Synthesis of Hexahydropyridazine-3-phosphonic Acid

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The synthesis of hexahydropyridazine-3-phosphonic acid (piperidazine-3-phosphonic acid) was performed via a hetero-Diels–Alder reaction followed by Lewis acid-catalyzed phosphorylation. This two-step procedure was improved to a one-pot reaction.

Key words hexahydropyridazine-3-phosphonic acid; phosphorylation; one-pot reaction; piperidazine-3-phosphonic acid; α-hydrazinophosphonic acid; hetero-Diels–Alder reaction

As analogues of α-aminophosphonic acids, α-hydrazinophosphonic acids (type 1, in Fig.1) and their derivatives are of potential biological importance. For example, several of these compounds provide safety against the phytotoxic action of chloroacetanilide herbicides.1) A few examples of the synthesis of α-hydrazinophosphonic acids have been reported; these include a nucleophilic phosphonylation to either preformed or in situ generated C=N bonds (aliphatic aldehyde azines,2) N-protected hydrazones,3) dimethylhydrazones4)), a selective reduction of α-hydrazonophosphonic acids,5) and a nucleophilic substitution of α-mesyloxyalkylphosphonates with hydrazine. 6) However, a simple and general synthetic method for cyclic hydrazine-type compounds (type 2) has not been established, and most of the reported methods concern acyclic compounds.

Recently, as a model of cyclic α-hydrazinophosphonic acid, we reported the first synthesis of simple hexahydropyridazine-3-phosphonic acid (piperidazine-3-phosphonic acid) 3 in preliminary form,7) employing the hetero-Diels–Alder (hetero-D–A) reaction and subsequent phosphorylation of the cycloadduct in the presence of a Lewis acid. Piperidazine-3-phosphonic acid is a phosphonic analogue of piperidazine-3-carboxylic acid 4, the enantiomeric forms of which have been encountered in numerous pharmacologically active molecules, such as the monamycin8) and azinothricin9) families. The details of the synthesis of 3 are described here.

In the initial stage, we examined the construction of the 3-substituted pyridazine rings by the application of the reported methods10,11) of the hetero-D–A reaction, as illustrated in Chart 1. Thus the hetero-D–A reaction of 1-methoxy-1,3-butadiene 5a with dialkyl azodicarboxylates 6a–c was carried out in dichloromethane (CH2Cl2) at room temperature to produce the cycloadducts of 3-methoxy-1,2,3,6-tetrahydropyridazine derivatives 7a–c in nearly quantitative yields. Conversion of the methoxyl group of the cycloadducts 7a–c into a phosphonyl group was conducted smoothly in CH2Cl2 at room temperature by treatment of 7a–c with trimethyl phosphite in the presence of trimethylsilyl triflate (TMSOTf) or boron trifluoride etherate (BF3 · OEt2) as a Lewis acid to afford the corresponding methyl 1,2,3,6-tetrahydropyridazine derivatives 8a–c in good yields. The results are summarized in Table 1. Despite these satisfactory results, a similar hetero-D–A reaction using trimethylsilyloxybutadiene 5b or acetoxybutadiene 5c was not quite as straightforward as expected. These cycloadducts are very unstable. Therefore our attention was directed toward a one-pot reaction including the hetero-D–A reaction and subsequent phosphorylation. After some trials, the one-pot reaction progressed well by slowly adding a Lewis acid to the CH2Cl2 solution of three components (diene 5, dienophile 6, and trimethyl phosphite) and gave 8a in satisfactory yields (Table 1), except for the case of acetoxybutadiene 5c, in which the reaction became complicated. In comparison with the two-step method, this one-pot method appears to be advantageous in terms of reaction efficiency, particularly for the unstable cycloadducts from the hetero-D–A reaction.

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Next, catalytic hydrogenation of tetrahydropyridazines 8a and 8c, which have tert-butyloxy carbonyl (Boc) and trichloroethoxy carbonyl (Trocl) groups, using Pd on charcoal in methanol gave the saturated compounds 9a and 9b in 89% and 40% yield, respectively, although the reduction of the Trocl group occurred in the latter. Finally, N-Boc derivative 9a was hydrolyzed in boiling 6 N HCl and then treated with propylene oxide (2) in methanol to obtain the salt-free product to give piperidazine-3-phosphonic acid 3 in 62% yield (Chart 2), the structure of which was supported by the analytical and spectral data.

Thus the synthesis of piperidazine-3-phosphonic acid has been accomplished. The present method is simple and will be applicable to the synthesis of a variety of 6-membered cyclic α-hydrizinophosphonic acids.

Experimental

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. NMR spectra were obtained on a JEOL JNM-GSX-400 spectrometer using tetramethylsilane (TMS, δ 0 ppm) or dioxane (δ 3.70 ppm for 1H-NMR and δ 67.4 ppm for 13C-NMR) as an internal standard. IR spectra were recorded on a Horiba FT-720 spectrophotometer. MS and HR-MS were obtained on a JEOL JMS-SX102A spectrometer. Column chromatography was carried out on silica gel (Kieselgel 60, 70—230 mesh, Merck). Diethyl azodicarboxylates and 1-substituted 1,3-butadienes were purchased from commercial sources.

**Di-tert-buty1 3-Methoxy-1,2,3,6-tetrahydropyridazine-1,2-dicarboxylate (7a)** A solution of di-tert-buty1 azodicarboxylate 6a (690 mg, 3 mmol) in CH2Cl2 (3 ml) was stirred under cooling at 0 °C. 1-Methoxy-1,3-butadiene 5a (0.33 ml, 3.3 mmol) was added to the solution. The reaction mixture was allowed to warm to room temperature, and stirring was continued for 2 h. The reaction solution was evaporated in vacuo to leave a residue, which was purified by column chromatography (CHCl3) to give 7a in 99% yield. Colorless oil. 1H-NMR (CDCl3) δ: 1.49 (9H, s, CH3), 1.50 (9H, s, CH3), 3.49 and 3.53 (3H, each s, OCH3), 3.55—3.83 (11H, m, CH-C6), 4.31 and 4.49 (1H, d, J = 17.8 Hz and d, J = 17.2 Hz, CH6-H6), 5.25—5.66 (11H, br, C4—H, C5—H), 5.77—6.15 (2H, m, C4—H, C5—H). 13C-NMR (CDCl3) δ: 28.26, 28.34 (q), 41.68, 43.64 (t), 56.24 (q), 80.25 (d), 80.84, 81.01, 81.63 (s), 123.82, 124.33 (d), 127.21, 127.73 (d), 154.19, 154.48 (s). IR (neat) cm⁻¹: 1716, 1705 MS m/z: 314 (M⁺). HR-MS m/z: 314.1842 (M⁺) (Calcd for C12H15Cl6N2O7P: 314.1844 M⁺). Bis(2,2,2-trichloroethyl) 3-Methoxy-1,2,3,6-tetrahydropyridazine-1,2-dicarboxylate (7b) Colorless oil. 1H-NMR (CDCl3) δ: 3.53 (3H, s, OCH3), 3.81—3.96 and 4.00—4.11 (11H, m, CH-C6), 4.53—5.05 (5H, m, C6-Hb and COOCH2×2), 5.57 (1H, br, CH3), 5.88—6.09 (2H, m, C4—H, C5—H). 13C-NMR (CDCl3) δ: 43.09, 44.17 (t), 56.72, 57.07 (q), 75.39, 75.62 (t), 81.18, 85.59 (d), 94.72, 95.04 (t), 123.60, 124.04 (d), 124.61, 128.88 (d), 152.17, 153.17 (s). IR (neat) cm⁻¹: 1718, 1705 MS m/z: 462 (M⁺). HR-MS m/z: 461.8884 (M⁺) (Calcd for C21H11Cl6N2O7P: 461.8877 M⁺).

Bis[2,3,3-trimethyl-1,2,3,6-tetrahydropyridazine-1,2-dicarboxylate (7c) Colorless oil. 1H-NMR (CDCl3) δ: 3.28 and 3.75 (3H, each br, OCH3), 3.65—4.00 (11H, m, CH-C6), 4.41—4.62 (2H, m, C6—Hb), 5.00—5.35 (4H, m, COOCH2×2), 5.50—5.60 (2H, br, C3—H), 5.81—5.99 (2H, m, C4—H, C5—H). 1H-NMR (CDCl3) δ: 42.50, 42.64 (t), 43.73, 43.97 (t), 56.41 (q), 67.93, 70.99 (d), 75.68 (t), 80.19, 80.86 (d), 123.65, 124.15 (d), 127.34, 127.58 (d), 127.87, 129.77, 128.11, 128.32, 128.43, 128.58 (d), 135.64, 135.87 (s), 154.50, 154.24 (s). IR (neat) cm⁻¹: 1716, 1705 MS m/z: 372 (M⁺). HR-MS m/z: 382.1529 (M⁺) (Calcd for C13H16N2O7P: 382.1529 M⁺).
added slowly to the reaction mixture under ice-cooling. The reaction mixture was allowed to warm to room temperature and stirred for a further 12 h. The work-up was carried out in a manner similar to that described above for the phosphonylethylamine moiety. The crude product 8a was recrystallized from hexane.

Yields of 8a from different butadienes 5a–c are summarized in Table 1.

Di-tert-butyl 3-Dimethylphosphono-hexahydropyridazine-1,2-dicarboxylate (9a) A solution of 8a (4.70 g, 12 mmol) in methanol (100 ml) was hydrogenated over 10% Pd–C (0.3 g) at 1 atm and room temperature for 20 h. The reaction mixture was filtered and concentrated under reduced pressure to leave a crude product, which was subjected to column chromatography (CHCl3), and then 3% MeOH–CHCl3 to give 9a. Yield 89%. Colorless oil. 1H-NMR (CDCl3) δ: 1.48 and 1.49 (each 9H, s, C4H9), 1.73—2.23 (4H, m, C4-Hb, C5-Hb), 2.83—3.08 (1H, m, C5-Ha), 3.71—3.94 (6H, m, OCH3×2), 3.79—4.22 (1H, m, C6-Hb), 4.43—4.84 (1H, br, C3-H). 13C-NMR (CDCl3) δ: 19.99 (t), 22.59 (t), 28.22 (q), 42.69, 45.02 (t), 47.74 (dd, 1JCP=159.8 Hz, C3), 52.50 (qd, 2JCP=7.4 Hz, OCH3), 52.74 (qd, 2JCP=6.1 Hz, OCH3), 80.32, 81.81 (s), 152.55, 153.92, 154.49, 154.87 (s). IR (KBr) cm⁻¹: 1712. MS m/z: 394 (M+). HR-MS m/z: 394.1869 (M⁺) (Calcd for C12H17Cl6N2O7P: C, 26.45; H, 3.14; N, 5.14. Found: C, 26.57; H, 3.05; N, 5.17.

Hexahydropyridazine-3-phosphonic Acid (Piperidine-3-phosphonic Acid) (3) A solution of 9a (789 mg, 2 mmol) in 6%HCl (20 ml) was refluxed under an argon atmosphere for 12 h to give 3 as HCl salt after evaporation to dryness, which was dissolved in MeOH (3 ml) and treated with propylene oxide (1 ml, 14 mmol). The precipitate that resulted was collected by filtration and recrystallized from MeOH–propylene oxide (3:1) to give 3 in 62% yield. White powder (MeOH–propylene oxide), mp 158—160°C. 1H-NMR (D2O) δ: 1.56—1.85 (2H, m, C4-Ha, C5-Ha), 1.90—2.05 (2H, m, C4-Hb, C5-Hb), 3.03—3.12 (1H, m, C6-Ha), 3.16—3.26 (1H, m, C3-H), 3.30—3.40 (1H, m, C6-Hb). 13C-NMR (D2O) δ: 21.30 (dd, 1JCP=12.2 Hz, C5), 23.72 (t, C4), 46.04 (t, C6), 54.88 (dd, 1JCP=146.5 Hz, C3). IR (KBr) cm⁻¹: 3400, 3255 (OH, NH), 1155 (P=O), 1061 (P–O). MS m/z: 167 (M⁺+1). HR-MS m/z: 167.0586 (M⁺+1) (Calcd for C12H17N2O7P: 167.0586).

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References and Notes
13) These signals were split due to the rotamers and/or the conformers.