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SYNTHESIS AND REACTIVITY OF BIS-LACTAMIC COMPOUNDS

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Abstract : A preparation of bis-lactams is described from α-ketols and bis-cyanamides in the presence of sodium ethoxide at room temperature. One of these compounds leads to an unsaturated derivative by condensation with furfural, or to a saturated analogue via catalytic hydrogenation.

We recently reported (1) the preparation of some α-carboxamido-γ-lactams of type I by condensation of an α-ketoalcohol with substituted cyanamides. The potentially useful biological activities exhibited by functionalized lactams (2,3) allied with two publications in 1993 (4,5) dealing with the synthesis and antitumoral activity of bis-lactones, have prompted us to expand access to derivatives with two lactam rings.

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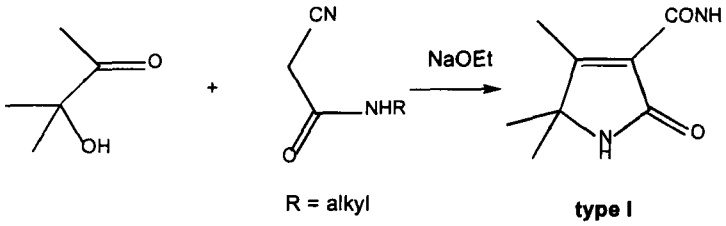
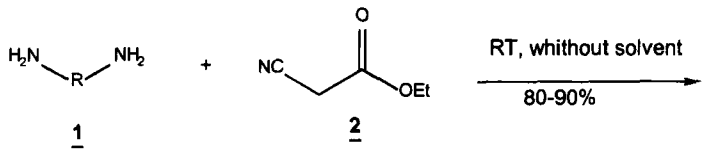
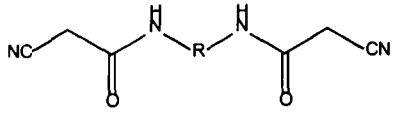


In order to obtain bis-cyanamides **3**, we started with various diamines that we condensed with ethyl cyanocetate **2**, these two compounds reacting at room temperature in 1:2 proportions without any solvent. In this manner, crystallized bis-amides **3** could be obtained in average 90% yield.



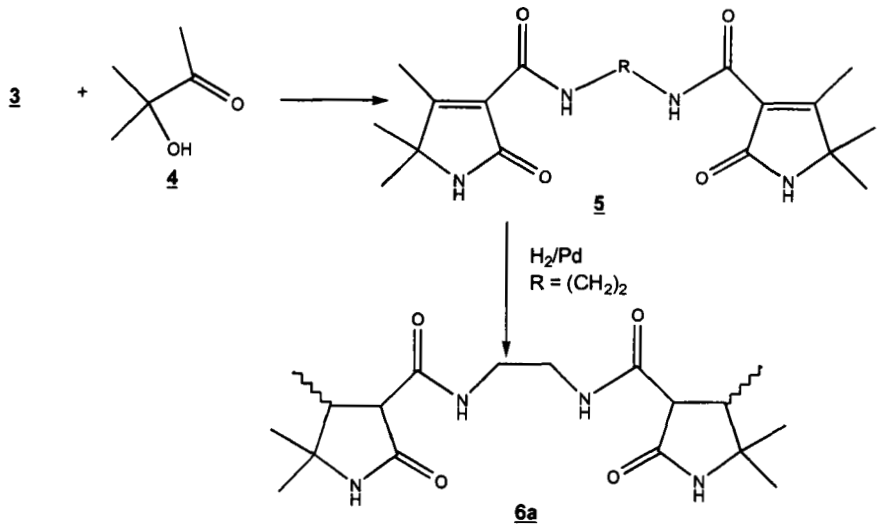


R = (CH2)n	n
3a	2
3b	3
3c	4
3d	5
3e	6
3f	7
3g	8

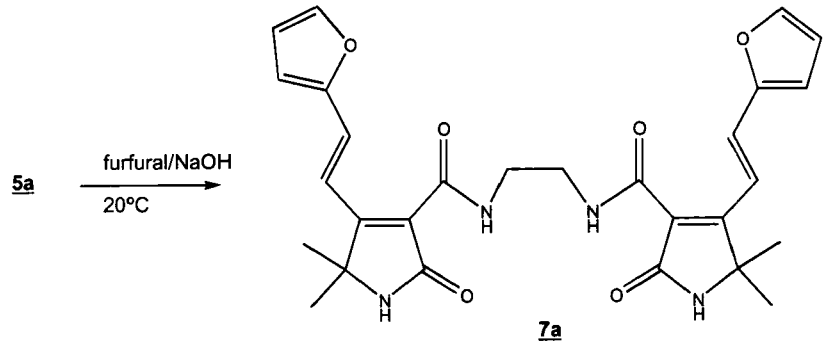
or R = -$CH_2CH(CH_3)$- **3h**

When **3** were treated with 3-hydroxy-3-methylbutan-2-one **4** in the presence of sodium ethoxide in ethanol, a Knoevenagel condensation occurred, followed *in situ*, by a cyclization of the two extremities of compounds **3**, leading to bis-lactams **5** in 70-80% yields. In our hands, attempts to obtain crystalline **3d** and **3f**, respectively generated from 1,5-diaminopentane and 1,7-diaminoheptane, failed.

Our studies in this area led us to revise the structures initially assigned (1). In contrast to what we thought at the outset, cyclization of the non-isolated intermediate from Knoevenagel reaction took place between the alcohol and nitrile groups, the amide being unchanged. As for monolactam homologues, bis-lactams **5** could be hydrogenated in ethanol in the presence of Pt/Pd as a catalyst. In such conditions, lactam **5a** gave the saturated bis lactam **6a**. This could be characterized as a mixture of cis/trans isomers, as shown by 1H NMR.



The 4-methyl group in the ring could be analyzed as two doublets. One other possible transformation of this structure lies upon the 4-methyl group hydrogens mobility in basic medium. The reaction of the unsaturated bis-lactam **5a** with furfural in basic conditions led to bis-lactam **7a** (isomer E) characterized by its 1H NMR spectrum.



Experimental section

General Methods.1H and 13C NMR were recorded with a Bruker AC400 (400 MHz) spectrometer. Chemical shifts were reported in ppm (d) relative to tetramethylsilane as internal standard, for solutions in CDCl3.; coupling constants (J) are given in Hz with the following abbreviations for splitting patterns:

s = singlet, ps = pseudo-singlet, d = doublet, t = triplet, q = quartet and m = multiplet. Flash chromatography was performed on 230-400 mesh Merck Silica gel 60. Elemental analyses were performed at the CNRS institute of Gif-sur-Yvette.

General Procedure for the Preparation of bis-cyanacetamides 3.

To the diamine 1 (one equivalent) stirred at room temperature, 2 equivalents of ethyl cyanocetate were added. Stirring was continued for 24 h. The crude mixture solid which on recrystallization from 95% ethanol gave bis-cyanacetamide 3 (90% yield). Experimental data for each product are presented in Table I.

Table I preparation of diamides 3

Entry	R	Compounds	m.p. (°C)[a]	IR (nujol) ν cm^{-1}
1	$-(CH_2)_2-$	**3a**	194.5-196	3295, 3079, 1689
2	$-(CH_2)_3-$	**3b**	160-161.5	3284, 3075, 1680
3	$-(CH_2)_4-$	**3c**	158-160	3270, 3064, 1691
4	$-(CH_2)_5-$	**3d**	122-126	3268, 3085, 1698
5	$-(CH_2)_6-$	**3e**	157-158	3257, 3090, 1695
6	$-(CH_2)_7-$	**3f**	134-136	3265, 3094, 1698
7	$-(CH_2)_8-$	**3g**	130-133	3297, 3102, 1687
8	$-CH_2-CHMe-$	**3h**	154-155	3302, 3074, 1685

[a] Uncorrected, measured with a Reichert apparatus.

General Procedure for the Preparation of bis-lactams 5.

In a 100-mL round-bottomed flask, a solution of sodium ethoxide was prepared by adding 0.23 g (10 mmol) sodium to 30 mL ethanol. To this solution 2.55 g (25 mmol) of 3-hydroxy-3-methylbutan-2-one and 25 mmol of bis-cyanacetamide **3** were added. The resulting mixture was stirred for 20 h at room temperature. After concentration in vacuo, the residue was acidified with 3M aqueous HCl then treated with potassium carbonate. The crude precipitate was filtered, then dissolved in ethanol. By addition of potassium carbonate to this solution bis-lactam **5** precipitated. The yields and physical data are given in Table II.

1,2-Bis-(4,5,5-trimethyl-2-oxopyrrolidine-3-carboxamido)ethane 6a.

A solution of 500 mg of bis-lactam **5a** in 20 ml 95% ethanol was stirred in the presence of a catalytic amount of Pt on charcoal, under 3 to 4 bars of hydrogen

Table II preparation of bis-lactames 5

Entry	R	Compounds	yield	m.p. (°C)[a]	IR (nujol) ν cm^{-1}	^1H NMR (δ, ppm)
1	$-(CH_2)_2-$	**5a**	71%	190-191	3266; 3181; 1679; 1648	1.42(s, 12H, $(CH_3)_2$); 2.41(s, 6H, CH_3); 3.56(d, 4H, CH_2N); 6.92 (ps 2H, NH); 9.73 (ps, 2H, NH).
2	$-(CH_2)_3-$	**5b**	86%	134.5-135.5	3264; 3191; 1670; 1635	1.42(s, 12H, $(CH_3)_2$); 1.88 (m, 2H, CH_2); 2.41(s, 6H, CH_3); 3.45(q, 4H, CH_2N); 6.92 (ps, 2H, NH); 9.66 (ps, 2H, NH).
3	$-(CH_2)_4-$	**5c**	88%	175-177	3286; 3155; 1678; 1627	1.42(s, 12H, $(CH_3)_2$); 1.68 (m, 4H, CH_2); 2.40(s, 6H, CH_3); 3.38 (m, 4H, CH_2N); 6.92 (ps, 2H, NH); 9.56 (ps, 2H, NH).
4	$-(CH_2)_6-$	**5e**	70%	89-90	3270; 3169; 1681; 1640	1.42(s, 12H, $(CH_3)_2$); 1.60 (m, 8H, CH_2); 2.41(s, 6H, CH_3); 3.32 (m, 4H, CH_2); 6.92 (ps, 2H, NH); 9.54 (ps, 2H, NH).
5	$-(CH_2)_8-$	**5g**	69%	78-80	3276, 3185, 1679, 1639	1.33 (m, 8H, CH_2); 1.42(s, 12H, $(CH_3)_2$); 1.57 (m, 4H, CH_2); 2.40(s, 6H, CH_3); 3.32 (m, 4H, CH_2); 6.92 (ps, 2H, NH); 9.52 (ps, 2H, NH).
6	$-CH_2-CH-$ Me	**5h**	73%	119-120	3290; 3164; 1686; 1625	1.28(d, 3H, CH_3); 1.42(s, 12H, $(CH_3)_2$); 2.40(s, 6H, CH_3); 3.33, 3.62, 4.28(3H, m, CH_xN); 6.92 (ps, 2H, NH); 9.65 et 9.76 (2 ps, 2H, NH).

[a] Uncorrected, measured with a Reichert apparatus.

during 5 h.The catalyst was then removed by filtration and the solvent was evaporated in vacuo at room temperature, leaving a yellow solid which was recrystallized from ether to give 480 mg of bis-lactam **6a** as a mixture of isomers (96% yield). mp. 223-225 °C .

1,2-Bis 4-(2-a-furylethenyl)-5,5-trimethyl-2-oxopyrrolidine-3-carboxamido)-ethane 7a.

In a 100-mL round-bottomed flask containing 10 mg of sodium hydroxyde in 20 mL ethanol, was added slowly a mixture of bis-lactam **5a** (5 mmol) nd 0.96 g of furfural (10 mmol). The solution was then refluxed for 4 h. After cooling, ethanol was evaporated under reduced pressure and the residue was recrystallized from ethanol to give 1.22 g of bis-lactam **7a** (3.5 mmol). Yield: 70% . m.p. = l20-l24°C.

References and notes

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