Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A Convenient Synthesis Of Substituted 3-Pyrrolin-2-ones from α-Cetols

Gaguik Melikian [a] , Francis Rouessac [a] & Christian Alexandre [a]
[a] Laboratoire de Synthese Organique, associé au CNRS, URA 482 Faculté des Sciences , Avenue O. Messiaen, BP 535, F-72017, Le Mans
Published online: 23 Sep 2006.

To cite this article: Gaguik Melikian , Francis Rouessac & Christian Alexandre (1993) A Convenient Synthesis Of Substituted 3-Pyrrolin-2-ones from α-Cetols, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 23:19, 2631-2638, DOI: 10.1080/00397919308013792

To link to this article: http://dx.doi.org/10.1080/00397919308013792

SYNTHETIC COMMUNICATIONS, 23(19), 2631-2638 (1993)

A Convenient Synthesis of Substituted 3-Pyrrolin-2-ones from α-Cetols

Gaguik Melikian[$], Francis Rouessac and Christian Alexandre*

Laboratoire de Synthèse Organique, associé au CNRS, URA 482
Faculté des Sciences, Avenue O. Messiaen, BP 535, F-72017 **Le Mans**

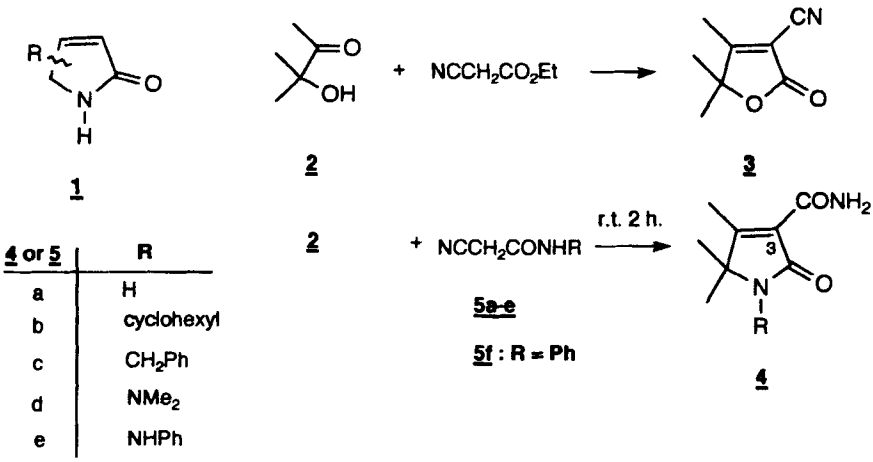
Abstract *: a simple and efficient method for the preparation of the title compounds is described from cyanoacetamides and 3-hydroxy-3-methyl-2-butanone in the presence of sodium ethylate at room temperature. The 3-carboxamido-N-alkyl-4,5,5-trimethyl-5-dihy dro-2H-pyrrol-2-ones lead to unsaturated derivatives by condensation with aldehydes, while hydrogenation give rise to the corresponding pyrrolidin-2-ones.*

In recent years, there has been considerable interest in the development of new processes for the synthesis of substituted 2-butenolides, because of their diverse biological activities (1). 3-Pyrrolin-2-ones **1**, regarded as nitrogen analogues of 2-butenolides represent also a diverse and important family of biologically active secondary metabolites, many of which have potential use in both medicine and agriculture (2). However, to our knowledge, no method is known to synthesize these 3-unsaturated γ-lactams in a facile way and in high yield (3). We report herein an efficient and straighforward synthetic approach to 3-pyrrolin-2-ones of type **4**.

In the past, we showed that the cetol **2** reacted with ethyl cyanoacetate to yield cyanobutenolide **3** (4). When **2** was treated in the same way with substituted 2-cyanoacetamides **5 a-e**, 3-pyrrolin-2-ones-2 **4 a-e** were formed in good yields (5,6) (scheme 1).

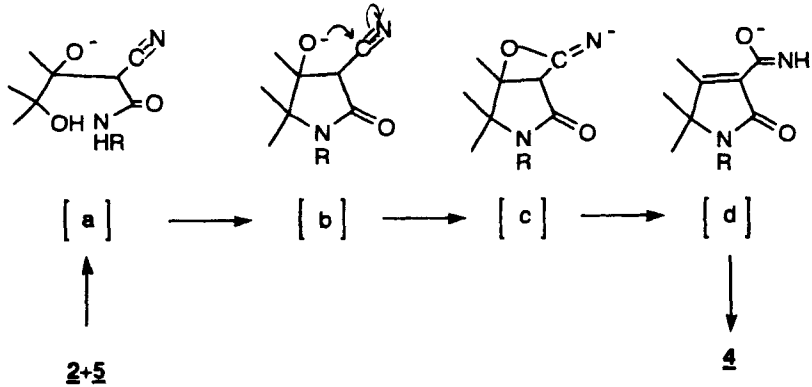
---

* to whom correspondence should be addressed.



Scheme 1

Instead of the normal Knoevenagel products, α-carboxamidolactams were obtained. We believe that **4** is formed in succession (scheme 2): the cyanoacetamide **5** attacks the hydroxyketone **2** (a), then suffers a nucleophilic cyclization with elimination of a water molecule (b); finally a transfer of the alcoolate oxygen to cyanide (c) provides the hydratation of the nitrile group into a carboxamide (d).

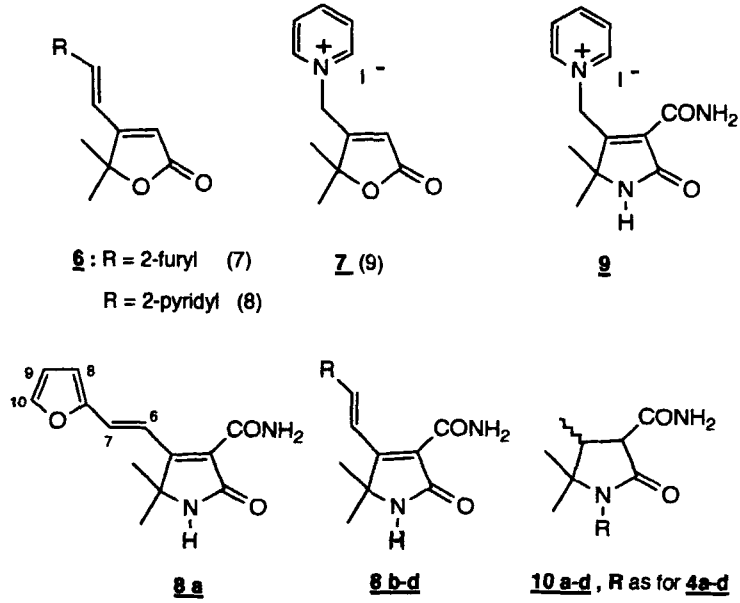


Scheme 2

This one-pot procedure, employing common intermediates has the advantage to furnish in fair yields and gram quantities, easily separable crystalline compounds which may be conveniently purified (Table I). We noticed that in each case, nitrile group was hydrolysed during the course of this reaction, excepted in the case of **5f** (R = Ph) which led to lactone **3**. No other product could be detected in this case.

In order to compare these 3-unsaturated γ-lactams with lactonic derivatives such as **6** (7,8) or **7** (9), we reacted **4a** with aromatics aldehydes, under reflux, with a solution of ethanolic sodium hydroxide to give the desired 4-substituted unsaturated 3-pyrrolin-2-ones **8 a-d** (Scheme 3 and Table II). The 4-methyl group could also be substituted according to King conditions (10) to give from **4a** for exemple, the pyridyl iodonium salt **9**. Experimental data are summarized in Table II.

Finally *cis/trans* mixture of saturated analogues **10** of **4** could be also easily obtained by catalytic hydrogenation run in the presence of a Pt/Pd catalyst (Scheme 3 and Table III).



Scheme 3

In conclusion, a new route to substituted 3-pyrrolin-2-ones has been accomplished, using a one step procedure from very simple starting compounds. These products served to synthetize 4-substituted derivatives. All compounds are presently tested to compare their biological activities to their lactonic counterparts.

Experimental section

General Methods. ^{1}H and ^{13}C NMR were recorded with a Bruker AC400 (400 MHz) spectrometer. Chemical shifts were reported in ppm (δ) relative to tetramethylsilane as internal standard, for solutions in $CDCl_3$.; 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 by the Department of Chemistry at the University of Bratislava (Slovenia).

General Procedure for the Preparation of Pyrrolin-2-ones 4

In a 100-mL round-bottomed flask, a solution of sodium ethoxide was prepared by adding 0.23 g (1 mmol) sodium to 30 mL ethanol. To this solution 2.5 g (5mmol) 3-hydroxy-3-methyl-2-butanone and 5 mmol of substituted cyanacetamide were added. The resulting mixture was stirred for 20 h at r. t. After concentration *in vacuo*, the residue was acidified with 6M aqueous HCl in order to remove the base. Then potassium carbonate was portionwise added until a precipitate was formed. The crude product was filtered and recrystallized from ethanol to give pure **4**. The yields and physical data are given in Table I.

General Procedure for the Preparation of 4-Alkylidenepyrrolin-2-ones 8.

In a 100-mL round-bottomed flask, containing 20 mL ethanol and 10 mg of sodium hydroxide a mixture of 0.85 g (5 mmol) pyrrolin-2-one **4a** and aldehyde (5 mmol) was slowly added. The resulting mixture was heated under reflux for 4 h and cooled to r.t. Ethanol was removed under reduced pressure and the residue was recrystallized from ethanol.The yields and physical data are given in Table II.

Table I. Preparation of 3-Pyrrolin-2-ones 4

entry	R	Cpd.	yield	m.p.(°C)[a]	Mol. formula[b]	IR (Nujol)	^{1}H RMN δ, J(Hz)
1	H	**4a**	82	163	$C_8H_{12}N_2O_2$ (168.20)	1630,1676, 3144, 3290	1.44(s, 5-Me), 2.42(s, 4-Me), 6.18(3-NH), 9.30(3-NH), 6.99(1-NH)
2	cyclohexyl	**4b**	75	58	$C_{14}H_{22}N_2O_2$ (250.34)	1630, 1676, 3236, 3310	1.41(s, 5-Me), 2.41(s, 4-Me), 6.94(3-NH), 9.57(3-NH), 1.2-2(m, 1-NC_6H_{11})
3	CH_2Ph	**4c**	75	66	$C_{15}H_{18}N_2O_2$ (258.32)	1602, 1638 1680, 3140, 3280	1.42(s, 5-Me), 2.43(s, 4-Me), 6.93(3-NH), 10.01(3-NH), 4.57(d, C$\underline{H_2}$Ph), 7.35(m, Ph)
4	NMe_2	**4d**	66	90	$C_{10}H_{17}N_3O_2$ (211.27)	1640, 1685, 3135, 3292	1.44(s, 5-Me), 2.43(s, 4-Me), 6.95(3-NH), 10.34(3-NH), 2.70(s, NMe_2)
5	NHPh	**4e**	63	117	$C_{14}H_{17}N_3O_2$ (259.31)	1625, 1680 3260, 3158	1.39(s, 5-Me), 1.91(s, 4-Me), 6.7-7.7(m, NHPh)

[a] Uncorrected. measured with a Reichert apparatus.

[b] For new compounds, satisfactory microanalyses obtained : C ± 0.32, H 0.20, N 0.27.

Table II. Preparation of alkylidene derivatives 8 of Pyrrolin-3-ones 4a

entry	R	Cpd.	yield	mp.(°C)[a]	Mol. formula[b]	IR (Nujol)	^{1}H RMN δ, J(Hz)
1	2-furyl	**8a**	87	190-193	$C_{13}H_{14}N_2O_3$ (246.27)	1636, 1678, 3150, 3285	1.68(5-Me), 6.49(8-H), 6.65(9-H), 6.91(d, J = 15 Hz, 6-H), 7.52(10-H), 8.30(d, J = 15 Hz, 7-H), 9.55(1-NH), 5.85 & 7.05($CONH_2$)
2	2-pyridyl	**8b**	84	200-202	$C_{14}H_{15}N_3O_2$ (257.29)	1638, 1670, 3152, 3305	1.75(5-Me), 5.68 & 7.15($CONH_2$), 7.18(d, J = 15 Hz, CH=CH-Pyr.), 7.23(Hβ-Pyr.), 7.76(Hβ & Hγ-Pyr.), 8.64(Hα-Pyr.),8.78(d, J = 15 Hz, CH=CH-Pyr.), 9.6(s,NH)
3	3-pyridyl	**8c**	78	160-163	$C_{14}H_{15}N_3O_2$ (257.29)	1640, 1672, 3140, 3294	1.76(5-Me), 5.7 & 7($CONH_2$), 7-7.4 (m, CH=CH-Pyr. & Hβ-Pyr), 7.8-8.1(m, Hγ-Pyr) 8.3-8.7(m, CH=CH-Pyr.& Hα-Pyr), 9.6(s,NH)
4	4-pyridyl	**8d**	76	261-264	$C_{14}H_{15}N_3O_2$ (257.29)	1630, 1681, 3138, 3270	1.58(5-Me), 5.60 & 6.95($CONH_2$), 7-7.4(m, CH=CH-Pyr. & Hβ-Pyr), 7.8-8(m, Hγ-Pyr.), 8.3-8.7(m, CH=CH-Pyr. & Hα-Pyr)
5	iodonium salt	**9**	82	149-150	$C_{13}H_{16}N_3O_2I$ (373.20)	1590, 1635, 1676	

[a] Uncorrected, measured with a Reichert apparatus.

[b] For new compounds, satisfactory microanalyses obtained : C ± 0.32, H± 0.20, N± 0.27.

Table III. Preparation of Pyrrolidinones 10.

entry	R	Cpd.	mp.(°C)[a]	Mol. formula[b]	IR (Nujol)	^{1}H RMN δ, J(Hz)
1	H	**10a**	126-128	$C_8H_{14}N_2O_2$ (170.21)	1690, 3150, 3310	1.2(d, J = 7 Hz, 4-Me), 1.25 & 1.48(2s, 5-Me Z+E),2.56 & 2.67(4-H Z+E), 3.22(d, J = 7 Hz, 3-H), 5.07 & 5.96(CONH$_2$), 8.17(1-NH)
2	cyclohexyl	**10b**	125-127	$C_{14}H_{24}N_2O_2$ (252.34)	1680, 3230, 3325	0.97(d, J = 7 Hz, 4-Me), 1.18 & 1.4(2s, 5-Me), 2.55(4-H), 3.4(d, J = 7 Hz, 3-H), 7.24 & 8.07(CONH$_2$)
3	CH_2Ph	**10c**	104-106	$C_{15}H_{20}N_2O_2$ (260.34)	1595, 1695, 3136, 3290	1.25(d, J = 7 Hz, 4-Me), 1.4 & 1.47(2s, 5-Me Z+E), 2.70(4-H), 3.15(d, J = 7 Hz, 3-H), 6.95 & 7.5(CONH$_2$)
4	NMe_2	**10d**	88-90	$C_{10}H_{19}N_3O_2$ (213.28)	1698, 3139, 3310	1.07 & 1.20(d, J =7 Hz, 4-Me), 1.28-1.31, 1.48-1.50 , 2.76-2.86(4H), 3.1(d, J = 7 Hz, 3-H), 2.53(NMe$_2$), 2.76 & 2.86(4-H), 6.74-7.70(CONH$_2$)

[a] Uncorrected, measured with a Reichert apparatus.

[b] For new compounds, satisfactory microanalyses obtained : C± 0.32, H± 0.20, N± 0.27.

Pyrrolinylpyridinium iodide 9

In a 200 mL round-bottomed flask, 1.68 g (0.01 mol) of lactam **4a**, 2.54 g of iodine, 6 mL of pyridin and 40 mL of ethanol were mixed together. The resulting mixture was heated under reflux for 3 h. After cooling, the off-white microcrystalline iodonium salt **9** was filtered (83 %), mp. 149-150 °C.

General procedure for Pyrrolidinones 10.

A stirred solution of 500 mg of the 3-pyrrolin-2-one **4** in 95 % ethanol (50 ml) was added in a hydrogenation apparatus (Parr), in the presence of 50 mg of Pt/Pd on charcoal.

The resulting mixture was maintained during 4 h under a pressure of 50-60 Psi of hydrogen. The catalyst was filtered off and after evaporation of the solvent under reduced pressure, the final product was crystallized from ether. The physical data are given in Table III.

References and Notes

[5] Department of Organic Chemistry, University of Erevan, 375049-Erevan (Armenia)

(1) J.S. Rao, *Chem Rev.* 1976, **75**, 625

(2) R. Fischer, H. Uhr, A. Widdig, S. Dutzmann, C. Erdelen, U. Wachendorff-Neumann and K. Schaller (Bayer A-G), **Ger. Offen.** DE 4,102,339 (1992).

(3) G. Rio and D. Masure, *Bull. Soc. Chim. France,* 1972, 4598.

(4) A. Avetisyan, S. Matsogan et G. Melikian, *Zh. Org. Chem.*, 1971, **7**, 962.

(5) the 2-cyanoacetamides used, were prepared from condenstion of ethyl cyanoacetate and substituted amines.

(6) a close resemblence has been found with the reaction of cyanothioacetamide upon benzoin : F.A. Khalifa, N.A. Ismail, A.H. Elghandour and H.F. Zohdi, *Tetrahedron,* 1991, **47**(38), 8243.

(7) M. Veveris, D. Jansone, L. Lietis, M. Shimanska, A. Aknazarian, G. Melikian and A. Aretisyan, *XII International Symposium on Medicinal Chemistry, Basel, Switzerland*, 1992, 327.

(8) G. Melikian, E. Solicaninova, A. Caplorski and A. Avetisyan, *Chem. Papers* (in press), Bratislava.

(9) G. Melikian, J. Nalgas, A. Avetisyan and P. Foltinova, *Chem. Papers,* Bratislava (Slovenia)

(10) - L.C. King, *J. Amer. Chem Soc.*, 1944, **66**, 894 and 1616.

(Received in UK 04 May 1993)