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A GENERAL AND CONVENIENT METHOD FOR THE SYNTHESIS OF UNESTERIFIED CARBAMOYL- AND THIOCARBAMOYL-PHOSPHONIC ACIDS[1)]

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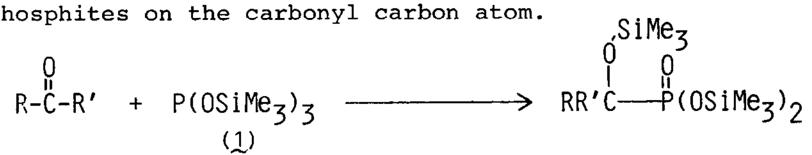
Summary: Unesterified carbamoyl- and thiocarbamoyl-phosphonic acids were prepared in high yields by the reaction of tris(trimethylsilyl) phosphite with isocyanates and isothiocyanates followed by treatment of the 1:1 carbonyl adducts with aniline-containing methanol.

Mukaiyama and his co-workers[2)] reported that trialkyl phosphites reacted with isocyanates or isothiocyanates at elevated temperatures (150-180°C) to give isonitriles.

$$\text{R-N=C=X} + \text{P(OR)}_3 \xrightarrow{\Delta} \text{R-N=C:} + \text{X=P(OR)}_3 \qquad \text{X= O or S}$$

Recently, it has been found[3-5)] that trimethylsilyl phosphites reacted smoothly with carbonyl compounds to afford the corresponding carbonyl addition products, where the trimethylsilyl phosphites act as strong nucleophiles toward the carbonyl compounds and the Si-O bond of the phosphites can be cleaved easily compared with the alkyl-O bond of trialkyl phosphites after the attacking of the silyl phosphites on the carbonyl carbon atom.

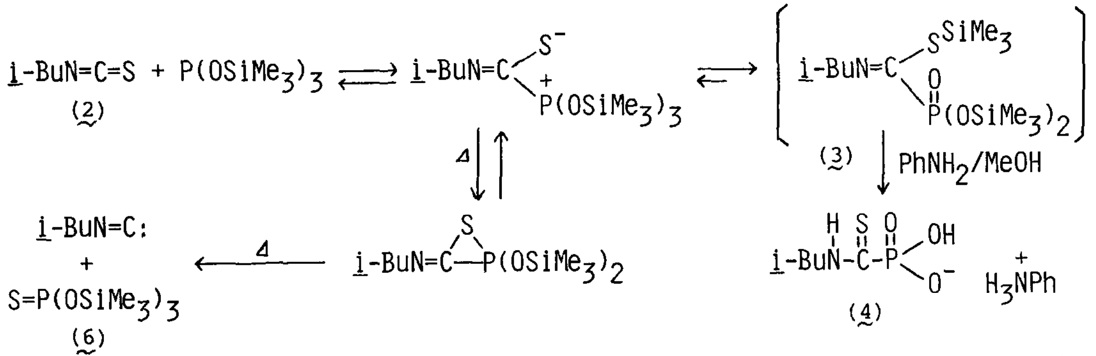


$$\text{R-}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{-R}' + \underset{(\mathbf{1})}{\text{P(OSiMe}_3)_3} \longrightarrow \text{RR}'\overset{\text{OSiMe}_3}{\overset{|}{\text{C}}}\text{—}\overset{\text{O}}{\overset{\|}{\text{P}}}\text{(OSiMe}_3)_2$$

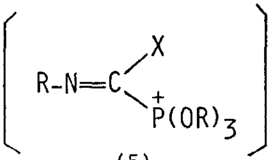
More recently, we have studied the synthesis of unesterified phosphonates in connection with the biological interests.[1,7)]

In this communication we wish to report a general and convenient method for the preparation of carbamoyl- and thiocarbamoyl-phosphonic acids by the reaction of tris(trimethylsilyl) phosphite (**1**) with isocyanates and isothiocyanates.

When **1** was allowed to react with i-butyl isothiocyanate (**2**) (1 equiv.), an alkyl isothiocyanate, an exothermic reaction took place even at room temperature giving a thiocarbonyl adduct (3).[6] The reaction mixture was further heated at 100°C for 3 h to afford i-butyl isonitrile in 90 % yield by distillation. Compound 3 could not be isolated. However, the formation of 3 was strongly suggested because a monoanilinium salt of i-butylthiocarbamoylphosphonic acid (4) was isolated in 60 % yield by treatment of the reaction mixture with aniline-containing methanol after the reaction was completed.[8]

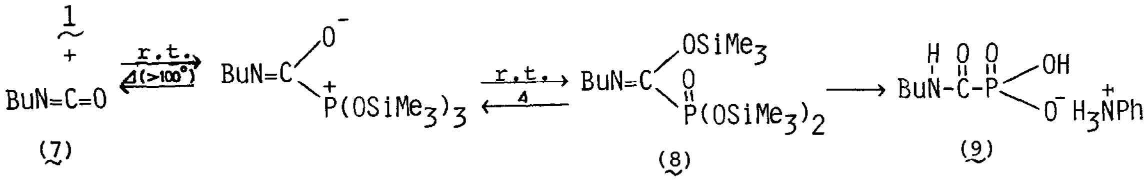


This result suggests the trapping of the hypothetical intermediate (5) discussed by Mukaiyama[2] in this type of desulfurization. Attempts to isolate 3 by distillation even under highly reduced pressures caused the partial decomposition to i-butyl isonitrile and tris(trimethylsilyl) thionophosphate (6).



(5)

On the other hand, in the case of the reaction of n-butyl isocyanate (7) (1 equiv.), an alkyl isocyanate, with 1 at room temperature for 1.5 h, the carbonyl adduct [8: 67-68°C (7.2 mm)][6] was successfully isolated in 93 % yield by rapid distillation under reduced pressure at lower temperatures than 100°C. Even when the distillation was conducted at higher tempratures, no deoxygenation reaction took place but the retro-reaction occured to give 1 releasing volatile n-butyl isocyanate (7). By similar treatment of 8, n-butylcarbamoylphosphonic acid (9) was isolated in 96 % yield as the monoanilinium salt.



When phenyl isocyanate (10a) (1 equiv.), an aromatic isocyanate, was employed in the above reaction, the reaction proceeded exothermically and the addition product [11a: 110-111°C (23 mm)][6] was obtained in an excellent yield

(94 %). The adduct was found to be quite stable at least to 200°C. Compound 11a was also readily converted to a monoanilinium salt of phenylcarbamoylphosphonic acid (12a) in 98 % yield.

Furthermore, the reaction of 1 with phenyl isothiocyanate (10b) at room temperature for 2 h resulted in the formation of the thiocarbonyl adduct (11b)[6] in quantitative yield. Distillation of 11b caused the retro-reaction to the starting materials as in the case of 8. However, when the reaction mixture was treated with aniline-containing methanolwithout distillation, a monoanilinium salt of phenylthiocarbamoylphosphonic acid (12b) was obtained in 95% yield.

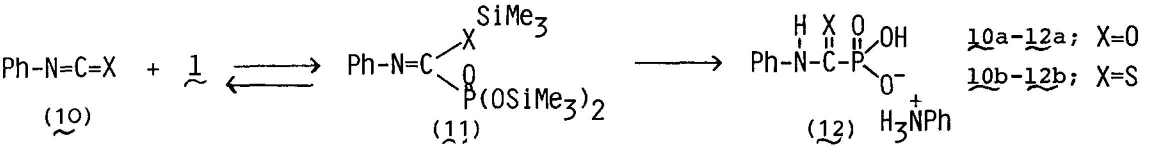
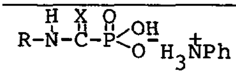


Table I Physical data of carbamoyl- and thiocarbamoyl-phosphonates

 $R{-}\overset{H}{N}{-}\overset{X}{\overset{\Vert}{C}}{-}\overset{O}{\overset{\Vert}{P}}\!<^{OH}_{O^-}\ H_3\overset{+}{N}Ph$ R	X	m.p.(dec.) (°C)	I.R.(KBr) (cm^{-1})	NMR (d^6-DMSO/$CDCl_3$/D_2O(1:1:0.1, v/v)) δ (ppm)
4 i-Bu	S	183-185	3354,2950 2600,1607, 1552,1400, 1385	0.90(d,6H,J_{H-H}=7Hz,$(C\underline{H}_3)_2C$), 2.07 (m,1H,$C\underline{H}$), 3.42(d,2H,J_{H-H}=7Hz,$C\underline{H}_2N$), 5.10(s,5H,acidic H), 6.85-7.38(m,5H, ArH)
9 Bu	O	160-164	3292,2610, 1629(νC=O), 1589,1562, 1500,1380	0.92(d,3H,J_{H-H}=7Hz,$C\underline{H}_3$), 1.13-1.63 (m,4H,$C\underline{H}_2$-$C\underline{H}_2$), 3.14(m,2H,$C\underline{H}_2$)
12a Ph	O	194-195	3260,2605, 1623(νC=O), 1600,1544	7.04-7.53(m,8H,ArH), 7.78-8.05 (m,2H,ArH)
12b Ph	S	186-187	3320,2590, 1590,1549, 1494	6.60-7.12(m,8H,ArH), 7.17-7.42 (m,2H,ArH)

All products gave satisfactory microanalysis (C ±0.18, H ±0.08, N ±0.17).

From these results, the thermal stability of the carbonyl and thiocarbonyl adducts of 1 would be ranked in the following order:

$$Ar\text{-}N{=}C(OSiMe_3)\text{-}P(O)(OSiMe_3)_2 > Alkyl\text{-}N{=}C(OSiMe_3)\text{-}P(O)(OSiMe_3)_2 >$$
$$Ar\text{-}N{=}C(SSiMe_3)\text{-}P(O)(OSiMe_3)_2 > Alkyl\text{-}N{=}C(SSiMe_3)\text{-}P(O)(OSiMe_3)_2$$

The adducts, **3**, **8**, and **11b**, were in equilibrium with the corresponding starting materials due to the instability of the S-Si bonds and/or the nonconjugated N=C bonds. The adduct **11a** was stabilized by the conjugation between the N=C bond and the benzene ring. The thermal desulfurization of **3** to *i*-butyl isonitrile might be due to the C-S bond cleavage through a three ring transition state. Desulfurization of isothiocyanates is known to be easier than deoxygenetion of isocyanates.$^{2)}$

In conclusion, it is noted that the present reactions provide the general and convenient method for the synthesis of a new class of organophosphorus compounds$^{9)}$, unesterified carbamoyl- and thiocarbamoyl-phosphonic acids, in high yields under very mild conditions.

References and Notes

(1) This paper participates as Part 13 in the series of Silyl Phosphites. Part 12: T. Hata, M. Nakajima, and M. Sekine, Tetrahedron Lett., in press (1979).

(2) T. Mukaiyama, H. Nambu, and M. Okamoto, J. Org. Chem., **27**, 3651 (1962).

(3) Z. S. Novikova and I. F. Lutsenko, J. Gen. Chem. USSR (Engl. Transl.), **40**, 2110 (1970); L. V. Nesterov, N. E. Krepysheva, R. A. Sabirova, and G. N. Romanova, ibid., **41**, 2449 (1971); Z. S. Novikova, S. N. Mashoshima, T. A. Sapozhnikova, and I. F. Lutsenko, ibid., 41, 2622 (1971); A. N. Pudovik, E. S. Batyeva, and G. U. Zameletdinova, ibid., 43, 2072 (1975); A. N. Pudovik, T. Kh. Gazizov, and Yu. I. Sudarev, ibid., **43**, 2072 (1973); A. N. Pudovik, T. Kh. Gazizov, and A. M. Kibardin, ibid., **44**, 1170 (1974); A. N. Pudovik, E. S. Batyeva, and V. A. Al'fonsov, ibid., **45**, 921 (1975); A. M. Kibardin, T. Kh. Gazizov, and A. N. Pudovik, ibid., **45**, 1947 (1975); I. V. Konovalova, L. A. Burnaeva, N. Sh. Sifulina, and A. N. Pudovik, ibid., **46**, 17 (1976).

(4) D. A. Evans, K. M. Hurst, L. K. Truesdale, and J. M. Takacs, Tetrahedron Lett., 2495 (1977); D. A. Evans, K. M. Hurst, and J. M. Takacs, J. Am. Chem. Soc., **100**, 3467 (1978).

(5) M. Sekine, I. Yamamoto, A. Hashizume, and T. Hata, Chem. Lett., 485 (1977); T. Hata, A. Hashizume, M. Nakajima, and M. Sekine, Tetrahedron Lett., 363 (1978); M. Sekine, K. Okimoto, T. Hata, J. Am. Chem. Soc., **100**, 1001 (1978).

(6) Adducts (**3**, **8**, **11a**, and **11b**) are described here as the compounds having Si-O or Si-S bond However, the isomers having Si-N bond may also exist. Their structures have not yet been assigned. Further investigation will be described elsewhere.

(7) T. Hata, K. Yamada, T. Futatsugi, M. Sekine, Synthesis, in press (1979).

(8) Two equiv, of *i*-butyl isothiocyanate was used and the reaction was carried out for 4 h since stoichiometric reaction could not afford **3** in quantitatave yield, even when the reaction time was prolonged to several days.

(9) Unesterified N,N-disubtituted carbamoylphosphonic acids was recently reported: T. Morita, Y. Okamoto, and H. Sakurai, Tetrahedron Lett., 2523 (1978).

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