Lawesson's Reagent: An Efficient 1,3-Dipole Trapping Agent

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Introduction

One of the best known thiation reagents is 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide, known as Lawesson's reagent (LR).[1] Studies of the thiation properties of LR have highlighted the possibility of a monomer–dimer equilibrium in solution (Scheme 1).[1b]

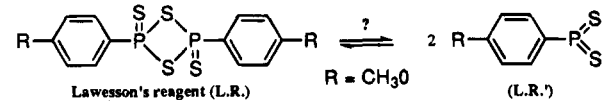
The possible existence of the monomeric form LR′ in solution led us to start investigating the potential of LR as a dipolarophile for [2 + 3]-cycloaddition reactions. It has been reported that the stable monomeric dithioxo(tri-*tert*-butylphenyl)phosphorane reacts with dimethyl 2,3-butadiene in a [4 + 2]cycloaddition process,[2] but to our knowledge, there have been no attempts to utilize LR as a dipolarophile in the synthesis of heterocycles with P–S incorporation. Lawesson's reagent was utilized in the synthesis of five-membered phosphorus heterocycles such as 1,3,5,2-oxathiazaphospholes[3] and 1,3,2-thiazaphospholines,[4] which formally result from a [2 + 3]cycloaddition process with nitrile oxides and nitrilimines, respectively. However, it was shown that the mechanism of these reactions involves the nucleophilic attack on phosphorus by the 1,3-dipole precursors, followed by ring closure and expulsion of HCl.[3,4]

Herein we report our first results on the reactivity of LR as a dipolarophile for [2 + 3]cycloaddition reactions with stable 1,3-dipoles. For this study we chose a nitrone (allyl type), two diazo compounds, and three nitrilimines (propargyl-allenyl type).

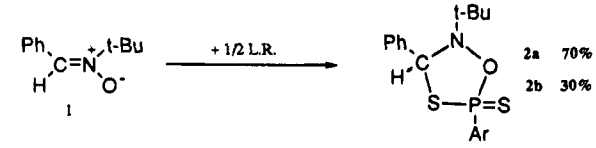
Results and Discussion

First, we investigated the cycloaddition behavior of LR with *N*-(*tert*-butyl)-*C*-phenyl nitrone **1**, nitrones representing a well established class of stable 1,3-dipoles.[5] When 2 equiv of nitrone 1 was added to a suspension of LR in THF, at room temperature, we observed the formation of oxathiazaphospholidines **2a** and **2b**. The reaction was complete after a few minutes, and rapid disappearance of the suspension made a titration feasible. From the ^{31}P NMR spectrum (a single resonance at + 102.4 ppm) it was obvious that only one regioisomer was obtained, the chemical shift being in agreement with the S–P–O sequence. The formation of two diastereomers can be explained by the *trans*/*cis* interconversion

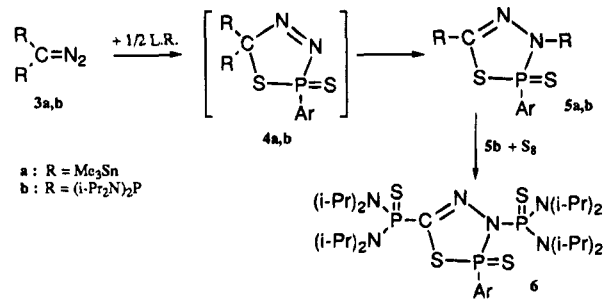
Scheme 1



Scheme 2



Scheme 3



of the nitrone in solution.[6] The ratio (70:30) was obtained from the integration of the two *tert*-butyl singlets in the ^1H NMR spectrum (Scheme 2).

To study the reactivity of LR with diazo compounds we chose two bis(hetero-substituted)diazomethanes: bis(trimethylstannyl)-[7] and bis[bis(diisopropylamino)phosphino]diazomethane[8] **3a** and **3b**, respectively. Half an equivalent of LR reacts under very mild reaction conditions (25 °C, THF) with **3a** and **3b**, leading to 1,3,4,2-thiadiazaphospholine-2-thiones **5a** and **5b**, in high yields. Again, reactions were almost instantaneous as observed with the nitrone. In each case the initial cycloadducts **4** were not detected, rapid migration of one C-substituent occurring. This result was confirmed by the presence of two signals in the ^{119}Sn NMR spectrum [−26.2 (SnC) and +70.7(J_{PSn} = 11.7 Hz) (SnN)] for **5a**, and an AMX system in the ^{31}P NMR spectrum [+92.7 (dd, J_{PP} = 87.0 and 5.0 Hz, ArP=S), +72.0 (d, J_{PP} = 87.0 Hz, PN), +51.4 (d, J_{PP} = 5.0 Hz, PC)] for **5b**. Moreover, these spectroscopic data indicated that the cycloaddition was completely regioselective. Addition of 2 equiv of elemental sulfur to **5b** led to the new thiadiazaphospholine **6**, which was isolated as yellow crystals (mp 211 °C) in 85% yield (Scheme 3).

For a long time nitrilimines were considered only as reactive intermediates.[9] Recently, we have shown that with judicious choice of substituents, nitrilimines can be isolated and stored at room temperature.[10] In order to check the scope and limitations of the reactivity of LR with propargyl-allenyl type 1,3-dipoles we chose three

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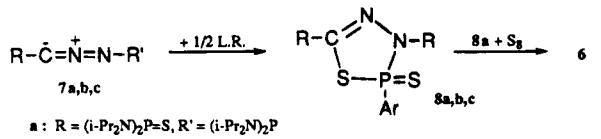
Scheme 4



stable nitrilimines each exhibiting very different behavior: *C*-thioxophosphoranyl *N*-phosphino nitrilimine **7a**[10a] which is nucleophilic, *C*-thioxophosphoranyl *N*-phosphino nitrilimine **7b**[10b,c] which is strongly electrophilic, and *C*- and *N*-boranyl nitrilimine **7c**[10d] which is totally unreactive toward classical electron-poor or electron-rich dipolarophiles.

LR reacts with nitrilimines **7a**, **7b**, and **7c**, under the same experimental conditions used for the other dipoles. The reactions were complete after a few minutes at room temperature affording the cycloadducts **8a–c** in high yields (Scheme 4). The *C*-thioxophosphoranyl *N*-phosphino thiadiazaphospholine **8a** showed an AMX system in the ^{31}P NMR spectrum [+97.1 (d, J_{PP} = 93.0 Hz, ArP), +72.7 (d, J_{PP} = 93.0 Hz, PN), +59.7 (s, P(S)C)] and was isolated after treatment with elemental sulfur and crystallization from pentane as heterocycle **6** in 88% yield. Heterocycle **8b** was obtained as white crystals from a pentane/THF solution in 93% yield (mp 163–164 °C). The ^{31}P NMR spectrum exhibited an AMX system [+101.4 (dd, J_{PP} = 11.5 and 2.3 Hz, ArP), +59.1 (dd, J_{PP} = 2.3 and 3.3 Hz, P(S)C), +51.4 (dd, J_{PP} = 11.5 and 3.3 Hz, PMe)]. The ring carbon (C=N) appeared in the ^{13}C NMR spectrum as a doublet of doublets at δ 153.3 ppm (J_{PC} = 131.9 and 14.3 Hz), one of the J_{PC} being unobservable. The most surprising result was the cycloaddition with *C*-[bis(diisopropylamino)boranyl]-*N*-[bis(diisopropylamino)boranyl]nitrilimine (**7c**), since as already mentioned, the 1,3-dipole **7c** is quite unreactive. Heterocycle **8c** was obtained, in nearly quantitative yield, as yellow crystals (mp 186 °C). The regioselectivity of this cycloaddition was obvious from the single resonance at +92.2 ppm, in the ^{31}P NMR spectrum; the ring carbon (C=N) appeared as a broad signal at +150.2 ppm in the ^{13}C NMR spectrum.

Conclusion

In conclusion, we have shown that 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide (LR) is a powerful dipolarophile. It reacts under mild conditions with a variety of electron-poor and electron-rich 1,3-dipoles, including those which show low reactivity. Therefore, Lawesson's reagent can be used as a "1,3-dipole indicator", the outcome of the reaction being easily verified using ^{31}P NMR spectroscopy.

Experimental Section

All experiments were performed under an atmosphere of dry argon or nitrogen. Melting points are uncorrected. 2,4-bis(4-Methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide and *N-tert*-butyl-α-phenyl nitrone were purchased from Aldrich Chemical Co. and were used as received.

Cycloadducts 2a and 2b from *N-tert*-Butyl-α-phenyl Nitrone. Lawesson's reagent (0.12 g, 0.28 mmol) was added to a THF solution (2 mL) of *N-tert*-butyl-α-phenyl nitrone (0.10 g, 0.56 mmol) at rt. After 1 h at rt, ^{31}P NMR spectroscopy indicated the quantitative formation of cycloadduct **2** as a mixture of two diastereoisomers **2a** and **2b** in 70:30 ratio according to ^{1}H NMR spectroscopy. Evaporation of the solvent led to the isolation of **2** as a spectroscopically pure yellow oil (0.16 g, 95% yield); all spectroscopic data were obtained from the mixture of isomers.

2a (70%): ^{31}P NMR{^{1}H} ($CDCl_3$) δ +102.4; ^{1}H NMR ($CDCl_3$) δ 1.11 (s, 9 H), 3.81 (s, 3 H), 6.17 (d, J_{PH} = 4.3 Hz, 1 H), 6.80–8.30 (m, 9 H); ^{13}C NMR ($CDCl_3$) δ 27.1 (s), 55.3 (s), 62.8 (d, J_{PC} = 5.4 Hz), 78.8 (s), 113.4 (d, J_{PC} = 15.9 Hz), 128.4 (s), 128.6 (s), 133.7 (s), 134.0 (d, J_{PC} = 14.8 Hz), 136.4 (s), 162.8 (d, J_{PC} = 4.5 Hz).

2b (30%): ^{31}P NMR{^{1}H} ($CDCl_3$) δ +102.4; ^{1}H NMR ($CDCl_3$) δ 1.55 (s, 9 H), 3.82 (s, 3 H), 6.80–8.30 (m, 9 H); ^{13}C NMR ($CDCl_3$) δ 28.2 (s), 55.5 (s), 62.7 (d, J_{PC} = 5.0 Hz), 78.9 (s), 114.0 (d, J_{PC} = 18.1 Hz), 129.1 (s), 129.2 (s), 134.2 (d, J_{PC} = 19.7 Hz), 164.1 (d, J_{PC} = 8.3 Hz).

Cycloadduct 5a from bis(Trimethylstannyl)diazomethane. Lawesson's reagent (0.11 g, 0.27 mmol) was added to a THF solution (2 mL) of bis(trimethylstannyl)diazomethane (0.20 g, 0.54 mmol) at rt. After 1 h at rt, ^{31}P NMR spectroscopy indicated the quantitative formation of cycloadduct **5a**. Evaporation of the solvent led to the isolation of compound **5a** as a yellow oil (0.23 g, 75% yield): ^{31}P NMR{^{1}H} ($CDCl_3$) δ +94.6; ^{119}Sn NMR ($CDCl_3$) δ −26.2 (s), +70.7 (d, J_{PSn} = 11.7 Hz); ^{1}H NMR ($CDCl_3$) δ 0.27 (s, 9 H), 0.31 (s, 9 H), 3.67 (s, 3 H), 6.79–6.82 (m, 2 H), 7.72 (dd, J_{HH} = 8.6 Hz, J_{PH} = 14.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ −10.0 (s, J_{SnC} = 355.1 Hz, J_{SnC} = 371.0 Hz), −3.7 (s, J_{SnC} = 374.7 Hz, J_{SnC} = 389.9 Hz), 55.5 (s), 113.3 (d, J_{PC} = 24.8 Hz), 129.6 (d, J_{PC} = 107.6 Hz), 134.2 (d, J_{PC} = 14.6 Hz), 148.4 (d, J_{PC} = 11.5 Hz), 162.4 (d, J_{PC} = 3.2 Hz); IR ($CDCl_3$) 1597 cm^{-1}. Anal. Calcd for $C_{14}H_{25}N_2PS_2OSn_2$: C, 29.50; H, 4.42; N, 4.91. Found: C, 29.59; H, 4.52; N, 4.79.

Cycloadducts 5b and 6 from Bis[bis(Diisopropylamino)-phosphino]diazomethane. Lawesson's reagent (0.08 g, 0.20 mmol) was added to a THF solution (2 mL) of bis[bis(diisopropylamino)phosphino]diazomethane (0.20 g, 0.40 mmol) in rt. After 1 h at rt, ^{31}P NMR spectroscopy indicated the quantitative formation of cycloadduct **5b** [+92.7 (dd, J_{PP} = 87.0 and 5.0 Hz), +72.0 (d, J_{PP} = 87.0 Hz), +51.4 (d, J_{PP} = 5.0 Hz)]. Addition of 2 equiv of sulfur led to compound **6** which, after crystallization from a pentane/THF solution, was obtained as yellow crystals (0.26 g, 85% yield): mp 211 °C; ^{31}P NMR{^{1}H} ($CDCl_3$) δ +98.3 (d, J_{PP} = 23.7 Hz), +61.7 (d, J_{PP} = 2.8 Hz), +58.4 (dd, J_{PP} = 23.7 and 2.8 Hz); ^{1}H NMR ($CDCl_3$) δ 1.09 (d, J_{HH} = 6.8 Hz, 12 H), 1.24 (d, J_{HH} = 6.8 Hz, 12 H), 1.37 (d, J_{HH} = 6.8 Hz, 12 H), 1.39 (d, J_{HH} = 6.8 Hz, 12 H), 3.79 (s, 3 H), 3.91 (sept d, J_{HH} = 6.8 Hz, J_{PH} = 23.6 Hz, 4 H), 4.17 (sept d, J_{HH} = 6.8 Hz, J_{PH} = 15.3 Hz, 4 H), 6.88 (dd, J_{HH} = 8.8 Hz, J_{PH} = 3.5 Hz, 2 H), 8.06 (dd, J_{HH} = 8.8 Hz, J_{PH} = 15.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 24.1 (s), 24.6 (s), 47.6 (d, J_{PC} = 5.7 Hz), 47.8 (d, J_{PC} = 6.5 Hz), 55.3 (s), 112.9 (d, J_{PC} = 17.4 Hz), 126.9 (d, J_{PC} = 113.3 Hz), 135.2 (d, J_{PC} = 14.9 Hz), 146.5 (ddd, J_{PC} = 149.2, 11.5 and 6.7 Hz), 162.5 (d, J_{PC} = 2.9 Hz); IR (THF) 1594 cm^{-1}; CIMS (m/z) 769 (M^+ + 1). Anal. Calcd for $C_{32}H_{63}N_6P_3S_4O$: C, 49.97; H, 8.26; N, 10.93. Found: C, 49.82; H, 8.20; N, 10.71.

Cycloadducts 8a and 6 from *C*-[Bis(Diisopropylamino)-thioxophosphoranyl]-*N*-[bis(diisopropylamino)phosphino]-nitrilimine (7a). Lawesson's reagent (0.09 g, 0.24 mmol) was added to a THF solution (2 mL) of nitrilimine **7a** (0.25 g, 0.47 mmol) at rt. After 1 h at rt, ^{31}P NMR spectroscopy indicated the quantitative formation of cycloadduct **8a** [+97.1 (d, J_{PP} = 93.0 Hz), +72.7 (d, J_{PP} = 93.0 Hz), +59.7 (s)]. Addition of 1 equiv of sulfur led to compound **6** which, after crystallization from a pentane/THF solution, was obtained as yellow crystals (0.32 g, 88% yield): mp 211–212 °C.

Cycloadduct 8b from *C*-[Bis(Diisopropylamino)thioxophosphoranyl]-*N*-bis[(diisopropylamino)methylphosphonio]nitrilimine (7b). Lawesson's reagent (0.08 g, 0.19 mmol) was added to a THF solution (2 mL) of nitrilimine **7b** (0.20 g, 0.37 mmol) at rt. After 1 h at rt, ^{31}P NMR spectroscopy indicated the quantitative formation of cycloadduct **8b**. Evaporation of the solvent and crystallization from a pentane/THF

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solution led to the isolation of compound **8b** as white crystals (0.31 g, 93% yield): mp 163–164 °C; ^{31}P NMR{^{1}H} ($CDCl_3$) δ +101.4 (d, J_{PP} = 11.5 and 2.3 Hz), +59.1 (dd, J_{PP} = 2.3 and 3.3 Hz), +51.4 (dd, J_{PP} = 11.5 and 3.3 Hz); ^{1}H NMR ($CDCl_3$) δ 1.18–1.36 (m, 48 H), 1.98 (d, J_{PH} = 13.9 Hz, 3 H), 3.68 (m, 8 H), 3.85 (s, 3 H), 7.04 (m, 2 H), 7.87 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 15.0 (d, J_{PC} = 100.7 Hz), 22.6, 23.7, 23.8, 24.3 (s), 48.1 (d, J_{PC} = 6.2 Hz), 48.2 (d, J_{PC} = 6.8 Hz), 48.8 (d, J_{PC} = 4.3 Hz), 49.9 (d, J_{PC} = 5.1 Hz), 56.0 (s), 115.1 (d, J_{PC} = 16.8 Hz), 120.4 (q, J_{FC} = 320.8 Hz), 121.2 (d, J_{PC} = 104.6 Hz), 135.1 (d, J_{PC} = 15.8 Hz), 153.3 (dd, J_{PC} = 131.9 and 14.3 Hz), 164.9 (d, J_{PC} = 2.8 Hz); IR ($CDCl_3$) 1598 cm^{-1}. Anal. Calcd for $C_{34}H_{66}N_6P_3S_4O_4F_3$: C, 45.32; H, 7.38; N, 9.32. Found: C, 45.02; H, 7.20; N, 9.03.

Cycloadduct 8c from *C*-[Bis(Diisopropylamino)boranyl]-*N*-[bis(diisopropylamino)boranyl]nitrilimine (7c). Lawesson's reagent (0.13 g, 0.33 mmol) was added to a THF solution (2 mL) of nitrilimine **7c** (0.30 g, 0.65 mmol) at rt. After 1 h at rt, ^{31}P NMR spectroscopy indicated the quantitative formation of cycloadduct **8c**. Evaporation of the solvent and crystallization from a pentane/THF solution led to the isolation of compound **8c** as yellow crystals (0.40 g, 93% yield): mp 186 °C; ^{31}P NMR{^{1}H} ($CDCl_3$) δ +92.2; ^{11}B NMR ($CDCl_3$) δ +27.7 (s br); ^{1}H NMR ($CDCl_3$) δ 1.12 (d, J_{HH} = 6.9 Hz, 24 H), 1.21 (d, J_{HH} = 6.9 Hz, 24 H), 3.49–3.72 (m, 8 H), 3.80 (s, 3 H), 6.91 (dd, J_{HH} = 8.8 Hz, J_{PH} = 14.8 Hz, 2 H), 8.01 (dd, J_{HH} = 8.8 Hz, J_{PH} = 3.1 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 23.4, 24.0, 25.3, 26.1, 48.0, 48.7 and 55.4 (s), 113.3 (d, J_{PC} = 16.1 Hz), 126.9 (d, J_{PC} = 106.2 Hz), 135.6 (d, J_{PC} = 15.1 Hz), 150.2 (s br), 162.5 (d, J_{PC} = 3.8 Hz); IR ($CDCl_3$) 1594 cm^{-1}. Anal. Calcd for $C_{32}H_{63}N_6B_2PS_2O$: C, 57.83; H, 9.55; N, 12.64. Found: C, 57.65; H, 9.48; N, 12.36.

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