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 diphenylmethylenetriphenylphosphorane 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 (Scheme 1).

![Scheme 1](image-url)
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 diphenylmethylenetriphenylphosphorane 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 (OCH₃),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 ¹³C NMR which indicates the presence of signals at δ =165.5 (C-OCH₃),140.56(C=N),114.34 ppm (N=CH), at 55.45(OCH₃) and at 56.5 corresponding to the S-CH(Ph)₂ group. The ¹³C 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, ¹³C 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-methylene triphenylphosphorane to give adducts 6a,b via intramolecular Hofmann rearrangement (3) followed by elimination of triphenylphosphine which considered as good leaving group (Scheme 2).

Worthy to mention that when phosphoniuom 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.

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 $^3$P NMR spectrum (in CDCl$_3$) showed a signal at $\delta = +22.6$ ppm that agrees with the dialkyl phosphonate adduct (Scheme 3) (4,5). Moreover, the $^1$H NMR spectrum of dimethyl [4-(dimethylamino)phenyl]{{5-(methylthio)-1,3,4-thiadiazol-2-yl] amino}methylphosphonate 8a showed signals at $\delta = 3.66$, 3.48[2d,6H,(O)P(OCH$_3$_2), $J_{HP} = 10$Hz],5.29ppm[dd,1H,$^2J_{HP} = 20.8$Hz, $J_{HH} = 10$ 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 $\delta_{C}$=54.3ppm with $J_{CP}=157.5$Hz and at 52.7(P-O-C,d,$J_{CP}=6.1$Hz),15.90(S-CH$_3$),39.5[N(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
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)methylene}-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 $\text{C}_{12}\text{H}_{14}\text{N}_{4}\text{S}_{2}$. The $^1$H NMR spectrum of 7b shows a singlet 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 $^1$H NMR of 7b reveals the presence of a singlet at 2.64 ppm (SCH$_3$) and absence of the SH broad singlet appeared at 10.5 ppm in the $^1$H 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 dimethylphosphonate 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, $^1$H 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$_3$PO$_4$ 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 diphenylmethylene triphenylphosphorane 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 °C. Calcd. For C$_{25}$H$_{19}$N$_2$S$_2$ (417.545): C 66.16, Η 4.59, Ν 10.06, S 15.36. Found :C 66.10, Η 4.61, Ν 10.03, S 15.31. MS: m/z = 417(15%). Triphenylphosphine was also isolated and identified.

Similarly, freshly prepared diphenylmethylene triphenylphosphorane 4 reacts with 1b, to give 5-(Benzhydrylsulfanyl)-N-[4-(dimethylamino)benzylidene]-1,3, 4-thiadiazol-2-amine 6b using eluent acetone / pterolue ether (12:88,v:v) as, yellow crystals (55%) yield, mp 181-182 °C. Calcd.for C$_{24}$H$_{22}$N$_4$S$_2$ (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:83.05[6H,N(CH$_3$)$_2$],6.25[1H,SCH(Ph)$_2$, s], 8.55[1H,N=CH,s],7.80 (2H,Ar-H,d),7.25-7.55 ppm[10, 2 (C$_6$H$_5$),m]. $^{13}$C NMR : δ 149.3[C-N(CH$_3$)$_2$],142.6(C=N),112.4(N=CH),40.1[N(CH$_3$)$_2$],56.8ppm[(Ph)$_2$CH]. 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}methylphosphonate 8a:

Eluent: acetone/petroleum ether(40:60,v:v) as white crystals, yield(30%), mp. 201-202 °C. Calcd for C_{14}H_{21}N_{4}O_{3}P_{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: 3400 cm\(^{-1}\) (NH), 1600 cm\(^{-1}\) (OC,Ar), 1240 cm\(^{-1}\) (P=O), 1045 cm\(^{-1}\) (P-O-CH\(_3\)). \(^1\)H NMR: 8.3.66, 3.48[6H,(0)P(0CH\(_3\)]), 2d,J\(_{HP}=10Hz\], 5.29[1H,(O)P-CH,dd,J\(_{HP}=20Hz\), J\(_{HH}=10Hz\), 2.89[5H,N(CH\(_3\)]], 2.58[3H,SCH\(_3\)], 6.68-6.73[2H,Ar-H,d], 7.24, 7.28[2H,Ar-H,d] and 8.69 ppm[1H,NH,dd]. MS: m/z = 388(25%).

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

Eluent: acetone/petroleum ether (12:88,v:v) as yellow crystals, yield (55%), mp.170-171 °C. Calcd for C_{12}H_{14}N_{4}S_{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°C for 3hr. The reaction mixture was evaporated under reduced pressure and the residue subjected 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 suspension of 1b (0.26g;0.001mol),1ml of diisopropyl phosphite 5c was heated in oil bath at 50°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 °C, yield (75%). Calcd for C$_{20}$H$_{33}$N$_4$O$_3$P$_2$ (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, S 13.56. IR: 3230cm$^{-1}$(NH),1235(P=O),1052 (P-0-CH),1602cm$^{-1}$(C=C,Ar). $^1$H NMR: δ 0.73 [1 H,CH(CH$_3$)$_2$,d], 1.10-1.25 {12H,P[0-CH(CH$_3$)$_2$], 4d},2.83[6H,N(CH$_3$)$_2$], 4.23[1H,SCHCH$_3$$_2$, s],4.65{2H,2[CH(CH$_3$)$_2$,m],5.20[1H,CH-P,dd,$^1$J$_{HP}$=27Hz,$^2$J$_{HH}$=10Hz],6.54(2H,Ar-H,d),7.22(2H, Ar-H,d) and 8.41 ppm(1H, NH,m).$^{13}$C NMR:δ 55.88(C-P,d,$^1$J$_{CP}$=161.1Hz),73.28[OCH(CH$_3$)$_2$], 2$^2$J$_{CP}$=7.3Hz],72.1[CH(CH$_3$)$_2$],40.4[N(CH$_3$)$_2$],24.2,23.8 [2[CH(CH$_3$)$_2$]],22.9[CH(CH$_3$)$_2$],150.0,1 29.4,121.3,112.3(C$_6$H$_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 °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$_3$O$_4$PS$_2$(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,S17.10.1IR: 3250cm$^{-1}$(NH),1230(-P=O),1056cm$^{-1}$(P-OCH$_3$). $^1$H NMR: δ 3.82,3.49 [6H,P(O CH$_3$)$_2$,2d,$^1$J$_{HP}$=11.54Hz],3.78(3H,OCH$_3$$_3$,s),2.61(3H,SCH$_3$$_3$,s),5.39(1H,C-H,d,$^1$J$_{CP}$ = 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,$^1$J$_{CP}$=157.0Hz),53.8[O(CH$_3$)$_2$, d,$^2$J$_{CP}$=6.98Hz],16.4(SCH$_3$) and 55.2ppm(OCH$_3$).$^{31}$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$_{16}$
H₂N₂O₄P₂S₂(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, P 7.38, S 15.31. IR: 3453 cm⁻¹ (NH), 1248 (P=O), 1023 cm⁻¹ (P-OC₂H₅), 5.40 (1H, C-H, d, J₁H₂P = 25.1 Hz), 6.85, 7.45 (4H, Ar, 2d) and 8.50 ppm (bd, 1H, NH).

¹³C NMR: δ 53.0 (C-P, d, J₁CP = 157.0 Hz), 63.3 [P(OCH₂CH₃)₂, d, J₁CP = 7.3 Hz], 55.0 (OCH₃), 28.7 (SCH₂ CH₃), 15.9 [(O)P(OCH₂CH₃)₂, d, J₁CP = 5.8 Hz] and 14.6 ppm (S-CH₂ CH₃).

H₂PS₂C₉H₆(417.4): 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), 990 cm⁻¹ (P[OCH(CH₃)₂]₂), 1608 cm⁻¹ (C=C, Ar).

NMR: δ 4.70, 4.35 {2H, 2[CH(CH₃)₂], m}, 1.25 {12H, (O)P[OCH(CH₃)₂]₂, m}, 3.50 [1H, SCH(CH₃)₂, m], 0.85 [6H, S-CH₂CH₃, d], 3.75 (3H, OCH₃, s), 5.30 (1H, C-H, d, J₁H₂P = 27 Hz), 6.75, 7.43 (4H, Ar, 2d) and 8.22 ppm (bs, 1H, NH exchangeable with D₂O). ¹³C NMR: δ 24.22 [OCH(CH₃)₂], 23.2 [SCH(CH₃)₂], 72.7 [P(OCH₂CH₃)₂, d, J₁CP = 7.48 Hz], 56.6 (C-P, d, J₁CP = 177.03 Hz), 40.3 [SCH₂CH₃], 54.28 (OCH₃), 169.2, 129.8, 127.0, 113.8 (C₆H₄), 169.9, 159.6 ppm (-C-S-C-).

³¹P NMR: δ +19.42 ppm. MS: m/z = 459 (25%).

Reference

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