PREPARATION OF PYRIMIDINES AND PYRIDINES FROM ALKYL KETONES AND NITRILES IN PRESENCE OF PHOSPHORYL CHLORIDE

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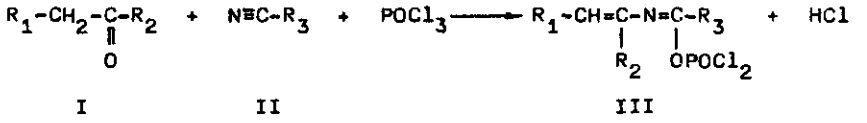
Abstract - The reaction of alkyl ketones with nitriles in the presence of $POCl_3$ has been examined. It has been found that N-vinylimidoyl dichlorophosphates initially formed react further with excess nitriles or ketones to afford pyrimidine or pyridine derivatives, respectively.

In contrast to basic catalysts which cause abstraction of the α-proton of nitrile group giving β-hydroxynitriles or α,β-unsaturated nitriles[1-4] in reactions of nitriles with carbonyl compounds, acid catalysts shall activate carbonyl carbon atom toward nucleophilic attack of nitrile nitrogen atom. These reactions, similar to the Ritter reaction[5], were carried out using such catalysts as H_2SO_4[6], $AlCl_3$[7] and $POCl_3$[8]. Imidoyl compounds[7,8] formed at the first stage of the reaction can be used to synthesize heterocycles. Thus, isoquinoline derivatives[9] were obtained by the reaction of benzyl ketones with nitriles in the presence of $POCl_3$, while acetophenone reacted with benzonitrile in the presence of $AlCl_3$ to yield a 1,3-oxazine derivative[7].

In this work, the reaction of alkyl ketones with nitriles in the presence of $POCl_3$ was explored to prepare pyrimidine and pyridine derivatives.

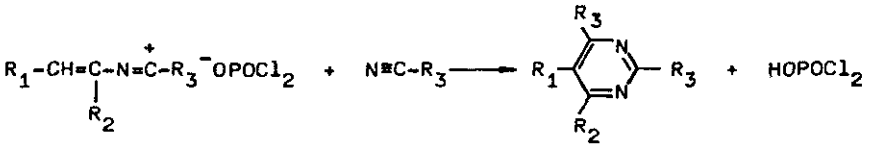
Alkyl ketones (I) and nitriles (II), upon heating in the presence of $POCl_3$, form *N*-vinylimidoyl dichlorophosphates (III) at the first stage of the reaction.



I II III

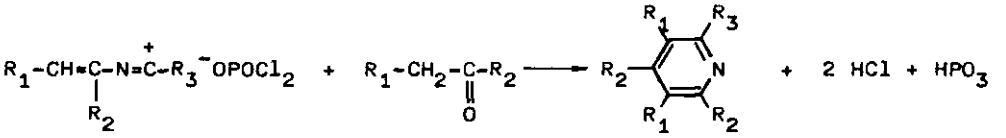
In fact, compound III was isolated when benzyl methyl ketone was reacted with acetonitrile[8], while N-acylvinylamines, alkaline hydrolysis products[8] of III, were obtained if $R_1 \neq H$[7,8]. Further courses of reaction suggest that the forma-

tion of N-vinylimidoyl dichlorophosphates from the reaction of alkyl ketones with nitriles in the presence of $POCl_3$ can be considered as a general process. Strongly polarized C-O bond in N-vinylimidoyl dichlorophosphates undergoes a heterolytic cleavage at elevated temperature yielding N-vinyliminocarbenium cations, which in turn may further react with nucleophiles present in the reaction medium. When an excess of nitrile is used, the reaction of N-vinyliminocarbenium cation with the nitrile nitrogen atom occurs to give pyrimidine derivative IV.



IV

On the other hand, pyridines V may be obtained when N-vinyliminocarbenium cation reacts with the α-carbon of ketone.



V

Most of pyrimidine and pyridine derivatives thus obtained (Table 1) were previously prepared by other methods. The structures of new compounds were determined by microanalyse, uv and ^1H nmr examinations (Table 2). The purity of prepared compounds was tested by TLC and GLC methods. The reaction of N-vinylimidoyl dichlorophosphates with nitriles or ketones giving pyrimidines or pyridines, respectively, proceeds very slowly on account of low basicities of nucleophiles and the reactants should be kept boiling for several hours. The yields of the pyrimidine and pyridine derivatives are not high and vary greatly depending on the structure of substrates. The yields are affected by the rates of reaction of N-vinylimidoyl dichlorophosphates with nitriles or ketones, giving pyrimidines or pyridines, respectively, and the rates of other reactions of imidoyl dichlorophosphates, such as the von Braun fragmentation reaction[8,10] or reaction with carbonyl oxygen atom[11] of ketones yielding 1,3-oxazines. The yields of pyrimidines IV (Table 1) were moderate, when N-vinylimidoyl dichlorophosphates were reacted with acetonitrile. When the rate of reaction of

Table 1. Pyrimidines IV and Pyridines V Prepared[a]

	Ketone I		Nitrile II	Pyrimidine IV					
	R_1	R_2	R_3	Yield %	bp °C/torr or mp °C	R_f[b]	t'_R[c]	mp of picrate °C	Ref
a	H	CH_3	CH_3	31	167-168/750	0.13	8.2	145-146	13
b	CH_3	CH_3	CH_3	52	196-197/750	0.18	11.5	129-130	14
c	H	C_6H_5	CH_3	19	145/5	0.11		209-210	
d	H	p-$NO_2C_6H_4$	CH_3	55	173-173.5	0.16		-	
e	CH_3	C_6H_5	CH_3	31	146-148/6 62-64	0.15		164-166	
f	H	CH_3	C_6H_5	2	93.5-94	0.30		155	15
g	H	CH_3	p-$CH_3OC_6H_4$	5	112-113	0.34		-	
h	H	CH_3	$C_6H_5CH_2$	-		0.20			
				Pyridine V					
a	H	CH_3	CH_3	12	169-170/750	0.22	7.2	157-158	16
b	CH_3	CH_3	CH_3	37	180-182/740	0.31	6.6	145-146	17
f	H	CH_3	C_6H_5	15	134-136/5	0.59		187	18
g	H	CH_3	p-$CH_3OC_6H_4$	10	167-168/3	0.52		203-204	
h	H	CH_3	$C_6H_5CH_2$	16	140-142/6	0.31		152-153	19

[a]The microanalyses of products and their picrates were in satisfactory agreement with the calculated values (C ± 0.28 %, H ± 0.24 %, N ± 0.32 %).

[b]TLC - stationary phase: silica gel; mobile phase: 3:1 v/v benzene/ethyl acetate

[c]GLC - packing of column: silica rubber SE-30 25% on Chromosorb W, column: 3 m long and 4 mm in diameter, carrier gas: hydrogen 100 ml/min, operating temperature: 68°C for IVa and Va, 80°C for IVb and Vb.

N-vinylimidoyl dichlorophosphates with nitrile decreases due to a steric hindrance or lower nucleophilicity of nitrile nitrogen atom (R_3 = C_6H_5, C_6H_5-CH_2), the yields of pyrimidines were much decreased. The pyridines V were formed only, when aliphatic ketones were used in the reaction with N-vinylimidoyl dichlorophosphates. When alkyl aryl ketones (R_1 = H, CH_3, R_2 = C_6H_5) were used, pyridines were not formed. In these cases the reaction yielded 4H-1,3-oxazines and small amounts of pyrimidines, which were formed from the reaction of N-vinylimidoyl dichlorophosphates with nitriles accompanied by the von Braun fragmen-

Table 2. Spectral Data of Pyrimidines IV and Pyridines V

Product	uv (methanol/water) medium[a] λ_{max} [nm] ($\varepsilon.10^{-3}$)	^{1}H nmr (CCl_4) δ [ppm]
IVa	basic 259 (4.1)	5.95 (s, 1H, 5-H); 2.22 (s, 3H, 2-CH_3);
	acidic 264 (5.6)	2.0 (s, 6H, 4-CH_3, 6-CH_3)
b	basic 259 (4.0)	2.48 (s, 3H, 2-CH_3); 2.26 (s, 6H, 4-CH_3, 6-CH_3);
	acidic 264 (5.6)	1.98 (s, 3H, 5-CH_3)
c	basic 251 (11.2) 278 (13.8)	8.35-7.53 (m, 5H, 6-C_6H_5); 7.46 (s, 1H, 5-H);
	acidic 254 (6.3) 302 (16.2)	2.92 (s, 3H, 2-CH_3); 2.68 (s, 3H, 4-CH_3)
d	basic 295 (18.1)	8.77-8.70 (q, 4H, 6-C_6H_4-NO_2-p); 7.87 (s, 1H,
	acidic 298 (22.2)	5-H); 3.20 (s, 3H, 2-CH_3); 3.0 (s, 3H, 4-CH_3)
e	basic 241 (5.4) 272 (8.9)	7.37 (s, 5H, 6-C_6H_5); 2.53 (s, 3H, 2-CH_3);
	acidic 291 (11.9)	2.40 (s, 3H, 4-CH_3); 2.17 (s, 3H, 5-CH_3)
f	basic 259 (36.0)	8.68-7.60 (m, 11H, 2-C_6H_5, 4-C_6H_5, 5-H);
	acidic 259 (31.7)	2.6 (s, 3H, 6-CH_3)
g	basic 292 (44.9)	8.77-7.30 (m, 9H, 2-$C_6\underline{H}_4$-OCH_3-p, 4-$C_6\underline{H}_4$-OCH_3-p,
	acidic 297 (21.3) 351 (36.0)	5-H); 4.15 (s, 6H, 2-C_6H_4-$OC\underline{H}_3$-p,
		4-C_6H_4-$OC\underline{H}_3$-p); 2.85 (s, 3H, 6-CH_3)
Va	basic 264.5 (3.0)	6.58 (s, 2H, 3-H, 5-H); 2.32 (s, 6H, 2-CH_3,
	acidic 268 (5.9)	6-CH_3); 2.17 (s, 3H, 4-CH_3)
b	basic 265.5 (2.3)	1.77 (s, 6H, 2-CH_3, 6-CH_3); 1.67 (s, 6H, 3-CH_3,
	acidic 270 (5.9)	5-CH_3); 1.45 (s, 3H, 4-CH_3)
f	basic 245 (11.9) 282 (10.4)	8.05-7.25 (m, 6H, 2-C_6H_5, 3-H); 6.80 (s, 1H,
	acidic 246 (6.0) 297 (14.0)	5-H); 2.50 (s, 3H, 6-CH_3); 2.33 (s, 3H, 4-CH_3)
g	basic 261 (11.6) 288 (14.4)	7.98-7.75 (q, 4H, 2-$C_6\underline{H}_4$-OCH_3-p); 7.18 (s, 1H,
	acidic 264 (6.2) 324 (14.6)	3-H); 6.70 (s, 1H, 5-H); 3.78 (m, 3H,
		2-C_6H_4-$OC\underline{H}_3$-p); 2.50 (s, 3H, 6-CH_3); 2.26 (s,
		3H, 4-CH_3)
h	basic 267 (5.1)	7.17 (s, 5H, 2-CH_2-$C_6\underline{H}_5$); 6.68 (s, 1H, 3-H);
	acidic 275 (8.4)	6.57 (s, 1H, 5-H); 3.98 (s, 2H, 2-$C\underline{H}_2$-C_6H_5);
		2.43 (s, 3H, 6-CH_3); 2.17 (s, 3H, 4-CH_3)

[a]Basic medium - 0.01 M NaOH in 10% methanol, acidic medium - 0.01 M HCl in 10% methanol.

tation. Yields of pyrimidines and pyridines increase, when the intermediate N-vinylimidoyl dichlorophosphates have an alkyl group in the 2-position ($R_1 \neq H$). It is shown that this group of N-vinylimidoyl dichlorophosphates is more stable in the reaction medium.

EXPERIMENTAL

Preparation of pyrimidines IV.

A mixture of alkyl ketone I (0.02 mole), nitrile II (0.1 mole) and $POCl_3$ (0.02 mole) was kept boiling until no initial ketone was observed in the samples (tested by means of TLC after their hydrolysis in acidic medium). The reaction mixture was then poured onto ice and distilled with steam. Distillate was discarded, the remainder was filtered to remove tars, then alkalized with NaOH solution. Pyrimidines (IVa, b, c, e) volatile in steam were separated by repeated steam distillation and extraction of distillate with ether. Pyrimidines (IVd, f, g) non-volatile in steam were separated by filtration or ether extraction. The solid products were purified by crystallization from hexane (IVd, e, f) or ethanol (IVg).

Preparation of pyridines V.

A mixture of alkyl ketone I (0.1 mole), nitrile II (0.03 mole) and $POCl_3$ (0.03 mole) was kept boiling for 10 h. The reaction mixture was worked up as above. All pyridine derivatives prepared were volatile in steam.

Reaction of acetonitrile with excess of acetophenone.

A mixture of acetophenone (0.1 mole), acetonitrile (0.03 mole) and $POCl_3$ (0.03 mole) was kept boiling for 10 h. The reaction mixture was hydrolyzed by pouring in a vigorously stirred solution of Na_2CO_3 (0.25 mole). The organic layer containing a mixture of several compounds was separated by preparative TLC method (2 mm thick silica gel plates; 3:1 v/v benzene/ethyl acetate). The following compounds were isolated:

a. 2,4-dimethyl-6-phenylpyrimidine (R_f = 0.11)

b. 2,4-dimethyl-4,6-diphenyl-4H-1,3-oxazine as an oil (R_f = 0.50), ^1H nmr ($CDCl_3$): δ [ppm] = 7.5-6.7 (m, 10H, 4-C_6H_5, 6-C_6H_5); 5.35 (s, 1H, 5-H); 1.85 (s, 3H, 4-CH_3); 1.4 (s, 3H, 2-CH_3). The structure of 4H-1,3-oxazine was assigned to this compound because it undergoes very easy hydrolysis in acidic medium[12] to 3-N-acetylamino-3-phenylbutyrophenone: mp 98°C (Ref.[6] 93-94°C),

^{1}H nmr ($CDCl_3$): δ[ppm] = 7.9-7.25 (m, 10H, arom); 6.96 (s, 1H, NH); 3.66 (d, 2H, CH_2, J = 8 Hz); 2.0 (s, 3H, CH_3); 1.88 (s, 3H, CH_3)

c. 1-chloro-1-phenylethene (R_f = 0.76) identified by ^{1}H nmr (product of fragmentation reaction).

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