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An α-Hydrazinoalkylphosphonate as Building Block for Novel *N*-Phosphonoalkylheterocycles

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ABSTRACT: *α-Hydrazinoalkylphosphonate* **3** *is a useful building block for the syntheses of novel* N-*phosphonoalkylheterocycles.* N-*phosphonoalkylpyrazoles* **8** *and* **9** *were prepared by the cyclization reaction of* **3** *with multifunctioned ethenes* **5** *and* **6** *in ethanol under reflux.* N-*Phosphonoalkyltriazole* **10** *was synthesized from* **3** *with* N-*dimethylthiomethylene benzoyl amide* **4** *in ethanol under reflux. The structures were confirmed by IR,* ^{1}*H NMR, mass spectroscopy, and elemental analysis. At the same time, the preparation of* **4** *was investigated.* © 2003 Wiley Periodicals, Inc. Heteroatom Chem 14:384–386, 2003; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10173

INTRODUCTION

For several years, we have been investigating the preparation and biological activities of α-aminophosphonic acid analogues that were regarded as one kind of isosteres of natural aminocarboxylic acids and could serve as antifungal agents, herbicides, plant regulators, and plant virucides [1]. Additionally, much attention has been recently devoted to the synthesis of substituted pyrazoles and triazoles as they are useful intermediates for the preparation of many kinds of pesticides [2]. Considering the wide application of these compounds and their potential serve as plant virucides, we designed and synthesized some α-aminophosphonic acid analogues containing pyrazoles and triazole rings.

RESULTS AND DISCUSSION

The synthesis of α-hydrazinoalkylphosphonate **3** has been reported by several methods [3], but its application in preparing α-aminoalkylphosphonates containing heterocycles has never been mentioned before. We found it convenient to synthesize phosphonoalkylheterocycles using **3** as building block, which was synthesized by a modified procedure of Yuan's report [3a]. For converting benzaldehyde **1** to α-hydroxyphenylmethylphosphonate **2**, an excess (four times) of catalyst (KF) was used, which caused it difficult to stir and incomplete to react. Instead, we used one equivalent of catalyst (KF) to avoid these shortcomings and achieved **2** with a better yield (90.6%, m.p. 80–81°C; Ref. [4], m.p. 83°C). However, the reaction time had to be prolonged to 120 min. The synthesis of α-hydrazinoalkylphosphonate **3** is shown in Scheme 1.

The preparations of 1,1-dicyano-2-ethoxylethene (**6**) [5], 1,1-di(benzylthio)-2,2-dicyanoethene (**5**) [6], and *N*-dimethylthiomethylene benzoyl amide (**4**) [7] have been reported before. *N*-Phosphonoalkylpyrazoles **8** and **9** were synthesized from the cyclization reaction of **3** with **5** and **6** respectively in mild conditions as shown in Scheme 2. The structure of **9** was confirmed on the basis of IR, ^{1}H NMR, mass

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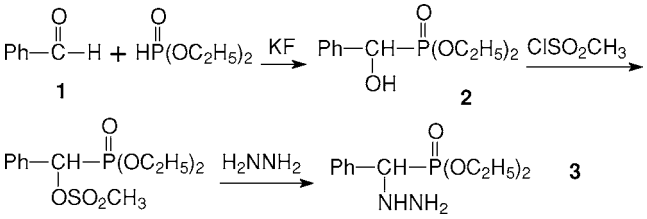
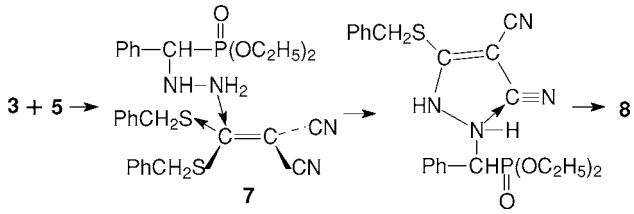


SCHEME 1

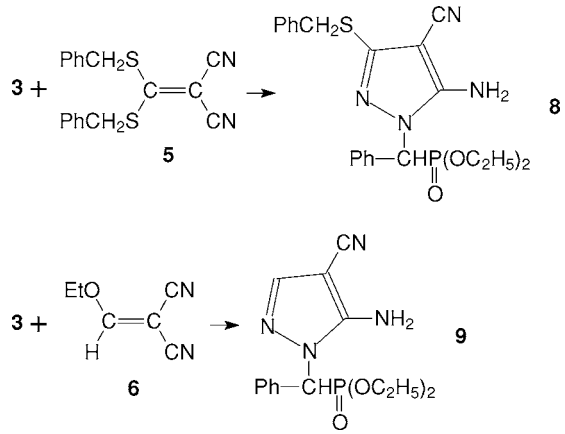


SCHEME 3

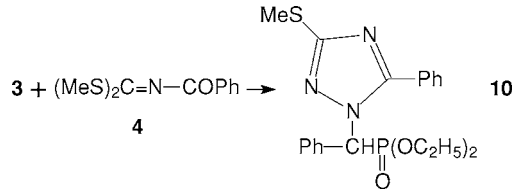
spectra, and elemental analysis. IR spectra showed conjugated C≡N and P=O stretching bands at 2208.0 cm^{-1} and 1233.2 cm^{-1}, respectively. The unusually low frequency of CN is reasonable in view of its conjugations with heterocycle. The IR spectra of **9** also showed two N—H absorptions at 3185.5 cm^{-1} and 3358.0 cm^{-1} characteristic of primary amines. ^{1}H NMR spectra of **8** and **9** showed one broad signal assignable to NH_2 protons in low field and a doublet characteristic of methylene protons attached to P atom.

Condensation reaction of **3** and **5** was assumed to go through two nucleophilic additions as shown in Scheme 3. The α-hydrazinoalkylphosphonate **3** attached to the double bond of **5** to form a transition state **7**. Although the more substituted nitrogen in α-hydrazinoalkylphosphonate **3** has more electronegativity, the steric effect of the neighboring alkyl group ought to reduce the nucleophilicity of this nitrogen, favoring the formation of the transition state **7**. Subsequent nucleophilic addition yields **8**. The syntheses of **9** and **10** go through the same reaction mechanism as above.

α-Hydrazinoalkylphosphonate **3** was cyclized with **4** to afford *N*-phosphonoalkyltriazole **10** in mild condition as shown in Scheme 4. Its structure was confirmed by ^{1}H NMR and elemental analysis.



SCHEME 2



SCHEME 4

^{1}H NMR spectra of **10** are in full agreement with our reported work as expected [8].

As for the synthesis of **4**, we found that all starting materials should be added together in one pot. If they were added stepwise, in addition to **4**, another three by-products, PhCO—NH—CS_2Me, PhCO—NMe—CS_2Me, and PhCO—NMe_2, would have been isolated successfully and identified by their melting points and ^{1}H NMR, which are consistent with the reported data [9]. We also found that compound **4** heated to more than 50°C could be partly converted to PhCO—NMe—CS_2Me.

EXPERIMENTAL

^{1}H NMR spectra were obtained at 200 MHz using a Bruker AC-P 200 spectrometer. Infrared spectra were recorded on a Shimadzu-435 spectrometer. Mass spectra were recorded with HP5988A spectrometer using the EI method. Elemental analyses were carried out with a Yanaco CHN Corder MT-3 elemental analyzer. Melting points were taken on a Thomas–Hoover melting point apparatus and are uncorrected. TLC was carried out on silica gel 60 F_{254} microplates.

4: A solution of benzamide (1.82 g, 15 mmol), carbon disulfide (4.5 g, 59 mmol), $(Me)_2SO_4$ (6.05 g, 48 mmol), and 60.0% NaH (1.08 g, 45 mmol) in THF (60 ml) was stirred at room temperature for 4 h. The reaction mixture was dissolved in 150 ml ice water, extracted with toluene. The organic phase was combined, dried by anhydrous $MgSO_4$, filtered, concentrated in vacuo, and then purified by chromatography on a silica to afford a brown oil

(1.6 g, 50.0% yield). ^{1}H NMR ($CDCl_3$) δ 2.60 (s, 6H, SCH_3), 7.40–8.20 (m, 5H, C_6H_5). (Ref. [7]: 43.0%, white solid, m.p. 46–47°C). At the same time, three by-products were also afforded: PhCO—NH—CS_2Me yield, 0.5%; m.p. 133–134°C; ^{1}H NMR ($CDCl_3$) δ 2.40 (s, 3H, SCH_3), 9.24 (s, 1H, N—H), 7.20–8.0 (m, 5H, C_6H_5); PhCO—NMe—CS_2Me yield, 10.4%; m.p. 68–69°C; ^{1}H NMR ($CDCl_3$) δ 2.60 (s, 3H, SCH_3), 3.70 (s, 3H, NCH_3), 7.20–7.80 (m, 5H, C_6H_5—); PhCO—NMe_2 yield, 35.8%; yellow oil; ^{1}H NMR ($CDCl_3$) δ 3.00 (s, 6H, $N(CH_3)_2$), 7.40 (s, 5H, C_6H_5—).

6: A solution of malononitrile (11.3 g, 0.172 mol), triethyl orthoformate (37 g, 0.25 mol), and acetic anhydride (41.7 g, 0.4 mol) was heated to 100°C for 4 h. The resulting mixture was distilled to afford the fractions: 110–114°C/0.9 mmHg, 16.5 g, yield: 78.6%; m.p. 65–67°C. (Ref. [5]: m.p. 67–68°C).

9: A mixture of **6** (2.36 g, 19.4 mmol), **3** (5.0 g, 19.4 mmol), and ethanol (30 ml) was heated under reflux for 5 h. The reaction mixture was cooled down to room temperature, concentrated in vacuo, and the residue was dissolved in CH_2Cl_2 (40 ml), which was washed with 5% sodium carbonate solution and water, dried with anhydrous Na_2SO_4, and concentrated in vacuo to give the crude product as viscous liquid. The addition of ether gave white solid (5.2 g, 68.4% yield). m.p. 117–118.5°C. IR (KBr) ν/cm^{-1} 3185.0 (N—H), 2208.0 (C≡N), 1662.7 (N—H), 1233.2 (P=O), 1020.1(P—O—C). ^{1}H NMR ($CDCl_3$) δ 1.21 (m, 6H, $OCH_2\underline{CH_3}$), 4.07 (m, 4H, $O\underline{CH_2}CH_3$), 5.33 (br, 2H, NH_2), 5.74 (d, $^2J_{PH} = 24$ Hz, 1H, PCH), 7.33–7.50 (m, 6H, Harom). Anal. Calcd for $C_{15}H_{19}N_4O_3P$: C, 53.89; H, 5.73; N, 16.76; Found: C, 53.49; H, 5.65; N, 16.75; MS (EI, 15 ev) *m/z* 334 (M, 13%), 197 ($C_{11}H_9N_4$, 100%), 91 (C_7H_7, 48%).

8: The compound was synthesized from the reaction of **5** and **3** as described for **9**. White crystal. Yield, 50.4%. m.p. 128.5–130°C. ^{1}H NMR ($CDCl_3$) δ 1.19 (m, 6H, $OCH_2\underline{CH_3}$), 3.99 (m, 4H, $O\underline{CH_2}CH_3$), 4.20 (s, 2H, SCH_2), 5.50 (br, 2H, NH_2), 5,76 (d, $^2J_{PH} = 23$ Hz, 1H, PCH), 7.17–7.50 (m, 10H, Harom). Anal. Calcd for $C_{22}H_{25}N_4O_3PS$: C, 57.88; H, 5.52; N, 12.27; Found: C, 57,98; H, 5.44; N, 12.05.

10: A solution of **3** (0.46 g, 1.8 mmol) and **4** (0.41 g, 1.8 mmol) in ethanol (20 ml) was refluxed for 2 h. The reaction mixture was evaporated in vacuo and then purified by chromatography on a silica. Elution with ethyl acetate and petroleum ether (60–90°C) gave **10** as a yellow liquid (0.41 g, 53.3% yield). ^{1}H NMR($CDCl_3$) δ 1.17 (m, 6H, $OCH_2\underline{CH_3}$), 2.66 (s, 3H, SCH_3), 4.01 (m, 4H, $O\underline{CH_2}CH_3$), 5.73 (d, $^2J_{PH} = 23$ Hz, 1H, PCH), 7.36 (m, 10H, C_6H_5—). Anal. Calcd for $C_{20}H_{24}N_{3O}O_3PS$: C, 57.43; H, 5.86; N, 10.18; Found: C, 57.54; H, 5.79; N, 10.07.

REFERENCES

[1] (a) Takematsu, T.; Konnai, M.; Tachibana, K.; Tsuruoka, T.; Inouye, S.; Watanabe, T. US Patent 4 265 654, 1981; (b) Schuster, G. Ger (East) DD 1991, 284, 155; (c) Ling, Y. X.; Zhang, K. S.; Qiu, D. W. Chem J Chinese Universities 1996, 17(8), 1247; (d) Borloo, M.; Jiao, X. Y.; Wojtowicz, H.; Rajan, R.; Verbruggen, C.; Augustyus, K.; Hacmers, A. Synthesis 1995, 1074; (e) Dai, Q.; Chen, R. Y. Heteroatom Chem 1997, 8(3), 203; (f) Wang, Q. M.; Li, Z. G.; Huang, R. Q.; Cheng, J. R. Heteroatom Chem 2001, 12(2), 68; (g) Wang, Q. M.; Chen, Z.; Zeng, Q.; Huang, R. Q. Heteroatom Chem 1999, 10(3), 209.

[2] (a) Kitazaki, T.; Tamura, N.; Tasaka, A.; Matsushita, Y.; Hayashi, R.; Obouogi, K.; Itoh, K. Chem Pharm Bull 1996, 44(2), 314–327; (b) Hutchinson, D. K. WO Patent 23, 788, 1996; (c) Morimoto, K.; Ogura, T.; Nagaoka, T. WO Patent 24, 589, 1996; (d) Chamberlain, K. Pestic Sci 1991, 31, 185; (e) Pirre, C. J. EP 258160, 1988.

[3] (a) Yuan, C. Y.; Li, C. Z. Synthesis 1996, 507; (b) Yuan, C. Y. Phosphorus Sulfur Silicon 1995, 106, 115; (c) Diel, P.; Maier, L. Phosphorus Sulfur Silicon 1988, 36, 85; (d) Rachon, J.; Wasielewski, C. Rocz Chem 1976, 50, 477.

[4] Texier-Boullet, F.; Foucaud, A. Tetrahedron Lett 1983, 21, 4847.

[5] Jones, R. G. J Am Chem Soc 1952, 74, 4889.

[6] Wang, X. J.; Huang, Z. T. Acta Chim Sinica 1989, 47, 890.

[7] Sato, M.; Fukada, N.; Kurauchi, M.; Takeshima, T. Synthesis 1981, 7, 554.

[8] (a) Li, Z. G.; Huang, R. Q.; Yang, Z.; Li, H. Y. Chem J Chin Universities 1998, 19(12), 1970; (b) Li, Z. G.; Huang, R. Q.; Shao, R. L.; Yang, Z.; Long, Y. X. Phosphorus Sulfur Silicon 1999, 155, 137.

[9] (a) Sadtler Research Laboratories. Inc. Nuclear Magnetic Resonance Spectra 16549M; (b) Kristian, P.; Kutschy, P.; Dzurilla, M. Coll Czech Chem Commun 1979, 44, 1324; (c) Ueno, Y.; Nakai, T.; Okawara, M. Bull Chem Soc Jpn 1971, 44, 841.