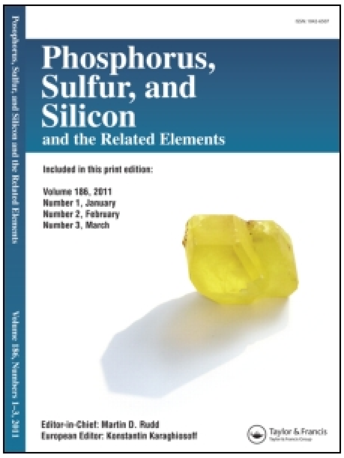

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STUDIES ON ORGANOPHOSPHORUS HETEROCYCLES PART X. SYNTHESIS OF 1,4-DIPHENYL-1,4,2-DIAZAPHOSPHOLIDIN-5-ONE-2-OXIDES AND THEIR QUANTITATIVE STRUCTURE-HERBICIDAL ACTIVITY RELATIONSHIP

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STUDIES ON ORGANOPHOSPHORUS HETEROCYCLES PART X. SYNTHESIS OF 1,4-DIPHENYL-1,4,2-DIAZAPHOSPHOLIDIN-5-ONE-2-OXIDES AND THEIR QUANTITATIVE STRUCTURE—HERBICIDAL ACTIVITY RELATIONSHIP

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A number of 1,4-diphenyl-1,4,2-diazaphospholidin-5-one-2-oxides (**4**) have been synthesized by the Mannich-type reaction of 1,3-diphenylurea (**1**), substituted benzaldehydes (**3**) and triphenyl phosphite (**2**) with anhydrous toluene as the solvent. Compounds **4** have been confirmed by microanalyses and spectroscopic methods. The bioassay indicates that some of compounds prepared have good selective herbicidal activity and the quantitative structure-herbicidal activity relationship (QSAR) of compounds **4** has also been studied.

Keywords: Synthesis; 1,4,2-diazaphospholidin-5-one; herbicidal activity; QSAR

INTRODUCTION

In our previous papers,[1–3] a number of 1,4,2-diazaphospholidinones and their corresponding thiones were synthesized by a Mannich-type reaction starting with 1-phenyl-3-(*p*-toluenesulfonyl) urea, substituted benzaldehydes and triphenyl phosphite. It was found that these rings possess good selective herbicidal activity. In order to investigate the Mannich-type reaction further with an attempt to look for a new herbicide, a series of new 1,4-diphenyl-1,4,2-diazaphospholidin-

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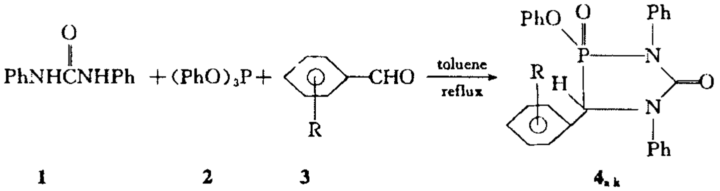


R: 4a, H; 4b, *p*-OMe; 4c, *o*-OH; 4d, *m*-OH; 4e, *o*-NO_2; 4f, *m*-NO_2; 4g, *p*-NO_2; 4h, 2,4-2NO_2; 4i, *m*-Cl; 4j, *p*-Cl; 4k, 2,4-2Cl

SCHEME 1

5-one-2-oxides (**4**) have been synthesized by the Mannich-type reaction of 1,3-diphenylurea, substituted benzaldehydes and triphenyl phosphite in anhydrous toluene. Their quantitative structure-herbicidal activity relationship is described in this paper.

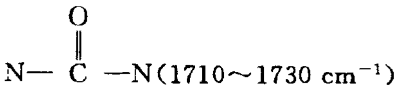
RESULTS AND DISCUSSION

Synthesis of Compounds 4

The Mannich-type reaction of trivalent phosphorus is a facile method for the preparation of new phosphorus heterocyclic compounds.[4–6] We allowed 1,3-diphenylurea (**1**) to react with triphenyl phosphite (**2**) and substituted benzaldehydes and synthesized compounds $\mathbf{4}_{\text{a-k}}$ in a yield of 30.74% ~ 65.82%. The synthetic route is shown in scheme 1.

Compounds **4** were confirmed by ^1H NMR, ^{31}P NMR, IR, MS spectroscopic and elemental analysis (see Table I). In the ^1H NMR spectra of compounds **4**, the proton in **PCH** appeared as a doublet in the range of δ 5.08 ~ 5.22 with the coupling constant split by the phosphorus atom $^2J_{PH}$ = 7.2 ~ 25.2 Hz. The chemical shift of the mobile proton in the **OH** of compounds **4c** and **4d** were 8.92 and 8.98, respectively, which disappeared when deuterated. The proton in $\mathbf{CH_3O}$ of compound **4b** appeared as a single peak at δ 3.76. The ^{31}P NMR spectra of compounds **4** revealed a singlet at the range of δ = 9.83 ~ 16.74.

The IR spectra for compounds **4** showed normal stretching absorption bands, indicating the existence of the groups P=O (1240 ~ 1280 cm^{-1}) and



$$N-\overset{\overset{\displaystyle O}{\|}}{C}-N\,(1710\sim1730\ cm^{-1})$$

TABLE I The physical and chemical data of compounds **4**

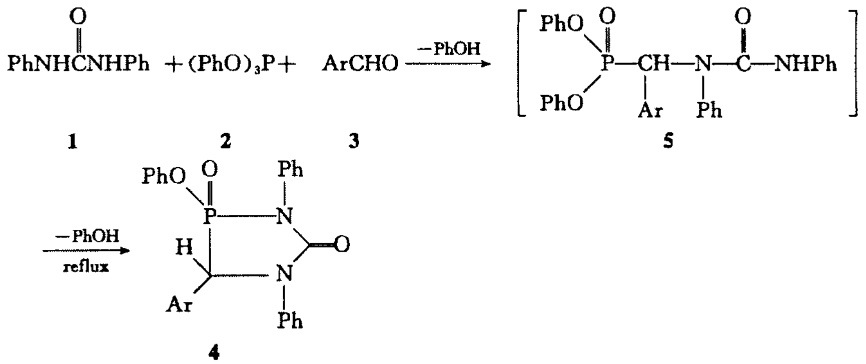
NO	*Yield* *(%)*	*MP* *(°C)*	*NMR*[a] *($CDCl_3$, δ)*	*Elemental Analysis/ Found (Cacld.)*			*MS* *(M^+)*	*IR* *(cm^{-1})*
				C *(%)*	*H* *(%)*	*N* *(%)*		
4a	43.70	203 ~ 204	7.36 ~ 7.58(m, 20H, Ar-H), 5.22 (d, 1H, PCH, $^2J_{PH}$ = 7.2Hz). ^{31}P NMR:11.07	70.98 (70.91)	4.83 (4.77)	6.52 (6.36)	440	1254(P=O) 1713(C=O)
4b	54.15	213 ~ 215	6.64 ~ 7.54 (m, 19H, Ar-H), 5.12 (d, 1H, PCH, $^2J_{PH}$ = 25.2Hz), 3.76(s,3H,OCH_3). ^{31}P NMR:10.07	68.58 (68.94)	4.62 (4.89)	6.08 (5.96)	470	1275(P=O) 1725(C=O)
4c*	39.45	202 ~ 203	6.92 ~ 7.86 (m, 19H, Ar-H), 8.92(s,1H,OH),5.14(d, 1H, PCH, $^2J_{PH}$ = 14.8Hz).	68.21 (68.42)	4.48 (4.61)	6.43 (6.14)	456	1260(P=O) 1730(C=O)
4d*	60.78	183 ~ 184	8.98(s, 1H, OH), 6.71 ~ 7.89 (m, 19H, Ar-H), 5.08 (d, 1H, PCH, $^2J_{PH}$ = 12.8Hz). ^{31}P NMR: 12.51	68.57 (68.42)	4.46 (4.61)	6.31 (6.14)	456	—[b]
4e	43.27	228 ~ 229	6.69 ~ 7.98(m, 19H, Ar-H), 5.08 (d, 1H, PCH, $^2J_{PH}$ = 16.4Hz)	64.64 (64.33)	4.22 (4.12)	8.35 (8.64)	485	1258(P=O) 1720(C=O)
4f	40.56	236 ~ 237	6.71 ~ 7.95(m, 19H, Ar-H), 5.14 (d, 1H, PCH, $^2J_{PH}$ = 14.2Hz)	64.69 (64.33)	4.24 (4.12)	8.37 (8.64)	—	1255(P=O) 1726(C=O)
4g	61.73	234 ~ 235	6.58 ~ 8.28 (m, 19H, Ar-H), 5.26 (d, 1H, PCH, $^2J_{PH}$ = 25.2Hz), ^{31}P NMR: 16.74	64.70 (64.33)	4.05 (4.12)	8.73 (8.64)	485	—

TABLE I *continued*

NO	*Yield (%)*	*MP (°C)*	*NMR*[a] *($CDCl_3$,δ)*	*Elemental Analysis/ Found (Cacld.)*			*MS (M^+)*	*IR (cm^{-1})*
				C (%)	*H (%)*	*N (%)*		
4h*	65.82	239 ~ 240	7.08 ~ 7.94(m, 18H, Ar-H), 5.10 (d, 1H, PCH, $^2J_{PH}$ = 14.4Hz), ^{31}P NMR:18.39.	58.94 (58.87)	3.49 (3.58)	10.49 (10.57)	—	1265(P=O) 1724(C=O)
4i	30.74	230 ~ 231	7.12 ~ 7.88 (m, 19H, Ar-H), 5.14 (d, 1H, PCH, $^2J_{PH}$ = 15.4Hz)	65.94 (65.82)	4.35 (4.22)	5.74 (5.91)	—	—
4j	32.95	234 ~ 236	7.18 ~ 7.86 (m, 19H, Ar-H), 5.19 (d, 1H, PCH, $^2J_{PH}$ = 15.4Hz), ^{31}P NMR:9.83	65.99 (65.82)	4.39 (4.22)	5.78 (5.91)	474	—
4k	49.81	243 ~ 245	7.21 ~ 7.92(m, 18H, Ar-H), 4.94 (d, 1H, PCH, $^2J_{PH}$ = 16.8Hz), 0^{31}P NMR: 11.86	61.52 (61.30)	3.64 (3.73)	5.36 (5.50)	509	1250(P=O) 1726(C=O)

[a] The solvent marked by asterisk is DMSO-d_6.

[b] Data were not recorded.



SCHEME 2

The EI-MS spectra of **4** demonstrated the existence of the weak molecular ion peak (M^+). The fragmentation ions were consistent with their structures and can be clearly assigned.

Mannich-type reaction involving benzaldehyde, urea derivatives and trivalent phosphorus species leads usually to substituted aminophosphonic acid. However, when phosphite esters were used with 1,3-dimethylurea[7] or 1,3-diphenyl or phenyl dichlorophosphine with phenylurea,[8-9] cyclic 1,4,2-diazaphospholidins (**4**) were the major products instead of linear structure (**5**). This process was described in scheme 2.

Herbicidal Activity and QSAR

The herbicidal activity of compounds **4** 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 the compounds **4** displayed good selective herbicidal activity against rape. The results are given in Table II in terms of activity indicator (D).

TABLE II The herbicidal activity of compounds **4** against rape

NO	*4a*	*4b*	*4c*	*4d*	*4e*	*4f*	*4g*	*4h*	*4i*	*4j*	*4k*
R_o	H	H	OH	H	NO_2	H	H	NO_2	H	H	Cl
R_m	H	H	H	OH	H	NO_2	H	H	Cl	H	H
R_p	H	OMe	H	H	H	H	NO_2	NO_2	H	Cl	Cl
D	2.73	2.91	3.76	3.02	2.92	2.76	2.88	3.14	2.53	2.36	2.04

TABLE III Correlation Coefficient

	$EN^2(Ro)$	$DP^2(Rm)$	$HO^2(Rp)$
$EN^2(Ro)$	1.0000		
$DP^2(Rm)$	0.2535	1.0000	
$HO^2(Rp)$	0.2591	0.04112	1.0000

$$D = \lg[a/(100 - a)] + \lg Mw$$

Where a refers to the inhibition percentage against rape at 1.5kg/ha. Mw is the molecular weight. Determinations of a 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 4-position phenyl, the quantitative structure-activity relationship (QSAR) of compounds **4** was studied.

The QSAR was performed on the CASAC software.[10] Ten parameters MR (Molecular Refraction), DP(Dipole Moment), EN(Electronegativity), HO(Energy of the Highest Occupied Orbital), OI(hydrophobicity value), $(MR)^2$, $(EN)^2$, $(DP)^2$, $(HO)^2$ and $(OI)^2$ were chosen. The lipophilicity and hydrophilicity values of the target molecules **4** are 534 and 420 respectively. After the stepwise regression analyses, the QSAR equation was obtained as follows:

$$D = 0.03436\, EN^2(Ro) - 0.01462 DP^2(Rm) + 0.01046 HO^2(Rp) - 0.69911 \quad (1)$$

Where $n = 11$, $r = 0.9524$, $F = 22.79$, $S = 0.0840$. The correlation was significant at a level of above 95%. The correlation coefficients are listed in Table III.

From the equation, It is found that the bigger EN value of the substituents at the ortho position, the bigger HO Value of those at para position and the smaller DP value of those at meta 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 CHN CORDERD MT-3 elementary analyzer. Mass spectra were recorded with a VG-7070E spectrometer. ^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. Colunm chromatography was performed on silica gel H (10–40μ. Hai Yang Chemical Factory of Qingdao).

The reagents and solvents were available commercially and purified according to conventional methods. *General procedure for synthesis of 1,4-diphenyl-1,4,2-diazaphospholidin-5-one-2-oxides* (**4**) Diphenylurea (2.12g, 0.01mol), triphenyl phosphite (3.10g, 0.01mol) and anhydrous toluene (15ml) 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 mole of substituted benzaldehydes (**3**) slowly at ambient temperature. The stirring was kept for 1h, then the solution was heated under reflux at 100–110°C for 6–8 h. After cooling, the mixture was filtered to yield the crude product that was recrystallized from toluene, compounds **4** were further purified by silica gel column chromatography using petroleum ether/dry ethyl ether mixtures as eluent. The physical and chemical data of compounds **4** are listed in Table I.

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