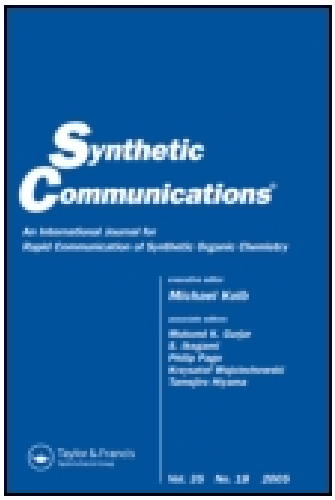

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A CONVENIENT AND EFFICIENT SYNTHESIS OF NOVEL 1-ETHOXYCARBONYLMETHYL-3-ETHYL-1,2,3,4-TETRAHYDRO-4-OXO-1,3,2-BENZODIAZAPHOSPHORIN-2-CARBOXAMIDE 2-OXIDES

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ABSTRACT

Some novel 1-ethoxycarbonylmethyl-3-ethyl-1,2,3,4-tetrahydro-4-oxo-1,3,2-benzodiazaphosphorin-2-carboxamide 2-oxides containing α-amino acid ester or α-aminophosphonate groups have been designed incorporating the proximate carbonyl and phosphoryl groups into the benzoannulated phosphidiamide heterocycle and synthesized by a convenient one-pot procedure in good yields, in which the hydrochlorides of α-amino acid esters or hydrobromides of α-aminophosphonates reacted smoothly with *bis*(trichloromethyl) carbonate with the help of four molar equivalents of triethylamine to give the corresponding isocyanates that then formed the products by the addition with the phosphorus reagent containing a P–H bond.

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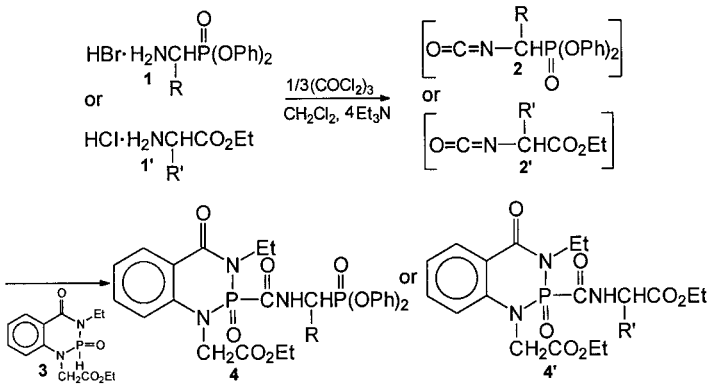
Key Words: Synthesis; 1,3,2-Benzodiazaphosphorin; α-ketophosphonates

During the past two decades, α-ketophosphonates and their derivatives have attracted considerable attention because these compounds are endowed with special physical, chemical and pharmacological properties due to the proximity of the carbonyl and the phosphoryl groups.[1–7] In the study on new pharmaceuticals and agrochemicals, the application of heterocycles is suggested to improve the biological activity. Moreover, benzoannulated and related analogs of cyclophosphamide possess antitumor activity.[8–11] As a part of our ongoing program aimed at searching for novel antitumor and antiviral agents with high activity and low toxicity, some 1-ethoxycarbonylmethyl-3-ethyl-1,2,3,4-tetrahydro-4-oxo-1,3,2-benzodiazaphosphorin-2-carboxamide 2-oxides containing α-amino acid ester or α-aminophosphonate groups were designed incorporating the proximate carbonyl and phosphoryl groups into the benzoannulated phosphdiamide heterocycle and synthesized by a convenient one-pot procedure in yields of 57.2–78.6%, as shown in Scheme 1, in which the appearance of the isocyanates (**2** and **2′**) and the reaction terminal point were monitored by IR spectroscopy.



Scheme 1.

We herein wish to report a simple and direct method utilizing the addition reaction of the phosphorus reagent (**3**) containing a P–H bond with the isocyanates that were prepared in a one-pot procedure from the

amine functionality of hydrochlorides of α-amino acid esters or hydrobromides α-aminophosphonates by the action of triphosgene [*bis*(trichloromethyl) carbonate]. Isocyanates are usually prepared by phosgene gas, which requires the hazards of handling of phosgene and drastic conditions. The improved method for the preparation of isocyanates involves the use of triphosgene that is a safe and stable replacement for phosgene. The hydrochlorides of α-amino acid esters or hydrobromides α-aminophosphonates could be prepared according to literature methods,[12,13] and reacted smoothly with *bis*(trichloromethyl) carbonate with the help of four molar equivalents of triethylamine to give the corresponding isocyanates (**2** or **2′**) that then formed the title compounds by the addition with **3**.

The structure of all of the title compounds was confirmed by ^{1}H NMR, ^{31}P NMR spectra, and elemental analyses. Preliminary bioassays indicated that the title compounds (**4** and **4′**) possess significant antiviral activity against Tobacco Mosaic Virus (TMV). The evaluations for the antitumor activity and the antiviral activities against HIV, HSV and HCMV of compounds **4** and **4′** are now in progress.

When R or R′≠ H, the title compounds may be discussed by recognition of the presence of two chiral centers, e.g., CH and P, and consequently existence of a pair of diastereoisomers. ^{31}P NMR spectra exhibited doublets of the chiral P in the range of δ 3.11–4.25 accounting for the pair of diastereoisomers, while **4a′** (R′=H) and **3** gave a single peak at δ 3.90 and δ 5.31, espectively, due to the presence of only one chiral phosphorus center. The separation of the diastereoisomers was not successful by the column chromatography method. The two diastereoisomers of compound **4a** were separated by partial recrystallization, and their ^{31}P NMR data were determined as δ 3.33, 16.83 and δ 4.25, 16.83 respectively. There is no ^{31}P–^{31}P coupling between the two phosphorus atoms in the title compounds **4**. The ratios of diastereoisomers were determined by integration of suitable signals in the ^{31}P NMR spectra of the crude products, which show that, unfortunately, the synthetic reactions are not significantly stereoselective in affording the products. In the ^{1}H NMR spectra of **4** and **4′**, the two methylene protons in the 3-ethyl group of the benzodiazaphosphorine resonated as two multiplets at δ 3.55–3.73 and δ 3.82–3.92, respectively. They are magnetically nonequivalent due to their orientation in the six-membered conformation of the benzadiazaphosphorine, which has been described in previous papers.[7,11] With regard to the corresponding methylene group attached to the 1-position of the benzadiazaphosphorine, the signals appeared as two multiplets at δ 4.01–4.51 and δ 4.65–4.93 because of the same reason. The chemical shift of the H atom in CH (R=aryl) is in the range of δ 5.80–5.85. Owing to the deshielding effect of the α-(substituted) benzene ring, these chemical shifts are at much larger

values of δ than those of CH (R=alkyl and H), which are in the range of δ 4.03–4.93.

EXPERIMENTAL

Melting points were determined with a model YANACO MP-500 apparatus and are uncorrected. IR spectra were recorded on a SHIMADZU-435 spectrometer, and band positions are reported in wavenumbers (cm^{-1}). 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. The nuclei that are deshielded relative to their respective standards are assigned a positive chemical shift. Coupling constants, *J*, are given in Hz. Elemental analyses were carried out on a Yana MT-3 instrument. Column chromatography was performed using silica gel H (10–40 μm, Haiyang Chemical Factory of Qingdao).

1-Ethoxycarbonylmethyl-3-ethyl-2,3-dihydro-1,3,2-benzodiazaphosphorin-4(1H)-one 2-oxide (**3**) has been described in previous papers.[7,11]

General Procedure for the Preparation of 1-Ethoxycarbonylmethyl-3-ethyl-1,2,3,4-tetrahydro-4-oxo-1,3,2-benzodiazaphosphorin-2-carboxamide 2-Oxides Containing α-Aminophosphonate or α-Amino Acids Ester Groups (4 and 4′)

A mixture of 3.0 mmol of the hydrobromides of α-aminophosphonates or hydrochlorides of α-amino acid esters and 12.0 mmol of dry triethylamine in 20 ml of anhydrous dichloromethane was added dropwise over a period of 20 min to a solution of 1.0 mmol of *bis*(trichloromethyl) carbonate in 10 ml of anhydrous dichloromethane at the temperature of −10°C (ice–salt bath). After completion of the addition, the temperature of the reaction mixture was maintained at 0°C for half an hour, and the appearance of the isocyanate groups, N=C=O (2200–2300 cm^{-1}) was monitored by IR spectroscopy. Then, another solution of 3.0 mmol of 1-ethoxycarbonylmethyl-3-ethyl-2,3-dihydro-1,3,2-benzodiazaphosphorin-4(1H)-one 2-oxide in 10 ml of anhydrous dichloromethane was added dropwise again. The mixture continued to react at ambient temperature for 2 h. Reaction terminal points could be detected by the disappearance of the isocyanate group in IR spectroscopy. Triethylamine hydrochloride and/or hydrobromide was filtered off, and the solvent was evaporated from the filtrate under reduced

pressure to produce the crude product, which was purified by column chromatography on silica gel; the eluent solvent bears ethyl acetate/light petroleum (b.p. 60–90°C) (v/v, 1 : 1). The physical and chemical data of compounds **4** and **4′** are given as follows.

4a′: R′ = H (Gly), yield: 61.1%; m.p. 96–98°C. ^{1}H NMR (200 MHz, $CDCl_3$, δ ppm, *J* Hz): 1.04–1.43 (m, 9H, $3 \times C\mathbf{H}_3$); 3.55, 3.82 (m, 2H, $NC\mathbf{H}_2CH_3$); 4.03–4.51 (m, 7H, $1/2 \times PNC\mathbf{H}_2CO_2CH_2CH_3 + PNCH_2CO_2C\mathbf{H}_2CH_3 + NHC\mathbf{H}_2CO_2C\mathbf{H}_2CH_3$); 4.81 (dd, 1H, $1/2 \times NC\mathbf{H}_2CO_2Et$, $^2J_{HH} = 18.0$, $^3J_{PH} = 8.6$); 6.58–7.55 (m, 3H, $C_6\mathbf{H}_3$); 7.84 (br, 1H, C(O)N**H**); 8.13 (dd, 1H, the H in 5-position of the benzodiazaphosphorine system, $^3J_{HH} = 7.7$, $^4J_H = 1.6$). ^{31}P NMR (80.96 MHz, $CDCl_3$, δ ppm): 3.90. Anal. calcd for $C_{18}H_{24}N_3O_7P$: C, 50.82; H, 5.69; N, 9.88. Found: C, 50.72; H, 5.84; N, 9.93.

4b′: R′ = i-Pr (DL-Val), yield: 75.8%; syrup. ^{1}H NMR (200 MHz, $CDCl_3$, δ ppm, *J* Hz): 0.75–0.92 (m, 6H, $CH(C\mathbf{H}_3)_2$); 1.03–1.44 (m, 9H, $3 \times CH_2C\mathbf{H}_3$); 2.02 (m, 1H, $C\mathbf{H}(CH_3)_2$); 3.56, 3.87 (m, 2H, $NC\mathbf{H}_2CH_3$); 4.01–4.46 (m, 5H, $2 \times CO_2C\mathbf{H}_2CH_3 + 1/2 \times PNC\mathbf{H}_2CO_2Et$); 4.59 (m, 1H, $NHC\mathbf{H}CO_2Et$); 4.67–4.93 (m, 1H, $1/2 \times PNC\mathbf{H}_2CO_2Et$); 6.64–7.53 (m, 3H, $C_6\mathbf{H}_3$); 7.79, 7.94 (br, 1H, C(O)N**H**); 8.12 (m, 1H, the H in 5-position of the benzodiazaphosphorine system). ^{31}P NMR (80.96 MHz, $CDCl_3$, δ ppm, Ratio of diastereoisomers). 3.96; 4.08 (0.96 : 1). Anal. calcd for $C_{21}H_{30}N_3O_7P$: C, 53.96; H, 6.47; N, 8.99. Found: C, 54.12; H, 6.20; N, 8.82.

4a: R = Me, yield: 57.2%; m.p. 162–164°C. ^{1}H NMR (200 MHz, $CDCl_3$, δ ppm, *J* Hz): 1.23–1.36 (m, 6H, $2 \times CH_2C\mathbf{H}_3$); 1.45–1.60 (m, 3H, $C\mathbf{H}_3$); 3.69, 3.84 (m, 2H, $NC\mathbf{H}_2C\mathbf{H}_3$); 4.05–4.30 (m, 3H, $1/2 \times NC\mathbf{H}_2CO_2Et + CO_2C\mathbf{H}_2CH_3$); 4.65–4.92 (m, 2H, $1/2 \times NC\mathbf{H}_2CO_2Et + C\mathbf{H}$); 6.58–8.21 (m, 14H, $2 \times C_6\mathbf{H}_5 + C_6\mathbf{H}_4$); 8.3, 8.5 (br, 1H, C(O)N**H**). ^{31}P NMR (80.96 MHz, $CDCl_3$, δ ppm, Ratio of diastereoisomers): 3.33, 16.83; 4.25, 16.83 (0.98 : 1). Anal. calcd for $C_{28}H_{31}N_3O_8P_2$: C, 56.10; H, 5.21; N, 7.01. Found: C, 56.00; H, 5.45; N, 7.14.

4b: R = i-Pr, yield: 64.5%; syrup. ^{1}H NMR (200 MHz, $CDCl_3$, δ ppm, *J* Hz): 0.82–1.16 (m, 6H, $CH(C\mathbf{H}_3)_2$); 1.21–1.35 (m, 6H, $2 \times CH_2C\mathbf{H}_3$); 2.25 (m, 1H, $C\mathbf{H}(CH_3)_2$); 3.67, 3.83 (m, 2H, $NC\mathbf{H}_2CH_3$); 4.08–4.32 (m, 3H, $1/2 \times NC\mathbf{H}_2CO_2Et + CO_2C\mathbf{H}_2CH_3$); 4.66–4.93 (m, 2H, $1/2 \times NC\mathbf{H}_2CO_2Et + NHC\mathbf{H}P$); 6.60–8.23 (m, 14H, $2 \times C_6\mathbf{H}_5 + C_6\mathbf{H}_4$); 8.3, 8.6 (br, 1H, C(O)N**H**). ^{31}P NMR (80.96 MHz, $CDCl_3$, δ ppm, Ratio of diastereoisomers): 3.45, 16.00; 3.83, 16.00 (0.97 : 1). Anal. calcd for $C_{30}H_{35}N_3O_8P_2$: C, 57.41; H, 5.62; N, 6.70. Found: C, 57.15; H, 5.87; N, 6.49.

4c: R = C_6H_5, yield: 78.6%; syrup. ^{1}H NMR (200 MHz, $CDCl_3$, δ ppm, *J* Hz): 1.20–1.32 (m, 6H, $2 \times CH_2C\mathbf{H}_3$); 3.70, 3.91 (m, 2H, $NC\mathbf{H}_2CH_3$); 4.05–4.42 (m, 3H, $1/2 \times NC\mathbf{H}_2CO_2Et + CO_2C\mathbf{H}_2CH_3$); 4.82 (m, 1H,

$1/2 \times NC\mathbf{H_2}CO_2Et$); 5.80 (m, 1H, C**H**); 6.64–8.25 (m, 19H, $3 \times C_6\mathbf{H}_5 + C_6\mathbf{H}_4$); 8.8, 9.2 (br, 1H, C(O)N**H**). ^{31}P NMR (80.96 MHz, $CDCl_3$, δ ppm, Ratio of diastereoisomers): 3.30, 12.63; 3.80, 12.45 (0.94 : 1) Anal. calcd for $C_{33}H_{33}N_3O_8P_2$: C, 59.91; H, 5.03; N, 6.35. Found: C, 59.72; H, 5.25; N, 6.13.

4d: R = *p*-MeC_6H_4, yield: 74.6%; syrup. ^{1}H NMR (200 MHz, $CDCl_3$, δ ppm, *J* Hz): 1.21–1.34 (m, 6H, $2 \times CH_2C\mathbf{H}_3$); 2.30 (s, 3H, $C_6H_4C\mathbf{H}_3$); 3.69, 3.90 (m, 2H, $NC\mathbf{H_2}CH_3$); 4.03–4.45 (m, 3H, $1/2 \times NC\mathbf{H_2}CO_2Et + CO_2C\mathbf{H}_2CH_3$); 4.85 (1H, $1/2 \times NC\mathbf{H_2}CO_2Et$); 5.82 (m, 1H, C**H**); 6.64–8.26 (m, 18H, $2 \times C_6\mathbf{H}_5 + 2 \times C_6\mathbf{H}_4$); 8.7, 9.1 (br, 1H, C(O)N**H**). ^{31}P NMR (80.96 MHz, $CDCl_3$, δ ppm, Ratio of diastereoisomers): 3.36, 12.87; 3.87, 12.67 (0.93 : 1). Anal. calcd for $C_{34}H_{35}N_3O_8P_2$: C, 60.45; H, 5.22; N, 6.22; Found: C, 60.07; H, 5.49; N, 5.96.

4e: R = *p*-ClC_6H_4, yield: 72.5%; syrup. ^{1}H NMR (200 MHz, $CDCl_3$, δ ppm, *J* Hz): 1.20–1.33 (m, 6H, $2 \times CH_2C\mathbf{H}_3$); 3.73, 3.92 (m, 2H, $NC\mathbf{H_2}CH_3$); 4.05–4.48 (m, 3H, $1/2 \times NC\mathbf{H_2}CO_2Et + CO_2C\mathbf{H}_2CH_3$); 4.88 (1H, $1/2 \times NC\mathbf{H_2}CO_2Et$); 5.85 (m, 1H, C**H**); 6.65–8.24 (m, 18H, $2 \times C_6\mathbf{H}_5 + 2 \times C_6\mathbf{H}_4$); 8.9, 9.3 (br, 1H, C(O)N**H**). ^{31}P NMR (80.96 MHz, $CDCl_3$, δ ppm, Ratio *f* diastereoisomers): 3.11, 12.05; 3.69, 11.92 (0.93 : 1). Anal. calcd for $C_{33}H_{32}ClN_3O_8P_2$: C, 56.95; H, 4.63; N, 6.04. Found: C, 56.47; H, 4.84; N, 5.77.

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REFERENCES

1. Breuer, E. *The Chemistry of Organophosphorus Compounds*. Hartley, F.R., Ed.; John Wiley & Sons, 1996; Vol. 4, 653–729.
2. Li, H.Y.; Chen, R.Y.; Ren, K.T. Phosphorus, Sulfur, and Silicon **1996**, *119*, 279.
3. Chen, R.Y.; Li, H.Y. Science in China (Series B) **1996**, *39*(4), 371.
4. Chen, R.Y.; Li, H.Y. Science in China (Series B) **1996**, *26*(2), 105.
5. Li, H.Y.; Chen, R.Y.; Ren, K.T. Science in China (Series B) **1997**, *40*(4), 365.
6. Li, H.Y.; Chen, R.Y. Science in China (Series B) **1997**, *27*(2), 112.
7. Huang, J.M.; Chen, R.Y. Chem. J. Chinese Univ. **2000**, *21*(8), 1216.

8. Rao, L.N.; Reddy, V.K.; Reddy, C.D. Heteroatom Chem. **2000**, *11*, 323.
9. Neda, I.; Melnicky, C.; Vollbrecht, A.; Schmutzler, R. Synthesis **1996**, (4), 473.
10. Viljanen, T.; Tähtinen, P.; Pihlaja, K.; Fülöp, F. J. Org. Chem. **1998**, *63*, 618.
11. Huang, J.M.; Chen, R.Y. Chem. J. Chinese Univ. **2000**, *21*(10), 1510. The compound **3**: m.p. 75–77°C. ^{1}H NMR ($CDCl_3$, δ ppm; *J*, Hz): 1.22–1.36 (m, 6H, $2 \times CH_2C\mathbf{H}_3$); 3.79 (m, 2H, $NC\mathbf{H}_2CH_3$); 4.09–4.28 (m, 3H, $CO_2C\mathbf{H}_2CH_3 + 1/2 \times NC\mathbf{H}_2CO_2CH_2CH_3$); 4.74 (dd, 1H, $1/2 \times PNC\mathbf{H}_2CO_2Et$, $^3J_{PH} = 8.7$, $^2J_{HH} = 18.3$); 6.60–8.22 (m, 4H, $C_6\mathbf{H}_4$); 7.95 (d, 1H, P(O)**H**, $^1J_{PH} = 649.8$), ^{31}P NMR $CDCl_3$, ppm): 5.31 (s). Anal. calcd for $C_{13}H_{17}N_2O_4P$: C, 52.70; H, 5.78; N, 9.46. Found: C, 52.72; H, 5.84; N, 9.53.
12. Wang, Q.M.; Zeng, Q.; Chen, Z. Heteroatom Chem. **1999**, *10*, 5.
13. Brenner, M.; Huber, W. Helv. Chim. Acta **1953**, *36*(5), 1109.

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