Synthesis and reactivity of enamines in pyridine series

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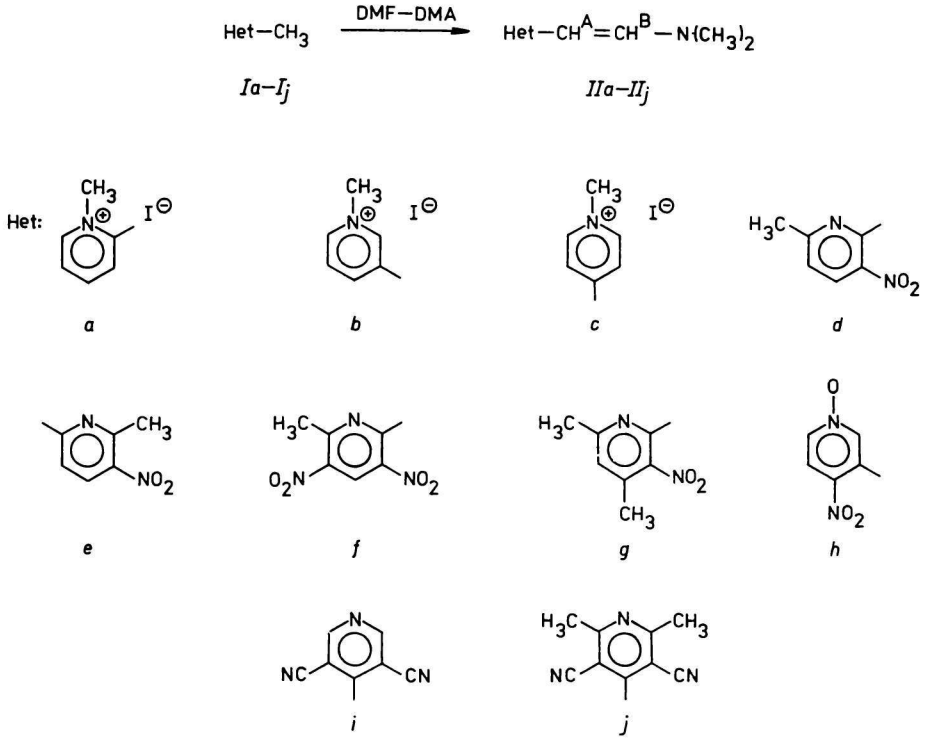
The paper describes synthesis of enamines, containing substituted pyridine moiety at the double bond, by the reaction of suitably substituted picolines, lutidines, and collidines with dimethylformamide dimethyl acetal. By the same method enamino ketones derived from acetylpyridines were prepared. Rotational barriers of enamino ketones were measured by dynamic ^{1}H NMR spectroscopy. Enamino ketones were cyclized with hydrazine and cyanoacetamide.

В работе описан синтез енаминов пиридинового ряда посредством реакции соответствующих замещенных пиколинов, лутидинов и коллидинов с диметилацеталем диметилформамида. Аналогичным образом были получены из ацетилпиридинов енаминокетоны. Изучались ротационные барьеры енаминокетонов с помощью динамической ^{1}H ЯМР спектроскопии. Проведены циклизации енаминокетонов с гидратом гидразина и цианоацетамидом.

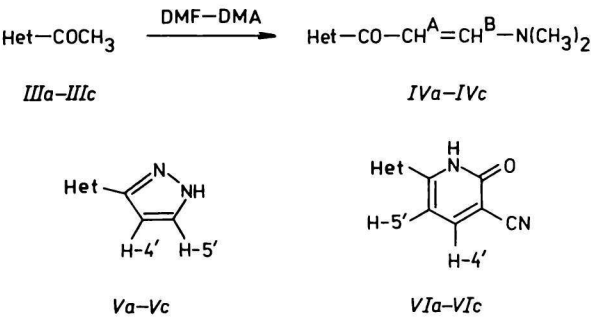
We have already described [1—3] the synthesis of heteroaryl enamines by the reaction of activated heteroarylvinyl halides with secondary aliphatic and cyclic amines, respectively. Such enamines are highly reactive starting compounds for further syntheses [4]. Enamines of the pyridine series have been prepared by multi-step complicated procedure [3].

Having recognized the synthetic potential of the title enamines we have sought simpler procedures for their preparation. Condensation of the suitably substituted picolines *Ia—Ic*, *Ih*, *Ii*, lutidines *Id*, *If*, and collidines *Ig*, *Ij* (prepared according to literature [5—11] with identical physicochemical constants) with dimethylformamide dimethyl acetal at 140—150 °C provided ten new enamines *IIa—IIj*, containing pyridine ring, in 37—80 % yield (Scheme 1). Based on the value of the coupling constant of ethylenic protons ($J_{A,B}$ = 12.5—12.8 Hz) in their ^{1}H NMR spectra, enamines were assigned *E* configuration.

Analogously enamino ketones *IVa—IVc* were synthesized from acetylpyridines [12, 13] *IIIa—IIIc* (Scheme 2). Hydrogens at the double bond of *IVa—IVc* were found to be in *E* configuration as well ($J_{A,B}$ = 12.5 Hz). Dynamic ^{1}H NMR spectroscopic studies were performed in order to determine rotational barriers



Scheme 1



a: Het = 2-pyridyl
b: Het = 3-pyridyl
c: Het = 4-pyridyl

Scheme 2

of enamino ketones *IVa*—*IVc*. Measured values of coalescence temperature T_c, band halfwidths b_E and of resonance frequencies $\Delta\nu_c$ are given in Table 1.

Table 1

^{1}H NMR coalescence values of compounds *IV* (c = 0.25 mol dm^{-3}) at 60 MHz in deuterochloroform

Compound	T_c/K	$\Delta\nu_c$/Hz	b_E/Hz	k_c/s^{-1}	$\Delta G_c^{\neq}$/kJ mol^{-1}
IVa	302	11.2	1.0	23.7	66.2 ± 0.5
IVb	302	14.1	1.0	30.1	65.6 ± 0.5
IVc	309	14.2	1.0	30.3	67.0 ± 0.5

Rotational barriers $\Delta G_c^{\neq}$ around the partial C—N double bond have been found to be almost identical within the experimental error $\Delta\Delta G_c^{\neq}$ (0.5 kJ mol^{-1}) for all derivatives *IV* The results thus entitle us to state that the position of substitution at the pyridine ring does not affect the reactivity of β-enamino ketone group. All enamino ketones *IV* underwent cyclization reaction [14], giving with hydrazine the corresponding pyridylpyrazoles *Va*—*Vc*. Similar cyclization with cyanoacetamide furnished pyridyl-substituted pyridones *VIa*—*VIc*, whereby the pyridone ring was created by C-alkylation and ring closure through the amino group of the amide. Assignment of proton signals in NMR spectra was based on both chemical shifts and multiplicity.

Experimental

Melting points were measured on a Kofler hot stage. Infrared spectra were taken with a Specord IR 71 spectrophotometer of either chloroform solutions or KBr discs. Ultraviolet spectra were measured with a Specord model M 40 in methanolic solutions (1×10^{-4} M). ^{1}H NMR spectra were taken with an 80 MHz Tesla spectrometer, model BS 487 C at 25 °C in dimethyl sulfoxide-d_6, using Me_4Si as internal standard. Rotational barriers were determined from measurements performed with a 60 MHz Tesla spectrometer, model BS 467, in deuterochloroform, containing 0.1 vol. % of pyridine, which removed traces of hydrogen chloride [15] and with hexamethyldisiloxane as internal standard. For NMR measurements of compounds *IVa*—*IVc* 0.25 M solutions were used.

Enamines of the pyridine series (IIa—IIj)

The requisite substituted picoline, lutidine, and collidine, respectively (0.005 mol) (*If* and *Ij* were treated in half amounts) was heated with 2 cm^3 of dimethylformamide

Table 2

Physical constants of enamines *IIa*—*IIj*

Compound	Formula	M_r	w_i(calc.)/% w_i(found)/%			Yield	M.p.	Reaction time/h
			C	H	N	%	°C	
IIa	$C_{10}H_{15}IN_2$	290.15	41.40	5.21	9.66	73	196—198[a]	10
			41.21	5.18	9.54		(decomp.)	
IIb	$C_{10}H_{15}IN_2$	290.15	41.40	5.21	9.66	37	204—207[a]	10
			41.25	5.15	9.60		(decomp.)	
IIc	$C_{10}H_{15}IN_2$	290.15	41.40	5.21	9.66	71	151—154[a]	10
			41.35	5.20	9.58		(decomp.)	
IId	$C_{10}H_{13}N_3O_2$	207.23	57.96	6.32	20.28	42	95—97[b]	16
			57.84	6.30	20.14			
IIe	$C_{10}H_{13}N_3O_2$	207.23	57.96	6.32	20.28	43	103—105[b]	16
			57.90	6.25	20.20			
IIf	$C_{10}H_{12}N_4O_4$	252.23	47.62	4.80	22.21	80	193—195[b]	5
			47.58	4.70	22.15			
IIg	$C_{11}H_{15}N_3O_2$	221.26	59.71	6.83	18.99	55	116—117[b]	16
			59.60	6.75	18.75			
IIh	$C_9H_{11}N_3O_3$	209.21	51.67	5.30	20.09	65	208—210[c]	5
			51.68	5.22	20.05			
IIi	$C_{11}H_{10}N_4$	198.23	66.65	5.09	28.26	64	193—195[b]	5
			66.62	5.15	28.23			
IIj	$C_{13}H_{14}N_4$	226.28	69.00	6.24	24.76	58	200—203[b]	10
			69.05	6.17	24.78			

a) Methanol—ether; *b*) heptane; *c*) benzene.

dimethyl acetal and 5 cm^3 of dimethylformamide at 140—150 °C for 2—16 h. After that the solvent was removed by vacuum distillation and the rest was then either crystallized or purified by chromatography at SiO_2 column, eluant prepared by mixing benzene, chloroform, and ethyl acetate.

Physical and spectral characteristics of compounds *IIa*—*IIj* are given in Tables 2—4.

Enamino ketones (IVa—IVc)

The corresponding acetylpyridines *IIIa*—*IIIc* (1.76 g; 0.01 mol) were heated with 2 cm^3 of dimethylformamide dimethyl acetal in 5 cm^3 of dimethylformamide at 140—150 °C for 2 h. The solvent was evaporated in vacuum and the solid rest crystallized. Physical constants and spectral data of compounds *IVa*—*IVc* are listed in Tables 5—7.

Table 3

UV and IR spectral data of compounds *IIa*—*IIj*

Compound	λ_{max}/nm (log {ε})	$\tilde{\nu}$/cm^{-1}				
		ν(C=C)	ν(pyr)	$\nu_s(NO_2)$	$\nu_{as}(NO_2)$	ν(C≡N)
IIa	200 (3.35), 220 (3.32), 333 (3.15), 381 (3.52)	1640	1580, 1620			
IIb	200 (3.13), 220 (2.98), 338 (3.28)	1640	1580, 1615	—	—	
IIc	200 (3.24), 220 (3.30), 400 (3.76)	1635	1575, 1615	—	—	—
IId	219 (3.11), 265 (3.04), 353 (2.96), 457 (2.39)	1625	1580, 1605	1345	1560	—
IIe	201 (3.21), 282 (2.89), 434 (3.47)	1640	1575, 1590	1340	1550	—
IIf	200 (3.27), 252 (3.21), 442 (3.67)	1625	1575, 1605	1350	1550	—
IIg	200 (3.25), 342 (2.93)	1645	1580, 1600	1345	1545	—
IIh	201 (3.23), 322 (3.28), 500 (2.69)	1640	1580, 1600	1345	1560	—
IIi	212 (3.40), 257 (2.88), 374 (3.56)	1640	1580, 1600	—	—	2240
IIj	214 (3.43), 385 (3.56)	1640	1580, 1600	—	—	2235

Table 4

^{1}H NMR spectra of enamines *IIa*—*IIc* (hexadeuterodimethyl sulfoxide), *IId*—*IIj* (deuterochloroform)

Compound	δ/ppm		$J_{A,B}$/Hz	δ/ppm	
	H^A	H^B		$-N(CH_3)_2$	Other protons
IIa	5.09 d	8.16 d	12.5	3.23 3.0	8.25 (d, 1H, H-6), 7.6—8.3 (m, 2H, H-3 and H-4), 6.7—7.1 (m, 1H, H-5), 3.84 (s, 3H, $\overset{\oplus}{N}$—CH_3)
IIb	5.05 d	7.59 d	12.5	2.89	8.71 (d, 1H, H-2), 8.0—8.4 (m, 2H, H-2 and H-6), 7.69 (dd, 1H, H-5), 4.19 (s, 3H, $\overset{\oplus}{N}$—CH_3)
IIc	5.26 d	8.04 d	12.8	3.10 2.93	8.04 (d, 2H, H-2 and H-6), 7.30 (d, 2H, H-3 and H-5), 3.84 (s, 3H, $\overset{\oplus}{N}$—CH_3)
IId	6.26 d	8.10 d	12.5	3.03	8.12 (d, 1H, H-4), 6.63 (d, 1H, H-5), 2.48 (s, 3H, CH_3), $J_{4,5}$ = 8.5 Hz
IIe	5.18 d	7.78 d	12.5	2.99	8.10 (d, 1H, H-4), 6.69 (d, 1H, H-5), 2.68 (s, 3H, CH_3), $J_{4,5}$ = 8.5 Hz
IIf	6.39 d	8.39 d	12.5	3.28 3.06	9.01 (s, 1H, H-4), 2.83 (s, 3H, CH_3)
IIg	4.83 d	7.09 d	12.8	2.89	6.93 (s, 1H, H-5), 2.41 (s, 6H, 2 × CH_3)
IIh	6.02 d	7.13 d	12.8	3.01	8.36 (d, 1H, H-2), 7.91 (d, 1H, H-6), 7.65 (d, 1H, H-5), $J_{5,6}$ = 8.3 Hz
IIi	5.39 d	8.33 d	12.5	3.14	8.53 (s, 2H, H-2 and H-6)
IIj	5.50 d	8.05 d	12.5	3.06	2.56 (s, 3H, CH_3), 2.61 (s, 3H, CH_3)

Table 5

Physical constants of enamino ketones *IVa—IVc*

Compound	Formula	M_r	w_i(calc.)/% w_i(found)/%			Yield	M.p.
			C	H	N	%	°C
IVa	$C_{10}H_{12}N_2O$	176.22	68.16	6.86	15.90	77	125—126[a]
			68.02	6.80	15.88		
IVb	$C_{10}H_{12}N_2O$	176.22	68.16	6.86	15.90	70	62—66[b]
			68.10	6.78	15.92		
IVc	$C_{10}H_{12}N_2O$	176.22	68.16	6.86	15.90	72	114—116[c]
			68.05	6.88	15.85		

a) Cyclohexane; *b*) benzene—petroleum ether ($\varphi_r = 3:1$); *c*) ethyl acetate.

Table 6

UV and IR spectral data of enamino ketones *IVa—IVc*

Compound	λ_{max}/nm (log {ε})	$\tilde{\nu}$/cm^{-1}	
		ν(CO)	ν(pyr)
IVa	200 (3.05), 243 (2.90), 355 (3.27)	1650	1570, 1600
IVb	200 (3.13), 234 (2.96), 348 (3.30)	1650	1570, 1602
IVc	200 (3.05), 227 (3.00), 355 (3.26)	1650	1580, 1605

3-(5)-Pyridylpyrazoles (Va—Vc)

To the solution of pyridylenamino ketone *IVa—IVc* (0.9 g; 0.0051 mol) in 10 cm^3 of methanol 0.65 g of 85 % aqueous solution of hydrazine monohydrate was added. Reaction mixture was then heated at the boiling point for 6 h. The solvent was subsequently removed by distillation and the solid residue crystallized from benzene—heptane mixture ($\varphi_r = 3:1$). Yield and physical constants of compounds *Va—Vc* are given in Table 8.

^{1}H NMR spectra of compounds *Va—Vc* (hexadeuterodimethyl sulfoxide), δ/ppm:

Va: 8.53 (d, 1H, H-6), 7.63—8.0 (m, 2H, H-3 and H-4), 7.20 (dd, 1H, H-5), 7.75 (d, 1H, H-5′), 6.81 (d, 1H, H-4′), $J_{5,6} = 4.8$ Hz, $J_{4',5'} = 2$ Hz.

Vb: 9.11 (d, 1H, H-2), 8.53 (dd, 1H, H-6), 8.21 (dt, 1H, H-4), 7.43 (dd, 1H, H-5), 7.83 (d, 1H, H-5′), 6.84 (d, 1H, H-4′), $J_{4',5'} = 2$ Hz.

Vc: 8.56 (d, 2H, H-2 and H-6), 7.78 (d, 2H, H-3 and H-5), 7.81 (d, 1H, H-5′), 6.89 (d, 1H, H-4′), $J_{2,3} = J_{5,6} = 6$ Hz, $J_{4',5'} = 2$ Hz.

Table 7

^{1}H NMR spectra of enamino ketones *IVa*—*IVc* (hexadeuterodimethyl sulfoxide)

Compound	δ/ppm		$J_{A,B}$/Hz	δ/ppm		
	H^A	H^B		$-N(CH_3)_2$		Other protons
IVa	6.29 d	7.72 d	12.5	3.09	2.84	8.55 (d, 1H, H-6), 7.3—8.0 (m, 3H, H-3, H-4 and H-5)
IVb	5.82 d	7.74 d	12.5	3.13	2.90	9.04 (d, 1H, H-2), 8.62 (dd, 1H, H-6), 8.19 (dt, 1H, H-4), 7.44 (dd, 1H, H-5)
IVc	5.79 d	7.76 d	12.5	3.11	2.89	8.64 (d, 2H, H-2 and H-6), 7.72 (d, 2H, H-3 and H-5)

Table 8

Physical constants of derivatives *Va*—*Vc*

Compound	Formula	M_r	w_i(calc.)/% w_i(found)/%			Yield	M.p.
			C	H	N	%	°C
Va	$C_8H_7N_3$	145.17	66.19	4.86	28.95	65	116—119
			66.15	4.75	29.10		
Vb	$C_8H_7N_3$	145.17	66.19	4.86	28.95	60	Oil
			66.12	4.84	29.04		
Vc	$C_8H_7N_3$	145.17	66.19	4.86	28.95	68	154—157[a]
			66.10	4.82	29.08		

a) Ref. [16] gives m.p. = 151—153 °C.

Table 9

Physical constants of 3-cyano-6-pyridyl-2-pyridones *VIa*—*VIc*

Compound	Formula	M_r	w_i(calc.)/% w_i(found)/%			Yield	M.p.
			C	H	N		°C
VIa	$C_{11}H_7N_3O$	197.20	67.00	3.58	21.31	50	241—244
			66.88	3.51	21.25		
VIb	$C_{11}H_7N_3O$	197.20	67.00	3.58	21.31	45	295—298
			66.95	3.45	21.20		
VIc	$C_{11}H_7N_3O$	197.20	67.00	3.58	21.31	48	303 (decomp.)
			66.98	3.54	21.30		

3-Cyano-6-pyridyl-2-pyridones (VIa—VIc)

To the aqueous solution (15 cm^3) of the starting pyridylenamino ketone *IVa*—*IVc* (0.9 g; 0.0051 mol) cyanoacetamide (0.43 g; 0.0051 mol) was added and the reaction mixture refluxed for 3 h. The separated crystalline compound was filtered off and crystallized from water. Physicochemical data of compounds *VIa*—*VIc* are given in Tables 9 and 10.

Table 10

IR and ^{1}H NMR spectral data of 3-cyano-6-pyridyl-2-pyridones *VIa*—*VIc* (hexadeuterodimethyl sulfoxide)

Compound	$\tilde{\nu}$/cm^{-1}		δ/ppm		$J_{4',5'}$/Hz	δ/ppm
	ν(CO)	ν(CN)	H-4′	H-5′		Other proton signals
VIa	1650	2220	8.25 d	7.24 d	7.8	8.74 (d, 1H, H-6), 7.43—8.4 (m, 3H, H-3, H-4, and H-5)
VIb	1660	2225	8.18 d	6.85 d	7.8	8.96 (d, 1H, H-2), 8.68 (dd, 1H, H-6), 8.12—8.3 (m, 1H, H-4), 7.51 (dd, 1H, H-5)
VIc	1660	2225	8.15 d	6.98 d	7.8	8.7 (d, 2H, H-2 and H-6), 7.79 (d, 2H, H-3 and H-5)

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