Cyclization of 5-(2-chloroethoxy)-1,5-dihydro-2*H*-pyrrol-2-ones

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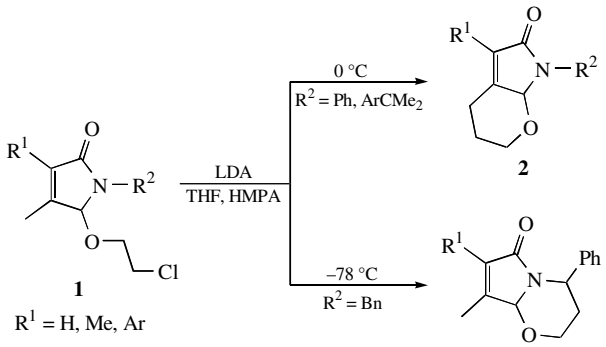
The intramolecular cyclization of substituted 5-(2-chloroethoxy)-1,5-dihydro-2*H*-pyrrol-2-ones in the presence of lithium diisopropylamide hexamethylphosphoramide in tetrahydrofuran gave tetrahydropyrano[2,3-*b*]pyrrol-6(2*H*)-ones and 3,4-dihydro-2*H*-pyrrolo-[2,1-*b*][1,3]oxazin-6(8a**H**)-ones in moderate to good yields.

Substituted 1,5-dihydro-2*H*-pyrrol-2-ones are of interest because of their pharmacological or pesticide activity.[1] We studied the incorporation of a fused heterocycle to these structures in order to get biologically important partially saturated fused pyrano-[2,3-*b*]pyrroles **2**[2,3] and pyrrolo[2,1-*b*][1,3]oxazines **3**.[4] Compounds **2** and **3** seem potent biologically active substances.[5–8]



Scheme 1

Carbon-carbon coupling cyclization is well known as a route to carbocycles.[9] Here we attempted to apply intramolecular coupling to the formation of an oxygen-containing ring.

We found that a six-membered ring fused to a pyrrolone ring can be formed in the presence of a strong base such as lithium diisopropylamide (LDA) thus giving substituted **2** or **3** (Scheme 1) in moderate to good yields. Starting material **1** is directly available by etherification of corresponding 5-hydroxy-1,5-dihydro-2*H*-pyrrol-2-ones.[10]

Preliminary data on the intramolecular cyclization of **1a** (R^1 = = 2-FC_6H_4, R^2 = 3,5-$Cl_2C_6H_3CMe_2$) are summarised in Table 1. The use of hexamethylphosphoramide (HMPA)[9] has drastically improved the cyclization (runs 1 and 2). Since the dilution of the initial reaction mixture increased the yield (run 3) it is anticipated that an intermolecular process competed with the main cyclization pathway.

The synthesis of compounds **2**† and **3**‡ (Table 2) has been carried out under optimum conditions (Table 1, run 3). It is noteworthy that the formation of **2** proceeds relatively slowly (1 h at 0 °C) and tolerates only phenyl or substituted α,α-dimethylbenzyl moieties at the nitrogen atom (Table 2, **2a**,**b**). In the presence of *tert*-butyl or isopropyl substituents at the nitrogen atom (Table 2, **2c**,**d**), the cyclization fails.

The cyclization of **1** containing a benzyl group at the nitrogen atom leads to **3** rather than **2** (Scheme 1). The process is unexpectedly fast compared to the formation of **2**. At –78 °C (Table 2, **3a**–**c**), the reaction furnishes **3** from N-benzylated **1** (R^2 = $PhCH_2$). Rapid intramolecular alkylation of the benzyl carbon (formation of **3**) may be accounted for a relatively high reactivity of the corresponding benzylic carbanion compared to the less reactive γ-anion of α,β-unsaturated amide (formation of **2**). Nuclear Overhauser enhancement (NOE) measurements showed that irradiation of the proton at C(8a) in **3a** has not

Table 1 Cyclization of **1a** into **2a** (R^1 = 2-FC_6H_4, R^2 = 3,5-$Cl_2C_6H_3CMe_2$, 0 °C, 1 mmol of **1a**, 2 mmol of LDA).

Run	Concentration/mol dm^{-3}	HMPA, mmol	*t*/h	Yield (%)
1	0.1	0	2	7
2	0.1	4	1	45
3	0.04	4	1	67

† *General procedure for the preparation of 3,4,7,7a-tetrahydropyrano-[2,3-*b*]pyrrol-6(*2H*)-ones* **2**. All reactions were carried out in a nitrogen atmosphere. To a mixture of a 2 M LDA solution in hexane (1 ml) and dry THF (12 ml) at –78 °C (a dry-ice bath) a solution of 5-(2-chloroethoxy)-1-(α,α-dimethyl-3,5-dichlorobenzyl)-3-(2-fluorophenyl)-1,5-dihydro-4-methyl-2*H*-pyrrol-2-one **1a** (0.439 g, 0.96 mmol) in dry THF (12 ml) was added with vigorous stirring. Then dry HMPA (0.72 g, 4 mmol) was added dropwise, and the mixture was stirred for 15 min at –78 °C. The mixture was allowed to warm to 0 °C and was stirred at this temperature for 1 h. The reaction mixture was quenched with a portion of 1 M HCl solution in methanol (2 ml), and the solvent was evaporated to give an oily residue. The residue was separated by flash chromatography using silica and hexane–ethyl acetate (4:1) to give 0.269 g (67%) of **2a** as a colourless solid, mp 135–136 °C (ethyl acetate). ^{1}H NMR ($CDCl_3$) δ: 1.76 (s, 3H, Me), 1.78 (s, 3H, Me), 1.85 (m, 2H, CH_2), 2.5 (m, 1H), 2.8 (m, 1H), 3.75 (m, 1H, CH_2O), 4.1 (m, 1H, CH_2O), 5.25 (s, 1H, 8-H), 7.0–7.5 (m, 7H, aryl protons). MS, *m*/*z*: 419 (M^+), 233 (M^+ – – CH_2=CMe–Ar). Found (%): C, 62.86; H, 4.82; N, 3.39. Calc. for $C_{22}H_{20}Cl_2FNO_2$ (%): C, 62.85; H, 4.76; N, 3.33.

*3,4,7,7a-Tetrahydro-5-methyl-7-phenylpyrano[2,3-*b*]pyrrol-6(*2H*)-one* **2b**: colourless solid, mp 109–110 °C (ethyl acetate). ^{1}H NMR ($CDCl_3$) δ: 1.8 (m, 2H, CH_2), 1.84 (s, 3H, Me), 2.35 (m, 1H), 2.85 (m, 1H), 3.7 (m, 1H, CH_2O), 4.1 (m, 1H, CH_2O), 5.29 (s, 1H, 8-H), 7.11 (t, 1H, Ph, *J* 8.3 Hz), 7.35 (t, 2H, Ph, *J* 8.3 Hz), 7.72 (d, 2H, Ph, *J* 8.3 Hz). MS, *m*/*z*: 229 (M+), 214 (M^+ – Me). Found (%): C, 73.31; H, 6.65; N, 6.11. Calc. for $C_{14}H_{15}NO_2$ (%): C, 73.36; H, 6.55; N, 6.11.

‡ *General procedure for the preparation of 3,4-dihydro-2*H*-pyrrolo[2,1-*b*]-[1,3]oxazin-6(8a*H*)-ones* **3**. All reactions were carried out in a nitrogen atmosphere. To the mixture of 2 M LDA solution in hexane (1 ml) and dry THF (10 ml) at –78 °C (a dry-ice bath) a solution of 1-benzyl-5-(2-chloroethoxy)-1,5-dihydro-4-methyl-2*H*-pyrrol-2-one (0.255 g, 0.96 mmol) in dry THF (5 ml) was added with vigorous stirring. Dry HMPA (0.90 g, 5 mmol) was added then dropwise, and the mixture was stirred at –78 °C for 1 h. The reaction mixture was quenched with a 1 M HCl solution in methanol (2 ml), and the solvent was evaporated to give an oily residue. The residue was separated by flash chromatography to give 0.088 g (40%) of 3,4-dihydro-8-methyl-4-phenyl-2*H*-pyrrolo[2,1-*b*][1,3]oxazin-6(8a*H*)-ones **3a** as a colourless solid, mp 114–115 °C (ethyl acetate). ^{1}H NMR ($CDCl_3$) δ: 2.02 (s, 3H, Me), 2.2 (m, 2H, 3-CH_2), 3.74 (m, 1H, CH_2O), 4.0 (m, 1H, CH_2O), 5.05 (s, 1H, 8a-H), 5.54 (s, 1H, 4-H), 5.98 (s, 1H, =CH), 7.1–7.5 (m, 5H, Ph). MS, *m*/*z*: 229 (M^+), 214 (M^+ – Me). Found (%): C, 73.32; H, 6.63; N, 6.17. Calc. for $C_{14}H_{15}NO_2$ (%): C, 73.36; H, 6.55; N, 6.11.

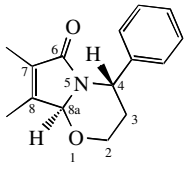
*3,4-Dihydro-7,8-dimethyl-4-phenyl-2*H*-pyrrolo[2,1-*b*][1,3]oxazin-6(8a*H*)-one* **3b**: colourless solid, mp 64–65 °C (ethyl acetate). ^{1}H NMR ($CDCl_3$) δ: 1.85 (s, 3H, Me), 1.92 (s, 3H, Me), 2.2 (m, 2H, 3-CH_2), 3.7 (m, 1H, CH_2O), 4.0 (m, 1H, CH_2O), 4.97 (s, 1H, 8a-H), 5.52 (s, 1H, 4-H), 7.2–7.4 (m, 5H, Ph). MS, *m*/*z*: 243 (M^+), 228 (M^+ – Me). Found (%): C, 74.04; H, 7.24; N, 5.78. Calc. for $C_{15}H_{17}NO_2$ (%): C, 74.07; H, 7.00; N, 5.76.

*3,4-Dihydro-8-methyl-4,7-diphenyl-2*H*-pyrrolo[2,1-*b*][1,3]oxazin-6(8a*H*)-one* **3c**: colourless oil. ^{1}H NMR ($CDCl_3$) δ: 2.14 (s, 3H, Me), 2.2 (m, 2H, 3-H), 3.85 (m, 1H, CH_2O), 4.1 (m, 1H, CH_2O), 5.14 (s, 1H, 8a-H), 5.64 (d, 1H, 4-H, *J* 4.5 Hz), 7.2–7.5 (m, 10H, Ph). MS, *m*/*z*: 305 (M^+), 290 (M^+ – Me). Found (%): C, 78.43; H, 6.48; N, 4.57. Calc. for $C_{20}H_{19}NO_2$ (%): C, 78.68; H, 6.23; N, 4.59.

Table 2 Synthesis of **2** and **3** from **1** in THF using 2 equivalents of LDA and 4 equivalents of HMPA.

Product	R^1	R^2 (in **1** or **2**)	*T*/°C	*t*/h	Yield(%)
2a	2-FC_6H_4	3,5-$Cl_2C_6H_3CMe_2$	0	1	67
2b	Me	Ph	0	1	40
2c	Me	Pr^i	0	0.5	0
2d	Me	Bu^t	0	0.5	0
3a	H		–78	1	40
3b	Me		–78	1	70
3c	Ph		–78	1	49

detectably enchanced the signal of the proton at C(4) (*i.e.*, benzylic position), compared to considerable enchancement of the signal of methyl protons. On the basis of NOE observations, we expect that product **3a** has a 4,8a-*trans* configuration.



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