REACTIONS OF 2-PYRIMIDINYL PHOSPHITES WITH ACYL CHLORIDES

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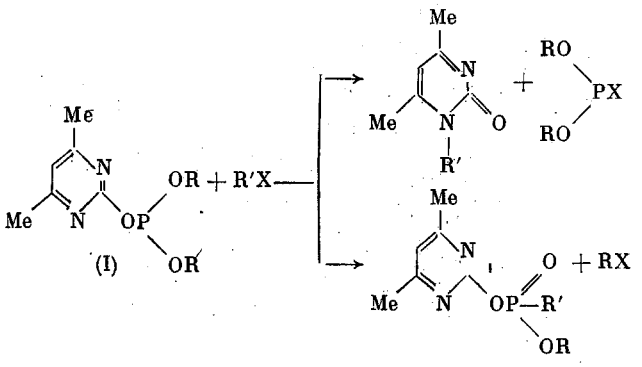
Alkoxypyrimidines react with acyl halides to form N-acylpyrimidones [1], while trialkyl phosphites react with acyl halides at 30-80°C to give the products of the Arbuzov rearrangement [2]. Triaryl phosphites react with acyl halides at 180-200°C to give chlorophosphites and aryl esters of carboxylic acids [3].

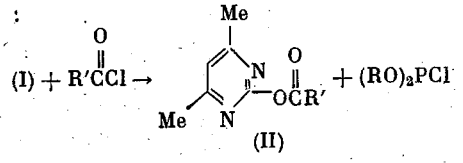
2-Pyrimidinyl phosphites (I), which have two isolated nucleophilic sites, viz., the nitrogen atom of the pyrimidine ring and the tricoordinated phosphorus atom, may react with electrophilic reagents either similarly to the Hilbert–Johnson reaction [pathway (1)] or to the Arbuzov reaction [pathway (2)]. We studied the reaction of (I) with acyl chlorides (AC):



(1)

(2)

At 40-50°C (I) react with AC to form dialkyl chlorophosphites and 2-acyloxypyrimidines (II):



(3)

The structure of the products formed was indicated by ^{31}P NMR and IR spectroscopy, comparison of the physical constants of the chlorophosphites with literature data, and the convergent synthesis of (II).

The IR spectra of (II) have bands at 1580-1600 cm^{-1} (pyrimidine ring) and 1760-1780 cm^{-1} (ester $\nu C{=}O$) and lack bands at 1660-1680 cm^{-1} (2-pyrimidone $\nu C{=}O$).

Monohydroxypyrimidines are acylated in the presence of organic bases at the oxygen atom [4]. The acylation of 4,6-dimethyldihydro-2-pyrimidone by AC in the presence of Et_3N leads to the preparation of (II) in 70-80% yield. The physical indices and spectral characteristics of (II) synthesized by both methods are identical.

The formation of (II) and chlorophosphites upon the reaction of (I) with AC may be attributed to one of the pathways in scheme (4):

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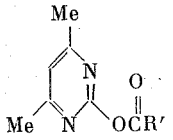
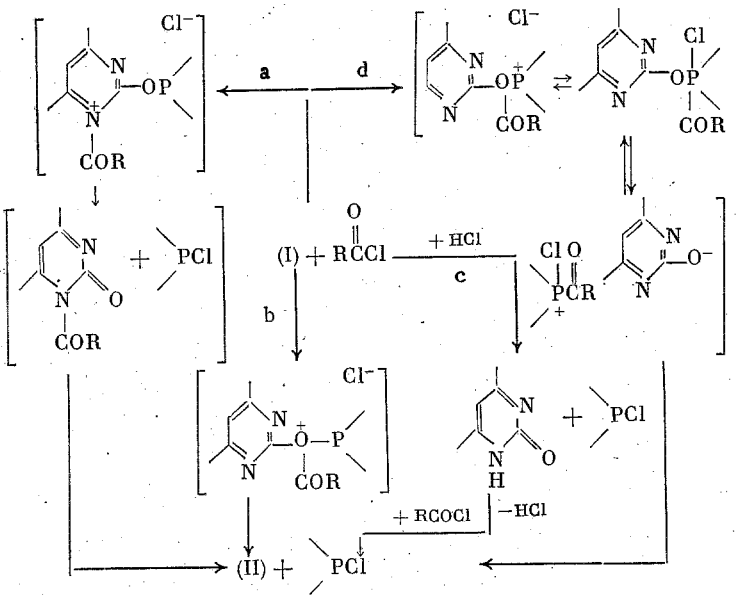
TABLE 1. 2-Acyloxy-4,6-dimethylpyrimidines



R′	Yield, %	bp, °C (pp, mm Hg) or mp	n_D^{20}	d_4^{20}	Chemical formula	Found / Calculated, % C	H	N
Me	83	70 (0,2)	1,4865	1,1204	$C_8H_{10}N_2O_2$	61,85 / 61,60	7,21 / 6,01	14,43 / 14,28
Pr	85	87 (0,2)	1,4843	1,0778	$C_{10}H_{14}N_2O_2$	57,83 / 57,56	6,02 / 6,24	16,86 / 16,62
Me_3C	84	41–42	–	–	$C_{11}H_{16}N_2O_2$	63,46 / 63,24	7,69 / 7,50	13,46 / 13,12



Pathway *a* involves nucleophilic attack of a pyrimidine ring nitrogen atom on the carbonyl carbon atom of the acid chloride, loss of a chlorophosphite, and rearrangement of N-acyl-2-pyrimidone to (II). Pathway b entails the nucleophilic reaction of the oxygen atom of the C_{pyr}—O—P bond with the carbonyl carbon atom with subsequent loss of (II). In pathway c, (I) initially reacts with HCl, which is always present in AC, with subsequent acylation of 2-pyrimidone by AC with the regeneration of HCl. Pathway d involves the nucleophilic attack of the phosphorus atom on the carbonyl carbon atom, anionic exchange in the phosphonium ion, and decomposition of the phosphonium pyrimidinolate formed into a chlorophosphite and (II).

Reaction by pathway *a* would involve the rearrangement of N-acyl-2-pyrimidone to (II). Although such acyl rearrangements have been found for pyridines [5] and sulfur-containing pyrimidines [6], Novacek [7] has reported that the condensation of acetylacetone with N-benzoylurea gives 1-benzoyl-4,6-dimethyl-1,2-dihydro-2-pyrimidone, which does not isomerize to benzoyloxy-4,6-dimethylpyrimidine.

Pathway b entails the nucleopyilic attack of the oxygen atom of the C_{pyr}—O—P fragment on the carbonyl group. However, the oxygen atom of the C_{alk}—OP bond is the more nucleophilic of the two types of oxygen atoms in (I) since it is bound to an electron-donor alkyl group and not to the electron-withdrawing pyrimidine ring. Thus, the formation of alkylpyrimidinyl chlorophosphites and alkyl esters of carboxylic acids, which were not detected in the reaction products, and not dialkyl chlorophosphites and (II) would occur if pathway b were realized.

In order to check the possibility that the reaction proceeds through pathway c, we carried out the reaction of (I) with trimethylacetyl chloride in the presence of Et_3N to bind HCl present in the AC. The reaction does not proceed in the presence of Et_3N to form chlorophos-

phite and (II) but rather is similar to the Arbuzov reaction and the pyrimidinyl ester of pivaloylphosphonic acid is formed in 92% yield. The structure of this ester was indicated by IR and ^{31}P NMR spectroscopy. The IR spectrum has bands at 1580-1600 cm^{-1} (pyrimidine ring), 900-1000 cm^{-1} (POC), 1270 cm^{-1} ($\nu P{=}O$), and 1740 cm^{-1} ($\nu C{=}O$).

Special experiments showed that $Et_3N{\cdot}HCl$ does not react with (I) at 80-120°C, while (II) is formed from dihydro-2-pyrimidone and AC in the absence of an organic base. The formation of a chlorophosphite and dihydro-2-pyrimidone in the reaction of (I) with HCl was shown in our subsequent work [8]. Thus, all the steps for pathway c are expermentally justified.

At present, we do not have experimental evidence to support or refute the possibility of the realization of pathway d for this reaction. The models for all the reaction steps for pathway c indicate that this pathway undoubtedly makes a contribution to the reaction of (I) with acyl halides.

EXPERIMENTAL

Reaction of Dialkyl-(4,6-dimethyl-2-pyrimidinyl) Phosphites with Acyl Chlorides (AC) in the Absence of Et_3N. A sample of dialkyl-(4,6-dimethyl-2-pyrimidinyl) phosphites was added dropwise with stirring to 0.1 mole AC over 20 min at 50°C. The mixture was heated for 1 h at 50°C and distilled. The yield of the dialkyl chlorophosphites was 75-85%. Their physical indices and ^{31}P NMR spectra correspond to the literature values. The yields and physical constants of previously unreported (II) are given in Table 1.

Reaction of Diethyl-(4,6-dimethyl-2-pyrimidinyl) Phosphite with Pivaloyl Chloride in the Presence of Et_3N. A sample of 8.3 g (34 mmoles) (I) (R = Et) was added dropwise to a mixture of 3.5 g (34 mmoles) Et_3N and 4.2 g (39 mmoles) pivaloyl chloride at 105-110°C and stirred at this temperature for 4 h at 100°C. The $Et_3N{\cdot}HCl$ precipitate was filtered off, and the residue was maintained for 2 h at 100°C (0.1 mm). The yield of 9.8 g (92%) ethyl-(4,6-dimethyl-2-pyrimidinyl)pivaloyl phosphonate was obtained as a viscous nondistilling oil. ^{31}P NMR spectrum δ = 3 ppm. Found: C 52.54; H 7.30; N 9.68; P 10.10%. Calculated for $C_{13}H_{21}N_2O_4P$: C 52.00; H 7.00; N 9.33; P 10.33%.

Acylation of 4,6-Dimethyl-1,2-dihydro-2-pyrimidone in the Presence of Et_3N. A sample of 3.2 g (0.4 mole) AcCl was added dropwise at 20°C to a mixture of 5.1 g (0.4 mole) 4,6-dimethyl-1,2-dihydro-2-pyrimidone and 4.1 g (0.4 mole) Et_3N in 50 ml acetonitrile and stirred for 30 min at 50°C. The $Et_3N{\cdot}HCl$ precipitate was filtered off, and the residue was distilled to give 5.8 g (85%) (II) (R = Me), bp 70°C (0.2 mm), n_D^{20} 1.4885, d_4^{20} 1.1185.

Acylation of 4,6-Dimethyl-1,2-dihydro-2-pyrimidone in the Absence of Et_3N. A sample of 3.2 g (0.4 mole) AcCl and 10 g (0.8 mole) 4,6-dimethyl-1,2-dihydro-2-pyrimidone were heated for 5 h at 50°C. The precipitate was filtered off, and the residue was distilled to give 5.3 (78.5%) (II) (R = Me), bp 70°C, n_D^{20} 1.4870, d_4^{20} 1.1186.

CONCLUSIONS

1. Dialkyl-(4,6-dimethyl-2-pyrimidinyl) phosphites react with acyl chlorides to form chlorophosphites and 2-acyloxy-4,6-dimethylpyrimidones.

2. Arbuzov rearrangement products are formed upon carrying out the reaction in the presence of an organic base.

LITERATURE CITED

1. H. Ballweg, Tetrahedron Lett., 2171 (1968).
2. M. B. Gazizov and A. I. Razumov, Tr. Kazansk. Khim.-Tekhnol. Inst., 34, 257 (1965).
3. W. Hawerston, R. A. Shaw, and B. C. Smith, J. Chem. Soc., 3267 (1962).
4. V. P. Mamaev and V. F. Sedova, Khim. Geterotsikl. Soedin., 787 (1965).
5. J. Fleming and D. Philippides, J. Chem. Soc., C, 2426 (1970).
6. G. I. Podzigun, N. G. Pashkurov, and V. S. Reznik, Izv. Akad. Nauk SSSR, Ser. Khim., 2564 (1980).
7. A. Nováček, Collect. Czech. Chem. Commun., 33, 3919 (1968).
8. M. A. Giniyatullina, G. I. Podzigun, and V. S. Reznik, Izv. Akad. Nauk SSSR, Ser. Khim., No. 12 (1985).