THE BEHAVIOR OF DIPHENYLMETHYLENETRIPHENYLPHOSPHORANE AND PHOSPHITES TOWARD 5-SUBSTITUTED -1,3,4-THIADIAZOL DERIVATIVES

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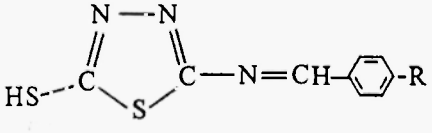
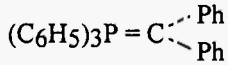
Abstract: Diphenylmethylenetriphenylphosphorane **4** reacts with 5-{[4-(methoxy-benzylidene)]amino}-1,3, 4-thiadiazol-2-thiol **1a** and 5-{[4-(dimethylamino)-benzylidene]amino}-1,3,4-thiadiazol-2-thiol **1b** to give adducts **6a** and **6b** respectively. On the other hand, dimethyl phosphite **5a** reacts with **1b** in presence of trace amount of TEA, yielding the dimethylphosphonate adduct **8a** and alkylated product **7b**, whereas diisopropyl phosphite **5c** reacts with **1b** to give diisopropylphosphonate adduct **8c**. Also,the reaction of dialkyl phosphites **5a-c** with **1a** has been investigated to give dialkyl phosphonate products **8d-f**. Structural reasoning for the new compounds are based on compatible analytical and spectral data.

Introduction

In our previous publication (1), we have reported that 5-substituted-1,3,4-thiadiazol derivatives **1** react with trialkyl phosphites **2** and trisdialkylaminophosphines **3** in different interesting courses depending on the stability of the addition products as well as the reaction conditions used. However, we have now extended our study on the behavior of diphenyl-methylenetriphenylphosphorane **4** and dialkyl phosphites **5** toward 5-{[4-(methoxy-benzylidene)]amino}-1,3,4-thiadiazole-2-thiol **1a** and 5-{[4-(dimethylamino)-benzylidene] amino}-1,3,4-thiadiazole-2-thiol **1b** (Scheme1).



1a, R = OCH_3
b, R = $N(CH_3)_2$



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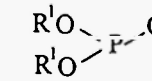
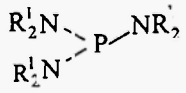
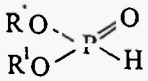


2a, $R^1 = CH_3$
b, $R^1 = C_2H_5$
c, $R^1 = CH(CH_3)_2$



3a, $R^1 = CH_3$
b, $R^1 = C_2H_5$



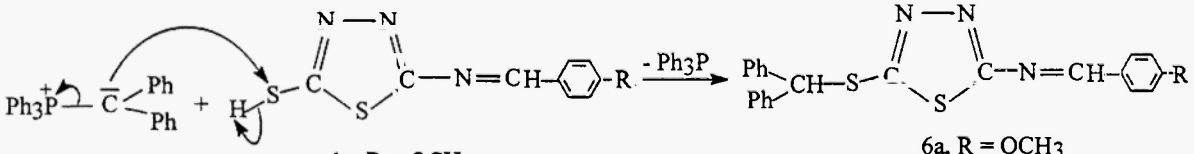
5a, $R^1 = CH_3$
b, $R^1 = C_2H_5$
c, $R^1 = CH(CH_3)_2$

Scheme 1

Results and Discussion

We have found that the reaction of 5-{[4-(methoxybenzylidene)]amino}-1,3,4-thiadiazole-2-thiol **1a** with mol equivalents of freshly prepared diphenylmethylenetriphenyl-phosphorane **4** (2) in dry toluene proceeds at reflux temperature to give yellow compound assigned structure **6a** (Scheme 2).

Triphenylphosphine was also isolated from the reaction in quantitative yield. Compound **6a** is chromatographically pure yellow crystals and possesses a sharp melting point. Structure elucidation of the new product is based on the following evidence. The IR spectrum of **6a** lacks the SH absorption band appearing in the spectrum of **1a** at 2650 cm^{-1}. Moreover, the IR spectrum of **6a** disclosed the presence of strong absorption bands at 1600 (C=C, Ar) and 1640cm^{-1}(C=N). The ^1H NMR spectrum of **6a** shows signals centered at δ 3.85 (OCH_3),6.15 ppm (1H,s,S-CH),8.70(1H,s,N=CH),two doublets at 6.95(2H,d) and 7.90 (2H,d) ppm for the four substituted aromatic ring, and at 7.20-7.50ppm (10H,two phenyl groups). Also, the ^1H NMR of **6a** shows the absence of the SH absorption band at 10.65ppm in the starting thiadiazol derivative **1a**. The structure assigned for compound **6a** was based on the ^{13}C NMR which indicates the presence of signals at δ =165.5 (C-OCH_3),140.56(C=N),114.34 ppm (N=



Scheme 2

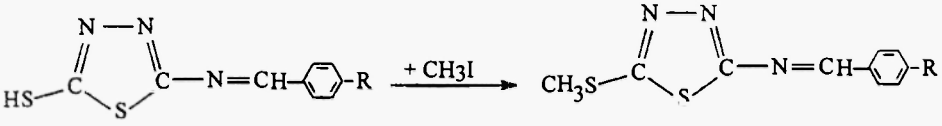
CH),at 55.45(OCH_3) and at 56.5 corresponding to the S-$CH(Ph)_2$ group. The ^{13}C NMR spectrum of **6a** lacks the C-SH absorption band at 187.53 ppm in **1a**. The mass spectrum of **6a** showed the ion peak at m/z = 417 [M^+].

Similarly, the reaction of **1b** with diphenylmethylenetriphenylphosphorane in dry toluene proceeds in reflux temperature for 8 hr to give a yellow crystalline product that was assigned the structure **6b**. Triphenylphosphine was also isolated (cf. Scheme 2). The identity of adduct **6b** was deduced from its elemental analysis, IR,^1H, ^{13}C NMR and mass spectral data (cf. Experimental).

A possible explanation for the formation of products **6a** and **6b** are illustrated in Scheme 2.

1,3,4-Thiadiazol derivatives **1a,b** reacts with diphenyl-methylenetriphenylphosphorane to give adducts **6a,b** via intramolecular Hofmann rearrangment (3) followed by elimination of triphenylphosphine which considered as good leaving group (Scheme 2).

Worthy to mention that when phosphonioum ylide **4** is allowed to react with the alkylated products **7a** and **7b** (prepared from **1a,b** and methyl iodide), no reaction is observed and the starting material is recovered unchanged (m.p, mixed m.p) which confirmed the addition via Hofmann rearrangement of the HS group.



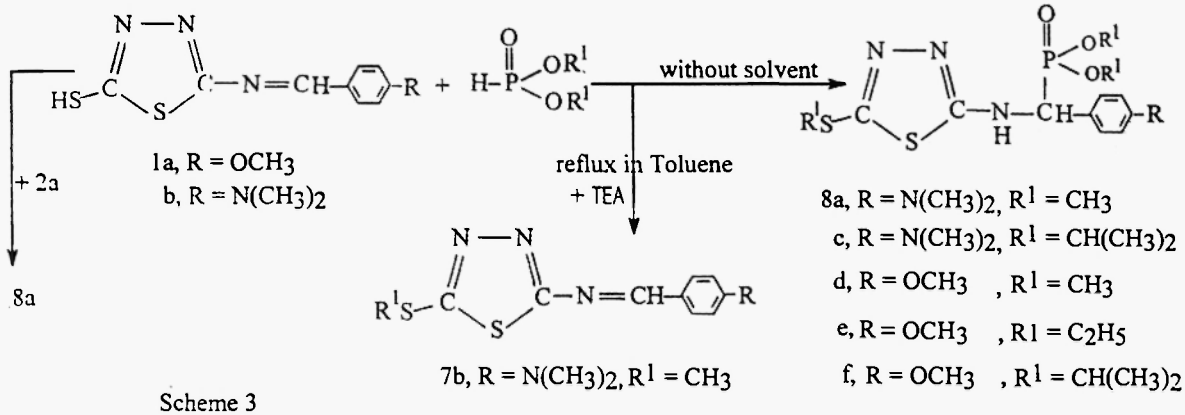
1a, R = OCH_3
b, R = $N(CH_3)_2$

7a, R = OCH_3
b, R = $N(CH_3)_2$

Furthermore, this study has been extended to include the reactions of **1a,b** toward dialkyl phosphites **5(a,c)**. We have found that 5-{[4-dimethylamino-benzylidene]amino}-1,3,4-thiadiazol-2-thiol **1b** reacts with excess dimethyl phosphite **5a**, in boiling toluene and in the presence of trace amount of triethylamine, for 10 hr to give a mixture of two main products (A+B), which could be separated by column chromatography.

The first product (A,~ 30%) was assigned structure **8a** because its ^{31}P NMR spectrum (in $CDCl_3$) showed a signal at δ = + 22.6 ppm that agrees with the dialkyl phosphonate adduct (Scheme 3) (4,5). Moreover, the ^1H NMR spectrum of dimethyl [4-(dimethylamino)phenyl]{[5-(methylthio)-1,3,4-thiadiazol-2-yl] amino}methylphosphonate **8a** showed signals at δ = 3.66, 3.48[2d,6H,(O)P(OCH_3)$_2$, J_{HP} =10Hz],5.29ppm[dd,1H,$^2J_{HP}$=20.8Hz, J_{HH} = 10 Hz],corresponding to the methine proton (CH-P),2.89[s,6H,N(CH_3)$_2$],2.58 (s,3H,SCH_3), 6.68-6.73 (d,2H, Ar),7.24-7.28(d,2H,Ar) and at 8.69ppm(dd,1H,NH). The main features of the IR spectrum of **8a** (in KBr, expressed in cm^{-1}) were the presence of absorption bands at 3400 cm^{-1} (NH),1600(aromatic), 1240cm^{-1}(P=O) (6). These assignments are also supported by ^{13}C NMR (7,8) which gave a doublet at δ_C=54.3ppm with J_{CP}=157.5Hz and at 52.7(P-O-C,d,J_{CP}=6.1Hz),15.90(S-CH_3),39.5[N(CH_3)$_2$],among others. The mass spectrum of **8a** yielded a prominent peak for M^+ at m/z 388.

Nomenclature according to IUPAC naming



Scheme 3

The second product (B,55%) has been found to be devoid of phosphorus as inferred from its elemental analysis and ^{31}P NMR measurements. It was identified as N-{(1E)-(4-dimethylamino) phenyl]methylidene}-5-(methylthio)-1,3,4-thiadiazol-2-amine **7b** for the following reasons: Its elemental analysis and molecular weight determination (MS) agreed with the molecular formula $C_{12}H_{14}N_4S_2$. The ^1H NMR spectrum of **7b** shows a singelet at 8.45 (s,1H, N=CH), and doublets at 2.55[d,6H,$N(CH_3)_2$],7.75(d,2H, Ar),6.65(d,2H, Ar). Moreover, the ^1H NMR of **7b** reveals the presence of a singelet at 2.64ppm (SCH_3) and absence of the SH broad singelet appeared at 10.5 ppm in the ^1H NMR spectrum of **1b**.

Worthy of mention is the fact that when **1b** was allowed to react with dimethyl phosphite in the absence of solvent at 50 °C, the dimethylphsphonate adduct **8a** is the sole reaction product which isolated in 85% yield. Moreover, when **1b** is allowed to react with trimethyl phosphite **2a** in refluxing toluene, the dimethylphosphonate adduct **8a** was isolated in 80% yield.

Similarly, the reaction of **1b** with diisopropyl phosphite proceeds without solvent and reflux for 10 hr giving rise to the dialkylphosphonate adduct **8c** in 75% yield. The structure of the diisopropylphosphonate adduct **8c** was deduced from its ^{31}P NMR, IR, ^1H NMR, ^{13}C NMR and mass spectral data (cf. Experimental).

Furthermore, we have found that 5-{[4-(methoxybenzylidene)]amino}-1,3,4-thiadiazole-2-thiol **1a** reacts with dialkyl phosphites **5(a-c)** to give the corresponding dialkylphosphonate adducts **8(d-f)**, respectively. The reaction products **8d**, **8e** and **8f** was found to be identical with the reaction products, previously obtained (1) from the reaction of **1a** with trialkyl phosphites (cf. Experimental).

Conclusion:

Significantly, the reaction of Wittig reagents here are indicative of the broad reaction spectrum of which ylides are capable in addition to the usual olefin-forming reactions. Moreover, the present study clearly shows that the reaction of alkyl phosphites **5** with **1a** and **1b** depends on the substituent at the benzylidene group as well as the reaction temperature used.

Experimental

All melting points are uncorrected. The IR spectra were obtained with a Perkin-Elmer Infracord Spectrometer Model 157(Grating) in KBr discs. The ^{1}H and ^{13}C-NMR spectra were recorded in $CDCl_3$ as solvent on a Joel- 270 MHz Spectrometer and the chemical shifts were recorded in δ ppm relative to TMS. The ^{31}P NMR spectra were taken with a Varian CFT-20 (vs. external 85% H_3PO_4 standered). The mass spectra were performed at 70 ev on a shimadzu GCS-OP 1000 Ex Spectrometer provided with a data system.

5-(Benzhydrylsulfanyl)-N-(4-methoxybenzylidene)-1,3,4-thiadiazol-2-amine **6a**

To a solution of **1a** (0.25g;0.001 mol) in dry toluene (30 ml) was added (0.43g; 0.001 mol) of freshly prepared diphenylmethylenetriphenylphosphorane **4**. The reaction was refluxed for 8hr and evaporated under reduced pressure. The residue was subjected to silica gel column chromatography using acetone / petroleum ether(60:40,v:v) as eluent to give **6a** as yellow crystals, yield (60%), mp.172-173 ^{0}C. Calcd. For $C_{23}H_{19}N_3OS_2$ (417.545): C 66.16, H 4.59, N 10.06, S 15.36. Found :C 66.10, H 4.61, N 10.03, S 15.31. MS: m/z = 417(15%).
Triphenylphosphine was also isolated and identified.

Similarly, freshly prepared diphenylmethylenetriphenylphosphorane **4** reacts with **1b**,to give 5-(Benzhydrylsulfanyl)-N-[4-(dimethylamino)benzylidene]-1,3, 4-thiadiazol-2-amine **6b** using eluent acetone / peterolum ether (12:88,v:v) as, yellow crystals (55%) yield, mp 181-182 ^{0}C. Calcd.for $C_{24}H_{22}N_4S_2$ (430.588):C 66.95,H 5.15,N 13.01,S14.90.Found: C 66.90,H 5.10,N13.03, S14.87.IR:1605cm^{-1}(C=C,Ar),1640cm^{-1}(C=N).^{1}HMNR:δ3.05[6H,N(CH_3)$_2$],6.25[1H,SC**H**(Ph)$_2$, s], 8.55(1H,N=C**H**,s),7.80 (2H,Ar-**H**,d),7.25-7.55 ppm[10,2 (C_6H_5),m]. ^{13}C NMR : δ 149.3[**C**-N (CH_3)$_2$],142.6(**C**=N),112.4(N=**C**H),40.1[N(**C**H_3)$_2$],56.8ppm[(Ph)$_2$**C**H]. MS: m/z = 430 (100%). Triphenylphosphine was also isolated and identified (mixed mp and comparative IR spectra).

Reaction of 5-{4-(dimethylamino)-benzylidene]amino}-1,3,4- thiadiazol-2-thiol **1b** with dimethyl phosphite **5a**.

A suspension of **1b** (0.26g, 0.001 mol), 0.5 ml of dimethyl phosphite **5a** and trace amount of triethylamine in 30 ml dry toluene was refluxed for 8hr. The reaction mixture was evaporated under reduced pressure and the residue was applied to silica gel column chromatography to give two products, formulated as **8a** and **7b**, respectively.

Dimethyl[4-(dimethylamino)phenyl]{[5-(methylthio)-1,3,4-thiadiazole-2-yl] amino}methyl-phosphonate **8a**:

Eluent: acetone/petroleum ether(40:60,v:v) as white crystals, yield(30%), mp. 201-202 ^{0}C. Calcd.for$C_{14}H_{21}N_4O_3PS_2$ (388.301):C 43.26,H 5.45,N 14.43,P 7.98, S 16.51. Found :C 43.20, H 5.47,N 14.41,P 7.96,S 16.49. IR: 3400cm^{-1} (NH),1600cm^{-1} (C=C,Ar),1240 cm^{-1}(P=O),1045cm^{-1} (P-O-CH_3). ^{1}H NMR:δ3.66,3.48[6H,(O)P(OC**H**$_3$),2d,J_{HP} = 10Hz],5.29(1H,(O)P-C**H**,dd,J_{HP} = 20 Hz,J_{HH}=10Hz),2.89[s,6H,N(C**H**$_3$)$_2$],2.58(3H,SC**H**$_3$,s),6.68-6.73(2H,Ar-**H**,d),7.24,7.28(2H,Ar-**H** .d) and 8.69ppm(1H,NH,dd). MS: m/z = 388(25%).

N-{(1E)-(4-dimethylamino)phenyl]methylidene}-5-(methyl)-1,3,4-thiadiazol-2-amino **7b**.

Eluet: acetone/ petroleum ether (12:88,v:v) as yellow crystals, yield (55%), mp.170-171^{0}C. Calcd for $C_{12}H_{14}N_4S_2$(278.27): C 51.75,H 5.07,N 20.13,S 23.04. Found: C 51.70, H 5.02, N 20.11,S 23.01. MS: m/z =278 (40%).

Reaction of dimethyl phosphite **5a** with compound **1b** (without solvent).

A mixture of **1b** (0.26g,0.01mol), 0.5 ml of dimethyl phosphite **5a** was heated in oil bath at 35^{0}C for 3hr. The reaction mixture was evaporated under reduced pressure and the residue subjecte to silica gel column chromatography ,using acetone/petroleum ether as eluent (40:60, v:v) to give **8a** as colourless crystals (mp, mix.mp. ^{1}H NMR, MS).

Reaction of trimethyl phosphite **2a** with **1b**.

Trimethyl phosphite(0.24g;0.002 mol) was added dropwise to a solution of **1b** (0.26; 0.001 mol) in dry toluene (20 ml) and the reaction mixture was refluxed for 3h. The reaction mixture was reduced and washed several times by petroleum ether. The substance that separated was

crystallized from ethyl acetate to give white crystals, which proved to be **8a** (mp, mix.mp., ^{1}H NMR, MS).

Diisopropyl[4-(dimethylamino)phenyl]{5-(isopropylthio)-1,3,4-thiadiazol-2-yl] amino}methylphosphonate **8c**.

A suspention of **1b** (0.26g;0.001mol),1ml of diisopropyl phosphite **5c** was heated in oil bath at 50^{0}C for 8hr. The reaction mixture was evaporated under reduced pressure and the residue was washed several times by petroleum ether. The substance that separated was crystallized from benzene to give colourless crystals **8c**, mp.194-195 ^{0}C, yield (75%). Calcd for $C_{20}H_{33}N_4O_3PS_2$(472.403): C 50.84,H 7.04,N 11.87,P 6.56,S 13.58. Found: C 5.80, H 7.02, N 11.84,P 6.52, S13.56. IR: 3230cm^{-1}(NH),1235(P=O),1052 (P-O-CH),1602cm^{-1}(C=C,Ar). ^{1}H NMR: δ 0.73 [1H,CH(C**H**$_3$)$_2$,d],1.10-1.25{12H,P[O-CH(C**H**$_3$)$_2$]$_2$, 4d},2.83[6H,N(C**H**$_3$)$_2$], 4.23[1H,SC**H**CH$_3$)$_2$, s],4.65{2H,2[C**H**(CH$_3$)$_2$],m},5.20[1H,C**H**-P,dd,J_{HP}=27Hz,J_{HH}=10Hz],6.54(2H,Ar-**H**,d),7.22(2H, Ar-H,d) and 8.41 ppm(1H,N**H**,m).^{13}C NMR:δ 55.88(C-P,d,$^1J_{CP}$=161.1Hz),73.28[O**C**H(CH$_3$)$_2$,d, $^2J_{CP}$=7.3Hz],72.1[**C**H(CH$_3$)$_2$],40.4[N(**C**H$_3$)$_2$],24.2,23.8{2[CH(**C**H$_3$)$_2$]},22.9[CH(**C**H$_3$)$_2$],150.0,1 29.4,121.3,112.3(C_6H_4),162.1,161.8ppm(**C**-S-C). ^{31}PNMR: δ +20.9. MS: m/z = 472 (15%).

Reaction of dialkyl phosphites **5a-c** with compound **1a**.

General Method:

A mixture of **1a** (0.25g;0.001mol) and 1ml of dialkyl phosphites **5a-c**, was heated in oil bath at 110-120 ^{0}C for 3 - 4 hr. The reaction mixture was evaporated under reduced pressure and the residue was applied to silica gel column chromatography. The eluent, yield and mp are given below for dialkyl phosphonate adducts **8d-f.**

8d: acetone/petroleum ether(50:50,v:v),colourless crystals,mp.162^{0}C,yield(85%).Calcd for $C_{13}H_{18}N_3O_4PS_2$(375.4):C 41.59,H 4.83,N 11.20,P 8.25,S 17.08. Found:C 41.53,H 4.80,N 11.16,P 8.23,S17.10.IR: 3250cm^{-1}(NH),1230(-P=O),1056cm^{-1}(P-OCH$_3$). ^{1}H NMR: δ 3.82,3.49 [6H,P(O C**H**$_3$)$_2$,2d,J_{HP}=11.54Hz],3.78(3H,OC**H**$_3$,s),2.61(3H,SC**H**$_3$,s),5.39(1H,C-**H**,d,J_{HP} = 25.0 Hz),7.49, 6.89(4H,Ar,2d) and 8.23 ppm(1H,NH,bs).^{13}C NMR:δ 54.2(C-P,d,$^1J_{CP}$=157.0Hz),53.8[P(CH$_3$)$_2$, d,J_{CP}=6.98Hz],16.4(S**C**H$_3$) and 55.2ppm(O**C**H$_3$).^{31}P NMR: δ+ 23.77ppm. MS:m/z =375 (50%) .

8e: acetone/ petroleum ether(60:50,v:v),colourless crystals yield 86 %,mp..112 ^{0}C.Calcd for C_{16}

$H_{24}N_3O_4PS_2$(417.4):C 46.03, H 5.79,N 10.06, P 7.41,S 15.36. Found C 46.01,H 5.73,N 10.02,P7.38,S15.31.IR:3453cm^{-1}(NH),1248(P=O),1023cm^{-1}(P-OC_2H_5).^{1}HNMR:δ 4.15[4H,(O)P(OC_2H_5)$_2$,q],1.32[6H,(O)P(OC_2H_5)$_2$,t],3.05(2H,SC_2H_5,q),1.01(3H,SC_2H_5,t),3.75(3H,OCH_3,s), 5.40(1H,C-H,d,$^2J_{HP}$=25.1Hz),6.85,7.45(4H,Ar,2d) and 8.50ppm (bd,1H,NH).^{13}CNMR: δ 53.0 (**C**-P,d,$^1J_{CP}$=157.0Hz),63.3[(O)P(O**C**H_2CH_3)$_2$,d,J_{CP}=7.3Hz],55.0(O**C**H_3),28.7(S**C**H_2 CH_3),15.9 [(O)P(OCH_2**C**H_3)$_2$,d,$^3J_{CP}$=5.8 Hz] and 14.6 ppm (S-CH_2 **C**H_3). ^{31}PNMR: δ = +21.19ppm. MS: m/z = 417(25%).

8f:ethyl acetate/petroleum ether(60:50,v:v),colourless crystals yield 86 %,mp126^{0}C. Calcd $C_{19}H_{30}N_3O_4PS_2$ (459.5): C 49.65, H 6.58,N 9.14,P 6.73,S 13.95.Found: C 49.59,H 6.54,N 9.10,P 6.70,S 13.89. IR: 3234 (NH),1228 (P=O), 990cm^{-1} P[OCH(CH_3)$_2$]$_2$,1608cm^{-1} (C= C, Ar).^{1}H NMR:δ 4.70,4.35{2H,2[CH(CH_3)$_2$],m},1.25{12H,(O)P[OCH(CH_3)$_2$]$_2$,m},3.50[1H,SCH(CH_3)$_2$,m],0.85[6H,S-CH(C**H**$_3$)$_2$,d],3.75(3H,OC**H**$_3$,s),5.30[1H,C-**H**,d,J_{HP} = 27 Hz),6.75,7.43 (4H, Ar, 2d) and 8.22 ppm(bs,1H,NH exchangeable with D_2O).^{13}C NMR: δ 24.22 [OCH (**C**H_3)$_2$], 23.2[SCH(CH_3)$_2$],72.7{P[O**C**H(CH_3)$_2$]$_2$,d,$^2J_{CP}$ = 7.48Hz},56.6(C-P,d,$^1J_{CP}$ = 177.03Hz),40.3[S-**C**H(CH_3)$_2$],54.28(O**C**H_3),169.2,129.8,127.0,113.8(C_6H_4),169.9,159.6ppm(-C-S-C-).^{31}P NMR: δ +19.42ppm. MS: m/z = 459 (25%).

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