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An Improved Synthesis of Fused 1,2,3-Benzothiadiphospholes and a Proposed Reaction Pathway

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ABSTRACT

A fresh look has been taken at the reaction of PCl_3 with thioanisole **1b** *and $AlCl_3$ that gives, after treatment with water, the title compounds cis-***2b** *in 38% yield together with small amounts of the isomeric cis-***3b** *(2%). The course of this reaction has been studied by ^{31}P-NMR spectroscopy. A multistep pathway, governed by the formation of several $AlCl_3$ complexes with sulfur and phosphorus containing intermediates, has been proposed. The crucial step of this reaction is very reasonably an intramolecular electrocyclic ring closure of a diphosphane intermediate. From this plausible mechanism, an improved procedure that gives only the cis-***2b** *isomer in 42% yield has been realized. In addition, an alternative synthesis using p-thiocresol that gives compounds cis-***2b** *and cis-***3b** *in a ratio of about 2:1 has been effected.* © 1997 John Wiley & Sons, Inc. Heteroatom Chem **8:**551–556, 1997

INTRODUCTION

In order to achieve the synthesis of new phosphorus and sulfur containing heterocycles by a simple procedure, we devised [1] the highly stereoselective one-pot synthesis of *cis*-[1,2,3]benzothiadiphospholo-[2,3-*b*] [1,2,3]benzothiadiphosphole (*cis*-**2**), a new fused heterocyclic system containing an unusual P–P(S_2) unit, by treating thioanisole **1** with $PCl_3/AlCl_3$. This method has also been generalized employing several alkyl aryl sulfides, providing in this way the corresponding fused 1,2,3-benzothiadiphospholes, such as *cis*-**2** [2]. This peculiar reactivity has also been applied to the synthesis of 1,2,3-benzothiadiphospholes **4** using $RPCl_2/AlCl_3$ and **1b,** but, in this case, the yields of **4** were lower, and the formation of a relevant amount of the corresponding P-oxide was also observed [3]. Subsequently [4], working on a larger scale, it was possible to isolate also the isomeric compounds ±*cis*-**3** in very small amounts. No appreciable amounts of the corresponding *trans* isomers were observed. The X-ray structures of *cis*-**2** and *cis*-**3** compounds showed that both of the molecules adopt a butterfly-like arrangement with the phosphorus electron lone pairs in an eclipsed conformation. As this conformation is unusual for a molecule containing a P(III)–P(III) single bond, a solid-state ^{31}P-NMR study was performed. The changes in ^1J(P,P) and δ^{31}P observed from solution to solid state indicated that crystal packing effects force the two "wings" of the butterfly molecule to open slightly in the solid state [5]. It should be noted that the best results (38% yields) were obtained in the synthesis of *cis*-**2b,** and for this reason, we began to study the reactivity of this heterocyclic system using prevalently this compound.

Dedicated to Prof. William E. McEwen on the occasion of his seventy-fifth birthday.

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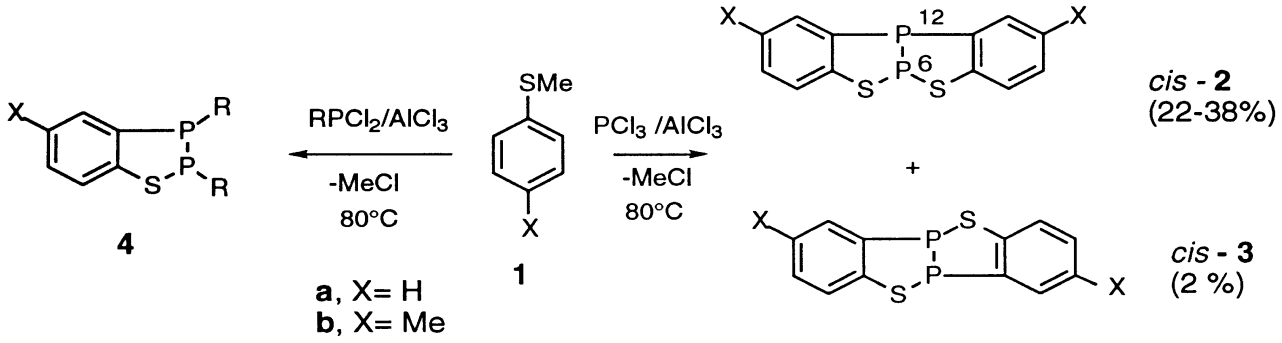


SCHEME 1

RESULTS AND DISCUSSION

Previously, the synthesis of *cis*-**2b** was carried out as a one-pot, one-step Friedel–Craft-type reaction in which **1b** was added to a mixture of PCl_3 and aluminum chloride with a 1:3:0.75 ratio, without solvent, by heating at 80°C for about 2 hours. It has long been known that the reaction of diphenyl sulfides with $PCl_3/AlCl_3$ gives heterocyclic compounds related to phosphathianthracenes [6], but no examples are reported in the literature in which this reaction is applied to *aryl alkyl sulfides*. Then, we speculated that this lack of information might be due to the complexity of the results that might include the formation of a tarry mixture containing a multitude of products, including the formation of some unexpected heterocyclic compounds, such as 1,2,3-benzothiaphosphole or benzothiaphosphete. Such compounds might be very difficult to characterize. Fortunately, we found that, even if the result of the reaction between **1** and $PCl_3/AlCl_3$ is a very complex cyclization, the separation and the characterization of the prevalent product (*cis*-**2**) was very easy. The breaking of two S–Me bonds, the formation of two C–P bonds, two P–S bonds, and one P–P bond are involved in this cyclization, but several pathways can a priori be written, and, up to date, it has not been possible to determine an unequivocal reaction pathway. In order to determine the most probable pathway, it is necessary to uncover some information regarding the demethylation process, the ortho- and S-phosphorylation, the P–P linkage formation and, if it is possible, to have some explanation for the facile regioselective and stereoselective formation of *cis*-**2**.

It is well documented in the literature [7] that, when a diphenyl sulfide is caused to react with $AlCl_3$, a sulfonium salt or complex is formed in a reversible manner, and evidence for methyl phenyl sulfide-$AlCl_3$ complex formation has also been reported [8]. In addition, when this complex is treated with other reagents, a cleavage of the C–S bond occurs presumably via a tetracovalent sulfur compound [7–9]. Furthermore, benzyl phenyl sulfide is known [9] to form a complex with $AlCl_3$, one which undergoes reaction with water to give thiophenol and benzyl chloride.

It is explicitly stated [10], on the basis of ^{31}P-NMR measurements, that, while molecular complexes are formed between dichlorophosphines and $AlCl_3$, no complex (ionic or molecular) is formed in detectable amounts from PCl_3 and $AlCl_3$.

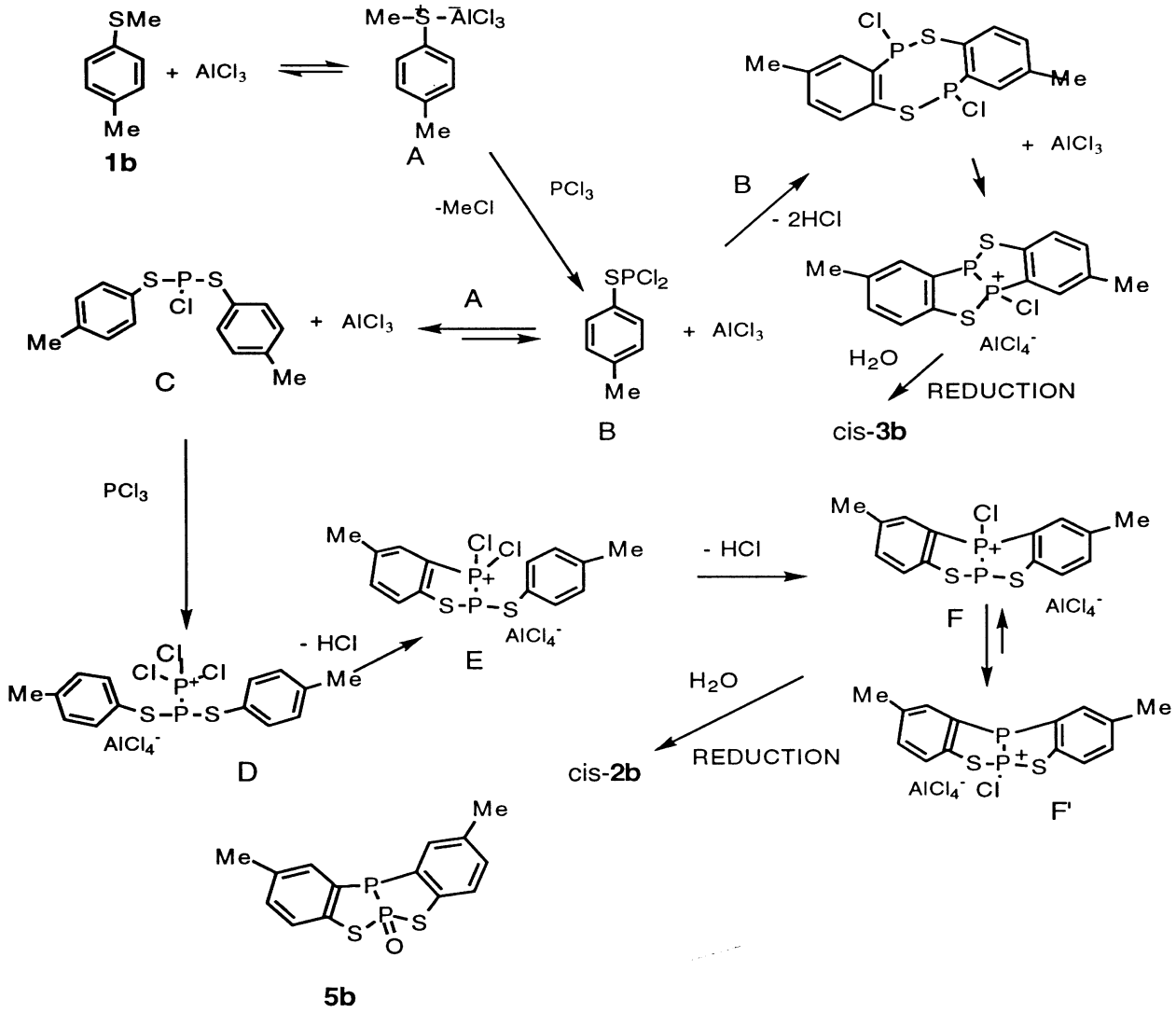
From this information in the literature, we understood that, presumably, the first step of our reaction might be the sulfide-$AlCl_3$ complex formation and that there is no competition with PCl_3 in the $AlCl_3$ complex formation.

After a series of reactions using various reagent ratios and various temperatures and times, we found that the best results were obtained by changing the order of addition of the reagents in a one-pot, two-step procedure.

In particular, we noticed an improvement by first adding $AlCl_3$ to the sulfide **1b** at room temperature. In this case, the development of a red-brown oil indicated the formation of a sulfonium salt or a complex such as A (Scheme 2). No gas evolution was observed in this step. The color changed from red-brown to yellow when an excess of PCl_3 was added dropwise to this mixture. At this stage, MeCl was evolved. At the end of the addition, a homogeneous reaction mixture was obtained, and this was gently heated at 50–60°C for about 5 hours until no more hydrogen chloride was evolved; after treatment with water, compound *cis*-**2b** was obtained in about 42% yield.

It should be noted that, for a good outcome of the reaction, it is necessary to use a fresh bottle of anhydrous $AlCl_3$ (otherwise it has to be sublimed just prior to use) and a sulfide/$AlCl_3$/PCl_3 ratio of 1:0.75:4.

From these observations, some conclusions can be reached. First, it is clear that, after the first step,



SCHEME 2

the true substrate is no longer the sulfide but its $AlCl_3$ complex A, which should deactivate the ortho electrophilic Friedel–Crafts aromatic substitution while activating the S-phosphorylation. Second, the demethylation step occurs after the addition of PCl_3, and the reaction can be conducted in several steps at different temperatures. Finally, at the end of the reaction, it is necessary to add water and work up the mixture in order to observe the formation of *cis*-**2b.** In consideration of the above-mentioned observations, we are proposing a multistep mechanism as depicted in Scheme 2.

The proposed *intramolecular* cyclization after the P–P linkage has formed is further supported by the results obtained from methyl phenyl sulfide **1a.** In this case, the *para* position is free to undergo an *intermolecular* electrophilic aromatic substitution, but, also in this case, the formation of the corresponding *cis*-**2a** is prevalent, even if in minor yield (22–25%) in comparison to *cis*-**2b** (38–42%). At the end, in situ reduction of intermediates F or/and F′ and decomplexation after addition of water gives *cis*-**2b** and a very small amount of the oxide **5b** [^{31}P-NMR: δ 21.4 (d, P_6); 103.1 (dt, P_{12}, $^3J_{P\text{-}H}$ = 9.5 Hz), $^1J_{PP}$ = 258.2 Hz)].

In order to obtain supporting evidence for the above-proposed multistep mechanism, we have conducted a series of reactions using various conditions (different reagents ratios and various temperatures), and aliquots of the reaction mixtures have been analyzed by ^{31}P- and ^{1}H-NMR spectroscopy and by GC-MS determinations.

The ^{1}H-NMR spectrum of the first step mixture confirmed the existence of the complex A in equilib-

rium with the sulfide. The aromatic protons and methyl protons are shifted downfield relative to those of the sulfide alone, as previously reported [14].

After the first step (formation of $AlCl_3$-complex A) and addition of PCl_3 (sulfide/$AlCl_3$/PCl_3 ratio of 1:0.75:4), the reaction was carried out at 50–60°C and the first aliquots showed several ^{31}P-NMR peaks that were difficult to assign, but, at the end of the reaction, there was observed only a strong pair of doublets that may be assigned to the final intermediate F′. The ^{31}P chemical shifts and P–P and PH coupling constants [δ 37.7 (d, P_6, J_{PP} = 349.5 Hz); 111.0 (dt, P_{-12}, $J_{P\text{-}H}$ = 8 Hz, J_{PP} = 349.5 Hz)] are in good agreement with the formulation of F′, as depicted in Scheme 2.

After treatment of the reaction mixture with water, the gradual disappearance of the peaks of F′ and the concomitant appearance of the peaks [δ 88.3 (d, P_6); 65.4 (dt, P_{12}, $^3J_{P\text{-}H}$ = 7.8 Hz, $^1J_{PP}$ = 211.5 Hz)] of *cis*-**2b** were observed.

Only a very small amount of the oxide **5b** was also found to be present. No traces of *cis*-**3b** were observed indicating that under these conditions, collateral reactions are minimized.

In contrast, when the second step of the reaction was also carried out at ambient temperature, as well for several minutes (20–30 min), but with minor amounts of $AlCl_3$ and PCl_3 (sulfide/$AlCl_3$/PCl_3 ratio of 1:0.3:2), we observed the appearance and disappearance of peaks (δ 206 and δ 184) assigned to compounds B and C, respectively. After further addition of $AlCl_3$, we observed the appearance of a new peak at δ 233 that can be attributed tentatively to the phosphenium cation derived from C [15], and the appearance of two pairs of doublets at δ 5.7 (dd, J_{PP} = 325 Hz, $^3J_{P\text{-}H}$ = 7.5 Hz), 121.2 (d, J_{PP} = 325 Hz) and at δ 36.4 (d, J_{PP} = 347.2 Hz), 126.0 (d, J_{PP} = 347.2 Hz) that may be assigned to the intermediates E and D, respectively. If at this stage, the reaction mixture was heated at 50–60°C, the doublets of D and E were gradually replaced by the doublets of F′. This fact suggests that the final phosphorylation (a Friedel–Crafts type of aromatic substitution) is the rate-determining step of this anomalous reaction. It should be noted that B and C were also observed by GC-MS determinations.

It should also be noted that, when the reaction was carried out as a one-pot, one-step procedure at 70–80°C (sulfide/$AlCl_3$/PCl_3 ratio of 1:0.75: 3), at the beginning of the reaction, after treatment with water, a *cis*-**2b**/*cis*-**3b** ratio of 4:1 was observed, while, at the end of the reaction, the ratio was about 20:1. This can be explained in the following manner. Initially the intermediate B or its $AlCl_3$ complex may prevail over the other intermediates. The simultaneous heating of the reaction mixture probably allowed an intermolecular cyclization of B (as depicted in Scheme 2) to occur to give *cis*-**3b.** After a few minutes, the equilibrium between B and C became operative. The formation of D, favored by the excess of PCl_3, now promoted the formation of *cis*-**2b** and drastically attenuated the formation of *cis*-**3b.** Then, in order to obtain only *cis*-**2b,** it was necessary to use a large excess of PCl_3 and the right amount of $AlCl_3$ (0.75 equiv.). An excess of $AlCl_3$ disfavored the reaction because all the sulfide was complexed. Since the S–Al coordination drives the sequence of reactions from the first steps, one can assume, from the proposed scheme and from the stoichiometry involved in the formation of the product F′, that the best $AlCl_3$:**1b** ratio should be 0.5:1.0 However, the best yields were obtained with a 0.75:1.0 ratio, probably due to the complexity of the mechanism, together with the effects of some impurities often present in $AlCl_3$. After the addition of PCl_3, it is necessary to allow the reaction to proceed at ambient temperature for several minutes so as to form D and to exclude the cyclization of B.

The proposed pathway also explains some of the results previously reported [2]. When isopropyl p-tolyl sulfide was used together with PCl_3/$AlCl_3$, the compound (4-$MeC_6H_4S)_2$(*i-pr*)PO was obtained as the major product. In this case, isopropyl chloride is formed, but its persistence in the reaction mixture can cause reaction with the intermediate C to give, after workup, the above compound.

The failure of other Lewis acids to catalyze these reactions, as reported [2], is now explained. This reaction is governed by the particular tendency of $AlCl_3$ to form complexes with sulfur and phosphorus compounds. Our reaction is not a simple Friedel–Crafts phosphorylation but is instead a multistep procedure in which $AlCl_3$ plays always a determinant role. Attempts to perform the reaction with several solvents (CH_2Cl_2, NO_2Ph, $CHCl_3$) failed.

In order to confirm the structure of F′, the final reaction mixture containing prevalently the supposed intermediate F′ was reduced and decomplexed in situ by addition of But_3P, giving immediately *cis*-**2b.**

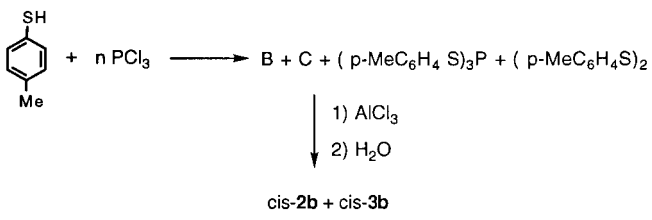
Furthermore, a reaction of *cis*-**2b** with 1 equiv of chlorine was performed: the ^{31}P-NMR spectrum of the reaction mixture showed some peaks, indicating that this reaction is very complex. Among other signals, a strong pair of doublets at δ 110 and δ 32 (J_{PP} = 305 Hz), which might result from the presence F′ or F without $AlCl_3$, is in equilibrium with its pentacoordinate form. Addition of $AlCl_3$ to this mixture did not give an appreciable variation of the shifts and

of the J_{PP} values. Presumably, the complexation in the presence of a solvent is very difficult as confirmed by the failure of this reaction to take place in the presence of any solvent. However, a conclusive proof for the structure of F′ was not found. It should be noted that the addition of $AlCl_3$ to *cis*-**2b** did not cause a variation in its ^{31}P signals, thus excluding the possibility that F′ can be a *cis*-**2b**-$AlCl_3$ complex.

Having proposed and partially confirmed a plausible pathway for this unexpected formation of the benzothiadiphosphole system, we proceeded to a rational exploitation for an alternative synthesis. The crucial intermediate of the above-mentioned multistep mechanism is compound C. We therefore prepared C by reaction of PCl_3 with p-thiocresol, obtaining a mixture of chlorodithiophosphite C, dichlorothiophosphite B, p-tolyltrithiophosphite, and the corresponding disulfide in different ratios depending [14] on the ratio of the starting reagents. The subsequent treatment of this mixture with $AlCl_3$ gave, after about 2 hours at 70°C, a mixture of *cis*-**2b** and *cis*-**3b** in a ratio that is related to the ratio of C and B obtained previously (Scheme 3). For example, when 2 equiv of PCl_3 were used, the C:B ratio was about 2:1.5, and the final *cis*-**2b**:*cis*-**3b** ratio was 2:1, but the overall yield was only 15%. This result confirms that C is the precursor of *cis*-**2b,** and presumably, B may be the precursor of *cis*-**3b,** as depicted in Scheme 4.

Work is still in progress to obtain more information regarding this hypothesized intermolecular cyclization. However, preliminary results show that when a large excess of PCl_3 (4–5 equiv.) is used, compound *cis*-**3b** is not formed: This result is in good agreement with an intermolecular cyclization and explains the necessity to use a large excess of PCl_3 when the synthesis starts from sulfide **1,** in which an intramolecular cyclization must be favored in order to have the exclusive formation of *cis*-**2b.**

In conclusion, the pathway proposed provides a rational explanation of the unexpected highly stereoselective formation of fused 1,2,3-benzothiadiphospholes *cis*-**2** by the simple reaction between sulfide **1** and $AlCl_3$ and PCl_3. In addition, from this plausible multistep pathway, an improved procedure



SCHEME 3

that gives only *cis*-**2b** and an alternative synthesis that permits also the formation in good yields of the isomeric *cis*-**3b** have both been realized.

EXPERIMENTAL

^1H- and ^{31}P-NMR spectra were recorded at 300.00 and 121.144 MHz, respectively, on a Varian Gemini 300 instrument. ^1H-NMR chemical shifts are given in ppm from Me_4Si, and ^{31}P-NMR chemical shifts are from H_3PO_4 (85%) as an external standard in $CDCl_3$ solutions and with downfield shifts positive. Mass spectra were recorded on a VG 7070 spectrometer or with an HP-5890 gas chromatograph equipped with a methyl silicone capillary column and by an HP-5970 mass detector. Commercial PCl_3 was used after distillation. Commercial sulfides and thiophenols were used without any purification. Aluminum trichloride had to be sublimed just prior to use.

One-pot–two-step Procedure. Reaction of Sulfide **1b** *with $AlCl_3$ and PCl_3*

The reaction was conducted in a 150 mL three-necked flask equipped with a condenser, a dropping funnel, and with provision for the ingress and egress of dry N_2. A mixture of sulfide **1b** (0.04 mol) and $AlCl_3$ (0.03 mol) was stirred for about 5 minutes during which the initial yellow color changed to red-brown. The subsequent dropwise addition of PCl_3 (0.16 mol) caused the reaction mixture color to change to yellow over about 30 minutes at room temperature. During this time, evolution of MeCl was observed. Aliquots of this reaction mixture were taken up in $CDCl_3$ for NMR analysis. The ^{31}P-NMR spectrum showed several weak signals.

Subsequently, the reaction mixture was gently heated at 50–60°C for about 5 hours until evolution of HCl ceased, then diluted with CH_2Cl_2 (30 mL), cooled to 0°C, and treated under stirring with water. Extraction with CH_2Cl_2 and subsequent crystallization of the crude product from CH_2Cl_2–Et_2O gave pure *cis*-**2b** (42%). No formation of the isomeric *cis*-**3b** was observed.

The ^{31}P-NMR spectrum of the final solution, before the addition of water, showed, in addition to the signal of PCl_3 (δ 219.5), a strong couple of doublets at δ 37.7 (d, P_6, J_{PP} = 349.5 Hz) and at δ 111.0 (dt, P_{12}, $J_{P\text{-}H}$ = 8 Hz, J_{PP} = 349.5 Hz). In order to obtain a good resolution of these signals, the excess of PCl_3 was removed under dry nitrogen.

Small amounts of the oxide **5** were isolated from the reaction mixture by flash chromatography over silica gel using light petroleum ether (40–60°C) / diethyl ether 1:3 as eluant.

Compound **5.** While solid; R_F 0.14; mp 181–184°C; ^{1}H NMR δ ($CDCl_3$) 2.39 (s, Me, 6H), 7.24–7.26 (m, 4H, ArH), 7.67 (bd, 2H, H^1, $^3J_{HP}$ 9.5 Hz); ^{31}P NMR δ 21.4 (d, P-6), 103.1 (dt, P-12), J_{PP} 258.2 Hz, $^3J_{PH}$ 9.5 Hz; *m/z* 321.321.9806, (M^+ calc. for $C_{14}H_{12}P_2S_2O$: 321.9804) 275, 259 (base-peak), 243, 211, 185, 121, 63 (Found: H, 3.7; C, 52.25; P, 19.15; S, 19.8; $C_{14}H_{12}P_2S_2O$ requires H, 3.7; C, 52.2; P, 19.2; S, 19.85%.)

Reaction of p-Thiocresol with PCl_3 and $AlCl_3$

A mixture of p-Thiocresol (0.04 mol) and PCl_3 (0.08 mol) was allowed to react for 1 hour at room temperature under stirring in an atmosphere of dry N_2 until no more HCl evolved. An equilibrium mixture of compounds B, C, trithiophosphite, and disulfide in the ratio 1.5:2:2:1 was obtained. Subsequently, this reaction mixture was treated with $AlCl_3$ (0.02 mol) and allowed to stand at 70–80°C for about 3 hours. After treatment of the mixture with water, a mixture containing *cis*-**2b** and *cis*-**3b** in the ratio 2:1 was obtained.

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