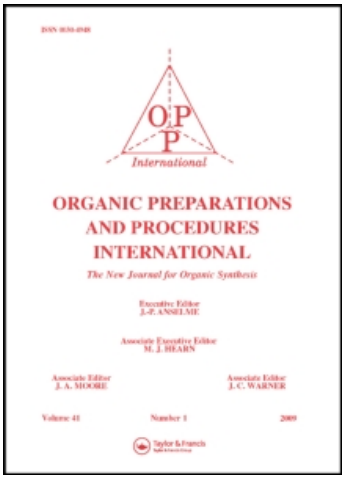

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PREPARATION OF SUBSTITUTED 1,6-DIAMINO-2-OXOPYRIDINES

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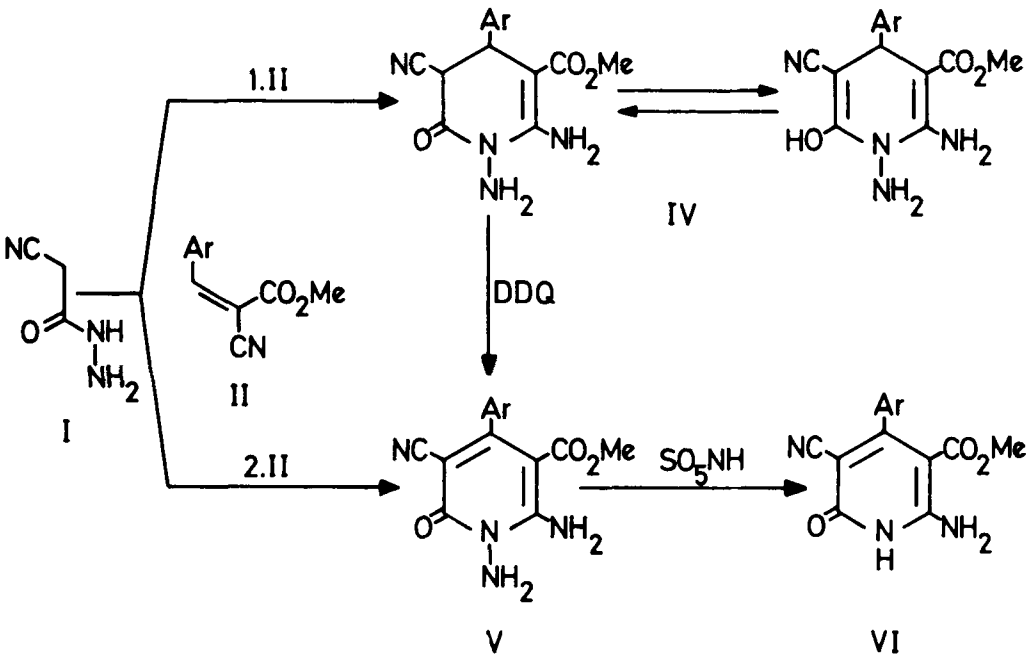
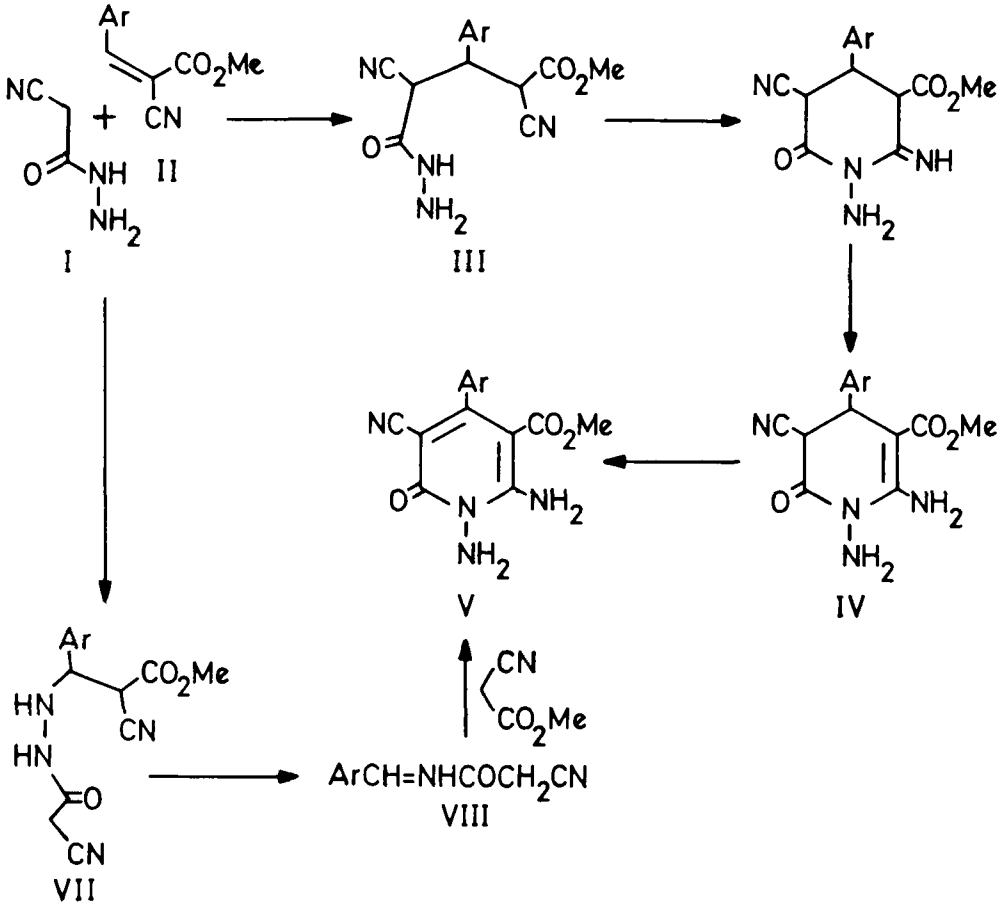
In a previous paper,[1] we reported a simple, one-step procedure for the synthesis of 1-amino-2-oxopyridines from benzylidenemalononitriles. Those compounds are useful synthetic intermediates,[2-5] but their synthesis is usually difficult.[6] Thus, we have now extended our synthesis to different 1,6-diamino-2-oxopyridines by using the reaction of cyanoacetohydrazide with methyl benzylidenecyanoacetates, which proved to be a somewhat different reaction.



Scheme 1

Methyl benzylidenecyanoacetates (II) react easily with cyanoacetohydrazide (I) to give a 1,6-diamino-2-oxopyridine system (Scheme 1). The reaction must be carried out in methanol at room temperature, even if it is a slow reaction, because higher temperatures result in lower yields. However, the compound actually obtained depends on the molar ratio of the reactants. If equimolar amounts of I and II are used, 3,4-dihydroderivatives IV are obtained. On the other hand, using two equivalents of benzylidenecyanoacetate per equivalent of cyanoacetohydrazide, the aromatic derivatives V are obtained. In either case, a Michael addition by cyanoacetohydrazide leads to adduct III, which cyclizes by attack at the cyano group and tautomerizes to dihydropyridine IV.



Scheme 2

However if a second molecule of II is present, it acts as the oxidant responsible for the aromatization (Scheme 2). This role for related unsaturated compounds as an aromatization reagent has been previously reported.[7] On the other hand, aromatization of IV to V can also be achieved in a separate reaction by treating it with dichlorodicyanoquinone (DDQ) according to the method of Duquette and Johnson.[8]

The cyclization reactions leading to IV and V are accompanied by a side-reaction involving the formation of cyanoacetohydrazones VIII which, in some instances, precipitate firts from the reaction medium. Formation of cyanocetohydrazones VIII can be explained as a 1,4-addition to II, followed by a retro-Michael elimination of a molecule of methyl cyanoacetate. Formation of VIII seems to be a reversible reaction and when VIII is treated with methyl cyanoacetate, 1,6-diamino-2-oxopyridine (V) is obtained.

Finally, the N-amino group of the 1,6-diamino-2-oxopyridines can be removed by means of a nitrous deamination using nitrosyl sulfuric acid in acetic acid as the reagent, using a method similar to the one reported by Overberger for other N-amino heterocycles.[9] 6-Amino-2-oxopyridines VI are obtained (Scheme 1).

EXPERIMENTAL SECTION

Melting points were determined in capillary tubes in a Büchi apparatus and are uncorrected. The ^{1}H-NMR spectra were recorded at 60 MHz on a Varian T-60A and chemical shifts are given in δ values against TMS as the internal standard. IR spectra were measured with a Perkin-Elmer 257 spectrophotometer in potassium bromide pellets. A Varian MAT-711 was used, for the recording of mass spectra. Microanalysis were performed by Centro Nacional de Química Orgánica de Madrid. The reactions and purity of compounds were monitored by TLC, performed on silicagel plates (Merck) and

using hexane-etanol as the eluent. Cyanoacetohydrazide and methyl cyanoacetate were obtained from Ega Chemie and used without further purification. Methyl benzylidenecyanoacetates (II) were prepared according to known methods.[13-16]

1,6-Diamino-4-aryl-5-carbomethoxy-3-cyano-2-oxopyridines (V). General Procedure.-

The corresponding methyl benzylidenecyanoacetate (II) (6mMol) and 3 mMol of cyanoacetohydrazide was suspended in ca 15 ml of dry methanol and a few drops of piperidine were added. The reaction mixture was allowed to stand at room temperature with magnetic stirring for the appropiate number of hours (see Table 1), until TLC shows no starting material left. The solid precipitate thus formed was collected by filtration. In most cases, this solid was the corresponding 1,6-diamino-2-oxopyridine (V) which was purified by means of several crystallizations in methanol. In some instances, however (reaction with IId), the first compound to precipitate was cyanoacetohydrazones (VIII) and the oxopyridine was recovered after concentration of the mother liquors (about half its initial volume).

1,6-Diamino-4-aryl-5-carbomethoxy-3-cyano-3,4-dihydro-2-oxopyridines (IV). General Procedure.-

A suspension of 12 mMol of the appropiate methyl benzylidenecyanoacetate (II) and 12 mMol of cyanoacetohydrazide in ca 30 ml of dry methanol with a few drops of piperidine was stirred at room temperature until the starting materials were exhausted (TCL). Compound IV were isolated by vacuum filtration and recrystallized from methanol. In the case (IIb) where the cyanoacetohydrazone precipitates first, this must be removed before IV can be isolated.

Transformation of 1,6-Diamino-5-carbomethoxy-3-cyano-4-phenyl-3,4-dihydro-2-oxopyridine (IVa) into 1,6-Diamino-5-carbomethoxy-3-cyano-4-phenyl-2-oxopyridine (Va).-To a warm solution of 17,5 mMol of IVa into

40 ml of methanol, were added 17,5 mMol of dichlorodicyanoquinone (DDQ) in small portions. The reaction mixture was refluxed for a few minutes and about one third of solvent was removed. The solution was allowed to stand at room temperature until precipitation occurs. The reaction product was collected by filtration and recrystallized from ethanol (yield 45%).

Transformation of 1,6-Diamino-5-carbomethoxy-3-cyano-4-phenyl-2-oxopyridine(Va) into 1-Hydro-6-amino-5-carbomethoxy-3-cyano-2-oxopyridine (VIa).-

A suspension of 1,6-diamino-2-oxopyridine Va (1 mMol) in 20 ml of acetic acid was treated with a solution of 1.1 mMol of nitrosyl sulfuric acid in ca. 10 ml of water. The reaction was stirred at room temperature for 24 hours and the resulting solution was then poured into crushed ice. The solid that precipitates was collected by filtration and washed with plenty of water, dried and purified by means of several crystallizations in methanol (yield 74%).

Reaction of Methyl cyanoacetate with p-Methylbenzylidenecyanoacetohydrazone (VIIIb).- A mixture of cyanoacetohydrazone VIIIb (0,5 mMol) and methyl cyanoacetate (0,5 mMol) was suspended in 5 ml of dry methanol containing a few drops of piperidine, and magnetic stirring was mantained until TLC shows no starting materials (about four days). After removing half the volume of solvent in vacuo 1,6-diamino-2-oxopyridine Vb precipitated and was isolated by filtration (yield 17%).

TABLE 1. Physical Data of Compounds IV-VIII

Comp.	Ar	Yield (%)	m.p.[a] (ºC)	Time (days)	Elemental Analysis:Calcd.(Found) C	H	N
IVa	C_6H_5	49	203-204	3	58.74	4.89	19.58
					(58.86)	(4.84)	(19.72)
IVb	p-$CH_3C_6H_4$	20[b]	181-182	2	60.00	5.33	18.67
					(59.94)	(5.59)	(18.88)
Va	C_6H_5	40[c]	247-248	3	59.15	4.22	19.72
					(59.45)	(4.36)	(19.83)
Vb	p-$CH_3C_6H_4$	45	246-247	6	60.40	4.69	18.79
					(60.31)	(4.80)	(18.94)
Vc	p-ClC_6H_4	35	242-243	21	52.75	3.45	17.58[d]
					(53.07)	(3.52)	(17.64)
Vd	p-$CH_3OC_6H_4$	19[b]	203-204	11	57.32	4.46	17.38
					(56.92)	(4.56)	(17.63)
Ve	p-$NO_2C_6H_4$	72	310-311	11	51.06	3.34	21.28
					(50.76)	(3.42)	(21.56)
VIa	C_6H_5	74	310-311	24	62.45	4.09	15.61
					(62.20)	(3.87)	(15.31)
VIIIb	p-$CH_3C_6H_4$	29	197-198	2		Ref. 17	
VIIId	p-$CH_3OC_6H_4$	60	210-212	11		Ref. 18	

a) All compounds were recrystallized from ethanol.

b) In these instances, the corresponding cyanoacetohydrazones must be removed before the oxopyridine can be isolated.

c) This yield is only 23% when the reaction is carried out at reflux temperatures.

d) Cl: Calc.: 11.14, Found: 11.28.

TABLE 2. Spectral Data of Compounds IV-VI

Comp.	NMR[a]					IR[b]		
	NH_2	N-NH_2[c]	ArH	CO_2Me	Other	NH[d]	C=O	C=O (ester)
IVa[e]	7.3-8.0	5.20	6.8-7.2	3.40		3440,3340 3300	1665	1685
IVb[e]	7.3-8.0	5.17	6.8-7.1	3.40	2.20(CH_3)	3440,3340 3220	1660	1660
Va[f]	8.20	5.53	6.9-7.4	3.17		3390,3270	1660	1685
Vb	8.13	5.50	6.8-7.2	3.17	2.30(CH_3)	3430,3300	1655	1685
Vc	8.20	5.50	6.9-7.4	3.20		3390,3270	1660	1685
Vd	8.27	5.63	6.8-7.3	3.30	3.80(CH_3O)	3400,3300	1650	1680
Ve	8.60	5.53	7.4-8.4	3.27		3400,3300	1650	1680
VIa[g]	7.46	--	7.0-7.5	3.20		3420,3320 2800	1670	1715

a) NMR spectra of all compounds were recorded in DMSO-d_6.

b) The cyano group gives rise to a band at 2220 cm^{-1} in compounds V and VI and 2250 cm^{-1} in compounds IV.

c) This protons are identified by addition of TFA and their chemical shifts agree with reported values for other N-amino heterocycles (Ref. 11,12).

d) A band at 1510-1540 is also present, and can be asigned to N-substitution (Ref. 10).

e) Hydrogens at position 3 and 4 of the ring appear as two doublets at 4.93 and 4.10 ppm in IVa and at 4.87 and 4.13 in IVb.

f) Mass spectrum of compound Va: m/e = 284(M+, 100), 269(12), 253(17), 252(49), 225(18), 224(19), 223(16), 195(11), 140(13), 128(14), 127(10).

g) Mass spectrum of compound VIa: m/e = 269(M+, 100), 238(39), 237(72), 204(16), 202(65), 201(30), 200(51), 199(38), 198(23), 114(14), 104(13), 101(18).

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