A Convenient Synthesis of 5-Cyano-6-dialkylamino-2-hydroxy-3-methoxycarbonyl-2-methyl-4-(2- or 4-nitrophenyl)-1,2,3,4-tetrahydropyridines and their Dehydration to 5-Cyano-6-dialkylamino-3-methoxycarbonyl-2-methyl-4-(2- or 4-nitrophenyl)-1,4-dihydropyridines

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The reaction of cyanoacetamidines with methyl 2-[(nitrophenyl)methylene]-3-oxobutanoates leads to 2-hydroxy-1,2,3,4-tetrahydropyridines in high yields. These compounds can be dehydrated to 1,4-dihydropyridines by heating in benzene containing a catalytic amount of *p*-toluenesulfonic acid.

Dihydropyridines are of considerable interest because of their pharmacological properties. It has been reported that alkyl 3-alkylamino-3-aminoacrylates react with methyl 2-[(nitrophenyl)methylene]-3-oxobutanoates **1** to give 2-alkylamino-4,5- and -3,4-dihydropyridines.[1] We describe here the use of cyanoacetamidines[2] **2** as synthetic building blocks for the synthesis of 6-amino-2-hydroxy-1,2,3,4-tetrahydropyridines **3** and the dehydration of **3** to 1,4-dihydropyridines **4**.

Thus, the reaction of cyanoacetamidines **2a–d** with an equimolecular amount of methyl 2-[(2- or 3-nitrophenyl)methylene]-3-oxobutanoate[3] **1** at room temperature in ethanol, leads to 6-amino-2-hydroxy-1,2,3,4-tetrahydropyridines **3a–d** in 80–90%

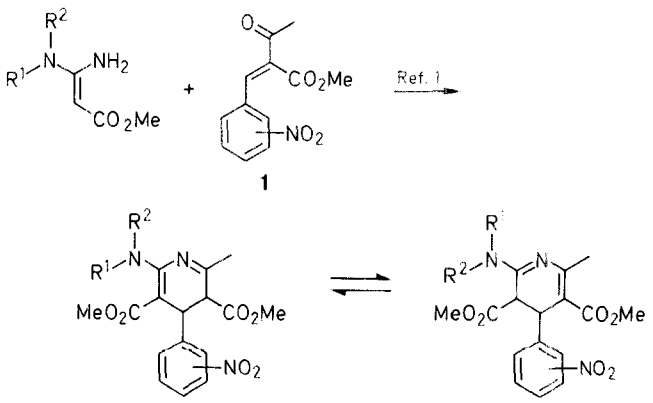


Table 1. Compounds **3** Prepared

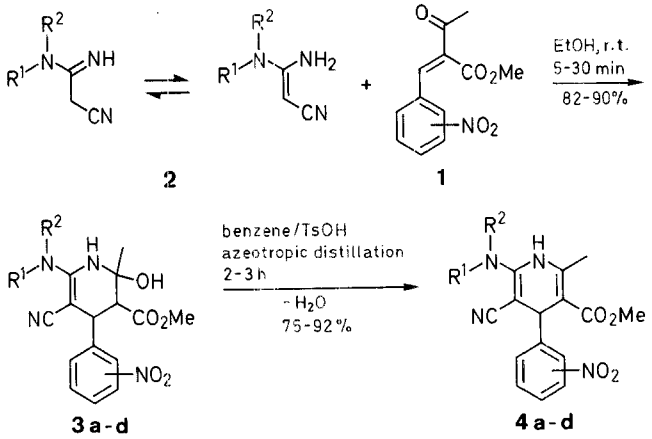
Product	R^1	R^2	$-NO_2$	Yield (%)	mp (°C)[a] (EtOH)	Molecular Formula[b]	^{1}H-NMR[c] (DMSO-d_6/TMS) δ
3a	Me	Me	3	85	138	$C_{17}H_{20}N_4O_5$ (360.3)	1.5 (s, 3H); 2.6 (d, 1H); 3 (s, 6H); 3.5 (s, 3H); 4.2 (d, 1H); 5.75 (s, 1H exchangeable with D_2O); 6.75 (s, 1H, exchangeable with D_2O); 7.75–8.15 (m, 4H)
3b	Et	Et	2	82	170	$C_{19}H_{24}N_4O_5$ (388.4)	1.1 (t, 6H); 1.45 (s, 3H); 2.7 (d, 1H); 3.22 (m, 4H); 3.4 (s, 3H); 4.6 (d, 1H); 5.72 (s, 1H, exchangeable with D_2O); 6.85 (s, 1H, exchangeable with D_2O); 7.6 (m, 4H)
3c	$(CH_2)_4$		2	90	172	$C_{19}H_{22}N_4O_5$ (386.4)	1.45 (s, 3H); 1.8 (m, 4H); 2.7 (d, 1H); 3.35 (m, 7H); 4.6 (d, 1H); 5.7 (s, 1H, exchangeable with D_2O); 6.3 (s, 1H, exchangeable with D_2O); 7.6 (m, 4H)
3d	$(CH_2)_2O(CH_2)_2$		3	88	180	$C_{19}H_{22}N_4O_6$ (402.4)	1.45 (s, 3H); 2.6 (d, 1H); 3.3 (m, 4H); 3.42 (s, 3H); 3.55 (m, 4H); 4.12 (d, 1H); 5.75 (s, 1H exchangeable with D_2O); 7 (s, 1H, exchangeable with D_2O); 7.7 (m, 2H); 8.05 (m, 2H)

[a] Melting points are uncorrected.
[b] Satisfactory microanalyses obtained: C ±0.16, H ±0.06, N ±0.05.
[c] Measured at 60 MHz using a Varian EM 360 spectrometer.

Table 2. Compounds **4** Prepared

Product	R^1	R^2	$-NO_2$	Yield[a] (%)	mp (°C)[b] (EtOH)	Molecular Formula[c]	^{1}H-NMR[d] (DMSO-d_6/TMS) δ
4a	Me	Me	3	75	206	$C_{17}H_{18}N_4O_4$ (342.3)	3.2 (s, 3H); 3.8 (s, 6H); 4.4 (s, 3H); 5.4 (s, 1H); 8.5 (m, 2H); 8.8 (m, 2H); 9.8s (s, 1H, exchangeable with D_2O)
4b	Et	Et	2	89	185	$C_{19}H_{22}N_4O_4$ (370.4)	1.1 (t, 6H); 2.35 (s, 3H); 3.4 (s, 3H + m, 4H); 5.1 (s, 1H); 7.4 (m, 4H); 8.9 (s, 1H, exchangeable with D_2O)
4c	$(CH_2)_4$		2	92	254	$C_{19}H_{20}N_4O_4$ (368.4)	2 (m, 4H); 2.5 (s, 3H); 3.6 (s, 3H); 3.7 (4H); 5.3 (s, 1H); 7.7 (m, 4H); 8.45 (s, 1H, exchangeable with D_2O)
4d	$(CH_2)_2O(CH_2)_2$		3	85	170	$C_{19}H_{20}N_4O_5$ (384.4)	2.35 (s, 3H); 3.35 (m, 4H); 3.6 (s, 3H + m, 4H); 4.55 (s, 1H); 7.68 (m, 2H); 8 (m, 2H); 9.2 (s, 1H, exchangeable with D_2O)

[a] Based on **3**.
[b] Uncorrected.
[c] Satisfactory microanalyses: C ±0.12, H ±0.06, N ±0.05.
[d] Measured at 60 MHz using a Varian EM 360 spectrometer.



yield (Table 1). The reaction proceeds fast and is complete after 5 to 30 min. The compounds isolated are stable and can be recrystallized from boiling methanol, ethanol or 2-propanol. The 6-amino-hydroxy-1,2,3,4-tetrahydropyridines **3** can be dehydrated to 1,4-dihydropyridines **4** by heating in boiling benzene containing a catalytic amount of *p*-toluenesulfonic acid with azeotropic removal of water (Table 2).

6-Dialkylamino-5-cyano-2-hydroxy-3-methoxycarbonyl-2-methyl-4-(2- or 3-nitrophenyl)-1,2,3,4-tetrahydropyridines 3a–d; General Procedure:
The *N,N*-dialkylcyanoacetamidine **2** (0.02 mol) and methyl 2-[(2- or 3-nitrophenyl)methylene]-3-oxobutanoate (**1**; 4.985 g, 0.02 mol) are stirred in EtOH (50 mL). A yellow precipitate forms within 5–30 min. The yellow product is isolated by suction and recrystallized from boiling EtOH.

6-Dialkylamino-5-cyano-3-methoxycarbonyl-2-methyl-4-(2- or 3-nitrophenyl)-1,4-dihydropyridines 4a–d; General Procedure:
A solution of the 1,2,3,4-tetrahydropyridine **3a–d** (0.015 mol) in benzene (100 mL) containing *p*-toluenesulfonic acid (50 mg) is heated to boiling with azeotropic removal of H_2O until the theoretical amount of H_2O (0.27 mL, 0.015 mol) has separated. The benzene solution of the product is then cooled and evaporated and the residue is extracted with $CHCl_3$ (100 mL). The extract is washed with 5% aqueous KOH (20 mL) and with H_2O (2 × 20 mL), dried (Na_2SO_4), and evaporated at reduced pressure. The remaining pale yellow product **4** is recrystallized from EtOH.

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(1) Meyer, H., Bossert, F., Vater, W., Stoepel, K. *German Patent* 2239815 (1974), Bayer AG; *C.A.* **1974**, *80*, 133275.
(2) Clark, J., Parvizi, B., Southon, I.W. *J. Chem. Soc. Perkin Trans. 1* **1976**, 125.
(3) Meyer, H., Bossert, F., Vater, W., Stoepel, K. *German Patent* 2235406 (1974), Bayer AG; *C.A.* **1974**, *80*, 120765.