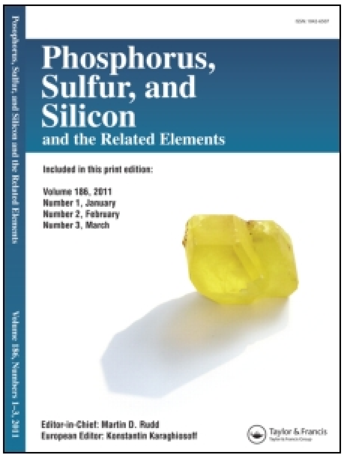

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SYNTHESIS OF 3,4-DIPHENYL-1,3,4-DIAZAPHOSPHOLIDIN-2-THIONE-4-OXIDES AND THEIR QUANTITATIVE STRUCTURE-HERBICIDAL ACTIVITY RELATIONSHIP

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SYNTHESIS OF 3,4-DIPHENYL-1,3,4-DIAZAPHOSPHOLIDIN-2-THIONE-4-OXIDES AND THEIR QUANTITATIVE STRUCTURE-HERBICIDAL ACTIVITY RELATIONSHIP

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A number of 3,4-diphenyl-1,3,4-diazaphospholidin-2-thione-4-oxides (4, 5) have been synthesized. The geometric isomers of compounds 4 are separated. However, for compounds 5 only the cis-isomer was found. All the products have been confirmed by microanalyses and spectroscopic methods. The bioassay indicates that some of the compounds prepared have high selective herbicidal activity and the quantitative structure-herbicidal activity relationship (QSAR) of compounds 5 has also been studied.

Key words: Synthesis, 1,3,4-diazaphospholidin-2-thione, geometric isomers, herbicidal activity, QSAR.

INTRODUCTION

In previous papers,[1-3] a number of 1,3,4-diazaphospholidinones and their corresponding thiones were synthesized by a Mannich-type reaction starting with phenylurea or phenylthiourea, phenyldichlorophosphine and various aliphatic aldehydes or ketones. It was found that straight chain and cyclic products were obtained respectively when different solvents were used. A mechanism involving addition of P—H to the imine derivatives was proposed for the Mannich-type reactions.[4] In this paper, the separation of the cis and trans geometric isomers for 4a is reported. Furthermore, in order to look for potent herbicides a series of new 3,4-diphenyl-1,3,4-diazaphospholidin-2-thione-4-oxides 5 have been synthesized by the Mannich-type reaction of phenyl thiourea with phenyl dichlorophosphine and various substituted benzaldehydes. Their quantitative structure-herbicidal activity relationship is described herein.

RESULTS AND DISCUSSION

A. Synthesis and Geometric Isomerism of Compounds 4 and 5

The Mannich-type reaction of trivalent phosphines is a facile method for the preparation of new phosphorus heterocyclic compounds.[5-7] We allowed phenylthiourea to react with phenyldichlorophosphine and aliphatic aldehyde or ketones and syn-

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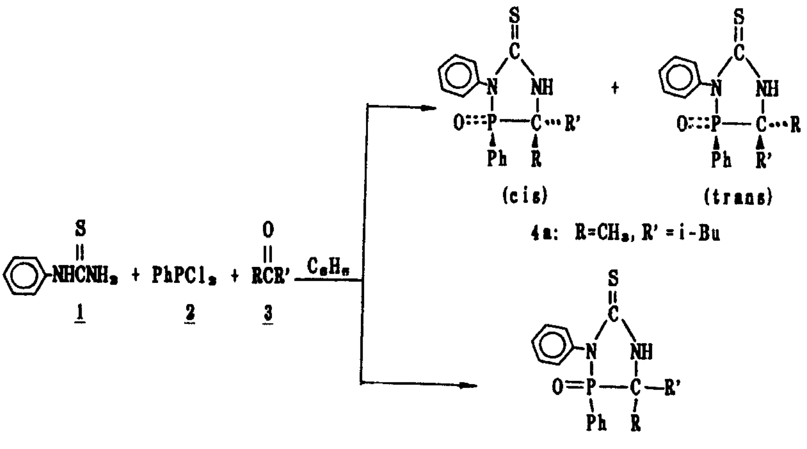
thesized compounds 4a–4c in a yield of 49.4%–81.1%. The synthetic route is shown in Scheme I. There exists two geometric isomers for 4a and they were separated by column chromatography on silica gel. However, from ^{1}H NMR and ^{31}P NMR no geometric isomerism was found for the other two compounds, 4b and 4c.

Compounds 5 were synthesized in a yield of 40.6%–83.8% by carrying out the reaction of phenylthiourea with phenyl dichlorophosphine and various substituted benzaldehyde in anhydrous benzene (Shown in Scheme II). To our great interest, only one geometric isomer was found for all compounds 5. The phosphorus coupling constant of the proton H(5) bonded to the 5-position carbon $^2J_{P-C-H}$ = 3.6 Hz, which is much lower than in straight chain compounds (10 ~ 30 Hz). From the analysis of the possible φ-dihedral angles using the corresponding Karplus relation,[8] it is demonstrated that the proton is located on the same side of the ring as the phenyl group linked with the phosphorus atom. Therefore, the isomer is concluded to be in the cis-configuration, which might be due to the apparent steric hindrance effect:

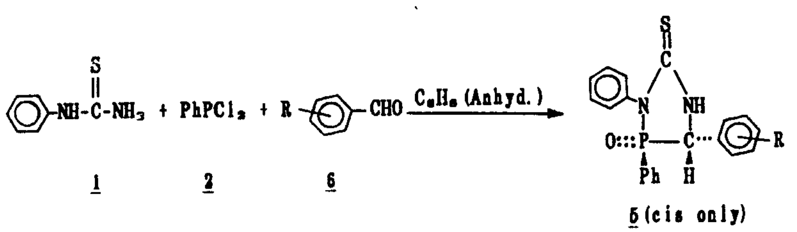
Besides the expected products, 3,4-diphenyl-1,3,4-diazaphospholidin-2-thione-4-oxides (4, 5), small amounts of other compounds, the corresponding 4-sulfides[4]



4a: R=CH$_3$, R' = i-Bu

4b: R=H, R' = i-Bu; 4c: R, R' = (CH$_2$)$_6$

SCHEME I



5a: R=H;
5b: R=p-CH$_3$;
5c: R=p-Cl;
5d: R=m-Cl;
5e: R=p-Br;
5f: R= p-F;
5g: R=o-CH$_3$O;
5h: R=p-CH$_3$O;
5i: R=p-NO$_2$;
5j: R=m-NO$_2$;
5k: R=p-PhO;
5l: R=2,4-Cl$_2$

SCHEME II

are observed by TLC(R_f = 0.8, chloroform as the developing solvent). The target compounds 4 and 5 are purified by recrystallization methods.

B. Spectral Properties and Structures of 4 and 5

All the compounds prepared were confirmed by ^{1}H NMR, ^{31}P NMR, IR, MS spectroscopy and elemental analysis (See Table I).

In the ^{1}H NMR spectra of 4a, there is much difference between the two geometric isomers. In the cis-isomer, the methyl group is syntonic to the phenyl group linked with the phosphorus atom, so that the chemical shifts of protons at the methyl group are at a higher field (δ 1.169–1.256 ppm) because the methyl is within the

TABLE I

The physical and chemical data of compounds 4 and 5

NO	Yield (%)	MP (°C)	NMR[a] (CDCl$_3$, δ, ppm)	Elemental Analysis/ Found (Cacld.) C (%)	H (%)	N (%)	IR (cm^{-1})	MS (M^{+})
4a (cis)	20.9	243–245	1.08 (d, 6H, 2CH$_3$), 1.169–1.256 (d, 3H, CH$_3$, $^3J_{PCCH}$ = 17.4 Hz), 2.00–2.05 (m, 3H, CH$_2$CH), 7.9 (d, 1H, NH), 7.29–7.75 (m, 10H, 2Ph), ^{31}P NMR: 46.3852	63.44 (63.69)	6.32 (6.42)	7.45 (7.82)	——[b]	358
4a (trans)	14.0	250–251	0.45–0.48 (d, 3H, CH$_3$), 0.87–0.90 (d, 3H, CH$_3$), 1.35–1.65 (m, 3H, CH$_2$CH), 1.75–1.82 (d, 3H, CH$_3$, $^3J_{PCCH}$ = 13.6 Hz), 7.26–7.82 (m, 11H, 2Ph and NH), ^{31}P NMR: 46.5700	63.66 (63.69)	6.41 (6.42)	7.46 (7.82)	——	358
4b	49.4	221–223	0.80–0.95 (m, 6H, 2CH$_3$), 1.7–2.0 (m, 3H, CH$_2$CH), 3.95–4.05 (t, 1H, CH), 7.21–7.81 (m, 11H, 2Ph and NH)	62.84 (62.79)	5.88 (6.10)	7.99 (8.14)	——	344
4c	81.1	249–251	1.37–2.1 (m, 12H, 6CH$_2$), 8.1–8.2 (d, 1H, NH), 7.32–7.85 (m, 10H, 2Ph)	64.74 (64.86)	6.44 (6.22)	7.22 (7.57)	——	370
5a*	65.9	236–238	5.44 (d, 1H, CH, $^2J_{PCH}$ = 4.3 Hz), 7.10–7.90 (m, 15H, 3Ph), 10.62 (d, 1H, NH, $^3J_{PCNH}$ = 21.6 Hz), ^{31}P NMR:P 35.00	65.89 (65.93)	4.46 (4.67)	7.88 (7.69)	1250 (P═O) 1516 (N—C═S)	364
5b*	66.1	244–246	2.40 (s, 3H, CH$_3$), 5.40 (d, 1H, CH, $^2J_{PCH}$ = 4.0 Hz), 7.10–7.90 (m, 14H, 2Ph and C$_6$H$_4$), 10.50 (d, 1H, NH, $^3J_{PCNH}$ = 21.6 Hz)	66.72 (66.67)	5.04 (5.03)	7.77 (7.41)	1250 (P═O) 1520 (N—C═S)	378
5c*	62.7	173–175	5.70 (d, 1H, CH, $^2J_{PCH}$ = 4.0 Hz), 7.00–7.80 (m, 14H, 2Ph and C$_6$H$_4$), 10.30 (d, 1H, NH, $^3J_{PCNH}$ = 21.6 Hz), ^{31}P NMR: 37.02	59.88 (60.23)	4.28 (4.02)	6.69 (7.03)	1250 (P═O) 1520 (N—C═S)	398

TABLE I (*Continued*)

5d	60.3	273–275	5.81–5.83 (d, 1H, CH, $^2J_{PCH}$ = 4.80 Hz), 8.2–8.3 (d, 1H, NH), 7.15–7.79 (m, 14H, 2Ph and C_6H_4)	60.10 (60.23)	3.85 (4.02)	7.11 (7.03)	——	398
5e*	40.6	249–251	5.60 (d, 1H, CH, $^2J_{PCH}$ = 4.0 Hz), 7.10–7.90 (m, 14H, 2Ph and C_6H_4), 10.20 (d, 1H, NH, $^3J_{PCNH}$ = 21.6 Hz)	54.13 (54.18)	3.37 (3.61)	5.97 (6.32)	1250 (P=O) 1520 (N—C=S)	440
5f*	73.4	254–256	5.56 (d, 1H, CH, $^2J_{PCH}$ = 4.0 Hz), 7.20–8.00 (m, 14H, 2Ph and C_6H_4), 10.60 (d, 1H, NH, $^3J_{PCNH}$ = 21.6 Hz)	63.04 (62.83)	4.22 (4.19)	6.98 (7.33)	1250 (P=O) 1500 (N—C=S)	382
5g	83.8	258–260	3.58 (d, 3H, OCH_3), 5.40–5.45 (d, 1H, CH), 7.80–7.90 (d, 1H, NH), 6.8–7.7 (m, 14H, 2h and C_6H_4)	63.82 (63.96)	4.98 (4.82)	7.02 (7.11)	——	394
5h*	58.4	216–217	3.76 (s, 3H, OCH_3), 5.36 (d, 1H, CH, $^2J_{PCH}$ = 4.0 Hz), 7.00–7.80 (m, 14H, 2Ph and C_6H_4), 10.10 (d, 1H, NH, $^3J_{PCNH}$ = 21.6 Hz)	58.54 (58.68)	3.78 (3.91)	9.97 (10.27)	1246 (P=O) 1516 (N—C=S)	409
5i*	73.3	230 (dec)	6.00 (d, 1H, CH, $^2J_{PCH}$ = 4.0 Hz), 7.20–8.20 (m, 14H, 2Ph and C_6H_4), 10.10 (d, 1H, NH, $^3J_{PCNH}$ = 21.6 Hz)	58.54 (58.68)	3.78 (3.91)	9.97 (10.27)	1246 (P=O) 1516 (N—C=S)	409
5j	68.5	259–261	5.83–5.86 (d, 1H, CH, $^2J_{PCH}$ = 4.78 Hz), 10.68–10.78 (d, NH, $^3J_{PCNH}$ = 21.1 Hz), 7.10–8.25 (m, 14H, 2Ph and C_6H_4)	58.77 (58.68)	3.74 (3.91)	9.99 (10.27)	——	409
5k	78.9	250–252	5.06–5.08 (d, 1H, CH, $^2J_{PCH}$ = 4.0 Hz), 6.2–6.3 (d, 1H, NH), 6.74–7.78 (m, 19H, 3Ph and C_6H_4)	68.49 (68.42)	4.93 (4.61)	5.86 (6.14)	——	456
5l	41.6	273–274	5.50–5.55 (d, 1H, CH), 8.1–8.2 (d, 1H, NH, $^3J_{PCNH}$ = 20 Hz), 7.18–7.87 (m, 13H, 2Ph and C_6H_3)	55.46 (55.43)	3.66 (3.46)	6.46 (6.47)	——	433

[a] The solvent marked by asterisk is DMSO-d_6.
[b] Data were not recorded.

shielding region of the benzene ring. In addition, the coupling constant $^3J_{PCCH}$ has a larger value (17.4 Hz). Nevertheless, the isobutyl group is far from the phenyl group and therefore, the chemical shifts of the protons at the isobutyl group are at a lower field. The two methyls of the isobutyl give one set of multiple peaks. However, the situation in the trans-isomer is on the contrary. Furthermore, the two methyls of the isobutyl group display two sets of multiple peaks with much difference ($\Delta\delta$ = 0.4 ppm) because they are located in the strong and weak shielding region of the benzene ring respectively. Noteworthy, there is little difference in the ^{31}P NMR of the two geometric isomers (cis: δ 46.3852 ppm and trans: δ 46.5700 ppm).

From the ^1H NMR and ^{31}P NMR of compounds 5, only one isomer was found. The cis-configuration of the isomer is confirmed by the smaller coupling constant

${}^2J_{PCH}$(~4.0 Hz). And the larger coupling constant ${}^3J_{PCNH}$(~22.0 Hz) indicates that the five-membered heterocycle is a coplanar structure.

The IR spectra of compounds 5 showed normal stretching absorption bands, indicating the existence of the —N—C═S (1500–1520 cm^{-1}) and P═O (~1250 cm^{-1}) groups. The other all could be rationalized.

The EI-MS spectra of 5 demonstrate the existence of the stable molecular ion peaks (see Table I) and that compounds 5 are always cleaved to give fragments

which are obtained via hydrogen-rearrangement and skeleton-rearrangement. All fragmentation ions are consistent with their structures and can be clearly assigned.

C. Herbicidal Activity and QSAR

The herbicidal activity of compounds 5 was tested. A set amount of each sample was dissolved in acetone to which a drop of an emulsifier was added. Then, the solution was diluted with water until it reached the concentration required. Some herbs such as rape, oats, flax and barnyard grass were subjected to the leaf treatment. Preliminary bioassays indicated that some of compounds 5 displayed potent selective herbicidal activity. The results are given in Table II in terms PI_{50}.

$$PI_{50} = -\lg(ED_{50}/Mw)$$

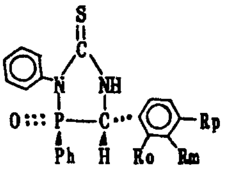
where ED_{50} refers to the drug dosage (gram/acre) inhibiting 50% of herbs and Mw is the molecular weight. Determinations of ED_{50} were repeated for at least three runs and averaged.

In order to know the correlation of structure to herbicidal activity, especially the contributions to the herbicidal activities by ortho-, meta- and para-substituents of the 5-position phenyl and other factors, the quantitative structure-activity relationship (QSAR) of compounds 5 was studied.

The QSAR was performed on the CASAC software. Ten parameters MR (Molecular Refraction), EN (Electronegativity), DP (Dipole Moment), HO (Energy

TABLE II

The herbicidal activity of compounds 5



NO	5a	5b	5c	5d	5e	5f	5g	5h	5i	5j	5k	5l
Ro	H	H	H	H	H	H	OMe	H	H	H	H	Cl
Rm	H	H	H	Cl	H	H	H	H	H	NO_2	H	H
Rp	H	Me	Cl	H	Br	F	H	OMe	NO_2	H	OPh	Cl
PI_{50}	0.7597	0.2765	0.4558	0.3621	0.8561	0.2810	0.8688	0.5975	0.4616	0.9042	0.3579	0.7163

of the Highest Occupied Orbital), GP (Energy Gap), $(MR)^2$, $(EN)^2$, $(DP)^2$, $(HO)^2$ and $(GP)^2$ were chosen. The lipophilicity and hydrophilicity values of the target molecules 5 are 470 and 350 respectively.After the stepwise regression analyses, the QSAR equation was obtained as follows:

$$PI_{50} = 0.3986HO(Rm) + 0.2414MR(Ro) - 0.0182EN^2(Rp) - 3.2376$$

where $n = 12$, $r = 0.767$, $s = 0.1791$, $F = 3.81$. The correlation was significant at a level of above 95%.

From the equation, we see that the bigger MR value of the substituents at the ortho position, the bigger HO value of those at the meta position and the smaller EN value of those at the para position are more favorable to the herbicidal activity. More or less, these results are of some significance for predicting herbicidal activity of new compounds and may help in designing some novel herbicides.

EXPERIMENTAL

Elemental analysis was performed with a CHNCORDERD MT-3 elementary analyzer. Mass spectra were recorded with a VG-7070E spectrometer using the GAB method. ^1H NMR spectra were recorded with a JEOL-FX-090Q spectrometer and BRUKER AC-P200. TMS was used as an internal standard for ^1H NMR, and 85% H_3PO_4 was used as an external standard for ^{31}P NMR. The IR spectra were measured by using a SHIMADZU-435 instrument. The QSAR was performed on the CASAC software (Version 2.0). Melting points were determined with a model YANACO MP-500 apparatus and were uncorrected. Column chromatography was performed on silica gel H (10–40 μ, Hai Yang Chemical Factory of Qingdao).

The reagents and solvents were available commercially and purified according to conventional methods.

3,4-Diphenyl-1,3,4-Diazaphospholidin-2-Thione-4-Oxides (4, 5). *(General procedure):* Phenylthiourea (1.52 g, 0.01 mol), phenyl dichlorophosphine (1.79 g, 0.01 mol) and anhydrous benzene (15 ml) were added to a four-necked flask equipped with a reflux condenser, a calcium chloride tube and a thermometer. To the stirred solution was dropped 0.01 mol of aliphatic aldehyde or ketone (3) or substituted benzaldehyde (6) slowly at ambient temperature. The stirring was kept for 0.5 h, then the solution was heated under reflux at 80–100°C for 10 h. After cooling, the mixture was filtered to yield the crude product that was recrystallized from proper solvents.

Solvents for recrystallization of 4a–c, 5d, 5g and 5j–l: chloroform-petroleum ether; for 5a–b; chloroform; for 5c and 5h: chloroform-benzene; for 5e–f and 5i: acetonitrile.

The physical and chemical data of compounds 4 and 5 are listed in Table I.

Separation of the Geometric Isomers of 4a: The product 4a obtained above in a yield of 69.8% was a mixture of cis and trans forms and subjected to separation. The sample was dissolved in chloroform and chromatographed on silica gel with a mixture of chloroform and dichloromethane (v/v 1:1) as the eluent. Two components were collected with R_f values of 0.45 and 0.50 in a yield of 20.9% and 14.0% respectively. Analyses data recorded also in Table I indicate that the former is a *cis*-isomer while the latter is a *trans* one.

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