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Synthesis of Substituted Dicyanomethylendihydrofurans

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ABSTRACT. A simple and efficient method for the preparation of the title compounds is described from α-ketols and malononitrile in the presence of sodium ethylate at room temperature. These compounds lead to unsaturated derivatives by condensation with aldehydes.

The furan ring is a versatile building block in the synthesis of many natural products which exhibit important biological activities [1,2]. Polyfunctionally substituted furans and α-methylenfurans have therefore found a lot of applications such as potential cytostatic and pesticidal agents. In this domain dihalogenomethylenfurans derived from butyrolactones are well known intermediates for the synthesis of chiral tetrahydrofurans such C-glycosides or 1-methylene sugars [3].

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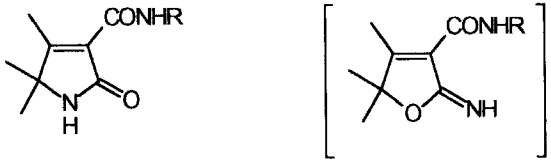
Recently [4] we have shown that unsaturated α-carboxamido-γ-lactams of 3-pyrrolin-2-one, type **1**, could be prepared by condensation of a tertiary α-ketol with substituted cyanacetamides in the presence of sodium ethylate (Scheme 1).

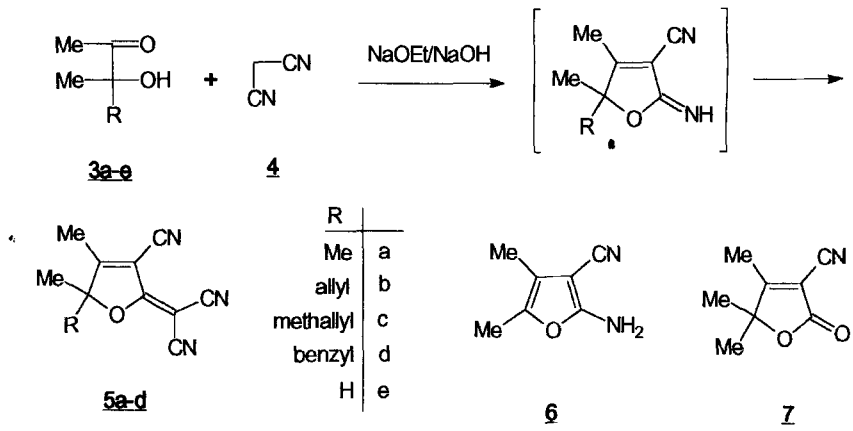


1 **2**

Scheme 1

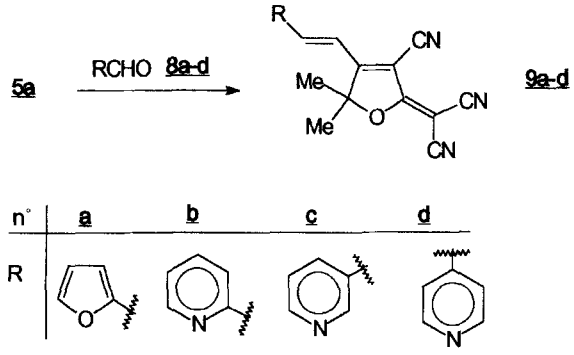
After a Knoevenagel reaction, the hydroxyl group attacks the nitrile function to form an intermediate iminolactone **2** which converts to the unsaturated lactam **1** [5]. A recent paper from Trogolo et al. [6] dealing with another route to such heterocycles from olefins by sonochemistry prompts us to report here some complementary results.

In our search for new condensations with tertiary α-ketols **3**, we have found that under the same basic conditions (NaOEt/EtOH), in the presence of malononitrile **4**, dicyanomethylendihydrofurans **5** were formed rapidly (Scheme 2 and Table I). Under these conditions, **5** was not formed when **4** was replaced by 2-amino-1,1,3-tricyano-1-propene (malononitrile dimer), which ruled out the dimerization of **4** before condensation with **3**. Surprisingly, this simple and almost quantitative transformation has been apparently unexplored until now. It is known that α-phenylbenzoin $PhC(O)CPh_2OH$ fails to undergo the Knoevenagel reaction, presumably due to steric hindrance [7]. Interestingly if the secondary ketol **3e** was used, a different behaviour leading to aminofuran **6** was observed by Gewald [8] or others [9]. Attempts to condense **4** with cyanolactone **7** were unsuccessfull : the starting material was recovered unchanged [10].



Scheme 2

In order to compare compounds **5** with 4-substituted pyrrolin-2-ones as earlier described [4], we reacted **5a** with 4 aromatics aldehydes (**8a-d**), under reflux, with a solution of ethanolic sodium hydroxide to give the desired 4-substituted unsaturated dihydrofurans **9 a-d** (Scheme 3 and Table II).



Scheme 3

In conclusion, a new route to substituted furans **5** and **9** has been accomplished, using a one step procedure from very simple starting compounds. These products served to synthesize 4-substituted derivatives. All compounds are pre-

Table I. Preparation of Dicyanomethylendihydrofurans 5a-d

entry	Cpd.	yield	m.p.(°C)[a]	Mol. formula[b]	IR (Nujol)	^{1}H RMN δ, J(Hz)
1	**5a**	75	199	$C_{11}H_9N_3O$ 199.23	2235; 2221; 1616; 1596	1.63 (s,6H, $2CH_3$ C_5); 2.37 (s,3H, CH_3 C_4)
2	**5b**	73	125-127	$C_{13}H_{11}N_3O$ 225.27	2225; 2218; 1614; 1590	1.58 (s,3H, CH_3 C_5); 2.39 (s,3H, CH_3 C_4) 2.73 (dd, 1H, CH_2); 2.80(dd, 1H, CH_2); 5.19 to 5.57 (m, 3H, H vinyl).
3	**5c**	71	148	$C_{14}H_{13}N_3O$ 239.30	2226; 2217; 1615; 1588	1.62 (s,3H, CH_3 C_5); 2.38 (s,3H, CH_3 C_4) 1.75 (s,3H, CH_3 C=);2.50 (d, 1H, CH_2); 2.74(d, 1H, CH_2); 4.78 and 5.04 (2s, large, 2H, H ethyl.)
4	**5d**	69	139	$C_{17}H_{13}N_3O$ 275.33	2230; 2220; 1618; 1602; 1581	1.70 (s,3H, CH_3 C_5); 2.38 (s,3H, CH_3 C_4) 3.08 (d,1H, CH_2Ph); 3.35 (d,1H, CH_2Ph) 7.06 (m, 2H, Ph); 7.35 (m,3H, Ph).

[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 9a-d of 5a

entry	R	Cpd.	yield	mp.(°C)[a]	Mol. formula[b]	IR (Nujol)	^{1}H RMN δ, J(Hz)
1	2-furyl	**9a**	80	245-246	$C_{16}H_{11}N_3O_2$ 277.30	2229; 2211; 1610; 1589; 1567	1.72 (s, 6H, 2 CH_3); 6.64 (m, 1H, $H_{furyl.}$); 6.85 (d, J = 17 Hz, 1H, $H_{ethyl.}$); 6.97 (m, 1H, H_{furyl}); 7.55 (d, 1H, $H_{ethyl.}$); 7.70 (m, 1H, H_{furyl}).
2	2-pyridyl	**9b**	72	260-261	$C_{17}H_{12}N_4O$ 288.33	2225; 2219; 1619; 1589; 1558	1.85 (s, 6H, 2 CH_3); 7.52 (m, 1H, $H_{pyridin}$); 7.72 (d, J = 17 Hz, 1H, $H_{ethyl.}$); 7.88 (m, 1H, $H_{pyr.}$); 7.94 (d, 1H, $H_{ethyl.}$); 8.77 (m, 1H, $H_{pyridin.}$).
3	3-pyridyl	**9c**	64	248-249	$C_{17}H_{12}N_4O$ 288.33	2223; 2215; 1617; 1590; 1560	1.82 (s, 6H, 2 CH_3); 7.58 (m, 1H, $H_{pyridin}$); 7.36 (d, J = 17 Hz, 1H, $H_{ethyl.}$); 8.38 (m, 1H, $H_{pyr.}$); 7.95 (d, 1H, $H_{ethyl.}$); 8.68 (m, 1H, $H_{pyridin.}$); 9.05 (m, 1H, $H_{pyr.}$).
4	4-pyridyl	**9d**	67	277-278	$C_{17}H_{12}N_4O$ 288.33	2227; 2217; 1615; 1587; 1562	1.80 (s, 6H, 2 CH_3); 7.45 (d, 1H, $H_{ethyl.}$); 7.88 (d, J = 17 Hz, 1H, $H_{ethyl.}$); 7.90 (m, 2H, $H_{pyr.}$); 8.76 (m, 2H, $H_{pyridin.}$).

[a] Uncorrected, measured with a Reichert apparatus.

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

sently being tested to compare their biological activities. The scope and limitations are now under investigation.

Aknowledgment. We wish to thank Professor R. Couffignal for a gift of the three α-ketols **3b**, **3c** and **3d**.

Experimental section

General Methods. ^1H 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 at the CNRS Gif-sur Yvette.

General Procedure for the Preparation of 2-dicyanomethylen-3-cyano-4,5-dimethyl-5-alkyl-2,5-dihydrofurans 5a-d.

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 10 mmol of α-cetol **3a-3d** and 1.32 g (20 mmol) of malononitrile **4** were added. The resulting mixture was stirred for 20 h at room temperature. After concentration *in vacuo*, the residue was acidified with 6M aqueous HCl in order to adjust the pH to 4-5. The crude precipitate was filtered and recrystallized from ethanol to give pure **5**. The yields and physical data are given in Table I.

General Procedure for the Preparation of 2-dicyanomethylen-3- cyano-4,5-dimethyl-4-Alkylidene-2,5-dihydrofurans 9a-d.

To a solution of 10 mg of sodium hydroxide in 20 ml ethanol, was added 1g of **5a** (5 mmol) and aldehyde (**8a-d**)(5 mmol). The mixture was stirred and refluxed for 4 hours. After cooling the precipitated solid was filtered and recrystallized from ethanol. The yields and physical data are given in Table II.

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