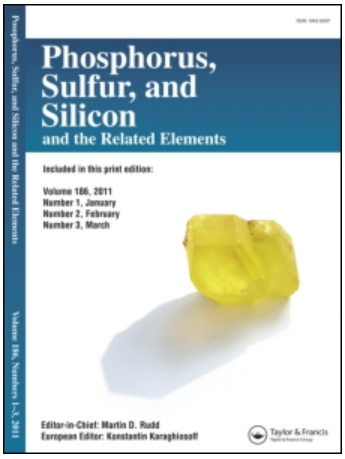

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SYNTHESIS OF DERIVATIVES OF [1,3,4]THIADIAZOLO[3,2-C]-1,2,3-TRIHYDRO-[1,3,5,2]THIADIAZAPHOSPHORINS

Tian-Bao Huang[a]; Ling-Fei Liu[b]; Wen-Qian Yang[a]; Xiao-Ming Yu[a]; Xu-Hong Qian[b]; Jingling Zhang[a]
[a] Institute of Organic Synthesis. Central China Normal University, Wuhan, People Republic of China [b] Institute of Pesticides and Pharmaceuticals, East China University of Science and Technology, Shanghai, People Republic of China

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SYNTHESIS OF DERIVATIVES OF [1,3,4]THIADIAZOLO[3,2-C]-1,2,3-TRIHYDRO-[1,3,5,2]THIADIAZAPHOSPHORINS

TIAN-BAO HUANG[a,*], LING-FEI LIU[b], WEN-QIAN YANG[a], XIAO-MING YU[a], XU-HONG QIAN[b] and JING-LING ZHANG[a]

[a]*Institute of Organic Synthesis, Central China Normal University, Wuhan 430070, People Republic of China;* [b]*Institute of Pesticides and Pharmaceuticals, East China University of Science and Technology, Shanghai 200237, People Republic of China*

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The first dicyclic fused thiadiazaphosphorin derivatives, namely, [1,3,4]thiadiazolo[3,2-c]-1,2,3-trihydro-[1,3,5,2]thiadiazaphosphorins (3 and 4), were synthesized by intermolecular cyclocondensation of [1,3,4]thiadiazole-2-yl-dithiocarbamic acid (1) or -dithio**peroxy**carbamic acid (2) with tri(dialkylamino)phosphine. 5-methyl[1,3,4]thiadiazolo[3,2-c]-2-dialkylamino-6-thiono-1,2,3-trihydro-[1,3,5,2]thiadiazaphosphorin (3) was easily oxided into the 5-methyl [1,3,4]thiadiazolo[3,2-c]-2-dialkylamino-6-thiono-2-**oxo**-1,2,3-trihydro-[1,3,5,2]thiadiazaphosphorin (4) and 5-methyl-[1,3,4]thiadiazolo[3,2-c]-2-dialkylamino-6-thiono-1,2-**dioxo**-1,2,3-trihydro-[1,3,5,2]thiadiazaphosphorin (5).

Keywords: [1;3;4]Thiadiazolo[3;2-c][1;3;5;2]thiadiazaphosphorin; Tris(dialkylamino)phosphine; Cyclocondensation

INTRODUCTION

Recently many interesting phosphorus-containing fused heterocyclic compounds were reported in the literature.[1,2,3] It encourage us to synthesize phosphorus containing heterocyclic compounds of which the ring-frame is novel. Characterization data for [1,3,5,2]thiadiazaphosphorin is available,[4,5] but a fused cycle including this monocycle has not yet been reported. As part of our interest in biologically active phosphorus containing fused heterocyclic compounds,[6,7,8] we synthesized the first representatives of dicyclic fused thiadiazaphosphorins,

*Corresponding author.

namely of the 5-methyl[1,3,4]thiadiazolo[3,2-c]-2-dialkylamino-6-thiono-1,2,3-trihydro-[1,3,5,2]thiadiazaphosphorins (3) and 5-methyl[1,3,4]thiadiazolo[3,2-c]-2-dialkylamino-6-thiono-2-**oxo**-1,2,3-trihydro-[1,3,5,2]thiadiazaphosphorin (4), through the cyclocondensation of 5-methyl-[1,3,4]thiadiazole-2-yl-dithiocarbamic acid (1) and -dithio**peroxy**carbamic acid (2) with tri(dialkylamino)phosphines. The oxidation of 3 (R=Et) gave rise to 5-methyl-[1,3,4]thiadiazolo[3,2-c]-2-diethylamino-6-thiono-1,2-**dioxo**-1,2,3-trihydro-[1,3,5,2]thiadiazaphosphorin (5). The preliminary bioassays indicated that 4 and 5 have 100% inhibiting effect against wheat leaf rust (*puccinia triticina eriks*) at 200 ppm and 500 ppm, respectively.

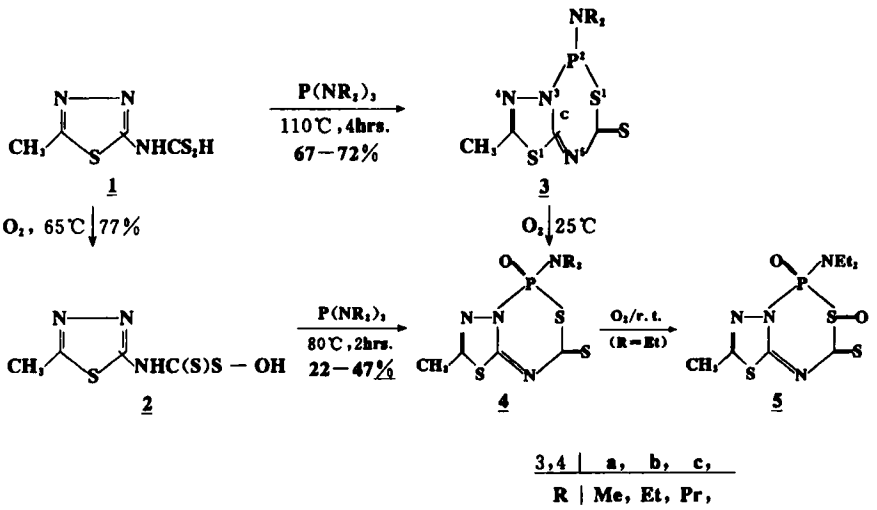
RESULTS AND DISCUSSION

The generally applied routes for the preparation of 3 and 4 are listed in Scheme 1.

Although 1 has been synthesized previously,[9] some new ^{1}H, ^{13}C NMR and MS data is presented in the experimental section. Tautomerism causes reactant 1 to have an unsaturated five-membered chain terminated by N-H, O-H and S-H groups which can condense with $P(NR_2)_3$. Compound 1 was treated with 2.5 equimoles of $P(NR_2)_3$ in xylene at 110°C to afford 3. Product 3 could be purified by chromatography on silica gel in 67–72% yield. They were oily with an unpleasant odor, and sensitive to air where they could be oxided (vide infra). The ^{1}H, ^{13}C, ^{31}P, IR and MS spectra were consistent with its formulation as a new fused-dicyclic system (C_2N_2S-C_2N_2PS). The ^{31}P chemical shifts of 3 were 109 $\sim$ 112 ppm, close to those of aminothiazaphosphines[10]. MS spectra gave peaks for M^+ as prominent signals, this implies that the cations of this fused dicycle have a considerable stability in the gas phase.

Compound 2, as a yellow solid, could be obtained through the oxidation of 1, is soluble in alkali water, insoluble in acidic water, and could be purified by recrystallization from DMSO-H_2O (1:1). In its MS spectrum, the signals at m/e 207 and m/e 158 as eminent peaks were respectively attributed to $M^+ + H$ and M^+-SOH. This suggested that the NHC(=S)S-H in 1 was converted into NHC(=S)S-O-H in 2. The IR spectrum, which displayed the N-H and O-H stretching absorption at 3200–3500 cm^{-1} as a strong broad band and showed the absence of the S-H stretching at 2500–2600 cm^{-1}, and ^{1}H and ^{13}C NMR data supported the assigned structure for 2 as shown in Scheme 1.

2 was treated with 2.5 equimoles of tri(dialkylamino)phosphine in benzene at 80°C to afford 4. As indicated by TLC and ^{31}P NMR, this reaction was faster



SCHEME 1

and more complex than that of 1 with $P(NR_2)_3$. 4 could be isolated by a centrifugal silica gel TLC using ether/petroleum ether (1 : 1) as eluent in 10–15% yields. In addition, known compounds $(R_2N)_3PS$ and $(R_2N)_3PO$ were obtained as byproducts 10–15% yield, and that should explain the relatively lower yield. Increasing the amounts of $P(NR_2)_3$ from 2.5 to 4 equimoles raised the yield of compound 4 from 10% to 22–47%. For 4, the very strong band at 1240–1280 cm^{-1} in the IR spectra, the M^+ peak with superior m/e 16 to that of 3 in MS and a signal at 67–77 ppm in the ^{31}P NMR spectra, confirm their phosphoryl (P=O) structure.

It was also observed that in air, compound 3b (R=Et) in CH_2Cl_2 solution was automatically oxidized into 4b and 5 at room temperature. The formation of the >S=O stemmed from the band at 1080 cm^{-1} in IR spectrum and MS peaks at m/e 232 (M^+-1), m/e 232 (M^+-CS-SO) and m/e 158 (M^+-CS-SO-$OPNEt_2$).

EXPERIMENTAL

Elemental analyses (C, H and N) were obtained with a PE-2400 elementary analyzer. Mass spectra were recorded with a HEWLETT-PACKARD HP-5988A spectrometer at 70ev ionization energy. ^1H, ^{13}C and ^{31}P-NMR were recorded in $CDCl_3$ or DMSO-d_6 with a Varian XL 200 spectrometer. Chemical shifts were

reported in ppm relative to the internal standard TMS for ^{1}H and ^{13}C NMR, and the external standard 85% H_3PO_4 for ^{31}P NMR. IR were recorded on a PE-983G spectrometer.

Ether was distilled from benzophenone ketyl; benzene and xylene were dried with sodium and calcium hydride.

PCl_3, and R_2NH were obtained commercially. $P(NR_2)_3$[11] were prepared according to reported procedures.

All manipulations were carried out under a dry nitrogen atmosphere.

5-methyl-[1,3,4]thiadiazole-2-yl-dithiocarbamic acid (1)[9]

A 250 ml three necked round bottom flask equipped with a dropping funnel, stirrer and thermometer, was charged with 2-amino-5-methyl-[1,3,4]thiadiazole (11.5 g, 0.1 mol), 80% KOH (8.25 g, 0.12 mol), 20 ml of DMF. After the reaction mixture was stirred for half an hour, 18 ml of CS_2 (0.3 mol) was added slowly at 20°C, refluxed for 6hrs. then cooled to room temperature and poured it into a ice cooled 1N hydrochloric acid (100 ml) under vigorous agitation. The solid collected by filtration was recrystallized from DMSO-H_2O (1:1) to afford white power 13 g (68.1%), m. p. 163°C. IR (KBr, cm^{-1}): 3400m (N-H), 2580w (S-H), 1590s and 1540s (C=N), 1420s (C=S), 1350s, 1300s (N-N), 1010s (C-N), 640m (C-S). ^{1}H NMR (DMSO-d_6, ppm): 2.08 (br, 1H, D_2O exchangable, S-H), 2.50 (s, 3H, CH_3), 12.40 (br, N-H, D_2O exchangable). ^{13}C NMR (DMSO-d_6, ppm): 16.02 (CH_3), 114.70 (C^2=N), 158.5 (C^5=N), 168.5 (C=S). MS m/z (int.): 192 (M^+ + H, 1.8), 159 (M^+-S, 2.4), 157 (M^+-SH_2, 55), 115 (M^+-CS_2, 100), 99, 74, 58.

5-methyl-[1,3,4]thiadiazole-2-yl-dithioperoxycarbamic acid (2)

A fine white power of **1** (5 g, 26.2 mmol) was irradiated with an infrared heat lamp (500w) in the precence of air at 65°C for 24 hrs to afford a yellow solid. The solid was recrystallized from DMSO-H_2O(1:1). Yellow crystals of **2** (4.2 g, 77.6% yield), m.p. 278.5–280°C, were obtained. IR (KBr, cm^{-1}): 3400s (N-H), 3250s and 3150s (O-H), 1580m, 1540s (C=N), 1425s (C=S), 1370s, 1300s (N-N), 990s (C-N), 640m (C-S). ^{1}H NMR (DMSO-d_6, ppm): 2.44 (s, 3H, CH_3), 3.51 (br, 1H, D_2O exchangable, O-H), 7.12 (br, NH, D_2O exchangable). ^{13}C NMR (DMSO-d_6, ppm): 16.48 (CH_3), 114.90 (C^2=N), 156.17 (C^5=N), 168.5 (C=S). MS m/z (int.): 208 (M^+ + H, 1.8), 159 (M^+-S, 45), 116 (M^+-CSSO, 100).

5-methyl-[1,3,4]thiadiazolo[3,2-c]-2-dialkylamino-6-thiono-1,2,3-trihydro-[1,3,5,2]thiadiazaphosphorins (3); Typical Procedure for 3b

Xylene (10 ml), tri(diethylamino)phosphine (1.8 ml, 6.5 mmol), and 5-methyl-[1,3,4]thiadiazole-2-yl-dithiocarbamic acid (1, 0.5 g, 2.6 mmol) were placed in a 25 ml round-bottom flask. This mixture was heated at 120°C under a nitrogen atmosphere of 100 torr for 4 hrs. The solvent was then evaporated in vacuo and the residual crude product was purified through rapid chromatographic technique[12] on silica gel using ether/petroleum ether (1/4) as eluent, yield of pure 3b: 0.512 g (67%); colorless oil. A similar procedure was used to synthesize 3a, and 3c.

For 3a (72%, colorless oil), $C_6H_9N_4PS_3$ (calcd.: C, 27.26; H, 3.43; N, 21.20; P, 11.72. Found: C, 27.11; H, 3.56; N, 21.09;). IR (Film, cm^{-1}): 2950 (C-H), 1550 and 1500 (C=N), 1380 (N-N), 930 (P-N), 830, 715 (C-S). ^{31}P NMR: 112.0. ^1H NMR: 2.50 (s, 3H, CH_3), 2.91 (d, $^3J_{P\text{-}N\text{-}C\text{-}H}$ = 8.4Hz, 6H, NMe_2). MS m/z (int.): 264 (M^+, 42.5), 220 (M^+-NMe_2, 89.6), 157 (M^+-NMe_2-PS, 69.2), 114 (157-CS, 83.4), 58 (CNS, 100).

For 3b (67%, colorless oil), $C_8H_{13}N_4PS_3$ (calcd.: C, 32.86; H, 4.48; N, 19.16; P, 10.59. Found: C, 32.71; H, 3.56; N, 21.10; P, 11.0.) IR (Film, cm^{-1}): 2950 (C-H), 1550 and 1500 (C=N), 1380 (N-N), 930 (P-N), 820, 730 (C-S). ^{31}P NMR: 109.2. ^1H NMR: 1.1 (t, $^3J_{H\text{-}H}$ = 7. 0Hz 6H, $2CH_3$), 2.50 (s, 3H, CH_3), 3.30 (m, 4H, N (CH_2-)$_2$). MS m/z (int.): 292 (M^+, 27.5), 220 (M^+-NEt_2, 68.6), 157 (M^+-NMe_2-PS, 54.8), 114 (157-CS, 88.6), 99 (C_2N_3S, 31), 72 (NEt_2, 100), 58 (CNS, 33.5).

For 3c (68%, colorless oil), $C_{10}H_{17}N_4PS_3$ (calcd.: C, 37.48; H, 5.35; N, 17.49; P, 9.67. Found: C, 37.63; H, 5.42; N, 17.30; P, 10.31.) IR (Film, cm^{-1}): 2950 (C-H), 1550, 1500 (C=N), 1440 (C=S), 940 (P-N), 720 (C-S). ^{31}P NMR: 110.0. ^1H NMR: 1.0–1.2 (m, 10H, $\underline{CH_2CH_3}$), 3.02 (m, 4H, N (CH_2-)$_2$), 2.50 (s, 3H, Me). MS (m/z, int) 320 (M^+, 17.8), 220 (M-NPr_2, 45), 157 (M^+-NEt_2-PS, 58.8), 114 (157-CS, 89.5), 100 (NPr_2, 77), 99 (C_2N_3S, 43).

5-methyl-[1,3,4]thiadiazolo[3,2-c]-2-dialkylamino-6-thiono-1,2,3-trihydro-[1,3,5,2]thiadiazaphosphorin-2-oxo (4); Typical Procedure for 4b

In a 25 ml round-bottom flask, 5-methyl-[1,3,4]thiadiazole-2-yl-dithioperoxycarbamic acid (2; 520 mg, 2.5 mmol) was added to tri(diethylamino)phosphine (2.8 ml, 10 mmol) in 5 ml of benzene at 0°C and stirred for half an hour. This mixture was heated at 85°C with stirring for 2 hrs. After removal of solvent, the oily residue was purified through preparative TLC on silica gel

using ether/petroleum ether (1/1) as eluent. Pure 4b was obtained in the yield of 0.21 g (27.1%). A similar procedure was used to synthesize 4a, and 4c.

For 4a (47%, colorless oil), $C_6H_9N_4OPS_3$ (calcd. C, 25.71; H, 3.24; N, 20.00; P, 11.46. Found C, 25.70; H, 3.26; N, 19.50; P, 11.00). IR (Film, cm^{-1}): 2950 (C-H), 1550, 1465 (C=N), 1280 (P=O), 1050 (C-N), 930 (P-N), 715 (C-S). ^{31}P NMR: 72.6. ^{1}H NMR: 3.38 (br, 6H, NMe_2), 2.45 (s, 3H, Me). ^{13}C NMR: 15.52 (s, Me), 42.2 (br, NMe_2), 154.72 (C=S), 167.46 (C^2=N), 182.6 (C^5=N). MS (m/z, int.): 280 (17, M^+), 236 (34.1, M-NMe_2), 158, 91, 65, 58 (100%).

For 4b (27%, colorless oil), $C_8H_{13}N_4OPS_3$ (calcd. C, 31.16; H, 4.25; N, 18.17; P, 10.04. Found C, 31.08; H, 4.19; N, 17.93; P, 10.27). IR (Film, cm^{-1}): 2950 (C-H), 1550–1250 (C=N, P=O, C-N), 940 (P-N), 725 (C-S). ^{31}P NMR: 67.1. ^{1}H NMR: 1.22 (t, $^{3}J_{H-H}$ = 7.2 Hz, 6H, $2CH_2$ $\underline{CH_3}$), 2.48 (s, 3H, Me), 3.81 (m, 4H, 2 $\underline{CH_2}CH_3$). ^{13}C NMR: 12.52, (s, $CH_2\underline{CH_3}$), 15.7 (s, Me), 39.39 ($\underline{CH_2}CH_3$), 153.90 (C=S), 167.7 (C^2=N), 182.4 (C^5=N). MS (m/z, int.): 308 (M^+), 158, 72, 58 (100%).

For 4c (24%, colorless oil), $C_{10}H_{17}N_4OPS_3$ (calcd. C, 35.70; H, 5.08; N, 16.66; P, 9.21. Found C, 35.40; H, 5.09; N, 16.37; P, 9.03). IR (Film, cm_{-1}): 2990 (C-H), 1560, 1485 (C=N), 1420 (C=S), 1240 (P=O), 1010 (C-N), 930 (P-N), 730 (C-S). ^{31}P NMR: 77.9. ^{1}H NMR: 0.86 (t, $^{3}J_{H-H}$ = 7.2 Hz, 6H, $2CH_2CH_2\underline{CH_3}$), 1.62 (m, 4H, $2CH_2\underline{CH_2}CH_3$), 2.44 (s, 3H, Me), 3.67 (m, 4H, 2 $\underline{CH_2}CH_2CH_3$). MS (m/z, int.): 336 (M^+), 299, 258, 225, 183, 158, 114, 100, 65.

5-methyl-[1,3,4]thiadiazolo[3,2-c]-2-diethylamino-6-thiono-1,2,3-trihydro-[1,3,5,2]thiadiazaphosphorin-1,2-dioxo (5)

Purified 3b (195 mg, 0.67 mmol) obtained above was dissolved in 10 ml of dichloromethane in 50 ml beaker. The mixture was stirred at 24°C for 48 hrs.

The ^{31}P NMR and TLC of the mixture indicated the formation of the 4b and 5. Solvent was removed and the residue was purified by preparative TLC on silica gel plates using ether/petroleum ether (2/1) as eluent. In addition to described 4b (142 mg, 69%), the yield of 5 (colorless viscous liquid) was 55 mg (25%). $C_8H_{13}N_4O_2PS_3$ (calcd.: C, 29.62; H, 4.04; N, 17.27; P, 9.55. Found: C, 29.57; H, 4.13; N, 17.10; P, 9.23) IR (Film, cm^{-1}): 2990 (C-H), 1550 and 1480 (C=N), 1420 (C=S), 1360 (N-N), 1260 (P=O), 1080 (S=O), 1030 (C-N), 940 (P-N), 820, 725 (C-S). ^{31}P NMR: 54.08. ^{1}H NMR: 1.25 (t, 6H, $2CH_3$), 2.50 (s, 3H, CH_3), 3.70 (m, 4H, N $(CH_2\text{-})_2$). ^{13}C NMR: 12.4 (s, CH_3), 13.3 (s, CH_2 $\underline{CH_3}$), 15.6 (s, SCH_3), 39.3 (d, $^{2}J_{PNC}$ = 15 Hz, $(CH_2\text{-})_2$), 153.1 (C=S), 167.66 (C^2=N), 182.55 (C^5=N). MS m/z (int.) 323 (M^+-1, 34.7), 232 (M^+-CS_2O, 100), 205 (M^+-$PONEt_2$), 158 (205-SO + H), 99 (C_2N_3S, 15), 72 (NEt_2, 86).

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