FORMATION OF THIOCYANATES BY RING CLEAVAGE FROM 2-IMINO-5,6-DIHYDRO-4H-1,3-THIAZINE

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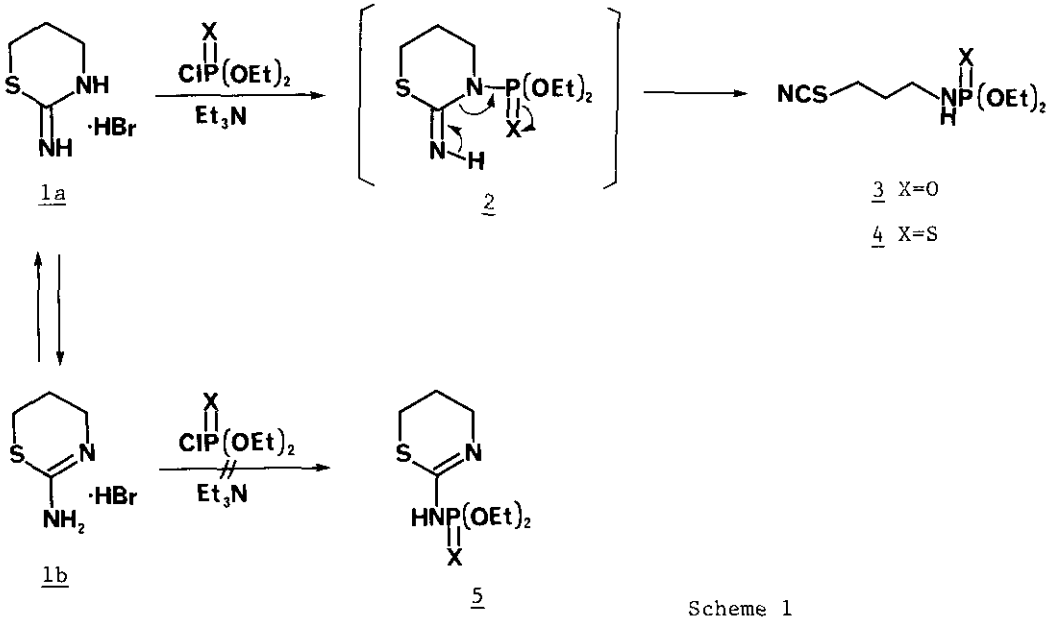
Abstract ——— The reaction of 2-imino-5,6-dihydro-4H-1,3-thiazine with diethyl chlorophosphate, diethyl chlorothiophosphate and p-toluenesulfonyl chloride in the presence of base gave N-propylthiocyanate derivatives of diethyl phosphoramide, diethyl phosphorothioamide and p-toluenesulfonamide, respectively, in good yield.

The 1,3-thiazine derivatives have been less intensively studied than their counterparts, 1,3-diazine and 1,3-oxazine derivatives. A few studies on the reactivity of 2-imino-1,3-thiazine have been reported. However, 1,3-thiazine derivatives are of interest biologically because they show insecticidal and fungicidal activity[1] and are used as radiation sickness drugs or as antiradiation agents.[2] In 1970, Schöberl and Magosh[3] reported that 2-imino-5,6-dihydro-4H-1,3-thiazine 1 reacts with acyl halides or anhydrides resulting in N-mono- and N,N'-diacylation products. Pilgram and Skiles[4] described the reaction of 1 with chlorothioformyl chloride, which leads to the formation of bicyclic thiadiazolone. The chemistry of 1 is complicated by the presence of two reactive nitrogen atoms in the molecule, and it is frequently difficult to obtain unequivocal chemical proof of the structure of reaction products. In our search for biologically active 2-imino-1,3-thiazine derivatives,[5-7] we became interested in the syntheses of 1,3-thiazinylphosphoramidates. Here we wish to report that the reaction of 1 with diethyl chlorophosphate afforded only thiocyanate 3, rather than the desired compound 5.

When 2-imino-1,3-thiazine hydrobromide (0.985 g), which was prepared from 3-bromopropylamine hydrobromide according to reported procedure,[8] was allowed to react with diethyl chlorophosphate (0.95 g) in the presence of triethylamine (1.11 g) in benzene at room temperature for 18 h, crude 3 (1.28 g) was obtained. The oily crude product

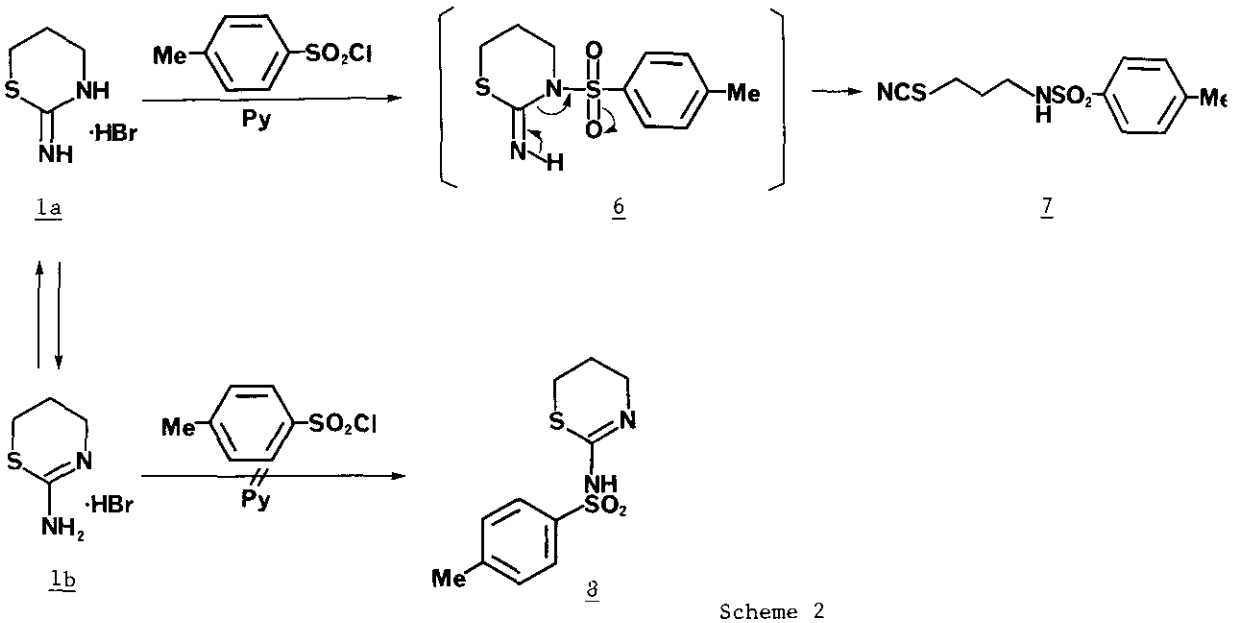
was subjected to chromatography on silica gel to give pure 3 (1.04 g, 82%) as a colorless oil. Diethyl phosphorothioamide thiocyanate 4 was obtained by the reaction of 1a with diethyl chlorothiophosphate as described above, in the 92% yield as a colorless oil. The structures of 3 and 4 were confirmed on the basis of the ir spectra which showed characteristic SCN absorption at 2150 cm^{-1} and 2145 cm^{-1} for 3 and 4, respectively. The ^1H nmr spectra of 3 and 4 were as follows: 3 ($CDCl_3$)δ 1.32 (6H,t,J=7Hz), 1.98 (2H,m), 3.06 (4H,m), 3.70 (1H,m), 4.07 (4H,dt,J=7.2,7Hz); 4 ($CDCl_3$)δ 1.30 (6H,t,J=7.5Hz), 1.98 (2H,m), 3.11 (5H,m), 3.95 (4H,q,J=7.5Hz). Mass spectra and elemental analyses for 3 and 4 also gave satisfactory data.[9] These results suggest a mechanism in which the formation of thiocyanates proceeds in two steps: the first involves the phosphoramidates 2 by nucleophilic attack of NH on 1a, and the second is proton abstraction from the endo NH on 2 with the base as shown in Scheme 1. Hard and soft acids and bases theory[10] supports this mechanism in which



Scheme 1

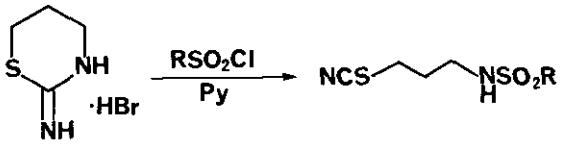
2-imino-1,3-thiazine, such as 1a (amino group in thiazine ring is a hard base) can be expected to react preferentially with the phosphoroxy group (P=O group is a hard acid) of the phosphorylating reagents, chloro-phosphate or thiophosphate. In order to explore this aspect, p-toluenesulfonyl chloride was chosen as the sulfonylating reagent and its reaction was examined by the similar method for the preparation of

3 and 4. To a suspension of 2-imino-5,6-dihydro-4H-1,3-thiazine hydrobromide (1.00 g) in dry pyridine (8 ml) was added p-toluenesulfonyl chloride (1.07 g), and the mixture was stirred for 15 h at room temperature. The reaction mixture was poured into cold 4 N H_3PO_4 and extracted with methylene chloride, giving an oily residue. The oily product was subjected to column chromatography on silica gel and gave a pure oily product 1.06 g (77%). The sole compound isolated was not 2-p-toluenesulfonylamino-1,3-thiazine 8, but compound 7 resulting from ring cleavage of intermediate 6 (Scheme 2), which showed an SCN absorption at 2150 cm^{-1} in its ir spectrum. The ^1H



Scheme 2

nmr spectrum of 7 was as follows: ($CDCl_3$) δ 1.97 (2H,m), 2.41 (3H,s), 3.05 (4H,m), 5.12 (1H,t,J=6Hz), 7.32 (2H,d,J=8.8Hz), 7.77 (2H,d,J=8.8Hz). Mass spectra and elemental analysis were also satisfactory.[11] In the same way, 9-12[12-15] were obtained by the reaction of 2-imino-1,3-thiazine with corresponding sulfonyl chlorides in good yield (Table 1).



1a 9-12

Table 1. Reaction of 1a with various sulfonyl chloride

Compound	R	Yield (%)
9 [12]	Me	61
10 [13]	ph	97
11 [14]	4-NO_2-ph	88
12 [15]	4-Cl-ph	91

The phosphoramidate described above, having the thiocyanate group, showed high insecticidal activity.

ACKNOWLEDGEMENT

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9. Mass spectrum for 3, m/z: 253(M^++1); (Found: C, 37.63; H, 6.86; N, 10.73; S, 12.52. Calcd for $C_8H_{17}N_2SO_3P$: C, 38.09; H, 6.79; N, 11.10; S, 12.71%). Mass spectrum for 4, m/z: 268(M^+); (Found: C, 36.21; H, 6.28; N, 10.14; S, 23.81. Calcd for $C_8H_{17}N_2S_2O_2P$: C, 35.81; H, 6.39; N, 10.44; S, 23.90%).
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11. Mass spectrum for 7, m/z: 270(M^+); (Found: C, 48.49; H, 5.26; N, 10.35; S, 23.46. Calcd for $C_{11}H_{14}N_2S_2O_2$: C, 48.87; H, 5.22; N, 10.36; S, 23.72%).
12. N-(3-Thiocyanopropyl)methanesulfonamide (9) — Oil; ir ($CHCl_3$) 2160 (SCN) cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.12 (2H,m), 3.00 (3H,s), 3.09 (2H,t,J=7Hz), 3.35 (2H,q,J=7Hz),

4.44 (1H,br); ms m/z: 195(M^++1); (Found: C, 30.60; H, 4.98; N, 14.22. Calcd for $C_5H_{10}N_2O_2S_2$: C, 30,91; H, 5.19; N, 14.42%).

13. N-(3-Thiocyanopropyl)benzenesulfonamide (10) — Mp 49.5-50.5°C (from benzene-n-hexane); ir ($CHCl_3$) 2160 (SCN) cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.03 (2H,m), 3.04 (2H,t, J=7Hz), 3.14 (2H,q,J=7Hz), 4.80 (1H,br), 7.60 (2H,m), 7.85 (2H,m); ms m/z: 257 (M^++1); (Found: C, 46.93; H, 4.80; N, 10.98. Calcd for $C_{10}H_{12}N_2O_2S_2$: C, 46.85; H, 4.72; N, 10.92%).

14. N-(3-Thiocyanopropyl)-4-nitrobenzenesulfonamide (11) — Mp 82-83°C (from benzene); ir ($CHCl_3$) 2160 (SCN) cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.09 (2H,m), 3.07 (2H,t,J=7Hz), 3.21 (2H,q,J=7Hz), 4.95 (1H,br), 8.07 (2H,m), 8.39 (2H,m); ms m/z: 302(M^++1); (Found: C, 39.78; H, 3.70; N, 14.10. Calcd for $C_{10}H_{11}N_3O_4S_2$: C, 39.86; H, 3.68; N, 13.94%).

15. N-(3-Thiocyanopropyl)-4-chlorobenzenesulfonamide (12) — Mp 88.5-89°C (from benzene-n-hexane); ir ($CHCl_3$) 2160 (SCN) cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.05 (2H,m), 3.05 (2H,t,J=7Hz), 3.15 (2H,q,J=7Hz), 4.67 (1H,br), 7.52 (2H,d,J=9Hz), 7.81 (2H,d, J=9Hz); ms m/z: 291(M^++1); (Found: C, 41.23; H, 3.84; N, 9.70. Calcd for $C_{10}H_{11}ClN_2O_2S_2$: C, 41.30; H, 3.81; N, 9.63%).

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