yield of dimer **5** and to the additional formation of α-cyanoenamine **2b**. In contrast, the yield of **2a** was highly dependent of the reaction conditions and oxidation agents. For instance, when the reaction was conducted in the presence of air, the major isolated product was the previously described lactam **4**. The best conditions for the obtention of **2a** were a molar solution and a short reaction time, while a longer reaction time afforded, in addition, the stereomeric α-cyanoenamine **2b** as a minor compound.

The difficulties of the purification resulting from the simultaneous formation of **1**, **2a**, **2b**, and **5** were solved by treating the reaction mixture with $AgBF_4$. We reasoned that the silver salt would remove the more labile cyano group borne by compounds **1** and **5** to yield water soluble salts, while α-cyanoenamines **2a** and **2b** would not react in this process. Treatment of the reaction mixture with $AgBF_4$ followed by extraction with water/CH_2Cl_2 provided exclusively the thermodynamically more stable **2b** (H-3/H-8a *trans*) (20%).

As previously mentioned, **2a** and **2b** were ideal substrates for γ-alkylation. Following Meyers's methodology,[3a,3d,18] the metalation of **2b** was carried out with LiTMP in THF/HMPA at −70°C. Addition of benzyl bromide followed by hydrolysis afforded the β-alkylated lactam **7** in 50% yield as a single diastereomer (Scheme 3).



Scheme 3.

The equatorial position of the benzyl chain C-7 was deduced from the ^{1}H NMR spectrum. Indeed, while the signal of H-7 showed a complex multiplet, a carefull NMR study including 2D experiments revealed the axial position of H-7 through the large coupling constants exhibited by the signals of the axial protons H-6 at 2.09 ppm (dd, J gem = 17 Hz, $J_{\text{H-6/H-7}} = 12$ Hz) and H-8 at 1.31 ppm (ddd, $J_{\text{gem}} = 12.5$ Hz, $J_{\text{H-8/H-7}} = 10$ Hz, $J_{\text{H-8/H-8a}} = 9.5$ Hz). In addition, the large coupling constant between H-8 axial and H-8a was in favor of the axial position of H-8a. The pseudo-chair conformation as depicted in Scheme 3 was deduced from nOe-difference experiments and was in good agreement with the stereoselectivity of the alkylation as previously reported.[3a] The same procedure applied to α-cyanoenamine **2a** failed to give an alkylated derivative and yielded the unsubstituted lactam **4** after hydrolysis.

Further studies are in progress in order to reach the isobenzomorphan skeleton[19] by the same alkylation procedure using a methoxy activated benzyl group in a Mannich type reaction with the C-8a iminium functionality.

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In summary we have described a very easy access to endocyclic chiral non-racemic α-cyanoenamines. Starting from building block **1** obtained in 85% yield by reacting glutaraldehyde and (*R*)-(-)-phenylglycinol in the presence of KCN,[20] the one-pot procedure consisting in metalation and iodine oxidation led to α-cyanoenamine **2a**, and dimer **5** in addition to the starting material. Further treatment with $AgBF_4$ afforded exclusively α-cyanoenamine **2b**. The modest yield of the reaction is counterbalanced by the simplicity and the versatility of the procedure.

EXPERIMENTAL

7,8-Dihydro-3-phenyl-3*R*-[3α,8aβ]-5*H*-oxazolo[3,2a]-pyridine-5-carbonitrile (2a)

To a solution of diisopropylamine (1.47 mL, 9.6 mmol) in 5 mL of dry tetrahydrofuran at 0°C was added *n*-butyllithium (3.9 mL, 9.6 mmol, 2.5 M in hexanes) under an argon atmosphere. The mixture was stirred for 20 min at 0°C and then cooled to −78°C. Compound **1** (1 g, 4.38 mmol) in 15 mL of dry tetrahydrofuran was added dropwise and the reaction mixture was stirred for 20 min. A solution of iodine in dry THF was transferred *via* canula into the mixture that was stirred for 5 min at −78°C. The reaction was quenched with an aqueous buffered phosphate solution (pH 6.2) and the aqueous solution extracted with methylene chloride. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to give a crude oil, which was purified by flash chromatography (8.5/1.5 hexane/acetone) to afford the diastereomers **2a** and **2b**, and the dimer **5** in 25% yield respectively.

7,8-Dihydro-3-phenyl-3*R*-[3α,8aβ]-5*H*-oxazolo[3,2a]-pyridine-5-carbonitrile (2a)

$[\alpha]_D^{20}$-297 (*c* 1 in $CHCl_3$); m.p. 100–104°C; IR ($\nu\,cm^{-1}$): 2250, 1725, 1675, 1620; ^1H NMR (300 MHz; $CDCl_3$): δ 1.72 (1H, m, H-8), 2.31 (3H, m, H-8 and H-7), 4.09 (1H, dd, $J = 1.5$, 8.5 Hz, H-2), 4.29 (1H, dd, $J = 6$, 8.5 Hz, H-2), 4.72 (1H, dd, $J = 1.5$, 6.0 Hz, H-3), 4.81 (1H, dd, $J = 4.0$, 10.0 Hz, H-8a), 5.32 (1H, br s, H-6), 7.3–7.5 (5H, m, aromatics); ^{13}C NMR (75 MHz; $CDCl_3$): δ 21.2 (C-8), 25.9 (C-7), 61.6 (C-3), 73.6 (C-2), 87.4 (C-8a), 114.0 (C-6), 115.1 (CN), 115.7 (C-5), 127.6, 127.9, 128.6 (CH aromatics), 141.0 (C aromatic); *m*/*z* (CI) 227 $(M+1)^+$; Anal.

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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.

7,8-Dihydro-3-phenyl-3*R*-[3α,8aα]-5*H*-oxazolo[3,2a]-pyridine-5-carbonitrile (2b)

$[\alpha]_D^{20}$-245 (*c* 1 in $CHCl_3$); IR ($\nu\,cm^{-1}$): 2224, 1720, 1670, 1610; ^1H NMR (300 MHz; $CDCl_3$): δ 1.7–1.8 (1H, m, H-8), 2.0–2.4 (3H, m, H-8 and H-7), 3.80 (1H, dd, $J = 7.0$, 8.0 Hz, H-2), 4.34 (1H, dd, $J = 7.0$, 8.0 Hz, H-2), 4.65 (1H, t, $J = 7.0$ Hz, H-3), 4.95 (1H, dd, $J = 3.0$, 7.0 Hz, H-8a), 5.67 (1H, t, $J = 4.5$ Hz, H-6), 7.3–7.5 (5H, m, aromatics); ^{13}C NMR (75 MHz; $CDCl_3$): δ 19.9 (C-8), 24.6 (C-7), 64.4 (C-3), 72.2 (C-2), 87.8 (C-8a), 115.5 (CN), 118.1 (C-6), 119.5 (C-5), 126.7, 127.9, 128.6 (CH aromatics), 139.5 (C aromatic); *m*/*z* (CI) 227 $(M+1)^+$; HRMS (CI, CH_4) *m*/*z* $(M+1)^+$; Calcd for $C_{14}H_{14}N_2O$: 227.1184 Found: 227.1177.

Dimer 5

$[\alpha]_D^{20}$-77 (*c* 1 in $CHCl_3$); m.p. 185–188°C (MeOH/aceton); IR ($\nu\,cm^{-1}$): 2177; ^1H NMR (300 MHz; $CDCl_3$): δ 1.6–2.3 (6H, m, H-6, H-7 and H-8), 3.94 (1H, d, $J = 9.0$ Hz, H-2), 4.13 (1H, dd, $J = 7.0$, 9.0 Hz, H-2), 4.81 (1H, d, $J = 7.0$ Hz, H-3), 4.98 (1H, t, $J = 7.0$ Hz, H-8a), 7.3–7.5 (5H, m, aromatics); ^{13}C NMR (75 MHz; $CDCl_3$): δ 17.5 (C-7), 29.3 (C-8), 30.8 (C-6), 58.7 (C-3), 64.1 (C-5), 75.1 (C-2), 86.8 (C-8a), 119.5 (CN), 126.9, 127.6, 128.6, (CH aromatics), 141.0 (C aromatic); *m*/*z* (CI) 455 $(M+1)^+$; 401 $(M+1\text{-}54)^+$; HRMS (CI, CH_4) *m*/*z* $(M+1)^+$; Calcd for $C_{28}H_{30}N_4O_2$: 455.2447 Found: 455.2456.

Alkylation of Cyanoenamine 2b

To a stirred solution of 2,2,6,6-tetramethylpiperidine (105 μL, 0.622 mmol) in 1.5 mL of anhydrous THF at −78°C were added successively *n*-BuLi (0.25 mL, 0.622 mmol, 2.5 M solution in hexanes) and HMPA (105 μL, 0.622 mmol) under an argon atmosphere. The reaction mixture was then allowed to warm to 0°C, stirred for 15 min and then cooled to −78°C. Cyanoenamine **2b** (86 mg, 0.389 mmol) in 0.5 mL of anhydrous THF was added dropwise. The mixture was stirred at −78°C for 20 min and benzylbromide (93 μL, 0.78 mmol) was added dropwise over 2 min. The mixture was stirred for 1 h at −78°C. The reaction was then quenched

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with saturated $KHCO_3$ (5 mL) and extracted with ethyl ether (2 × 15 mL). The combined organic layers were concentrated under reduced pressure, treated with 5 mL of THF and 5 ml of a 1N aqueous solution of HCl (5 mL) and stirred for 15 h at room temperature. After extraction with ethyl ether and evaporation to dryness the crude residue was purified by flash chromatography (6 : 1 hexanes : ethyl acetate) and provided 66 mg (55%) of lactam 7 and 8 mg (10%) of lactam **4**.

Lactam 7

$[\alpha]_D^{20}$-24 (*c* 1 in $CHCl_3$); IR ($\nu\,cm^{-1}$): 1644; ^1H NMR (300 MHz; $CDCl_3$): δ 1.31 (1H, ddd, $J = 12.5$, 10, 9.5 Hz, H-8ax), 2.09 (1H, dd, $J = 17$, 12 Hz, H-6ax), 2.15–2.30 (1H, m, H-7), 2.35 (1H, ddd, $J = 12.5$, 4.5, 2 Hz, H-8eq), 2.55 (1H, dd, $J = 17$, 4.5 Hz, H-6eq), 2.69 (1H, dd, $J = 13.5$, 6.5 Hz, Ph-CH_2), 2.72 (1H, dd, $J = 13.5$, 6 Hz Ph-CH_2), 4.49 (1H, dd, $J = 9$, 8 Hz, H-2), 4.98 (1H, dd, $J = 9.5$, 4.5 Hz, H-8a), 5.24 (1H, dd, $J = 8$ Hz, H-3, 1H), 7.1–7.4 (5H, m, aromatics); ^{13}C NMR (75 MHz; $CDCl_3$): δ 31.7 (C-7); 34.1 (C-8); 38.0 (C-6); 41.8 (Ph-CH_2); 57.8 (C-8a); 72.6 (C-2); 88.2 (C-3); 125.9; 126.4; 127.5; 128.4; 128.7; 129.0 (CH aromatics); 138.5; 139.3 (C aromatics); 168.3 (C=O); *m/z* (CI) 308 $(M+1)^+$; HRMS (CI, CH_4) *m/z* $(M+1)^+$; Calcd for $C_{20}H_{21}NO_2$: 308.1650 Found: 308.1655.

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