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AN EFFICIENT SYNTHESIS OF 1,2-DITHIOLANES AND 1,2,4-TRITHIOLANES BY THE REACTION OF PHOSPHORUS YLIDES WITH ELEMENTAL SULFUR

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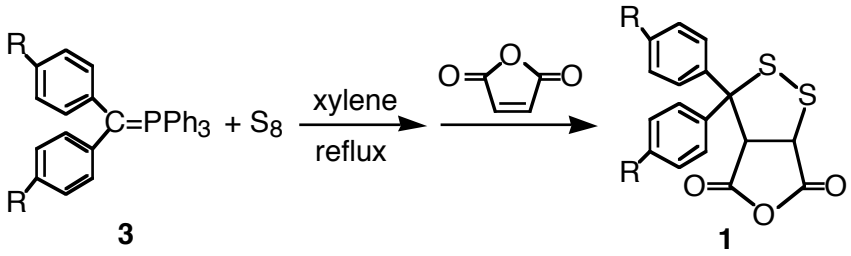
Abstract-Reaction of diarylmethylenetriphenylphosphoranes with elemental sulfur followed by the addition of maleic anhydride afforded 1,2-dithiolanes in good yields. When the reaction was carried out in the presence of adamantane-2-thione, two types of 1,2,4-trithiolane were formed. Thiation of thiobenzophenones with elemental sulfur also afforded the corresponding 1,2-dithiolanes.

The chemistry of cyclic polysulfides is of current interest.[1] 1,2-Dithiolanes (**1**) and 1,2,4-trithiolanes (**2**) are an important class of compounds because of their biological activity and structural interest.[2] The synthesis of **1** includes the oxidation of 1,3-dithiols,[3] and the intramolecular cyclization of thiosulfine with double bond.[4] 1,2,4-Trithiolanes **2** were prepared by the reaction of thiobenzophenone with *o*-chloranil,[5] the reaction of thiobenzophenones with 1,1-diphenylethylene sulfide,[6] the reaction of thiones with Lowesson reagents,[7] the reaction of dialkyl ketones with hydrogen sulfide, elemental sulfur, and amines,[8] and the fragmentation of 1,2,3-thiadiazoles.[9] Recently, Senning and coworkers reported that reaction of α-chlorosulfenyl disulfides with morpholine afforded the corresponding dispirotrithiolanes.[10] Previously, we have reported the synthesis of 1,2-dithiolanes **1** from Wittig reagents (**3**), elemental sulfur, and maleic anhydride.[11] Recently, we have reported that the reaction of pivalophenones with tetraphosphorus decasulfide afforded *cis*- and *trans*-3,5-di-*tert*-butyl-3,5-diaryl-1,2,4-trithiolanes, which equilibrated to give other isomers in refluxing toluene *via* thiopivalophenones and thiopivalophenone S-sulfides.[12] We report a synthesis of **1** and **2** from diarylmethylenetriphenylphosphoranes (**3**) and elemental sulfur.

Results and Discussion

Treatment of diphenylmethylenetriphenylphosphorane (**3a**) with excess sulfur in the presence of maleic anhydride resulted in the formation of 5,5-diphenyl-1,2-dithiolane-3,4-dicarboxylic acid anhydride (**1a**) in good yield. Reactions of other phosphoranes (**3b**-**d**) with elemental sulfur and maleic anhydride were carried out in a similar manner (Scheme 1, Table 1).

The reaction required relatively elevated temperature for completion. When the reaction was carried out in refluxing benzene, 50% of thiobenzophenone (**4a**) was remained unreacted.

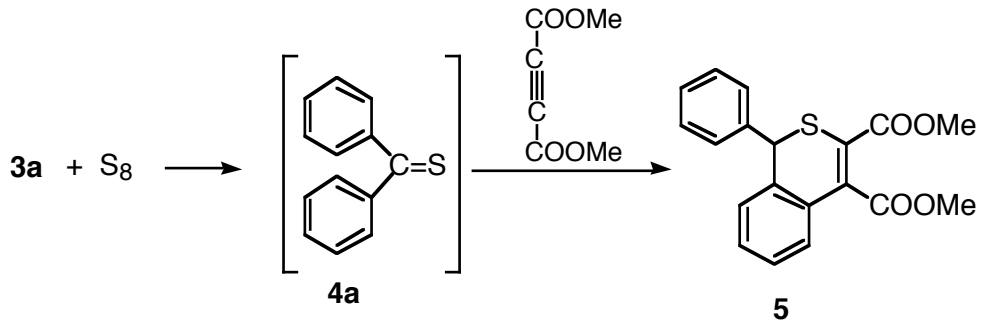


Scheme 1.

Table 1. Reaction of **3** with 7 Equivalents of Elemental Sulfur Followed by Maleic Anhydride in Xylene under Reflux

		Conditions			
3	R	Solvent	Time/day	**1**	Yield (%)
3a	H	Xylene	1	**1a**	74
3a	H	Toluene	1	**1a**	25
3b	Me	Xylene	1	**1b**	90
3c	MeO	Xylene	1	**1c**	79
3d	Cl	Xylene	1	**1d**	35
3d	Cl	Xylene	3	**1d**	60

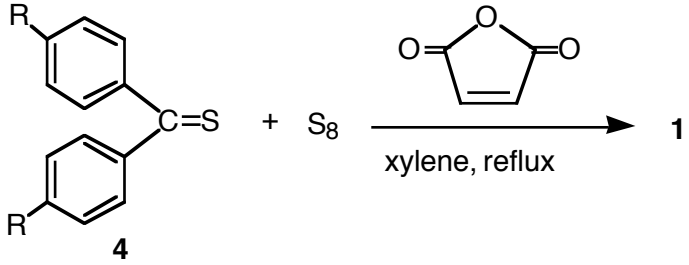
1,2-Dithiols were prepared by a cycloreversion and cycloaddition reaction of trithiolanes with Dimethyl acetylenedicarboxylate (DMAD) or by the reaction of ketone hydrazone with S_2Cl_2 followed by the addition of DMAD.[6,13] Recently, we have reported the reaction of 4,4'-dimethylthiobenzophenone (**4b**: R=CH_3) with 2,5-norbornadiene; the initial [4+2] cycloaddition product was obtained without 1,3-prototropy.[14] We tried the reaction of **3a** with elemental sulfur in the presence of DMAD in the hope of obtaining the [3+2] cycloadduct of thiosulfine with DMAD. However, only cyclic sulfide (**5**), a [4+2] cycloadduct of **4a** with DMAD was obtained, suggesting that, the reactivity of DMAD was quite different from that of maleic anhydride (Scheme 2).



Scheme 2.

Since **4a** is generally produced by the reaction of **3a** with elemental sulfur,[15] we then tried the reaction of **4** with elemental sulfur in the presence of maleic anhydride. When 4,4'dimethoxythiobenzophenone (**4c**) was treated with elemental sulfur in the presence of maleic anhydride, the cycloadduct (**1c**) was obtained in 30 % yield (Scheme 3, Table 2).

The lower yields for **1** is probably due to low concentration of activated sulfur. If activated sulfur plays an important role in this reaction, addition of triphenylphosphine could improve the yields of cycloadducts **1**. When the reaction of **4c** with excess sulfur was carried out in the presence of triphenylphosphine, the yield of adduct (**1c**) was increased to 65 %.

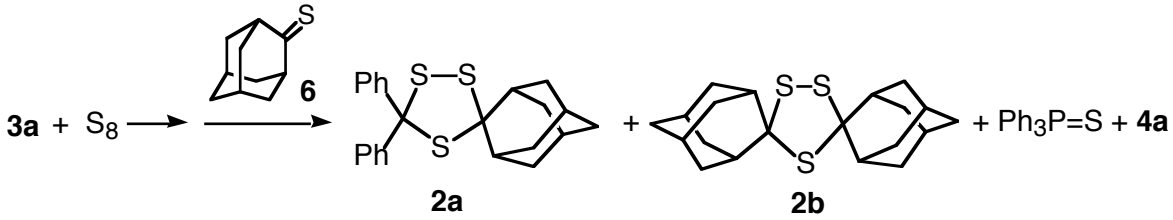


Scheme 3.

Table 2. Reaction of Thiobenzophenones (**4**) with Sulfur in the Presence of Maleic Anhydride in Xylene under Reflux

	R	Time/day	**1**	Yield (%)
4a	H	3	**1a**	13
4c	MeO	2	**1c**	30
4c	MeO	5	**1c**	48

Huisgen and Rapp reported the synthesis of 1,2,4-trithiolanes (**2**) by the reaction of thiobenzophenone-S-sulfides with adamantane-2-thione (**6**).[6] To check the scope and limitation of the present methodology, we then tried the reaction of **3a** with elemental sulfur and **6** under these conditions in the hope of the formation of the corresponding **2**. Treatment of **3a** with elemental sulfur followed by the addition of **6** resulted in tha formation of spiro-adamantane-1,2,4-trithiolanes (**2a**) and spiro-diadamantane-1,2,4-trithiolane (**2b**) in 15 % and 44 % yields, respectively. Thiobenzophenone (**4a**) and triphenylphosphine sulfide were also obtained in 35 % and 84 % yields (Scheme 4, Table 3).



Scheme 4.

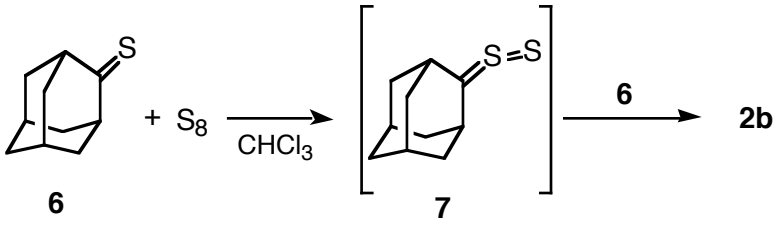
Table 3. Reaction of **2** with Sulfur in the Presence of Adamantane-2-thione in Toluene unde Reflux

	R	Time/day	Products/ Yield (%) **2**			**4**	
3a	H	1	**2a**	15	**2b** 44	**4a**	35
3c	MeO	2	**2c**	12	**2b** 38	**4c**	35

Analogously, thiation of 4,4'-dimethoxythiobenzophenone (**4c**) by elemental sulfur and catalytic amount

of triphenylphosphine sulfide in chloroform followed by treatment with adamantane-2-thione led to the adamantane-spiro-1,2,4-trithiolanes (**2c**) (14 %) and (**2b**) (35 %) along with starting **4c** (45 %).

The above results suggest that initially formed thiosulfines reacted **6** to afford unsymmetrical trithiolanes (**2c**), which decomposed to give 4,4'-dimethoxythiobenzophenone and adamantane-2-thione S-sulfide (**7**). The obtained **7** further reacted with **6** to give the most stable symmetrical trithiolane (**2b**). To confirm this possibility, we then tried the reaction of elemental sulfur with **6** in the presence of catalytic amount of triphenylphosphine sulfide in chloroform. As expected, the corresponding trithiolane (**2b**) was obtained in 59 % yield. Thus, this method will be also applicable to the synthesis of 1,2,4-trithiolanes (Scheme 5).



Scheme 5.

In summary, we have succeeded in the synthesis of 1,2-dithiolanes from diarylmethylene-triphenylphosphorane, elemental sulfur, and maleic anhydride. We have also synthesized 1,2,4-trithiolanes from adamantane-2-thione, elemental sulfur, and thiobenzophenones.

ACKNOWLEDGMENT

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EXPERIMENTAL

General: Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained with a JEOL FX-90Q or a JEOL GSX-400 spectrometer. Chemical shifts are given in ppm units downfield from tetramethyl-silane. TLC analyses were performed using Merck silica gel 60 F254 aluminum plates. Gel-HPLC was performed on a JAI Model 908 by elution with chloroform.

Material: Thiobenzophenones (**4**) were prepared by the reaction of benzophenone with P_4S_{10}.[16] Adamantane-2-thione (**6**) was prepared by a method in a literature.[17]

Reaction of Diphenylmethylenetriphenylphosphorane (3a) with Elemental Sulfur Followed by the Addition of Maleic Anhydride To a refluxing solution of **3a** (0.428 g, 1 mmol) in xylene (30 mL) was added elemental sulfur (0.224 g, 7.0 mg-atom) in one portion. After refluxing for 5 min, maleic anhydride (0.294 g, 3.0 mmol) was added in one portion and the solution was refluxed for 36 h. The reaction mixture was concentrated to give a dark brown oil, which was chromatographed over silica gel by elution from hexane-dichloromethane (1:1) to give triphenylphosphine sulfide (0.223 g, 76 %) and pale yellow crystals of 5,5-diphenyl-1,2-dithiolane-3,4-dicarboxylic acid anhydride (**1a**, 0.244 g, 74 %). **1a**: mp 86-88 °C (MeOH), ^{1}H NMR (400 M Hz, $CDCl_3$) δ= 4.61 (d, *J*= 8.0 Hz, 1 H, CH), 4.81 (d, *J*= 8.0 Hz, 1 H, CH), 7.20-7.42 (m, 10 H, Ph). Anal. Calcd for $C_{17}H_{12}O_3S_2$. C; 62.17, H; 3.68. Found. C; 62.27, H; 3.86. Other reaction was carried out in a similar manner. 3,3-di-*p*-tolyl-1,2-dithiolane-4,5-dicarboxylic acid anhydride (**1b**): mp 87-90 °C (MeOH). ^{1}H NMR (400 M Hz, $CDCl_3$) δ= 2.22 (s, 6 H, Me), 4.46 (d, *J*= 7.4 z 1 H, CH), 4.67 (d, *J*= 7.4 Hz, 1H, CH), 7.00-7.22 (m, 8 H, Ar). HRMS: Found. 356.0545. Calcd for $C_{19}H_{16}O_3S_2$ (M^+) 356.0541. 5,5-di-*p*-methoxyphenyl-1,2-dithiolane-3,4-dicarboxylic acid anhydride (**1c**): mp 55-58°C. ^{1}H NMR (400 M Hz, $CDCl_3$) δ=3.77 (s, 3 H, MeO), 3.79 (s, 3 H, MeO), 4.54 (d, *J*= 7.3 Hz, 1 H, CH), 4.62 (d, *J*= 7.3 Hz, CH), 6.82 (br d, *J*=7.2 Hz, 4 H, Ar), 7.16 (d, *J*=7.2 Hz, 2 H, Ar), 7.24 (d, *J*=7.2 Hz, 2 H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ=53.65 (CH), 55.16 (OMe), 55.26 (OMe), 58.03 (CH), 79.89 (Ar_2C), 113.48, 113.57, 128.26, 129.21, 130.64, 134.13, 159.11,

159.24 (Ar), 166.10 (C=O), 167.54 (C=O). Anal. Calcd for for $C_{19}H_{16}O_5S_2$. C; 58.75, H; 4.25. Found. C; 59.01, H; 4.53. 5,5-di-*p*-chlorophenyl-1,2-dithiolane-3,4-dicarboxylic acid anhydride (**1d**): mp 73-76 ˚C (MeOH). ^{1}H NMR (400 MHz, for $C_{19}H_{16}O_3S_2$) δ= 4.61 (d, 1 H, *J*=7.4 Hz, CH), 4.70 (d, 1 H,*J*=7.4Hz, CH), 7.10-7.42 (m, 10 H, Ar). ^{13}C NMR (100 MHz, for $C_{19}H_{16}O_3S_2$) δ = 53.11 (CH), 57.85 (CH), 79.14 (Ar_2C), 118.25, 128.26, 128.68, 128.82, 129.28, 130.14, 130.62, 134.38, 134.62, 136.47, 137,57, 140.29, 166.06, 168.79. HRMS: Found; 395.9448. Calcd for $C_{17}H_{10}O_3{}^{35}Cl_2S_2$ (M^+) ; 395.9448.

Reaction of 3 with Elemental Sulfur followed by Addition of DMAD To a refluxing solution of **3a** (0.428 g, 1 mmol) in xylene (30 mL) was added elemental sulfur (0.224 g, 7.0 mg-atom) in one portion. After refluxing for 5 min, DMAD (0.57 g, 4.0 mmol) was added in one portion and the solution was refluxed for 16 h. The reaction mixture was concentrated to give a dark brown oil, which was chromatographed over silica gel by elution from hexane-dichloromethane (1:3) to give triphenylphosphine sulfide (0.228 g, 78 %) and colorless crystals of dimethyl 1-phenyl-1*H*-2-benzothiopyrane-3,4-dicarboxylate (**5**, 0.201 g, 56 %). mp 90-91˚C (MeOH) (lit.[18] 91-92 ˚C). ^{1}H NMR ($CDCl_3$) δ=3.77 (s, 3 H, OMe), 3.94 (s, 3 H, OMe), 5.21 (s, 1 H, CH), 6.95-7.50 (m, 9 H, Ph).

Reaction of Thiobenzophenone (4a) with Elemental Sulfur in the Presence of Maleic Anhydride To a refluxing solution of **4a** (0.201 mg, 1.0 mmol) in xylene (20 mL) was added elemental sulfur (0.160 g, 5 mg-atom). After refluxing for 1 h, maleic anhydride (0.98 g, 10 mmol) was added to this blue solution and the solution was refluxed for 3 days. The reaction mixture was concentrated to give a dark brown oil, which was chromatographed over silica gel by elution from hexane-dichloromethane (1:1) to afford pale yellow crystals of **1a** (0.043 g, 13 %): mp 86-88 ˚C (MeOH).

Reaction of 4a with Elemental Sulfur Followed by Addition of Maleic Anhydride in the Presence of Catalytic Amount of Triphenylphosphine To a refluxing solution of **4a** (0.201 mg, 1.0 mmol) in xylene (20 mL) were added elemental sulfur (0.160 g, 5 mg-atom) and triphenylphosphine sulfide (0.029 g, 0.1 mmol). After refluxing for 1 h, maleic anhydride (0.98 g, 10 mmol) was added to this blue solution and the solution was refluxed for 24 h. The reaction mixture was concentrated to give a dark brown oil, which was chromatographed over silica gel by elution from hexane-dichloromethane (1:1) to afford pale yellow crystals of **1a** (0.213 g, 65 %): mp 86-88 ˚C (MeOH).

Reaction of 3a with Elemental Sulfur Followed by Addition of Adamantane-2-thione (6) To a refluxing solution of **3a** (0.428 g, 1 mmol) in toluene (20 mL) was added elemental sulfur (0.128 g, 4.0 mg-atom) in one portion. After refluxing for 30 min, **6** (0.165 g, 1.0 mmol) was added in one portion and the solution was refluxed for 24 h. The reaction mixture was concentrated to give a blue oil, which was chromatographed over silica gel by elution from hexane-dichloromethane (1:3) to give colorless crystals of 5',5'-diphenylspiro[adamantane-2,3'-(1,2,4)-trithiolane] (**2a**) (0.061 g, 15 %), dispiro[adamantane-2,3'-(1,2,4)-trithiolane-5',2'-adamantane] (**2b**) (0.080 g, 44 %), triphenylphosphine sulfide (0.252 g, 84 %), and benzophenone (0.064 g, 35 %). **2a**: mp 126-129 ˚C (THF-pentane) (lit.[1] 131-132 ˚C) ^{1}H NMR (400 MHz, $CDC1_3$) δ=1.78 (br, 4 H, Ad-H)), 1.86 (br s, 1 H, Ad-H), 1.97 (br d, 3 H, *J*= 16 Hz, Ad-H), 2.20 (br d, 2 H, *J*= 16 Hz, Ad-H), 2.27 (br d, 2 H, *J*= 16 Hz, Ad-H), 2.49 (br s, 2 H, Ad-H), 7.25-7.32 (m, 5 H, Ph), 7.60-7.63 (m, 5 H, Ph). **2b**: colorless crystals; mp 191-193 ˚C (THF-pentane) (lit.[1] 189-191 ˚C).

The reaction of **3c** with elemental sulfur and **6** was carried out in a similar manner. The reagents used in the preparation were: **3c** (0.481 g, 1.0 mmol), elemental sulfur (0.128 g, 4.0 mg-atom), **6** (0.165 g, 1.0 mmol) and toluene (20 mL). Flush chromatography followed by Gel-HPLC afforded 5',5'-di-*p*-methoxyphenylspiro[adamantane-2,3'-(1,2,4)-trithiolane] (**2c**) (0.061 g, 12 %), **2b** (0.080 g, 38 %), triphenylphosphine sulfide (0.252 g, 84 %), and **4c** (0.064 g, 35 %). **2c**: palebrownoil. ^{1}H NMR (400 MHz, $CDC1_3$) δ=1.78 (br, 4 H, Ad-H), 1.85 (br s, 1 H, Ad-H), 1.96 (br d, 3 H, *J*= 16 Hz), 2.17 (br d, 2 H, *J*= 12 Hz, Ad-H), 2.27 (br d, 2 H, *J*= 12 Hz), 2.46 (br s, 2 H, Ad-H), 3.79 (s, 6 H, OMe), 6.81 (d, 4 H, *J*=9 Hz, Ar), 7.53 (d, 4 H, *J*= 9 Hz, Ar). ^{13}C NMR (100 M Hz, $CDC1_3$) δ= 26.58, 26.74, 36.73, 37.77,

40.03, 55.26 (MeO) , 89.01, 93.49, 1 13.00 (meta, Ar), 130.31 (ortho, Ar), 134.36 (ipso, Ar), 158.79 (para, Ar). IR (KBr) v (cm^{-1}): 2910, 2853, 1604, 1579,1504, 1463, 1451, 1302, 1252, 1175, 1097, 1035, 961, 821. HRMS: Found; 456.1236. Calcd for $C_{25}H_{28}O_2S_3$ (M^+); 456.1251.

Reaction of 4c with Elemental Sulfur Followed by Addition of 6 in the Presence of Catalytic Amount of Triphenylphosphine Sulfide To a solution of **4c** (0.050 g, 0.2 mmol) in chloroform (5 mL) were added elemental sulfur (0.016 g, 0.5 mg-atom) and triphenylphosphine sulfide (0.010 g, 0.03 mmol). After refluxing for 1 h, **6** (0.033 g, 0.2 mmol) was added in one portion and the solution was refluxed for 24 h and stirred for 15 days at rt. The reaction mixture was evaporated to give a blue oil, which was subjected to a preparative TLC by elution of hexane, hexane-dichloromethane (1:1), and dichloromethane to give **2c** (0.0091 g, 14 %). Trithiolane (**2b**) was also obtained (0.013 g, 35 %). Thioketone (**4c**) was recovered in 45 %.

Reaction of 6 with Elemental Sulfur in the Presence of Catalytic Amount of Triphenylphosphine Sulfide To a solution of **6** (0.066 g, 0.4 mmol) in chloroform (5 mL) were added elemental sulfur (0.016 g, 0.5 mg-atom) and triphenylphosphine sulfide (0.010 g, 0.03 mmol). After refluxing for 2 days, the reaction mixture was evaporated to give pale orange crystals, which was subjected to a preparative TLC by elution of hexane and hexane-dichloromethane (1:1) to afford colorless crystals of **2b** (0.043 g, 59 %).

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