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2,4-Di-*t*-butyl-6-methoxyphenyldithioxophosphorane as a Probe for the Mechanistic Studies of Lawesson's Reagent

Masaaki Yoshifuji,* De-Lie An, Kozo Toyota, and Masafumi Yasunami

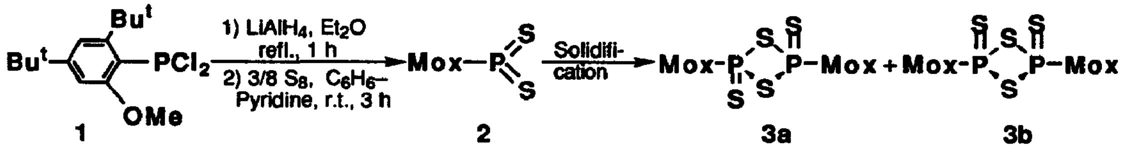
Department of Chemistry, Faculty of Science, Tohoku University, Aoba, Sendai 980, Japan

Abstract: *The chemical conversion of carbonyl to thiocarbonyl compound was directly achieved by the treatment of benzophenone with 2,4-di-t-butyl-6-methoxyphenyldithioxophosphorane, which was prepared by the thermolysis of the corresponding dimeric species, 1,3,2,4-dithiadiphosphetane 2,4-disulfides.*

The chemical conversion of carbonyl to thiocarbonyl compounds has long been an attractive area for synthetic chemists and a variety of the preparative methods have been developed.[1] Lawesson's reagent (LR: the dimer of *p*-methoxyphenyldithioxophosphorane) is one of the most successful reagents among them.[2] However, compared to extensive studies on the utility of LR, much less attention has been paid to the mechanism of the thionation reaction. A species of the $RP(=S)_2$ type has been postulated as a reactive intermediate, but this is not yet proved so far because of the difficulty in detecting such an unstable monomeric species.[3]

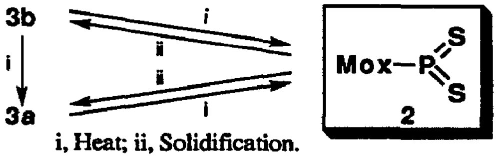
In order to obtain insight into a reaction mechanism of the LR reaction, we have been interested in a direct reaction of $RP(=S)_2$ with carbonyl compounds as a thionation reagent. Recently we have synthesized some stable dithioxophosphoranes, $ArP(=S)_2$ (Ar: 2,4,6-tri-*t*-butylphenyl)[4] and $MxP(=S)_2$ (Mx: 2,4-di-*t*-butyl-6-(dimethylamino)phenyl),[5] but these compounds, enjoying much steric protection, did not react with carbonyl compounds such as benzophenone and 1,1,3,3-tetramethylurea.[6,7] Very recently, on the other hand, we have developed a new sterically protecting group, 2,4-di-*t*-butyl-6-methoxyphenyl (hereafter abbreviated to Mox: methoxy-*m*-xylene derivative) and by utilizing this group we have obtained a moderately stable and at the same time rather reactive dithioxophosphorane, $MoxP(=S)_2$ (**2**, in Scheme I).[7] In fact, under an inert atmosphere, the dithioxophosphorane **2** in solution was stable for several days in non-polar solvents, whereas in the solid state or on concentration it gave dimeric products of the LR type, **3a** (*trans* isomer) and **3b** (*cis* isomer) in a 1 : 0.8 molar ratio. We now found that the dimers **3a** and **3b** returned to its monomer **2** on heating.

Scheme I



Mox = 2,4-Bu$^t_2$-6-MeO-C$_6$H$_2$

Scheme II



i, Heat; ii, Solidification.

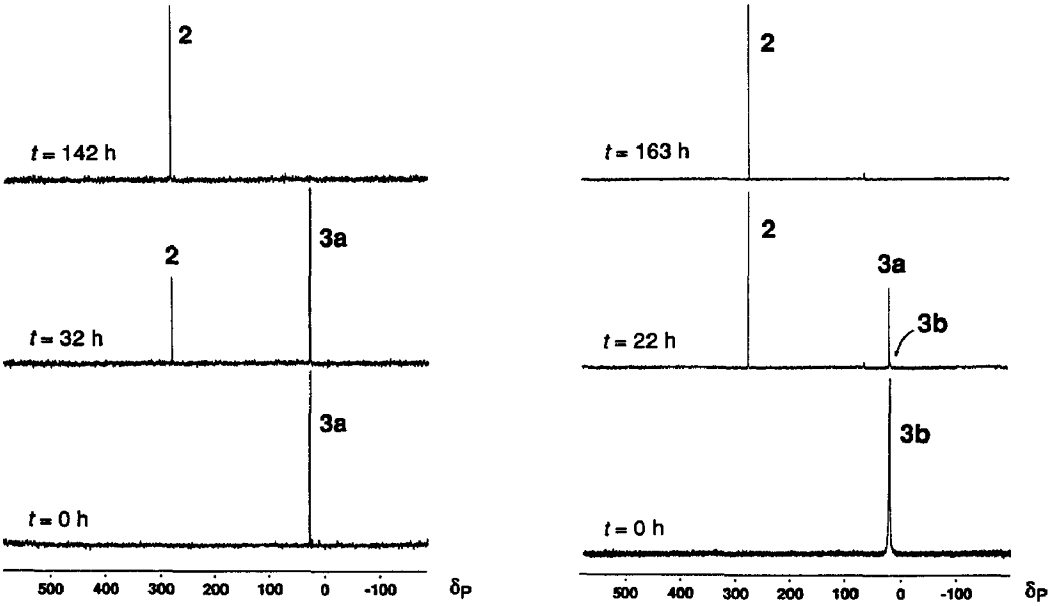
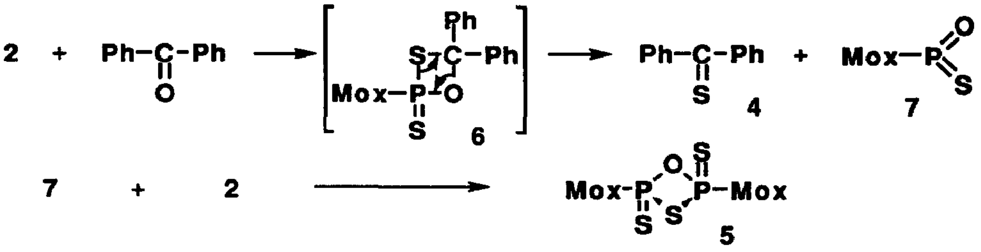


Figure 1. ^{31}P NMR spectra during the thermal reactions of **3a** (left) and **3b** (right) to **2** in C_6D_6.

When **3a** was heated at 80 °C in benzene-d_6 under argon in a sealed tube, a clean reaction occurred and the ^{31}P NMR indicated that the product was the monomer **2** (δ_P 280.05), although the reaction required a long time (6 days) to be completed. According to the similar NMR monitoring of the thermolysis of **3b**, the *cis* isomer **3b** seemed to be transformed to the monomer either directly to **2** or indirectly to **2** through an isomerization process to **3a**. Figure 1 shows the ^{31}P NMR spectra during the thermal reactions of **3a** (δ_P 27.70) at 80 °C and **3b** (δ_P 26.07) at 90 °C starting from 20.4 mg and 29.6 mg in benzene-d_6, respectively. Since we have noticed that either **3a** or **3b** is a good source to the monomer **2** (Scheme II), we now turned our attention to the reactivity of **2** toward carbonyl compounds. In fact, the monomer **2**, derived from **3a** (20.4 mg, 0.0324 mmol) by the thermal reaction as mentioned above, reacted with benzophenone (11.4 mg, 0.0628 mmol) in refluxing benzene (1 mL) for 6 days to give thiobenzophenone (**4**)[8] in 63% isolated yield based on benzophenone together with 2,4-bis(2,4-di-*t*-butyl-6-methoxyphenyl)-1,3,2,4-oxathiadiphosphetane 2,4-disulfide (**5**) in 24% yield (Scheme III).

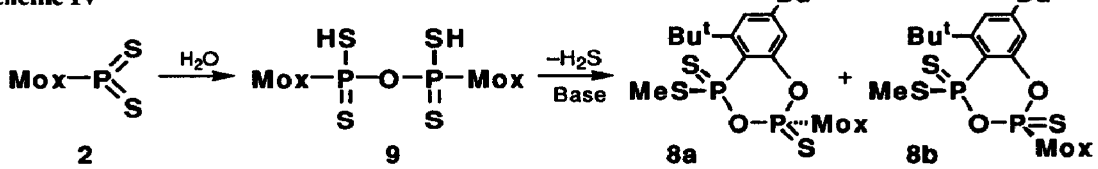
Scheme III



The reaction of dithioxophosphorane **2** with benzophenone is considered to proceed *via* a four-membered ring intermediate **6**. Thus, **2** reacts with benzophenone, leading first to **6**, followed by cleavage of the ring into one of the final products **4** together with oxothioxophosphorane **7**, which then reacts with unreacted **2** to afford the oxathiadiphosphetane *P,P'*-disulfide **5** (Scheme III).

On the other hand, when the reaction was carried out using **2** which was directly prepared from **1** without isolation,[7] the reaction products became somewhat complicated. Benzophenone (91.1 mg, 0.501 mmol) was refluxed for 24 h with **2**,[9] freshly prepared from **1** (191.5 mg, 0.596 mmol) in a mixture of benzene (15 mL) and pyridine (2 mL) as shown in Scheme I, to give the corresponding thioketone **4** (14% based on benzophenone) and **5** (5% based on **1**) together with unchanged benzophenone (80% recovery). In addition, by-products **8a** (14%) and **8b** (11% yield based on **1**, respectively) were formed as stable compounds and it seemed likely that the reaction had been carried out not under strictly anhydrous conditions. Mainly on the basis of NMR data,[10] the configurations of the cyclic products thus obtained were assigned: **8a** as *trans P,P'*-disulfide, **8b** as *cis P,P'*-disulfide, and **5** as *trans P,P'*-disulfide, by the following reasons. Both ^{1}H and ^{13}C NMR chemical shifts of the SMe group for **8b** showed significantly a high-field shift (δ_H 1.84 and δ_C 12.95) compared to those for **8a** (δ_H 2.67 and δ_C 15.03), probably the SMe for **8b** is located in the shielding region induced by the ring current of the Mox group on the other phosphorus atom and the configuration is further confirmed by an NOE experiment between the SMe and OMe protons for **8b**. As for **5**, the ^{31}P NMR signal appeared as a sharp peak indicating that **5** is in a *trans* configuration as observed for **3a** (Fig. 1) and *trans*-2,4-bis(2,4,6-tri-*t*-butylphenyl)-1,2,4-thiadiphosphetane 2,4-disulfide,[11] whereas the signal due to the *cis* isomer is expected to appear in a broad peak like **3b**.

Scheme IV



The formations of the cyclic phosphonic acid anhydrides **8a** and **8b** were unexpected. As a plausible mechanism for the formations of **8**, the monomer **2** might first give a mixed anhydride **9** in the presence of water and a base[12] and successive elimination of hydrogen sulfide accompanied by methyl transfer might eventually give **8** as shown in Scheme IV. It is interesting that the methyl group of methoxy in the Mox group is transferred to thioxo sulfur resulting in the formation of a methylthio phosphate as in **8**, although it is not clear whether the reaction proceeds intramolecularly or intermolecularly.

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9. No significant reaction was observed when benzophenone was heated with the dimers **3** under similar reaction conditions in refluxing benzene for 24 h, in contrast to the results with the monomer **2**.
10. **5**: mp 200–201 °C; ^1H NMR (200 MHz, C_6D_6) $\delta = 1.10$ (18H, s, Bu^t), 1.86 (18H, s, Bu^t), 3.32 (6H, s, OMe), 6.57 (2H, bs, arMox), and 7.33 (2H, bs, arMox); ^{31}P NMR (81 MHz, $CDCl_3$) $\delta = 74.81$; IR (KBr) 1045, 764, 694, 459, and 440 cm^{-1}; Found: C, 58.81; H, 7.57; S, 16.00%. Calcd for $C_{30}H_{46}O_3P_2S_3$: C, 58.80; H, 7.57; S, 15.70%. **8a**: mp 207–209 °C; ^1H NMR (600 MHz, $CDCl_3$) $\delta =$ 1.23 (9H, s, Bu^t), 1.26 (9H, s, Bu^t), 1.53 (9H, s, Bu^t), 1.65 (9H, s, Bu^t), 2.67 (3H, d, $^3J_{PH} = 17.66$ Hz, SMe), 4.08 (3H, s, OMe), 6.85 (1H, dd, $^4J_{PH} = 5.76$ Hz, $^4J_{HH} = 1.51$ Hz, arMox), 6.91 (1H, ddd, $^4J_{PH} = 5.03$ Hz, $^4J_{HH} = {}^4J_{P'H} = 2.04$ Hz, arMox'), 7.17 (1H, dd, $^4J_{PH} = 7.02$ Hz, $^4J_{HH} = 1.53$ Hz, arMox), and 7.38 (1H, ddd, $^4J_{PH} = 6.71$ Hz, $^4J_{HH} = 2.04$ Hz, $^6J_{P'H} = 1.12$ Hz, arMox'); $^{31}P\{^1H\}$ NMR ($CDCl_3$) $\delta = 86.00$ and 78.39 (AB, $^2J_{PP} = 47.10$ Hz); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) $\delta =$ 15.03 (d, $^2J_{PC} = 4.83$ Hz, SMe), 30.70 (s, $C\underline{Me}_3$), 30.90 (s, $C\underline{Me}_3$), 33.47 (s, $C\underline{Me}_3$), 33.59 (s, $C\underline{Me}_3$), 38.11 (d, $^3J_{PC} = 1.66$ Hz, o-$\underline{C}Me_3$), 38.48 (d, $^3J_{PC} = 1.46$ Hz, o-$\underline{C}Me_3$), and 57.12 (s, OMe); IR (KBr) 1057, 989, 868, 715, 690, and 499 cm^{-1}; Found: C, 58.63; H, 7.53; S, 15.97%. Calcd for $C_{30}H_{46}O_3P_2S_3$: C, 58.80; H, 7.57; S, 15.70%. **8b**: mp 252.5–254.5 °C; ^1H NMR (600 MHz, $CDCl_3$) $\delta = 1.25$ (9H, s, Bu^t), 1.29 (9H, s, Bu^t), 1.56 (9H, s, Bu^t), 1.62 (9H, s, Bu^t), 1.84 (3H, d, $^3J_{PH} =$ 17.12 Hz, SMe), 3.97 (3H, s, OMe), 6.86 (1H, dd, $^4J_{PH} = 5.54$ Hz, $^4J_{HH} = 1.53$ Hz, arMox), 7.05 (1H, ddd, $^4J_{PH} = 5.50$ Hz, $^4J_{HH} = {}^4J_{P'H} = 1.87$ Hz, arMox'), 7.23 (1H, dd, $^4J_{PH} = 7.52$ Hz, $^4J_{HH} =$ 1.57 Hz, arMox), and 7.45 (1H, ddd, $^4J_{PH} = 6.80$ Hz, $^4J_{HH} = 1.87$ Hz, $^6J_{P'H} = 1.12$ Hz, arMox'); $^{31}P\{^1H\}$ NMR ($CDCl_3$) $\delta = 84.09$ and 78.67 (AB, $^2J_{PP} = 56.13$ Hz); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) $\delta = 12.95$ (d, $^2J_{PC} = 4.35$ Hz, SMe), 30.83 (s, $C\underline{Me}_3$), 30.99 (s, $C\underline{Me}_3$), 32.93 (s, $C\underline{Me}_3$), 33.66 (s, $C\underline{Me}_3$), 38.21 (d, $^3J_{PC} = 1.62$ Hz, o-$\underline{C}Me_3$), 38.48 (d, $^3J_{PC} = 1.42$ Hz, o-$\underline{C}Me_3$), and 57.97 (s, OMe); IR (KBr) 1054, 982, 872, 862, 712, 685, 521, and 497 cm^{-1}; Found: *m/z* 612.2080. Calcd for $C_{30}H_{46}O_3P_2S_3$: M, 612.2084.
11. Toyota, K.; Ishikawa, Y.; Shirabe, K.; Yoshifuji, M.; Okada, K.; Hirotsu, K. *Heteroatom Chem.* **1993**, *4*, 279–285.
12. Under the control reaction conditions in the absence of benzophenone but in the presence of water (0.25 equiv.) and pyridine (2 equiv.), heating of pure **2**, generated from thermal reaction of **3** in benzene, gave **8a** and **8b** in 31% yield based on **3** in a 1 : 0.8 molar ratio. By monitoring the reaction by ^{31}P NMR an intermediary peak appeared at δ_P 73.23 and changed to **8** on heating.

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