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A Convenient Synthesis of Phosphorines and Phospholidins by *Lawesson*'s Reagent and Microwave Irradiation

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Summary. A new and simple method for the synthesis of 1,3,2-diazaphosphorines and 1,3,2-oxazaphosphorine was developed based on the reactions of *Lawesson*'s reagent with β-aminopropionitriles and β-hydroxypropionitrile. In addition, a rapid and facile synthesis of 1,3,2-diazaphospholidin-4-ones by the reaction of $P(NEt_2)_3$ with hindered diamino substrates under microwave irradiation was also achieved. The prepared phosphorines show herbicidal activity to some extent in the preliminary bioassays.

Keywords. Phosphorine; Diazaphospholidin; *Lawesson*'s reagent; Microwave; Herbicidal activity.

Introduction

Phosphorus heterocycles continue to attract a great interest because of the diversity of structures and the biological activities they present [1, 2]. Many classes of phosphorus heterocyclic compounds bearing P-O or P-N moieties have proven to be important biological molecules [3–5]. The bioactivity of these heterocyclic compounds may be associated with the particular arrangement of heteroatoms and the size of the ring [6]. This point of view prompts us to exploit continuously new methodologies for the synthesis of more structurally different phosphoroheterocycles and to study their biological activities. Recently, we have been attracted by the versatility and synthetic applicability of *Lawesson*'s reagent (2,4-bis(*p*-methoxyphenyl)-1,2,3,4-dithiadiphosphetane-2,4-disulfide) in construction of functionalized phosphoroheterocycles [7–10]. In order to establish access to more functional phosphorus heterocycles with this convenient method, in this paper the reactions of *Lawesson*'s reagent with β-aminopropionitriles and β-hydroxypropionitrile were examined.

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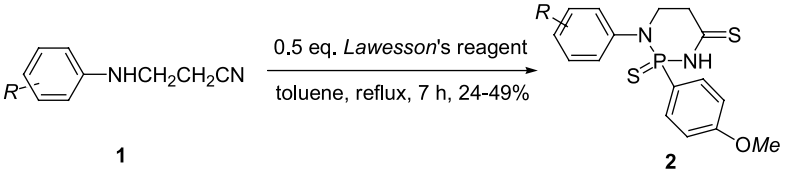
On the other hand, a convenient method for the synthesis of 1,3,2-diazaphospholidin-4-ones has been developed by using microwave technology. It is reported that 1,3,2-diazaphospholidin-4-one (or thione) derivatives have interesting biological activities, such as herbicidal and fungicidal properties [11, 12]. Their potential application as agricultural chemicals has attracted considerable attention. A literature search revealed that only a few synthetic ways to those heterocycles have been published [13–17]. Most of them involved the reaction of $P(NEt_2)_3$ with substituted glycinamides [12, 17]. However, in those cases the yields of the products are rather low due to the poor reactivity of the amino groups and the steric effect of substituents. Moreover, long reaction times are often required. Therefore, there is still an urgent need to exploit new methodologies for the synthesis of such heterocycles. Recently, microwave-promoted synthesis of 1,3,2-diazaphospholidin-4-ones was performed successfully in our laboratory. To the best of our knowledge, there is no microwave-aided synthesis of phosphorus heterocycles reported until now. Hereby we wish to describe the convenient synthesis of some phosphorines by *Lawesson*'s reagent together with the microwave-accelerated synthesis of 1,3,2-diazaphospholidin-4-ones.

Results and Discussion

Synthesis of Phosphorines by Lawesson's Reagent

The starting materials *N*-aryl-β-aminopropionitriles **1** were routinely prepared according to literature by *Michael* reaction of amines with acrylonitrile in the presence of $Cu(OAc)_2$ as catalyst [18, 19]. The reaction of **1** with *Lawesson*'s reagent in a molar ratio of 2 to 1 in refluxing toluene for 7 h readily afforded the six-membered 1,3,2-diazaphosphorine-4-thione 2-sulfides **2**, as depicted in Scheme 1. Attempts to optimize the reaction conditions revealed that half an equivalent of *Lawesson*'s reagent was sufficient to transform β-aminopropionitriles into **2** with yields of 24–49%, whereas with an excess of *Lawesson*'s reagent (>0.5 eq.) the yields of the expected products were not improved. Additionally, we found that the reaction temperature was a decisive factor for the formation of desired products. In the range of 90–110°C the reaction proceeded smoothly as expected, whereas at lower temperatures (≤ 80°C) no product was observed.

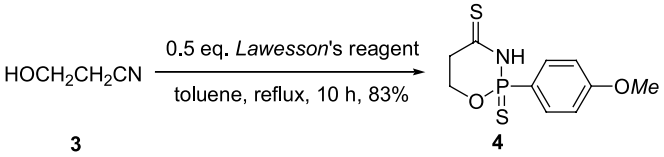
Compounds **2** were characterized by spectroscopy and microanalysis. For each of the compounds **2**, its ^{31}P NMR spectrum showed a pair of peaks, indicating the



1
1a: *R*= H
1b: *R*= *p-Me*
1c: *R*= *m-Me*
1d: *R*= *o-Me*

2
2a: *R*= H
2b: *R*= *p-Me*
2c: *R*= *m-Me*
2d: *R*= *o-Me*

Scheme 1



3 4

Scheme 2

existence of nearly equal amounts of conformational isomers (the ratio of isomers was measured by integration of signals in the ^{31}P NMR spectrum of the isolated crude product). Its ^{1}H NMR spectrum further confirmed this point on the basis of two existing single peaks around $\delta = 3.80$ ppm corresponding to a methoxy group and a pair of peaks close to 2.2 ppm corresponding to the methyl substituent on the phenyl ring.

The reaction of β-hydroxypropionitrile (**3**), which was prepared by treatment of 2-bromoethanol with sodium cyanide [20], with *Lawesson*'s reagent was also examined under similar conditions as shown in Scheme 2. After a prolonged reaction time (10 h), the expected 1,3,2-oxazaphosphorine **4** was obtained by column chromatography in 83% yield. The structure of **4** was elucidated by ^{1}H NMR, ^{31}P NMR, EI-MS, and elemental analysis. Its ^{31}P NMR spectrum showed a pair of peaks (71.15 and 71.71 ppm) and its ^{1}H NMR spectrum exhibited two single peaks ($\delta = 3.84$ and 3.82 ppm) corresponding to the methoxy moiety, implying the existence of two conformational isomers.

The preliminary bioassays indicated that the synthesized phosphoroheterocycles possessed herbicidal activity below 100 and 10 mg/dm^3. The testing of herbicidal activity was conducted upon the plants *Brassica campestris* and *Echinochloa*, and the results are summarized in Table 1.

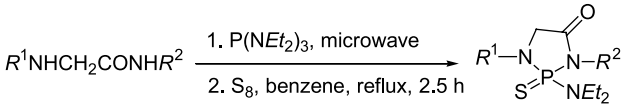
Microwave-Assisted Synthesis of 1,3,2-Diazaphospholidins

According to literature [12, 17], the cyclization of P(N*Et*$_2$)$_3$ with intermediate **5** (0.7 eq.) mainly depends on both the size of the substituents (R^1 and R^2) and the reactivity of the two amino groups. The present intermediates **5** do have bulky

Table 1. Herbicidal activity of **2a**–**2d** and **4**

No.	A/%		B/%	
	C	D	C	D
2a	0	0	14.6	0
2b	0	0	36.5	16.8
2c	18.4	8.6	20.8	0
2d	26.5	17.8	23.7	0
4	6.1	0	28.1	0

A: inhibition against *Brassica campestris*, B: inhibition against *Echinochloa*, C: bio-testing concentration 100 mg/dm^3, D: bio-testing concentration 10 mg/dm^3



5 6

Scheme 3

Table 2. Results under microwave irradiation conditions

Compounds	R^1	R^2	t/min	Yield/%
6a	*Ph*	*Ph*	1.5	62.3
6b	*m-Me-Ph*	*Ph*	1.5	60.5
6c	Isoindolylacetyl	*Ph*	1.5	43.7
6d	*p-Me-Ph*OCH(*Me*)CO	*Ph*	1.5	66.5
6e	*Ph*OCH(*Me*)CO	*Ph*	1.5	68.8

substituents and poorly reactive amino groups, which are unfavorable for the cyclization even at high temperatures for a long reaction time. However, by means of microwave irradiation this cyclocondensation easily proceeded. After thiation of the trivalent phosphorus intermediate, it was found that the products could be easily isolated and purified, and the yields of the products **6** were much higher than that previously reported. The reaction appeared to be clean and rapid. Table 2 illustrates the results. In comparison with the reported methodology, microwave-aided reaction appeared to be simple, convenient, and effective for the synthesis of 1,3,2-diazaphospholidin-4-ones.

In conclusion, a convenient synthesis of 1,3,2-diazaphosphorines and 1,3,2-oxazaphosphorine was achieved by the reaction of β-aminopropionitriles and β-hydroxypropionitrile using *Lawesson*'s reagent. The preliminary bioassays show that the prepared phosphorines possess herbicidal activity to some degree. In addition, a simple, convenient, and fast reaction of tris(diethylamino)phosphine with hindered substrates with diamino groups was performed under microwave irradiation, affording comparatively higher yields of desired 1,3,2-diazaphospholidins than by conventional heating.

Experimental

All reagents were obtained commercially and used without further purification unless otherwise indicated. Toluene was dried over sodium before use. Melting points were determined with a model YANACO MP-500 apparatus and are uncorrected. IR spectra were recorded on a SHIMADZU-435 spectrometer. The ^{1}H and ^{31}P NMR spectra were recorded on a BRUKER AC-P200 instrument. Tetramethylsilane (*TMS*) was used as an internal standard for ^{1}H NMR, and 85% phosphoric acid (H_3PO_4) was used as an external standard for ^{31}P NMR spectroscopy. Elemental analyses were carried out on a Yanaco MT-3 instrument. They were found to agree favorably with the calculated values. EI-MS spectra were recorded with a VG-7070E spectrometer. Column chromatography was performed using silica gel H (10–40 μm, Haiyang Chemical Factory of Qingdao, China). Microwave-promoted reaction was carried out on Soxwave 100 unit (Prolab co., Environmental Technology Centre, Environmental Canada). *Lawesson*'s reagent was synthesized according to Ref. [21].

General Procedure for the Synthesis of Compounds ***2***

A suspension of 4 mmol of β-aminopropionitrile **1** and 2 mmol of *Lawesson*'s reagent in a 25 cm^3 of anhydrous toluene in a 50 cm^3 flask was heated with vigorous stirring. The reaction was allowed to reflux for 7 h and then cooled to room temperature. The solvent was removed by evaporation at reduced pressure and the residue was subjected to chromatography by a silica gel column using a mixture of ethyl acetate and petroleum ether (1/1, *v*/*v*) as eluent, affording the desired product ($R_f = 0.2$). Further recrystallization of the crude product from a mixture of chloroform and petroleum ether (1/5, *v*/*v*) gave a white solid.

1-Phenyl-2-(4-methoxy)phenyl-1,3,2-diazaphosphorine-4-thione 2-sulfide
(**2a**, $C_{16}H_{17}N_2OPS_2$)

Yield 49%; mp 189–191°C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 8.56$ (br, NH), 7.86–6.95 (m, H_{arom}), 3.90 (s, OCH_3, isomer), 3.80 (s, OCH_3), 3.56–2.95 (m, CH_2CH_2) ppm; ^{31}P NMR (81 MHz, $CDCl_3$): $\delta = 56.58$, 52.11 ppm; IR (KBr): $\bar{\nu} = 3391$, 3343 (ν_{N-H}), 1529 ($\nu_{C=S}$), 1464, 1493, 1582 (ν_{Ar}), 627 ($\nu_{P=S}$) cm^{-1}.

1-(4-Methyl)phenyl-2-(4-methoxy)phenyl-1,3,2-diazaphosphorine-4-thione 2-sulfide
(**2b**, $C_{17}H_{19}N_2OPS_2$)

Yield 24%; mp 134–136°C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 8.65$ (br, NH), 7.96–6.90 (m, H_{arom}), 3.89 (s, OCH_3, isomer), 3.81 (s, OCH_3), 3.42–2.87 (m, CH_2CH_2), 2.31 (s, CH_3, isomer), 2.23 (s, CH_3) ppm; ^{31}P NMR (81 MHz, $CDCl_3$): $\delta = 56.27$, 51.46 ppm; EI-MS: m/z (%) = 362 (M^+, 100), 329 (M^+-HS, 80), 276 (17), 223 (30), 159 (36), 144 (51), 139 (27), 107 (30), 91 (57), 77 (26), 63 (29).

1-(3-Methyl)phenyl-2-(4-methoxy)phenyl-1,3,2-diazaphosphorine-4-thione 2-sulfide
(**2c**, $C_{17}H_{19}N_2OPS_2$)

Yield 25%; mp 180–182°C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 8.52$ (br, NH), 7.96–6.88 (m, H_{arom}), 3.88 (s, OCH_3, isomer), 3.81 (s, OCH_3), 3.52–2.82 (m, CH_2CH_2), 2.23 (s, CH_3, isomer), 2.14 (s, CH_3) ppm; ^{31}P NMR (81 MHz, $CDCl_3$): $\delta = 56.42$, 51.47 ppm.

1-(2-Methyl)phenyl-2-(4-methoxy)phenyl-1,3,2-diazaphosphorine-4-thione 2-sulfide
(**2d**, $C_{17}H_{19}N_2OPS_2$)

Yield 27%; mp 167–169°C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 8.57$ (br, NH), 7.94–6.86 (m, H_{arom}), 3.87 (s, OCH_3, isomer), 3.80 (s, OCH_3), 3.50–2.78 (m, CH_2CH_2), 2.35 (s, CH_3, isomer), 2.22 (s, CH_3) ppm; ^{31}P NMR (81 MHz, $CDCl_3$): $\delta = 56.45$, 51.32 ppm.

2-(p-Methoxy)phenyl-1,3,2-oxazaphosphorine-4-thione 2-sulfide (**4**)

To a solution of 5 mmol of β-hydroxypropionitrile in 20 cm^3 of anhydrous toluene was added 2.5 mmol of *Lawesson*'s reagent. The resulting mixture was subsequently refluxed with vigorous stirring for 10 h and then cooled to room temperature. The solvent was evaporated under reduced pressure and the residue was subjected to column chromatography using a mixture of ethyl acetate and petroleum ether (2/1, *v*/*v*) as eluent, giving 1.13 g of a yellow sticky oil. Yield 83%; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 8.32$–7.82 (m, H_{arom}), 7.02–6.94 (m, H_{arom}), 3.24–2.69 (m, CH_2CH_2), 3.84 (s, OCH_3, isomer), 3.82 (s, OCH_3) ppm; ^{31}P NMR (81 MHz, $CDCl_3$): $\delta = 71.15$, 71.71 ppm; EI-MS: m/z (%) = 273 (M^+, 35), 240 (100) 208 (23), 187 (34), 172 (20), 139 (34), 108 (50), 77 (17), 63 (18).

1,3,2-Diazaphospholidin-4-ones (**6**)

To a dry glass tube (20 cm × 1.5 cm) was added 2.5 mmol of **5** and 1 cm^3 of $P(NEt_2)_3$. The mixture was then placed into the microwave reactor. After irradiation by microwave under a controlled program at 250°C for 1.5 min, the reaction mixture became homogeneous. The solution was then poured into a 100 cm^3 flask with addition of 30 cm^3 of anhydrous benzene and 0.1 g of S_8. The mixture was then refluxed with stirring for another 2.5 h. The products **6** were obtained by flash chromatography using a mixture of ethyl acetate and petroleum ether (1/3, *v*/*v*) as eluent and purified by recrystallization from a mixture of chloroform and petroleum ether (1/4, *v*/*v*).

1,3-Diphenyl-2-diethylamino-1,3,2-diazaphospholidin-4-one 2-sulfide (**6a**, $C_{18}H_{22}N_3OPS$)

Colorless crystals, mp 134–136°C, yield 62.3%; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.45$–7.15 (m, H_{arom}), 4.34 (qq, $J_{H-H} = 3.42$ Hz, $^3J_{P-H} = 7.68$ Hz, CH_2), 3.68–3.40 (m, CH_2), 3.24–2.88 (m, CH_2), 0.78 (t, $^3J_{H-H} = 7.42$ Hz, $2CH_3$) ppm.

1-(m-Methyl)phenyl-3-phenyl-2-diethylamino-1,3,2-diazaphospholidin-4-one 2-sulfide (**6b**, $C_{19}H_{24}N_3OPS$)

Colorless crystals, mp 114–116°C, yield 60.5%; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.45$–6.86 (m, H_{arom}), 4.33–4.29 (m, CH_2), 3.68–3.31 (m, CH_2), 3.22–2.89 (m, CH_2), 2.34 (s, CH_3), 0.81 (t, $J_{H-H} = 7.68$ Hz, $2CH_3$) ppm.

1-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)acetyl-3-phenyl-2-diethylamino-1,3,2-diazaphospholidin-4-one 2-sulfide (**6c**, $C_{22}H_{23}N_4O_4PS$)

Colorless crystals, mp 226–228°C, yield 43.7%; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.92$–7.01 (m, H_{arom}), 5.23 (d, $^2J_{H-H} = 5.48$ Hz, $C\mathbf{H}_aH_b$), 4.68 (q, $^2J_{H-H} = 13.5$ Hz, $^3J_{P-H} = 15.6$ Hz, $C\mathbf{H}_CH_d$), 4.41 (d, $^2J_{H-H} = 5.48$ Hz, $CH_a\mathbf{H}_b$), 4.07 (q, 1H, $^2J_{H-H} = 13.50$ Hz, $^3J_{P-H} = 15.7$ Hz, $CH_C\mathbf{H}_d$), 3.64–3.02 (dm, $2CH_2$), 1.04 (t, $^3J_{H-H} = 7.02$ Hz, $2CH_3$) ppm; ^{31}P NMR (81 MHz, $CDCl_3$): $\delta = 59.02$ ppm; MS: *m*/*z* (%) = 470 (M^+, 2), 437 (5), 366 (24), 188 (4), 179 (5), 160 (52), 122 (10), 104 (6), 72 (100), 56 (15).

1-(2-p-Tolyloxy-propionyl)-3-phenyl-2-diethylamino-1,3,2-diazaphospholidin-4-one 2-sulfide (**6d**, $C_{22}H_{28}N_3O_3PS$)

Colorless crystals, mp 108–110°C, yield 66.5%; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.44$–6.79 (m, H_{arom}), 5.55 (brs, OCH), 4.44 (d, $^3J_{P-H} = 5.72$ Hz, $NCH_2C{=}O$), 3.41–2.64 (dm, $N(C\mathbf{H}_2CH_3)_2$), 2.25 (s, CH_3), 1.61 (d, $^3J_{H-H} = 6.26$ Hz, $OCHC\mathbf{H}_3$), 0.85–0.71 (m, $N(CH_2C\mathbf{H}_3)_2$) ppm.

1-(2-Phenoxy-propionyl)-3-phenyl-2-diethylamino-1,3,2-diazaphospholidin-4-one 2-sulfide (**6e**, $C_{21}H_{26}N_3O_3PS$)

Colorless crystals, mp 179°C, yield 68.8%; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.40$–6.93 (m, H_{arom}), 5.67 (brs, OCH), 4.45 (d, $^3J_{P-H} = 5.82$ Hz, $NCH_2C{=}O$), 3.38–2.63 (dm, $N(C\mathbf{H}_2CH_3)_2$), 1.63 (d, $^3J_{H-H} = 6.06$ Hz, $CHC\mathbf{H}_3$), 0.86–0.73 (m, $N(CH_2C\mathbf{H}_3)_2$) ppm.

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References

[1] a) Ashley GW, Bartlett PA (1982) Biochim Biophys Acta **108**: 1467; b) Liotta LJ, Gibss RA, Taylor SD, Benkovic PA, Benkovic SJ (1995) J Am Chem Soc **117**: 4729
[2] a) Hewitt DG, Newland GL (1997) Aust J Chem **30**: 579; b) Zhou J, Qiu Y, Feng K, Chen R (1999) Synthesis **1**: 40; c) Karp GM (1999) J Org Chem **64**: 8156
[3] a) Brassfield HA, Jacobson RA, Verkade JG (1975) J Am Chem Soc 4143; b) Gilard V, Martino R, Malet-Martino M, Niemeyer U, Pohl J (1999) J Med Chem **42**: 2542
[4] Darrow JW, Drueckhammer DG (1994) J Org Chem **59**: 2976
[5] Morita I, Kunimoto K, Tsuda M, Tada S-I, Kise M, Kimura K (1987) Chem Pharm Bull **35**: 4144
[6] Hetherington L, Greedy B, Gouverneur V (2000) Tetrahedron **56**: 2053
[7] Pedersen BS, Lawesson S-O (1979) Tetrahedron **35**: 2433
[8] Testa MG, Perrini G, Chiacchio U, Corsaro A (1994) Phosphorus Sulfur Silicon Relat Elem **86**: 75
[9] Deng SL, Liu DZ (2001) Synthesis **16**: 2445
[10] Deng SL, Chen RY (2002) Synthesis **17**: 2527
[11] He LN, Zhuo RX, Chen RY, Li K, Zhang YJ (1999) Heteroatom Chem **10**: 105
[12] Deng SL, Chen RY, Yang XF (2000) Chem J Chinese Univ **21**: 1679
[13] Korshin EE, Eliseenkova RM, Zyablikova TA, Zakharova LG, Akhmadullin AG, Nusinovich VD, Levin YaA (1993) Izv Akad Nauk Ser Khim **6**: 1116
[14] Chen RY, Li CX, Wang HG, Yao XK (1991) Chinese J Struct Chem **10**: 52
[15] Mulliez M (1985) Bull Soc Chim Fr **6**: 1211
[16] He LN, Cai F, Qin XH, Li K (1997) Chin Chem Lett **8**: 751
[17] Deng SL, Chen RY, Yang XF (2001) Chin J Appl Chem **18**: 647
[18] John CS (1958) Organic Synthesis, vol 38. John Wiley & Sons, New York, p 14
[19] Braunholtz JT, Mann FG (1952) J Chem Soc 3046
[20] Gilman H (1941) Org. Syn. Coll, vol. I. John Wiley & Sons, New York, p 256
[21] Pederson BS, Scheibye S, Nilsson NH, Lawesson SO (1978) Bull Soc Chim Belg **87**: 223