

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

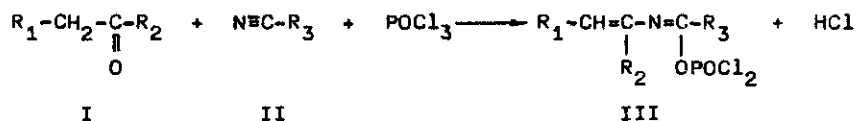
Wojciech Zieliński

Institute of Organic Chemistry and Technology, Silesian
Politechnical University, 44-101 Gliwice, Poland

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.

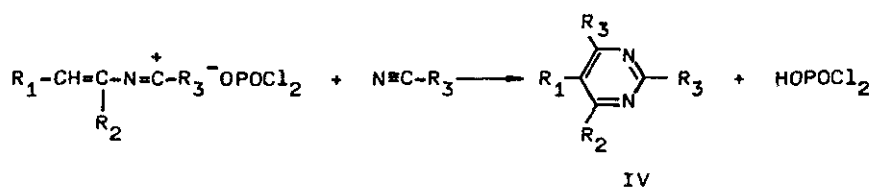
In contrast to basic catalyts which cause abstraction of the α -proton of nitrile group giving β -hydroxynitriles or α,β -unsaturated nitriles¹⁻⁴ in reactions of nitriles with carbonyl compounds, acid catalyts shall activate carbonyl carbon atom toward nucleophilic attack of nitrile nitrogen atom. These reactions, similar to the Ritter reaction⁵, were carried out using such catalyts 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 derivatives⁹ 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 derivative⁷.

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.

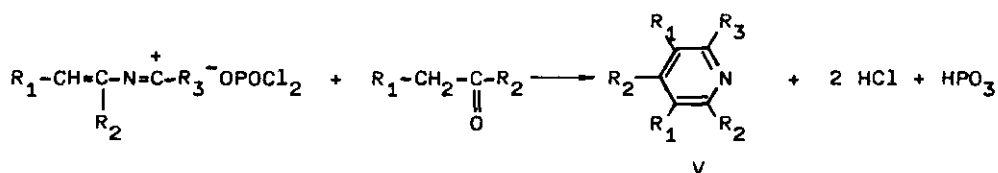


In fact, compound III was isolated when benzyl methyl ketone was reacted with acetonitrile⁸, while N-acylvinyllamines, alkaline hydrolysis products⁸ of III, were obtained if $\text{R}_1 \neq \text{H}$ ^{7,8}. Further courses of reaction suggest that the forma-

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.



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



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 atom¹¹ 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 | 31 | 167-168/750 | 0.13 | 8.2 | 145-146 | 13 |
| b | CH ₃ | CH ₃ | 52 | 196-197/750 | 0.18 | 11.5 | 129-130 | 14 |
| c | H | C ₆ H ₅ | 19 | 145/5 | 0.11 | | 209-210 | |
| d | H | p-NO ₂ C ₆ H ₄ | 55 | 173-173,5 | 0.16 | | - | |
| e | CH ₃ | C ₆ H ₅ | 31 | 146-148/6 62-64 | 0.15 | | 164-166 | |
| f | H | CH ₃ | 2 | 93.5-94 | 0.30 | | 155 | 15 |
| g | H | CH ₃ | 5 | 112-113 | 0.34 | | - | |
| h | H | CH ₃ | - | | 0.20 | | | |
| | | | Pyridine V | | | | | |
| a | H | CH ₃ | 12 | 169-170/750 | 0.22 | 7.2 | 157-158 | 16 |
| b | CH ₃ | CH ₃ | 37 | 180-182/740 | 0.31 | 6.6 | 145-146 | 17 |
| f | H | CH ₃ | 15 | 134-136/5 | 0.59 | | 187 | 18 |
| g | H | CH ₃ | 10 | 167-168/3 | 0.52 | | 203-204 | |
| h | H | CH ₃ | 16 | 140-142/6 | 0.31 | | 152-153 | 19 |

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

^bTLC - stationary phase: silica gel; mobile phase: 3:1 v/v benzene/ethyl acetate

^cGLC - 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 (R₃ = C₆H₅, C₆H₅-CH₂), 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 (R₁ = H, CH₃, R₂ = C₆H₅) 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

| Prod- uct | uv (methanol/water) | | ^1H nmr (CCl_4) |
|--------------|---------------------|--|--|
| | medium ^a | λ_{max} [nm] ($\epsilon \cdot 10^{-3}$) | 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 ₆ H 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 ₆ H 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 ₆ H 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 ₆ H ₅ , 4-C ₆ H 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 H ₄ -OCH ₃ -p, 4-C ₆ H ₄ -OCH ₃ -p, |
| | acidic | 297 (21.3) 351 (36.0) | 5-H); 4.15 (s, 6H, 2-C ₆ H ₄ -OCH ₃ -p, 4-C ₆ H ₄ -OCH 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 ₆ H 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 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 ₆ H ₄ -OCH 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 H ₅); 6.68 (s, 1H, 3-H); |
| | acidic | 275 (8.4) | 6.57 (s, 1H, 5-H); 3.98 (s, 2H, 2-CH ₂ -C ₆ H ₅); 2.43 (s, 3H, 6-CH ₃); 2.17 (s, 3H, 4-CH ₃) |

^aBasic 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 medium¹² to 3-N-acetylamino-3-phenylbutyrophenone: mp 98°C (Ref.⁶ 93-94°C),

- ^1H 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 ^1H nmr (product of fragmentation reaction).

REFERENCES

1. C. Ivanov and G. Angelova, Compt. Rend. Acad. Bulgare Sci., **19**, 739 (1966).
2. K. V. Popandova and C. Ivanov, ibid., **24**, 621 (1971).
3. Org. Synth., Coll. Vol. III, 715.
4. S. A. Di Biase, B. A. Lipisko, A. Haag, R. A. Wolak and G. W. Gokel, J. Org. Chem., **44**, 4640 (1979).
5. L. I. Krimen and D. J. Cota, Org. React., **17**, 213 (1969).
6. A. Y. Khorlin, O. S. Chizov and N. K. Kochetkov, Zh. Obshch. Khim., **29**, 3411 (1959).
7. S. Auricchio, O. Vajna De Pava and E. Vera, Synthesis, **1979**, 116.
8. W. Zieliński, Polish J. Chem., **56**, 93 (1982).
9. W. Zieliński, Roczniki Chem., **46**, 1455 (1972).
10. W. Zieliński, Polish J. Chem., **54**, 745 (1980).
11. H. O. House, "Modern Synthetic Reactions", Benjamin, Menlo Park, 1972, 2nd ed.
12. M. Lora-Tamayo, R. Mandronero, G. G. Munoz and H. Leipprand, Chem. Ber., **97**, 2234, 2244 (1964).
13. D. J. Brown, "The Pyrimidines", A. Weissberger Ed., Interscience Publishers, New York, 1962, p. 505.
14. J. C. Roberts, J. Chem. Soc., **1952**, 3065.
15. T. D. Heyes and J. C. Roberts, J. Chem. Soc., **1951**, 328.
16. D. Rostafińska, Roczniki Chem., **29**, 803 (1955).
17. E. D. Vasilieva and all., Izv. Akad. Nauk SSSR, Ser. Khim., **1965** (2), 322.
18. G. J. Janz and W. J. H. McCulloch, J. Am. Chem. Soc., **77**, 3134 (1955).
19. K. Tsuda, T. Sato and S. Saeki, Pharm. Bull. Japan, **1**, 307 (1953).

Received, 14th January, 1985