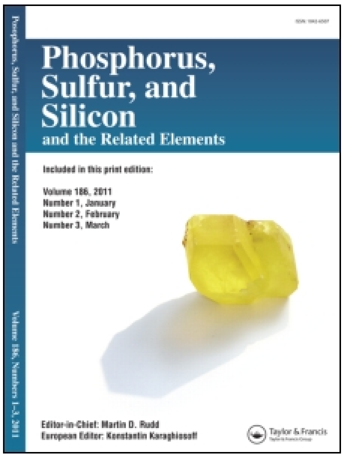

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

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To cite this Article Kaushik, Mahabir P. , Gupta, Arvind K. , Lal, Basant and Vaidyanathaswamy, Ramamoorthy(1992) 'UNUSUAL REACTION OF TRIETHYLPHOSPHITE WITH PYRIDOYL CHLORIDES', Phosphorus, Sulfur, and Silicon and the Related Elements, 71: 1, 175 — 177

To link to this Article: DOI: 10.1080/10426509208034508

URL: http://dx.doi.org/10.1080/10426509208034508

Phosphorus, Sulfur, and Silicon, 1992, Vol. 71, pp. 175–177
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UNUSUAL REACTION OF TRIETHYLPHOSPHITE WITH PYRIDOYL CHLORIDES

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(Received February 18, 1992; in final form May 11, 1992)

Reaction of 2-pyridoyl chloride with triethylphosphite provided a bis-phosphorus compound **2** arising out of Perkow reaction of the initially formed pyridoylphosphonate. However, 3- and 4-pyridoylchlorides with triethylphosphite gave rise to **4** and **6** probably due to ingress of moisture in the reaction medium.

Key words: Phosphites; Michaelis-Arbusov reaction.

INTRODUCTION

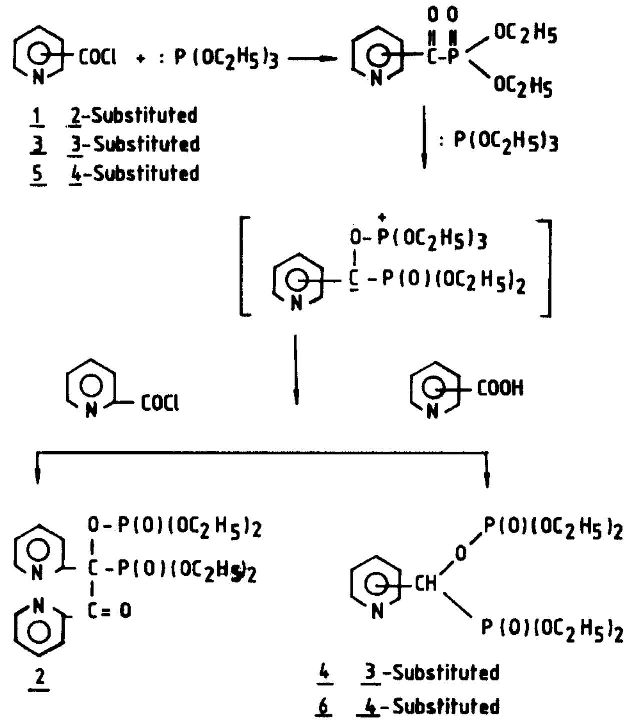
The best procedure for the preparation of α-ketophosphonate is to follow the familiar Michaelis-Arbuzov reaction wherein an acid chloride is allowed to react with trialkylphosphite.[1] Since a large quantity of pyridoylphosphonate was required by us for subsequent oximation and therapeutic evaluation against organophosphate poisoning, we attempted the reaction between 2, 3 and 4 pyridoyl chlorides and triethylphosphite. The reaction took an unusual course and this paper describes our results.

RESULTS AND DISCUSSION

The required **2**, **3** and **4** pyridoyl chlorides were prepared from the corresponding potassium salt of the acid and thionyl chloride.[2] Because of the limited storage stability, these acid chlorides were used immediately after distillation.

Reaction of 2-Pyridoylchloride (**1**) with an equivalent amount of triethylphosphite unexpectedly provided a viscous liquid which was not comparable to the aroylphosphonates prepared earlier by us.[3] This defied distillation and therefore was chromatographed which provided an analytically pure sample. Though the elemental analysis confirmed the correct ratio of phosphonate to aroyl group, the characteristic IR absorption at 1650 cm^{-1} for aroylphosphonate was not present. Instead a strong absorption at 1718 cm^{-1} was observed indicating a different chemical environment of the carbonyl group. That the compound obtained is **2** (Scheme I) is based on further evidence such as mass spectrum (*m/z* 487), singlets at δ 15.49 and δ -2.49 ppm in ^{31}P NMR and the proton NMR (see Experimental section). Variation of temperature, dilution with a variety of solvents or reverse addition had little effect on the course of this reaction as observed by TLC.

The product **2** presumably arises from a Perkow like reaction between a second molecule of triethylphosphite and the initially formed aroylphosphonate (Scheme



SCHEME I

I). Though precedented,[4] this unusual reaction is observed for the first time in a heterocylic system.

The reaction of trialkylphosphite with 3- and 4-pyridoyl chlorides provided still more interesting results as the products obtained did not show any absorption in the carbonyl region. This observation was indicative of the fact that neither pyridoyl phosphonate nor phosphonophosphate similar to **2** is the product obtained in these cases. Proton decoupled ^{31}P NMR however, showed the presence of two different kinds of phosphorus atoms in these compounds.[5] Further spectral and analytical data (see Experimental section) revealed that the products obtained from **3** and **5** are indeed **4** and **6** (Scheme I) respectively.

Though the initial step for the formation of **4** and **6** should take place by a mechanism similar to the one operative for **2**, it is not clear how the second pyridoyl group is "missing" from the molecule. It is likely that the reaction may follow a mechanism as depicted in Scheme I, wherein protonation of initially formed carbanion occurs through the acid, which would have been formed by hydrolysis of the corresponding pyridoyl chloride or pyridoylphosphonate. In order to confirm this mechanism, a control experiment was carried out by adding one equivalent of picolinic acid into 2-pyridoyl chloride before the addition of triethyl phosphite. The reaction was monitored with ^{31}P NMR and the spectrum showed that diphosphorus compound **2** was no longer formed and the major product was now the diphosphorus compound. with one pyridoyl ring similar to **4** or **6**. Some minor products (about 10%) were also observed in the case of **3** and **4** pyridoyl derivatives, but were not analyzed further.

EXPERIMENTAL

Pyridoyl chlorides were prepared following the method of Zinner *et al.*[2] Because of limited storage stability, the acid chlorides were used immediately after distillation. Triethylphosphite (Aldrich) was distilled before use. IR spectra were recorded on a Perkin-Elmer 577 Spectrophotometer. NMR spectra were obtained from Jeol FX-90Q at 89.55 MHz for ^{1}H with TMS as an internal standard and 36.25 MHz for ^{31}P with 85% H_3PO_4 as an external standard. Mass spectra were obtained on a Jeol JMS-DX-300 Mass spectrometer. Elemental analyses were performed on a Carlo-Erba elemental analyzer model 1106.

Reaction of triethylphosphite with 2-pyridoylchloride. 2-Pyridoylchloride 14.1 g (0.1 mole) was taken in a 250 ml two necked round-bottom flask fitted with a reflux condenser and a $CaCl_2$ guard tube. Freshly distilled triethylphosphite 16.6 g (0.1 mole) was added at such a rate that the temperature of the reaction did not exceed 35°C. Yellow color developed in the beginning but turned intense brown after complete addition of triethylphosphite. The viscous product was chromatographed on a silica gel column (10% acetone in benzene) to isolate **2** as an oily product yield; 12.4 g (25.5%). IR (neat) ν cm^{-1} 1718 (C=O), 1262 (P=O), 1030 (P—O—C); ^{1}H NMR (DMSO) δ 8.6 to 7.3 (*m*, 8H, arom), 4.10 (*m*, 8H, —CH_2), 1.20 (*m*, 12H, —CH_3); ^{31}P (DMSO) δ 15.49 (s); −2.49 (s) *m/z* 487, 381, 244, 155, 137, 109, 108; Anal. (Found C, 49.01; H, 5.62; N, 5.41. Calculated for $C_{20}H_{28}O_8N_2P_2$: C, 49.38; H, 5.76; N, 5.76%).

Reaction of triethylphosphite with 3-pyridoylchloride. Freshly distilled triethylphosphite 16.6 g (0.1 mole) was added to 3-pyridoylchloride 14.1 g (0.1 mole) at such a rate that the temperature did not exceed 35°C. The viscous product was purified by two different methods, one by solvent extraction. Acetone was added to the viscous material and a solid was isolated which was identified as nicotinic acid and the acetone fraction gave 90% pure **4**. Another method of purification was by column chromatography on silica gel (10% acetone in benzene) which gave 9.8 g (25.7%) of 4. IR (neat) ν cm^{-1} 1262 (P=O), 1023 (P—OC); ^{1}H NMR (DMSO) δ 8.7 to 7.5 (*m*, 4H, arom), 5.7 (dd, J = 14 Hz and 12 Hz, 1H, —CH), 4.1 (*m*, 8H, —CH_2), 1.3 (12H, *m*, —CH_3); ^{31}P (DMSO) δ 14.40 (d, P—C, J_{PP} 29.3 Hz), −2.03 (d, P—O—C, J_{PP} 29.3 Hz); *m/z* 382, 244, 227, 155, 137, 109, 108; Anal. (Found C, 44.45; H, 6.72; N, 4.06. Calculated for $C_{14}H_{25}O_7NP_2$: C, 44.09; H, 6.56; N, 3.67%).

Reaction of triethylphosphite with 4-pyridoylchloride. Triethylphosphite 16.6 g (0.1 mole) was added slowly to 4-pyridoylchloride 14.1 g (0.1 mole). The viscous product obtained was purified by column chromatography as in the case of 3-pyridoyl derivative to give **6**, 10.0 g (26.0%) IR (neat) ν cm^{-1} 1260 (P=O), 1030 (P—OC); ^{1}H NMR (DMSO) δ 8.8 to 7.45 (*m*, 4H, arom), 5.5 (dd, J = 15 Hz, 11 Hz, 1H, —CH), 4.06 (*m*, 8H, —CH_2), 1.2 (*m*, 12H, —CH_3); ^{31}P (DMSO) δ 14.85 (d, P—C, J_{PP} 31.7 Hz), 1.77 (d, P—O—C, J_{PP} 31.8 Hz); *m/z* 381, 244, 228, 155, 137, 109, 106; Anal. (Found C, 44.26; H, 6.69; N, 3.70. Calculated for $C_{14}H_{25}O_7NP_2$: C, 44.09; H, 6.56; N, 3.67%).

ACKNOWLEDGEMENT

We thank Drs. D. K. Jaiswal and S. K. Raza for critical comments. Thanks are also due to Mr. Mitthanlal and Mr. Hari Afley for secretarial assistance.

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5. It is interesting to note that the ^{31}P NMR of **2** showed two singlets while for **4** and **6** two doublets are observed. This difference is perhaps due to variation in dihedral angle.