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THIOCYANATION OF DIALKYL PHOSPHITES AND THEIR STRUCTURAL ANALOGUES BY THIOCYANOGEN $(SCN)_2$: MECHANISM AND STEREOCHEMISTRY†

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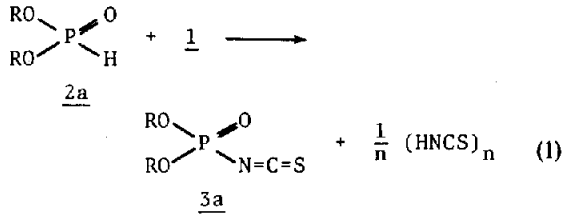
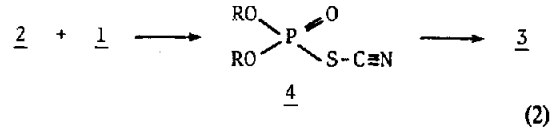
Abstract—The thiocyanation of organophosphorus compounds containing >P(X)H functional groups (X = O, S) has been reinvestigated. The reaction was shown to be highly stereospecific and proceeds with the retention of configuration at P via the thiocyanidate >P(O)SCN structure. The thiocyanidates rearrange into the isothiocyanidates >P(O)NCS with a rate depending on structure of substrates and reaction conditions. The thiocyanation reaction of dialkyl phosphite and their structural analogues offers an excellent route to the isothiocyanidates >P(X)NCS and in some cases also to the thiocyanidates >P(X)SCN.

One of the most known and versatile of pseudohalogens is thiocyanogen (**1**). This highly reactive and readily available compound has been widely used as an electrophilic reagent for introducing a -SCN group into aromatic and other organic systems.[1] It is of interest to note that among numerous reactions of thiocyanogen with nucleophiles the reaction between **1** and dialkylphosphites (**2a**) was the only one which led to the isothiocyano structure (**3a**).[2]



(1)

In early work from this Laboratory an unusual course of the reaction **1** was explained by the fast isomerisation of the initially formed phosphorothiocyanidate (**4a**) into phosphoroisothiocyanidate (**3a**) under reaction conditions.[2]



(2)

The thiocyanidates **4** were hypothetical species until 1972 when the first compound of this class was described and its great susceptibility to isomerisation demonstrated.[3]

The thiocyanidates **4** were synthesised from oxophosphoranesulphenyl chlorides **5** by displacement reactions at the S centre by silver cyanide[3] or, more conveniently, by trimethylsilyl cyanide.[4]

†Dedicated to Prof. Dr. Tadeusz Urbański on the occasion of his 80th birthday.

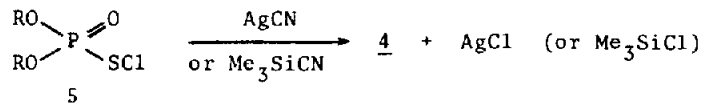
The stereochemistry of the isomerisation >P(O)SCN→>P(O)NCS was studied in this Laboratory with the aid of cyclic diastereoisomeric[5] and optically active acyclic[6] model systems. It has been shown that this rearrangement proceeds with full inversion of configuration at the P atom and is autocatalysed by nucleophilic partners, e.g. SCN^- ion, most likely via a penta-coordinated intermediate of trigonal bipyramid geometry.

With advanced understanding of the **4**→**3** isomerisation mechanism it is now possible to demonstrate the stepwise character of the reaction (**1**) and elucidate its stereochemistry. The present paper includes also new synthetic aspects of reactions between thiocyanogen (**1**) with phosphites (**2**), thiophosphites $(RO)_2P(S)H$, phosphinates R'(RO)P(O)H and phosphine oxides $R_2P(O)H$.

RESULTS

Thiocyanation of dialkyl phosphites. Previous work had shown that reaction of dialkyl phosphites with thiocyanogen resulted in formation of dialkylphosphoroisothiocyanidates **3** in good yield (70–80%)[2]. Earlier results were confirmed and extended. High purity of **3** prepared by this method was demonstrated by ^{31}P NMR spectroscopy.

The reaction of **1** with **2** (**a**, **b**) (*a*, R = Et; *b*, R = Bu^tCH_2–) was carried out by adding a methylene chloride solution of **1** in 0.001 mole excess to **2** in methylene chloride at −10° in ^{31}P NMR tube. In both cases three signals were observed the low field signals at 9.3 ppm and 10.5 ppm correspond to the thiocyanatidates **4a,b** while the middle and high field signals to the substrates **2a,b** while the middle and high field signals to the substrates **2a,b** and the isothiocyanidates **3a,b**, respectively. The ^{31}P chemical shifts of **4a,b** and **3a, b** observed were identical with those of authentic samples prepared by independent routes. After 20 min full isomerisation of **4a** into **3a** was observed. The neopentyl phosphorothiocyanidate **4b** is more stable and its isomerisation leading to **3b** was complete after 10 hr. The



(3)

heterodecoupled ^{31}P-NMR spectra of the reaction products the phosphites **2a** and **2b** with thiocyanogen after several minutes after the mixing of reagents are given in Fig. 1.

Thiocyanation reactions of sterically hindered hydrogen phosphinates **2c** *and sec-phosphine* **2d** *oxides and their stereochemistry.* It was demonstrated[5,6] that isomerisation >P(O)SCN→ >P(O)NCS proceeds by an autocatalytic nucleophilic attack of the SCN^- anion on the P centre. In consequence the steric hindrance ought to stabilise the >P(O)SCN structure. For this reason the following model compounds, t-butyl-hydrogen-O-methyl phosphinate $Bu^t(MeO)P(O)H$ **2c** and t-butyl-phenylphosphine oxide $Bu^tPhP(O)H$ **2d** were thiocyanogenated under similar conditions as those mentioned above for dialkyl phosphites. The relative high stability of the thiocyano structure was indeed confirmed on racemic compounds **4c** and **4d**. We took advantage of the possibility of thiocyanation of optically active **2c** and **2d** of known stereochemistry which can be prepared by

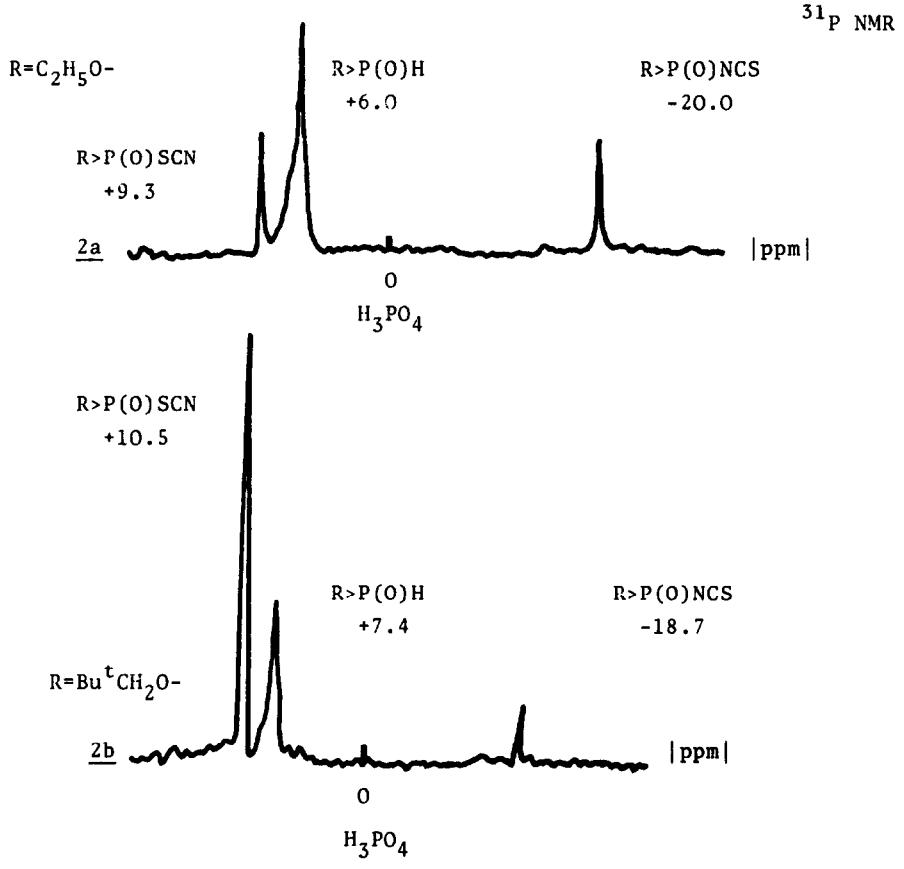
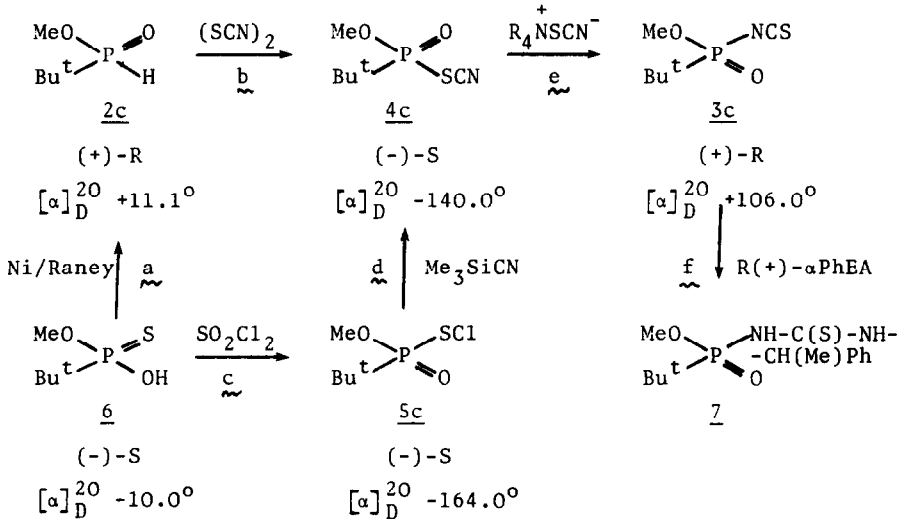


Fig. 1.



Scheme 1.

Raney Ni reduction from the monothioacids **6** and **8**. It has been established that the reduction proceeds with full retention of configuration at the P atom.[7]

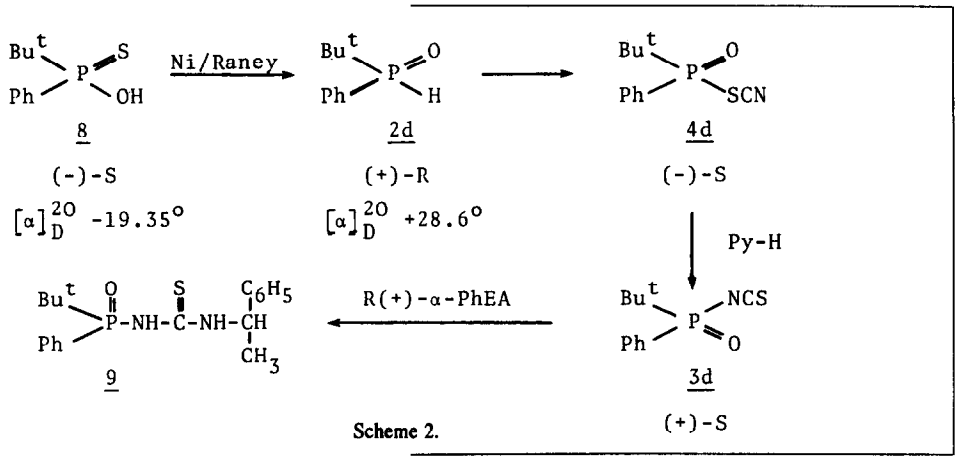
To follow the stereochemistry of thiocyanation of **2c** (reaction *b*) it was necessary to transform the same thioic acid **6**, from which the hydrogen phosphinate **2c** was obtained (reaction *a*), into oxophosphoranesulphenyl chloride **5c** (reaction *c*) and consequently into **4c** (reaction *d*). Both reactions *c* and *d* proceed with retention of configuration as well as the reaction *a*. Both the reaction *c* and *d* proceed without bond breaking and ligand methathesis at P centres. In consequence of these chemical transformations we were able to demonstrate that the thiocyanidate **4c** prepared by reaction *a* is of the same sign in optical rotation as those prepared via reaction *c* and *d*. It can therefore be concluded that the thiocynogenation reaction under discussion proceeds with retention of configuration at the P centre.[8] The stereoselectivity of the reaction was determined by ^{1}H NMR spectroscopy of the thiourea derivatives obtained by addition of *R*(+)-α-phenylethylamine (PhEA) to the isothiocyanidate **3c**. The diastereoisomeric purity of **3c** was found to be 85% demonstrating the high stereoselectivity 97% of both the thiocyanation reaction *a* as well as the isomerisation **4c**→**3c**.[9] A similar sequence of reactions has been carried out starting from the optically active acid **8**.

The reaction presented is clear cut and no other products containing phosphorus were observed by ^{31}P NMR spectroscopy. The relatively high stability of the thiocyanidate **11** $^{31}P\delta$ +75 ppm is to be explained by lower susceptibility of the thiophosphoryl group to nucleophilic displacement which is in agreement with the mechanism for *thiocyanidate-isothiocyanidate* rearrangement established in previous work[5,6]. Transformation of **11** into isothiocyanidate **12** proceeds by warming and is complete during the distillation *in vacuo*.

CONCLUDING REMARKS

New insight has been gained concerning the mechanism of the reaction between thiocyanogen **1** and dialkyl phosphites and their structural analogues. It was firmly established that the reaction proceeds with formation of a P–S bond and leads to the thiocyanidate structure **13** which undergoes *thiocyanidate-isothiocyanidate* isomerisation. The high stereoselectivity of the reaction and the retention of configuration at P is in good agreement with the following mechanistic scheme.

The reactive species in the prototropic system >P(O)H⇄P–OH seems to be the tri-coordinate form[13] which reacts with **1** to give hydroxyphosphonium salt **13**. The fast proton abstraction by SCN^- anion leads to the thiocyanidate. The proton transfer ought to be faster than ligand exchange which would lead to the isomerised

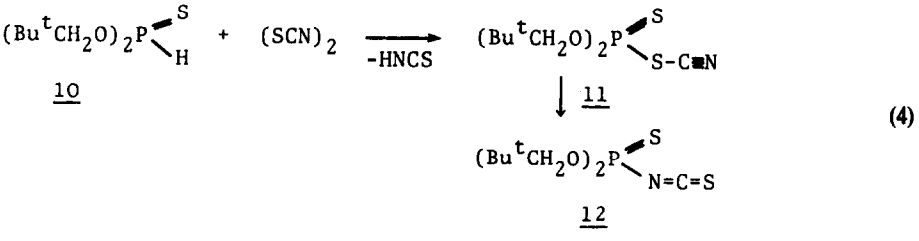


Scheme 2.

High stereoselectivity of the thiocyanation reaction (Scheme 2) was demonstrated with an aid of ^{31}P NMR spectroscopy. The thiourea **9** derivatives obtained by addition of *R*(+)-α-PhEA to the **3d** were shown to have 76% diastereoisomeric purity. The optical purity of thioic acid **8** was 80.4% (-)-*S* therefore stereoselectivity of the thiocyanation was estimated as 94%.

Thiocyanation of dineopentyl thiophosphite **10**. The reaction was carried out at room temperature in methylene chloride solution.

phosphonium salt **14**. For this reason it is unlikely to expect the isomerisation of salt **13** could contribute towards formation of **15**. It is of interest to note, that in the reaction of **1** with "true" trisubstituted organophosphorus compounds like tertiary phosphine or trialkylphosphite to give only structures which were detected by ^{31}P NMR studies were phosphoranes $\gtrless$P(NCS)$_2$ or phosphonium salts $\gtrless\overset{+}{\text{P}}$–NCS SCN^-[14,15].



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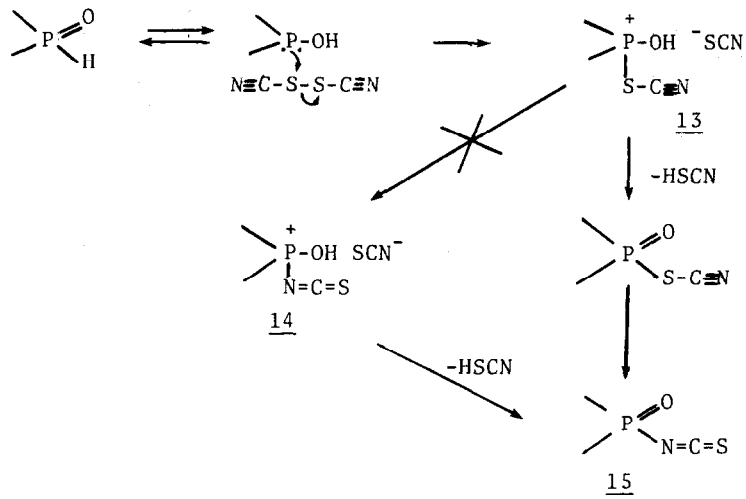

EXPERIMENTAL

Solvent and commercial reagents were purified by conventional methods before use. ^{1}H NMR spectra were recorded on a Perkin–Elmer R12B instruments with Me_4Si as internal standard. ^{31}P NMR spectra were measured with INM-FX60 Fourier transform spectrometers with 85% H_3PO_4 as internal standard. The negative values ^{31}P shift correspond to compounds absorbing at higher fields than that of H_3PO_4. Optical activity measurements were made with a Perkin–Elmer 141 photopolarimeter in benzene soln. The organophosphorus starting materials as **2a,b,c,d**, **5c**, **6**, **8** and some reaction products have been previously described.[5,6] Cyanotrimethylsilane[11] and benzyltri-n-butylammonium thiocyanate[12] were prepared as described.

The general procedure for the synthesis of phosphoroisothiocyanidate from >P(X)H *and thiocyanogen.* Into the soln of freshly prepared thiocyanogen (1.1 mole) in CH_2Cl_2, benzene, chloroform and another aprotic solvent at temp 5–10° (X = O,S,Se) was added dropwise with stirring the soln of the corresponding >P(X)H (1 mole) in the same solvents. After addition *ca.* half amount of >P(X)H a yellow ppt of the polymer of HSCN was observed. Stirring was continued for *ca.* 2–3 hr and the mixture was kept overnight at room temp. The polymeric material was filtered off, the solvent was evaporated *in vacuo* and the residual isothiocyanidate >P(X)NCS was purified by distillation *in vacuo*, yield 70–85%.

The reaction of diethylphosphite **2a** *with* **1**. To a soln of 1.38 g (0.01 mole) **2a** in 2 ml CH_2Cl_2 placed in ^{31}P NMR tube was added at −10° the soln of 0.011 mole freshly prepared **1** in 2 ml CH_2Cl_2. The ^{31}P NMR spectrum recorded after 5 min showed three signals: 9.3 ppm, 6.0 ppm and −19.5 ppm rel. intensity 1:7:2 which corresponds to **4a**, **2a** and **3a**, respectively. The temp of the mixture increase during *ca.* 20 min to the 15° and only one signal of **3a** and a small amount of substrate was observed. The mixture was kept overnight at +15°. The polymer of HSCN was filtered off and the crude **3a** was purified by distillation, b.p. 63°/0.5 mmHg, yield 1.3 g (70%).

The reaction of dineopentylphosphite **2b** *with* **1**. In the manner described for **2a**, after mixing the soln 2.2 g (0.01 mole) of **2b** with 0.011 mole of **1** in 4 ml CH_2Cl_2, the ^{31}P NMR spectrum showed the presence of **4b** δ + 10.5 ppm, phosphite **2b** δ + 7.4 ppm and isothiocyanidate **3b** δ − 18.7 ppm with relative amount 7:2:1. The mixture was kept at room temp and after *ca.* 10 hr only **3b** was observed. The 2.2 g (80%) of **3b** was separated by distillation b.p. 85°/0.2 mmHg.

The reaction of (+)-R **2c** *with* **1**. Into a soln of 0.031 mole **1** in 15 ml CH_2Cl_2, the 4.1 g (0.03 mole) (+)-*R* **2c** $[\alpha]_D^{20}$ + 11.1° in 10 ml CH_2Cl_2 prepared by reduction of (-)-*S* **6** $[\alpha]_D^{20}$ − 10.0°, was added dropwise at 10° with stirring. The ^{31}P NMR spectrum recorded after 6 hr showed the presence of only one product which according to chemical shift + 62.8 ppm was identified as (-)-*S* **4c**. The compound was stable for several hours and the isomerisation into **3c** was not observed.

The rearrangement of (-)-S **4c** *in the presence of benzyl tri-n-butylammonium thiocyanate.* Into a soln of crude (-)-*S* **4c**, (0.2 g) finely powdered benzyl tri-n-butylammonium thiocyanate was added at + 15°. After *ca.* 25 min only the presence of **3c** was observed by ^{31}P NMR. The crude **3c** was purified by distillation, yield 4.4 g (77%), $[\alpha]_D^{20}$ + 106.0°, b.p. 56–58/0.1 mm Hg. The sample of (+)-*R* **3c** was treated with excess of *R*(+)-α-PhEA, $[\alpha]_D^{20}$ + 39.0° in pyridine soln and the crude **7** was examined by ^{1}H NMR, two doublets for protons P-Bu^t in ratio 92:8, δ_1 1.13 ppm, δ_2 1.27 ppm was detected.

The optically active **4d** *by action of* **1** *on* (+)-R **2d** *and its isomerisation in presence of pyridine.* According to a procedure described for thiocyanation of (+)-*R* **2c**, from (+)-*R*-**2d** (1.8 g; 0.01 mole) $[\alpha]_D^{20}$ + 28.6° and **1** (0.011 mole) in 15 ml CH_2Cl_2 soln only (-)-*S* **4d** ^{31}P NMR + 73.8 ppm was obtained. To a soln of **4d** anhydrous pyridine (0.1 ml) was added and after *ca* 5 min the complete isomerisation of **4d** into (+)-*S* **3d** was observed by ^{31}P NMR. The immediate addition to a sample of **3d**, (1.3 g; 0.011 mole) of *R*(+)-α-PhEA to give **8** as a mixture of two diastereoisomers δ_1 + 42.69 ppm and δ_2 + 42.14 ppm in ratio 88:12 which was detected by ^{31}P NMR.

The chlorination of (−)-S **6**. The reaction of **6** (4.0 g; 0.023 mole) $[\alpha]_D^{20}$ − 10.0° with SO_2Cl_2 (3.2 g; 0.023 mole) at 0 − 5° in 20 ml CH_2Cl_2 gave (-)-*S* **5c**, yield 4.5 g (96%) $[\alpha]_D^{20}$ − 164.0°.

The reaction of (−)-S **5c** *with trimethylsilylcyanide.* Into a soln of **5c** (4.0 g; 0.019 mole) $[\alpha]_D^{20}$ − 164.0 in CH_2Cl_2, 20 ml (2.5 g; 0.025 mole) Me_3SiCN was added dropwise with stirring at 0–5°. The excess cyanide and Me_3SiCl was removed *in vacuo* and the distillation of residue gave pure **4c**, (3.1 g; 85%), b.p. 58°/0.1 mmHg, $[\alpha]_D^{20}$ − 140.0°, ^{31}P NMR δ + 62.8 ppm.

The reaction of dineopentylthiophosphite **9** *with* **1**. To a soln of **9** (2.4 g; 0.01 mole) in 3 ml CH_2Cl_2, **1** (0.011 mole) was added at + 5° with stirring. After 30 min the recorded ^{31}P NMR spectra showed the presence of two signals at + 75.0 ppm and 71.2 ppm which are characteristic for **10** and the substrate **9**. The thiocyanation was complete after 12 hr and only the presence of **10** was observed. The crude **10** was distilled *in vacuo* and **11** (2.2 g; 76%) b.p. 84°/0. 2 mm Hg ^{31}P NMR δ + 47.2 ppm was obtained.

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8. The optical purity of the thiocyanidate obtained by reaction *b* is diffcult to determine for technical reasons due to the presence of a yellow highly dispersed solid derived from the polymer of HSCN. However, the same compound prepared by reaction *d* can be readily characterised and the rotation value given in the Scheme 1 for **4c** applies for the compound prepared by the route *d*.
9. The possibility of kinetic selection was avoided by the use of an excess of PhEA. Furthermore, the entire product **7**, without purification was analysed by ^{1}H NMR to determine the diastereometric purity.[6]
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