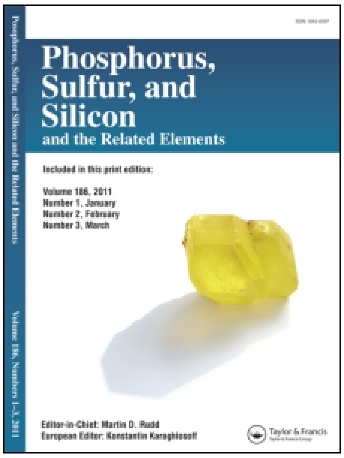

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

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To cite this Article Huang, Tian-Bao , Liu, Ling-Fei , Yu, Xiao-Ming , Yang, Wen-Qian , Qian, Xu-Hong and Zhang, Jingling(1997) 'REACTION OF SCHIFF BASE OF THIOHYDRAZIDES WITH $P(NR_2)_3$', Phosphorus, Sulfur, and Silicon and the Related Elements, 122: 1, 307 — 312

To link to this Article: DOI: 10.1080/10426509708043519

URL: http://dx.doi.org/10.1080/10426509708043519

Phosphorus, Sulfur, and Silicon, 1997, Vol. 122, pp. 307-312
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REACTION OF SCHIFF BASE OF THIOHYDRAZIDES WITH $P(NR_2)_3$

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(Received 2 May 1996; In final form 25 January 1997)

Three pathways were observed in the reactions of Schiff bases of Thiohydrazides with $P(NR_2)_3$. (a) MeS-R_2N exchange: MeS-C(=S)-NHN=CHPh (1) reacted with $P(NR_2)_3$ led to new Schiff bases, R_2N-C(=S)-NHN=CH=Ph (2). (b) Cleavage of C=S bond and the formation of P=S bond: H_2N-C(=S)-NHN=CH=Ph (3) reacted with $P(NR_2)_3$ gave rise to the thiophosphoric amide, $(Et_2N)_2P(=S)$-NH-CH=N-N=CH-Ph (4). (c) Formation of thiadiazole and triazole: Schiff bases 2a and $H_2N(MeS)C$=N-N=CH-Ph (6) reacted with $P(NR_2)_3$ respectively and produced 5-dimethylamino-2-phenyl-2,3-(2H)-1,3,4-**thiadiazole** (5) and 5-methylthio-2-phenyl-2,3-(2H)-1,3,4-**triazole** (7).

Keywords: Schiff base; thiosemicarbazide; thiohydrazide; tris(dialkylamino)phosphine

INTRODUCTION

Much success has been achieved on the versatile use of unsaturated four-membered chains terminating with -N(R)H, -OH, or -SH groups as substrates for heterophospholes synthesis.[1,2] Recently, the reaction[3–5] of thiohydrazides and thiosemicarbazide with phosphorus-containing reagents has been carried out, but the attempt to produce neutral σ^2-phosphorus species with -S-P=N- and >N-P=N- skeletons failed. This is probably because of the strong nucleophilicity of the P=N bond to amine or HX. J. P. Majoral and coworkers[6] described a interesting route to 1,2,4,3-triazaphospholes from Schiff bases of amidrazones via the elimination of PhCH $(NR_2)_2$. In order to seek a practical synthetic route

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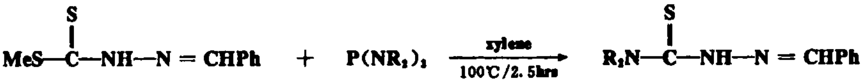
from the Schiff base of thiohydrazides (R-C(=S)-NH-N=CHPh) to thiazaphosphole, the reaction of these Schiff bases with $P(NR_2)_3$ has been studied. The experimental results showed that these reactions occurred either with MeS-R_2N exchange, or with migration of the thiono group from carbon to phosphorus, or with intramolecular cyclization, leading to 2, 4, 5 and 7, but no thiazaphosphole is formed by condensation.

RESULTS AND DISCUSSION

Treatment of Schiff base 1 with $P(NR_2)_3$ in xylene at 100°C for 2.5 hrs gave 80–85% yields of new Schiff bases 2 via substitution of MeS group by R_2N, as showed in Scheme I. It demonstrated that the C-SMe bond is weak.



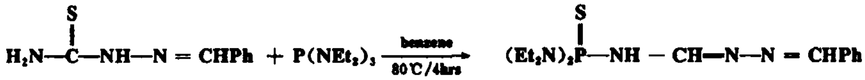
$$\underset{\mathbf{1}}{\mathrm{MeS{-}\overset{S}{\overset{|}{C}}{-}NH{-}N=CHPh}} + \mathrm{P(NR_2)_3} \xrightarrow[\mathrm{100^\circ C/2.5hrs}]{\mathrm{xylene}} \underset{\mathbf{2}}{\mathrm{R_2N{-}\overset{S}{\overset{|}{C}}{-}NH{-}N=CHPh}}$$

No. 2a, 2b.
R= Me, Et.

SCHEME I

When the MeS group was replaced by NH_2 group in 1, the Schiff base 3 with a stronger C-N bond was refluxed with $P(NEt_2)_3$. A complicated process, which proceeded subsequently by substitution on phosphorus, C=S bond cleavage, P=S bond formation and [1,2]-H shift, led to thiophosphoric amide **4**, a red oily compound (Scheme II).

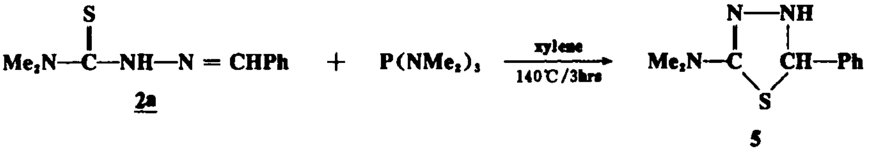
The structure of 4 was confirmed by MS, IR, ^{1}H, ^{13}C, ^{31}P NMR and elemental analyses. In the ^{31}P-NMR spectrum, the chemical shift (85.5 ppm) is close to that of $(R_2N)_3P{=}S$. In the IR spectrum, there is $\nu_{N\text{-}H}$ absortion at 3240 Cm^{-1}. The ^{1}H-NMR Data showed NH, NEt_2 and $-C_6H_5$ as well as two kinds of =CH- (7.93 ppm, d, $^3J_{PNHCH}$ = 7.3 Hz; 8.30 ppm, s). The ^{13}C NMR data were also consistent with the proposed structure for 4 in Scheme II.



$$\underset{\mathbf{3}}{\mathrm{H_2N{-}\overset{S}{\overset{|}{C}}{-}NH{-}N=CHPh}} + \mathrm{P(NEt_2)_3} \xrightarrow[\mathrm{80^\circ C/4hrs}]{\mathrm{benzene}} \underset{\mathbf{4}}{\mathrm{(Et_2N)_2\overset{S}{\overset{|}{P}}{-}NH-CH{-}N{-}N=CHPh}}$$

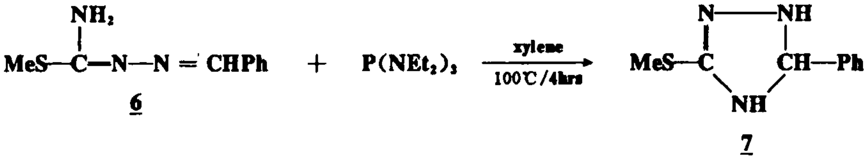
SCHEME II

When pure 2a was allowed to further react with $P(NMe_2)_3$ at 140°C, dramatic change of the product appeared, it afforded 95% yield of 5-dimethylamino-2,3-(2H)-1,3,4-thiadiazole 5 (Scheme III).



SCHEME III

When 3 was transformed into 6 by methylation. Under similar condition, the reaction of 6 with $P(NEt_2)_3$ afforded the 5-methylthio-2-phenyl-2,3-(2H)-1,3,4-triazole (7) in 86.1% yield (Scheme IV).



SCHEME IV

The results in Scheme III and in Scheme IV are very similar. It is of interest that thiadiazole and triazole could be formed from Schiff base in the presence of $P(NR_2)_3$ in good yield by intramolecular cyclization. Reducing the equiv. of $P(NR_2)_3$ from 1.5 to 0.1 or replacing it with 0.1 DBU, the yield of product 5 and 7 was still over 80%. But Et_3N (0.1–1 equiv.) did not lead to the products under reflex. These facts showed that $P(NEt_2)_3$ only functions as a catalytic agent through its well known strong Lewis basity in the reactions described in Scheme III and IV.

A series of ^{31}P NMR studies on four reaction solutions, heated at 80°C, 100°C and 120°C for 1h, 2h and 3h and then cooled, showed that in addition to a little broadening of peaks at 120.1 ppm ($P(NEt_2)_3$) or 123.7 ppm ($P(NMe_2)_3$, no signals appeared both below −20 ppm and above 150 ppm, indicative of both no acyclic phosphoranes (σ^5) as stable intermediates and no heterophospholes (σ^2) persistence. The results suggest that the remaining groups in 1, 2a, 3 and 6 (such as thiocarbamoyl group and carbodithioic ester) are more reactive to aminophosphines than the -N=CHPh moiety, therefore dominate the pathway which is characteristically different from the process in the literature.[6]

EXPERIMENTAL

Elemental analyses were obtained with a PE-2400 elementary analyzer. Mass spectra were recorded with a HP 5988A spectrometer at 70 ev Ionization energy. The ^{1}H, ^{13}C, ^{31}P NMR were recorded with Varian XL-200 spectrometer. The chemical shifts were reported in ppm relative to the internal standard TMS for ^{1}H, and ^{13}C NMR, and external standard 85% H_3PO_4 for ^{31}P NMR. IR were recorded on PE-983G spectrometer.

Ether was distilled from benzophenone ketyl. Hexane, benzene and xylene were dried with sodium. PCl_3, R_2NH, Et_3N, $H_2N\text{-}C(=S)\text{-}NH\text{-}NH_2$ and $H_2N\text{-}C(\text{-}SMe)=N\text{-}NH_2$ were obtained commercially. $MeS\text{-}C(=S)\text{-}NH\text{-}N=CHPh$ (1),[7] $H_2N\text{-}C(=S)\text{-}NH\text{-}N=CHPh$ (3),[8] $H_2N\text{-}C(\text{-}SMe)=N\text{-}N=CHPh$ (6)[8] and $P(NR_2)_3$ [9] were respectively prepared according to reported procedure. 1,8-diazabicyclo-[5,4,0]-undec-7-ane ("DBU") was purchased from ALDRICH.

All manipulations were carried out under an atmosphere of dry nitrogen.

Reaction of Schiff Base 1 With $P(NR_2)_3$

The general procedure for preparation of 2, as exemplified by the preparation of 2b, is as follows: To a 25 ml round-bottom flask with $P(NEt_2)_3$ (1.50 g, 6 mmol), Schiff base 1 (0.84 g, 4.5 mmol) and 10 ml of xylene were added. The mixture was heated at 100°C for 2.5 hrs, and then cooled to ambient temperature, the residual crude product was purified in a rotary TLC apparatus on silica gel using ether/petroleum ether (1:4) as eluent to afford 2b as a pale yellow solid. For 2a (81.4%), yellow solid, m.p. 121.5–123°C (benzene). $C_{10}H_{13}N_3S$ (Calcd.: C, 57.97; H, 6.8; N, 20.29. Found: C, 57.92; H, 6.35; N, 20.24.). ^{1}H-NMR: 3.45 (s, 6H, NMe_2), 7.0–7.50 (m, 5H, Ph), 7.75 (s, 1H, -CH=), 9.15 (br, <1H, NH). ^{13}C-NMR: 41.9 (s, NMe_2), 127.0, 127.1, 128.7, 1130.0, 133.7 (Ph), 142.7 (s, -CH=), 178.5 (C=S). MS (m/e, rel. intensity): 208 (M + H, 4.9), 193 (4.1), 103 ($Me_2NC(=S)NH$ or PhCN, 100), 77 (38, Ph). IR (cm^{-1}): 3160 (N-H), 3010 (Ph-H), 1550 (C=N), 1380 (C=S), 775 and 695 (Ph-). For 2b (84.4%), pale yellow solid, m.p. 132.5–133°C (benzene). $C_{12}H_{17}N_3S$ (Calcd.: C, 71.49; H, 7.23; N, 17.87. Found: C, 71.54; H, 7.28; N, 17.81.). ^{1}H-NMR: 1.37 (t, 6H, ^{3}J = 7.1 Hz, 2 CH_3CH_2), 3.50 (q, 4H, 2CH_3 CH_2), 7.40–7.60 (m, 5H, Ph), 7.80 (s, 1H, -CH=), 9.46 (br, <1H, NH). ^{13}C-NMR: 12.5 (Me), 47.0 (s, NCH_2), 127.0–134 (Ph), 143.1 (-CH=), 178.0 (C=S). MS (m/e, rel. intensity): 236 (M + H, 11.3), 178 ($M\text{-}CH_2CH_3\text{-}CH_2CH_2$, 100), 105 (PhCHNH, 43), 91 ($PhCH_2$, 28.1), 77 (45, Ph). IR (cm^{-1}): 3200 (N-H), 3010 (Ph-H), 1535 (C=N), 1500 and 1450 (C=C), 1380 (C=S), 760 and 695 (Ph-).

Reaction of Schiff Base 2a With $P(NMe_2)_3$

The mixture of 2a (0.52 g, 2.5 mmol), obtained above, 45 ml of xylene and $P(NMe_2)_3$ (1 ml, 3.75 mmol) were refluxed for 3 hrs, and then cooled to ambient temperature, the residual crude product was purified on a flash silica gel using ether/petroleum ether (1:4) as eluent to afford 5 (0.49 g, 95%) as a white solid. m.p. 137–138°C. $C_{10}H_{13}N_3S$ (Calcd.: C, 57.97; H, 6.28; N, 20.29. Found: C, 57.88; H, 6.33; N, 20.25). ^{1}H-NMR: 2.25 (s, 3H, MeN), 2.30 (s, 3H, MeN), 4.90 (br, <1H, NH), 5.30 (s, CH), 6.96–7.50 (m, 5H, Ph). ^{13}C-NMR: 29.51 (Me), 53.1 (CH), 125.0–130.5 (Ph), 147.8 (C=N). IR (cm^{-1}): 3400 (N-H), 3010 (Ph-H), 2950 (C-H), 1530 (C=N), 4160 (C=C), 750 and 690 (Ph).

Reaction of Schiff Base 3 With $P(NEt_2)_3$

To a 25 ml round-bottom flask containing schiff base 3 (1.00 g, 5.6 mmol) and 10 ml of benzene, 2.5 ml of $P(NEt_2)_3$ (8.4 mmol) was added. The mixture was refluxed for 4 hrs, and then cooled to ambient temperature, the residual crude product was purified by rotary TLC apparatus on silica gel using ether/petroleum ether (3:2) as eluent to afford 4 (1.5 g, 83%) as a red oily. $C_{16}H_{28}N_5PS$ (Calcd.: C, 54.39; H, 7.93; N, 19.83. Found: C, 54.53; H, 8.03; N, 19.74). ^{1}H-NMR: 0.74 (t, 6H, ^3J = 6.95 Hz, 2 CH_3CH_2), 0.86 (t, 6H, ^3J = 7.21 Hz, 2 CH_3CH_2), 2.97–3.23 (m, 8H, $4CH_3CH_2$), 5.90 (br, 1H, NH), 7.20–7.45 (m, 5H, Ph), 7.93 (d, $^3J_{PNHCH}$ = 7.33 Hz, PNH=CH), 8.30 (s, 1H, =CHPh). ^{13}C-NMR: 15.1, 15.3, 15.6 and 16.0 (Me), 47.2 (d, $^2J_{PNC}$ = 19.5Hz, $PNCH_2$), 51.0 (d, $^2J_{PNC}$ = 19.3 Hz, $PNCH_2$), 126.0–129 (Ph), 135.8 (d, $^2J_{PNC}$ = 34.7 Hz, P-N=CH), 147.8 (C=N). ^{31}P-NMR: 85.5. MS (m/e, rel. intensity): 353 (M, 11.9), 281 (M-NEt_2, 22), 271 (M-2Et-CH_2CH_2, 16), 218 (M-SP $(NEt_2)_2$, 5.5), 207 ($SP(NEt_2)_2$, 60), 134 ($SPNEt_2$, 24), 103 (NEt_2P, 60), 72 (Et_2N, 78), 58 (NCS, 100). IR (cm^{-1}): 3240 (N-H), 3010 (Ph-H), 1610 and 1580 (C=N), 1500 and 1450 (C=C), 948 (P-N), 760 and 695 (Ph-).

Reaction of Schiff Base 6 With $P(NEt_2)_3$

To a stirring solution of 5 ml of xylene and 1 ml of $P(NEt_2)_3$ (3.8 mmol), schiff base 6(0.50g, 2.6 mmol) was added. The mixture was heated at 100°C for 4hrs, and then cooled to ambient temperature, the residual crude product was purified on a flash silica gel using ether/petroleum ether (1:1) as eluent to afford 7 (0.70g, 86.1%) as a white solid. m.p. 147.5–148°C. $C_9H_{11}N_3S$ (Calcd.: C, 55.96; H, 5.70; N, 21.76. Found: C, 56.05; H, 5.77; N, 21.59). ^{1}H-NMR: 2.63 (s, 3H, MeS), 4.85 (br, <1H, NH), 5.23 (s, CH), 6.98–7.45 (m, 5H, Ph), ^{13}C-NMR: 21.2

(Me), 52.2 (CH), 125.6–137.5 (Ph), 148.1 (C=N). MS (m/e, rel. intensity): 191 (M-2, 1.9), 106 ($PhCH_2NH$, 40), 91 ($PhCH_2$, 100) 77 (Ph, 16). IR (cm^{-1}): 3360 (N-H), 3010 (Ph-H), 1605 (C=N), 1050 (C-N), 755 and 690 (Ph).

Acknowledgements

This work was supported by the National Natural Science Foundation of Peoples Republic of China (29602001) and Wuhan Natural Science Foundation for Young Scientist (95138-2). We thank Prof. J. E. Shi and Prof. W. F. Huang for helpful discussion.

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