Heteroatom Chemistry
Volume 12, Number 6, 2001

Synthesis of Derivatives of 1,3,2-Diazaphospholidin-4-ones and the Corresponding 2-Sulfides

Liangnian He,[1] Yanping Luo,[1,3] Mingwu Ding,[1] Aihong Lu,[1] Xiaopeng Liu,[2] Tianjie Wu,[2] and Fei Cai[2]

[1]*Institute of Organic Synthesis, Central China Normal University, Wuhan, 430079, P. R. China*

[2]*Center of Analysis and Testing, Central China Normal University, Wuhan, 430079, P. R. China*

[3]*College of Plant Protection, South China University of Tropical Agriculture, Danzhou, Hainan, 571737, P. R. China*

Received 13 December 2000; revised 26 February 2001

ABSTRACT: *Aromatic-substituted derivatives of 1,3,2-diazaphospholidin-4-ones* **2a–g** *were readily prepared from 1,3-diaryl glycinamides* **1** *by the reaction with hexaethylphosphoric triamide. Their chemical transformation was selectively effected with different thionation reagents to afford thionated products at the phosphorus atom to give* **3a–g** *and at the carbonyl group to give* **4a**. *An oxidation reaction at phosphorus to produce* **5a** *was effected with 10% hydrogen peroxide. Preliminary bioassays revealed that some of the title compounds,* **2a–g** *and* **3a–g**, *possess selective herbicidal activity against rape.* © 2001 John Wiley & Sons, Inc. Heteroatom Chem 12:497–500, 2001

INTRODUCTION

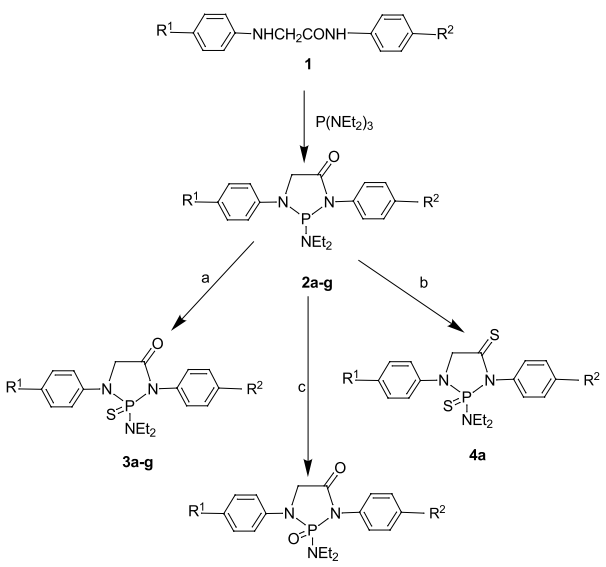
In recent years, our research interest has focused on the development of new synthetic methodology centered around biologically active phosphorus heterocycles [1] because such products are of great interest as bioactive substances [2–6]. In preceding articles [1], we disclosed a methodology for the synthesis of phosphorus heterocycles with biological activity by use of Lawesson's reagent, 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disufide, with bifunctional substrates. This procedure has been applied to glycinamides for the preparation of derivatives of 1-aryl-1,3,2-diazaphospholidin-4-thione-2-sulfides, which were found to have significant herbicidal activity [1,7,8]. In addition, phosphoramides, such as hexamethylphosphoric triamide and hexaethylphosphoric triamide, are known to have extensive applications in organic chemistry [9], and 1,3-diaryl glycinamides **1** have been found to have good biological activity [1,7]. We report in this article the synthesis of 1,3-diaryl-2-diethylamino-1,3,2-diazaphospholidin-4-ones **2a–g** by reaction of hexaethylphosphoric triamide with 1,3-diaryl glycinamides and the subsequent chemical conversions of these compounds with thionation reagents and an oxidation agent.

RESULTS AND DISCUSSION

1,3-Diaryl glycinamides **1** were treated with an excess of hexaethylphosphoric triamide at 100°C

Correspondence to: Present address: Department of Molecular Engineering, National Institute of Materials and Chemical Research, 1-1 Higashi, Tsukuba, Ibaraki 305-8565, Japan; Fax: +81 298 61 4511; E-mail: helini@nimc.go.jp

Contract Grant Sponsor: Dawn Plan of Science and Technology for Young Scientists of Wuhan City.
Contract Grant Sponsor: Natural Science Foundation of Hubei Province.



(a) R^1, R^2 = H, H; (b) *p*-Me,*p*-Cl; (c) *p*-Cl, H; (d) *p*-Cl, *p*-Me; (e) *p*-Cl, *p*-Cl; (f) *p*-Br, H; g: *p*-Br, *p*-Me.

(a) s_8, benzene, reflux; (b) Lawesson's reagent, toluene, reflux; (c) H_2O_2, r,t.

SCHEME 1

under nitrogen for 5–7 hours to afford 1,3-diaryl-2-diethylamino-1,3,2-diazaphospholidin-4-ones **2a–g** in good yields, as depicted in Scheme 1.

Furthermore, 1,3-diaryl-2-diethylamino-1,3,2-diazaphospholidin-4-one-2-sulfides **3a–g** were obtained by in situ thionation with 2 molar equivalents of sulfur under nitrogen in benzene at 80°C for 4 hours, and **2a** was treated with more than 2 mol of Lawesson's reagent in anhydrous toluene at 100°C under a nitrogen atmosphere for 10 hours to form 1,3-diaryl-2-diethylamino-1,3,2-diazaphospholidin-4-thione-2-sulfide **4a**, which is a product thionated at both the phosphorus atom and at the carbonyl group. Compound **2a** is readily converted to the corresponding oxygenated product 1,3-diaryl-2-diethylamino-1, 3, 2-diazaphospholidin-4-one-2-oxide, **5a**, by in-situ oxidation with 10% hydrogen peroxide at room temperature in acetone in a yield of 70% (Scheme 1).

All the new compounds were identified satisfactorily by analytical results and spectral data, IR NMR, and mass spectrometry, as listed in Tables 1 and 2. Compound **2a** (taken as a representative example) gave correct elemental analyses, and the IR spectrum of **2a** showed peaks at 1670 cm^{-1} (C=O), 1150 cm^{-1} (P–N), and 3030 cm^{-1} (C–H). The ^1H NMR spectrum exhibited (δ_H in $CDCl_3$) a triplet at 0.75–0.87 (t, 6H, $2 \times CH_3$), three kinds of multiplet's at 6.87–7.52 (m, 10H, aromatic protons,

TABLE 1 Physical Properties and IR Spectra for Compounds **2a–g** and **3a–g**

Entry	*State*	*m.p. (°C)*	*Yield (%)*	*IR (cm^{-1})*
2a	White crystal	117–119	67	3030, 1670, 1150
2b	White powder	123–125	63	3035, 1672, 1155, 735
2c	White powder	120–122	60	3033, 1665, 1150, 763
2d	White powder	100–103	61	3035, 1687, 1139, 729
2e	White powder	156–158	52	3034, 1719, 1179, 678
2f	White powder	112–113	58	3025, 1699, 1138, 547
2g	Brown powder	117–119	64	3082, 1720, 1140, 550
3a	Colorless crystal	128–129	70	1714, 1590, 1025, 745
3b	Colorless crystal	190–191	72	1720, 1565, 1050, 728
3c	Colorless crystal	150–151	70	1725, 1574, 1055, 730
3d	Colorless crystal	165–167	52	1710, 1590, 1020, 755
3e	Brown powder	148–149	57	1710, 1590, 1050, 750
3f	Colorless crystal	164–165	65	1720, 1595, 1065, 755
3g	Yellow crystal	176–177	59	1720, 1595, 1060, 760

Ar-H), 4.21–4.41(m, 2H, CH_2 in the ring of 5-membered P-heterocycle), 2.87–3.12 (m, 4H, $\underline{CH_2}CH_3$). The ^{31}P NMR spectrum ($CDCl_3$) showed a singlet peak: δ_P 107.18. The EI-MS spectra showed *m/z* (%): 327 (M^+, 44.69).

Preliminary biological screening of these compounds was carried out. 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. The results indicated that some of title compounds **2a–g** and **3a–g** have significant selective herbicidal activity against rape. A systematic survey of the biological activity and chemical properties of 1,3-diaryl-2-diethylamino-1,3,2-diazaphospholidin-4-ones and their related derivatives is under way.

EXPERIMENTAL

Melting points were determined with a model X_4 apparatus and were uncorrected. ^1H NMR spectra and ^{31}P NMR spectra were recorded on a Varian XL-200

TABLE 2 ^{1}H NMR and ^{31}P NMR and MS data for compounds **2a–g** and **3a–g**

Entry	*^{1}H NMR δ_H ($CDCl_3$)*	*^{31}P NMR δ_P ($CDCl_3$)*	*EI-MS m/z (%)*
2a	0.75–0.87 (t, 6H, 2 × CH_3), 2.87–3.12 (m, 4H, 2 × CH_2, $^3J_{PH}$ = 9.4 Hz), 4.21–4.41 (m, 2H, CH_2 in the ring), 6.87–7.52 (m, 10H, Ar-H).	107.18	327 (M^+, 44.69), 255 (84.27), 122(100), 105 (20.37), 77 (54.19), 72 (9.36)
2b	0.78–0.85 (t, 6H, 2 × CH_3), 2.29 (s, 3H, Me), 2.91–3.09 (m, 4H, 2 × CH_2,$^3J_{PH}$ = 9.5 Hz), 4.17–4.38 (m, 2H, CH_2 in the ring), 6.8–7.5 (m, 8H, Ar-H).	107.10	375 (M^+, 62.02), 303 (100), 156 (96.50), 91 (52.23), 119 (39.30), 72 (13.12)
2c	0.75–0.82 (t, 6H, 2 × CH_3), 2.86–3.10 (m, 4H, 2 × CH_2, $^3J_{PH}$ = 9.4 Hz), 4.08–4.36 (m, 2H, CH_2 in the ring), 6.85–7.47 (m, 9H, Ar-H).		361 (M^+, 13.51), 289 (20.77), 122 (100), 139 (10.96), 77 (64.32), 72 (12.56)
2d	0.77–0.88 (t, 6H, 2 × CH_3), 2.96–3.11 (m, 4H, 2 × CH_2,$^3J_{PH}$ = 9.1Hz), 4.16–4.33 (m, 2H, CH_2), 7.02–7.34 (m, 8H, Ar-H), 1.29 (s, 3H, Me).	107.25	375 (M^+, 21.00), 303 (27.65), 136 (74.96), 91 (100), 72 (30.67)
2e	0.77–0.84 (t, 6H, 2 × CH_3), 2.93–.08 (m, 4H, 2 × CH_2, $^3J_{PH}$ = 9.0 Hz), 4.14–4.35 (m, 2H, CH_2), 6.84–7.38 (m, 8H, Ar-H).		395 (M^+, 47.90), 322 (82.65), 324 (54.82), 156 (100), 139 (43.75), 111 (40.07)
2f	0.71–0.82 (t, 6H, 2 × CH_3), 2.86–3.10 (m, 4H, 2 × CH_2, $^3J_{PH}$ = 9.6 Hz), 4.15–4.28 (m, 2H, CH_2), 6.81–7.46 (m, 9H, Ar-H).	106.38	405 (M^+, 42.29), 333 (79.71), 335 (80.63), 122 (100), 185 (23.22), 77 (24.66)
2g	0.77–0.84 (t, 6H, 2 × CH_3), 2.90–3.16 (m, 4H, 2 × CH_2, $^3J_{PH}$ = 9.2 Hz), 4.12–4.25 (m, 2H, CH_2), 6.78–7.40 (m, 8H, Ar-H), 2.34 (s, 3H, Me).	105.97	419 (M^+, 49.95), 347 (95.73), 349 (95.67), 136 (100), 183 (28.41), 91 (39.53)
3a	0.57–0.67 (t, 6H, 2 × CH_3), 2.98-3.20 (m, 4H, 2 × CH_2), 4.15–4.20 (m, 2H, CH_2 in the ring), 6.85–7.31 (m, 10H, Ar-H)	62.90	359 (M^+, 23.92), 287 (4.87), 255 (86.4), 154 (20.57), 122 (85.64), 72 (100)
3b	0.76–0.86 (t, 6H, 2 × CH_3), 2.98–3.32 (m, 4H, 2 × CH_2), 4.26–4.32 (m, 2H, CH_2 in the ring), 7.10–7.46 (m, 8H, Ar-H).	62.86	407 (M^+, 38.64), 409 ($M^+ + 2$,14.66), 335 (4.16), 303 (100), 156 (11.90), 72 (31.15)
3c	0.75–0.82 (t, 6H, 2 × CH_3), 3.01–3.48 (m, 4H, 2 × CH_2), 4.26–4.32 (m, 2H, CH_2 in the ring), 7.10–7.44 (m, 9H, Ar-H).	62.53	393 (M^+, 49.91), 395 ($M^+ + 2$,20.61), 360 (6.65), 289 (100), 122 (30.84), 72 (27.47)
3d	0.77–0.88 (t, 6H, 2 × CH_3), 2.38 (s, 3H, CH_3), 7.09–7.34 (m, 8H, Ar-H), 2.99–3.38 (m, 4H, 2 × CH_2), 4.26–4.31 (m, 2H, CH_2 in the ring).	62.54	407 (M^+, 44.20), 409 ($M^+ + 2$,16.89),375 (4.67), 335 (6.50), 303 (100), 136 (23.78), 72 (24.01)
3e	0.76–0.86 (t, 6H, 2 × CH_3), 2.98–3.32 (m, 4H, 2 × CH_2), 4.26–4.32 (m, 2H, CH_2 in the ring), 7.10–7.46 (m, 8H, Ar-H).	62.18	427 (M^+, 34.72), 429 ($M^+ + 2$,25.23), 355 (5.27), 357 (4.54), 323 (100), 156 (14.02), 72 (34.72)
3f	0.73–0.83 (t, 6H, 2 × CH_3), 3.13–3.48 (m, 4H, 2 × CH_2), 4.27–4.32 (m, 2H, CH_2 in the ring), 7.05–7.48 (m, 9H, Ar-H).	62.51	437 (M^+, 36.30), 366 (8.83), 335 (100), 122 (28.93), 72 (25.21).
3g	0.77–0.86 (t, 6H, 2 × CH_3), 2.99–3.41 (m, 4H, 2 × CH_2), 2.39 (s, 3H, CH_3), 4.26–4.31 (m, 2H,CH2 in the ring), 7.06–7.48 (m, 8H, Ar-H)	62.42	451 (M^+, 42.86), 421 (5.14), 381 (9.42), 349 (100), 136 (22.67), 72 (22.97).

MHz spectrometer. Mass spectra were measured on a HP 5988A spectrometer. Elemental analysis was measured with a PE-2400 elementary analyzer. The IR spectra were measured by using a Shimadzu-408 instrument. Column chromatography was performed on silica gel II (10-40μ, Hai Yang Chemical Factory of Qingdao). All solvents and materials were reagent grade and purified as required. 1,3-diaryl glycinamides **1** were prepared according to the reported procedure [7,10].

*General Procedure for Synthesis of 1,3-Diaryl-2-diethylamino-1,3,2-diazaphospholidin-4-ones **2a–g***

A three-necked flask equipped with a dropping funnel, stirrer, drying $CaCl_2$ tube, and nitrogen gas inlet was charged with 1 mmol of 1,3-diaryl glycinamides **1**. Then hexaethylphosphoric triamide (10 mmol) was added dropwise to the flask at room temperature. When the addition was complete, the reaction mixture was heated and refluxed under dry nitrogen with stirring for 5–7 hours until no more of the starting materials could be detected by thin-layer chromatography (TLC). Evaporation of the solvent followed by column chromatography on silica gel using light petroleum ether (b.p. 40–60°C)–dry ethyl ether as eluent yielded the corresponding heterocycles **2a–g**. Yields were determined after separation on a silicon gel column. The structures of new compounds were confirmed by correct elemental analyses and spectral results. The physical data and IR, NMR, and MS data are listed in Tables 1 and 2.

*General Procedure for Synthesis of 1,3-Diaryl-2-diethylamino-1,3,2-diazaphospholidin-4-one-2-sulfides **3a–g***

One mmol of **2a–g** was treated with sulfur (2 mmol) in 10 mL of anhydrous benzene under dry nitrogen with stirring at reflux temperature for 4 hours until no more of the starting materials could be detected by TLC. Evaporation of the solvent under reduced pressure and purification of the products on a silicon gel column using light petroleum ether (b.p. 40–60°C)–anhydrous ethyl ether as eluent to gave **3a–g**. Yields were determined after separation on the silicon gel column. Their physical data and IR, NMR, and MS data are listed in Tables 1 and 2.

*Typical Procedure for Thionation of **2a** via Lawesson's Reagent*

A mixture of 1 mmol each of **2a** and Lawesson's reagent in anhydrous toluene was stirred at 100°C for 10 hours until no more of the starting materials could be detected by TLC. The solvent was evaporated under reduced pressure. The residue was purified by passing it through a short column with silica gel in petroleum ether and anhydrous ethyl ether to give **4a**. The yield was determined after separation on a silicon gel column. **4a**: Colorless solid, m.p. 138–139°C; yield 60%; ^{1}H NMR δ_H ($CDCl_3$): 0.59–0.65 (t, 6H, 2 × CH_3), 2.99–3.22 (m, 4H, 2 × CH_2), 4.12–4.20 (m, 2H, CH_2 in the ring), 6.95–7.34 (m, 10H, Ar-H). ^{31}P NMR δ_P ($CDCl_3$): 78.42. IR ν (KBr, cm^{-1}): 750 (P=S), 1230 (C=S), 1590, 1505, 1435 (aromatic ring). EI-MS (int.rel) *m/z* (%): 375(M^+, 50.82).

*Typical Procedure for Oxidation of **2a** by 10% Hydrogen Peroxide*

To a mixture of **2a** (1 mmol) and 20 mL of acetone was slowly added 10% hydrogen peroxide (1.2 mmol). After the vigorous exothermic reaction, the mixture was stirred for an additional 5 hours at room temperature. The acetone was allowed to evaporate, and the product was taken up in benzene, washed until peroxide free with ferrous ammonium sulfate solution, and dried. Evaporation of the benzene left **5a** as a crystalline solid. Further purification was effected by recrystallization from methanol and ethyl ether. m.p. 110–111°C; yield 70%; ^{1}H NMR δ_H ($CDCl_3$): 0.60–0.69 (t, 6H, 2 × CH_3), 3.01–3.21 (m, 4H, 2 × CH_2), 4.12–4.18 (m, 2H, CH_2 in the ring), 6.90–7.30 (m, 10H, Ar-H). ^{31}P NMR δ_P ($CDCl_3$): 25.74. IR ν (KBr, cm^{-1}): 1150 (P=O), 1055 (P–N), 1590, 1500, 1425 (aromatic ring). EI-MS (int. rel) *m/z* (%): 343(M^+, 40.56).

REFERENCES

[1] (a) He, L.-N.; Chen, R.-Y. *Phosphorus Sulfur Silicon* 1997,129, 111–120.
(b) He, L.-N.; Zhuo, R.-X. *Heteroatom Chem* 1999, 10(2), 105–111.
(c) He, L.-N.; Zhuo, R.-X.; Li, K.; Liu, X.-P. *Phosphorus Sulfur Silicon* 1999, 147, 111.
(d) Li, K.; He, L.-N.; Qing, X. H.; Luo, Y.-P.; Ding, M.-W. *Heterocyclic Comm* 1999, 5(2), 189–192.

[2] Quin, D. L. *The Heterocyclic Chemistry of Phosphorus*, Wiley & Sons: New York, 1981; pp 82–96.

[3] Prishchenko, A. A.; Livantsov, M. V. *In Abstracts of XIVTH International Conference on Phosphorus Chemistry*, July 12–17, 1998, Cincinnati, Ohio, p 213.

[4] Cava, M. P.; Levinson, M. I. *Tetrahedron* 1985, 41, 5061–5087.

[5] Cherkasov, R. A.; Kutyrev, G. A.; Pudovik, A. N. *Tetrahedron* 1985, 41, 2588–2624.

[6] Shabann, R.; Osman, F. H.; Atress, S. S. *Tetrahedron* 1994, 50, 6975–6988.

[7] Li, K.; Luo, Y.-P.; He, L.-N. Journal of *Central China Normal University (Nat. Sci. Ed)* 2000, 34(1), 53–57.

[8] He, L.-N.; Li, K.; Liu, X.-P.; Luo,Y.-P.; Lu, A.-H.; Ding, M.-W. *Phosphorus Sulfur Silicon* 2000, 158, 117–123.

[9] Denmark, S. E.; Su, X.; Nishigachi, Coe, Y.; D. M.; Wong, K.-T.; Winter, S. B. D.; Choi, J. Y. *J Org Chem* 1999, 64, 1958–1967.

[10] (a) Takeda, A. *J Org Chem* 1957, 22, 1096–1103. (b) Meriwether, L.; Wetheimer, F. H. *J Am Chem Soc* 1956, 78, 5119–5123.