Studies on Conjugated Nitriles. VII.[1] Lewis Acid-Promoted Reaction of Active Methylene Compounds with Diethyl Phosphorocyanidate; Preparation of α,β-Unsaturated α-Aminophosphonates

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Reaction of diethyl phosphorocyanidate (DEPC) with dimethyl malonate (1a) and ethyl cyanoacetate (1b) in the presence of zinc chloride and triethylamine resulted in selective addition of 1a,b to the cyano group of DEPC to give α,β-unsaturated α-aminophosphonates (2a,b). In contrast, similar treatment of enolizable methyl acetoacetate (1c) and acetylacetone (1d) with DEPC gave the corresponding enolphosphates (4c,d) as a result of nucleophilic displacement on the phosphorus atom of DEPC. Conversion of the resulting α-aminophosphonate (2a) to uracil-6-phosphonates (6a,b) was achieved by treatment with phenyl isocyanate (5a) and isothiocyanate (5b), respectively.

Keywords diethyl phosphorocyanidate; zinc chloride; α-aminophosphonate; uracil-6-phosphonate; enolphosphate

Diethyl phosphorocyanidate (DEPC)[2] is a useful reagent in organic synthesis, especially for mild condensations[2–4] and cyanations.[5–8] In general, nucleophiles initially attack the phosphorus atom of DEPC, leading to elimination of the cyano group.[9] If nucleophilic attack occurs at the cyano carbon atom of DEPC without P–CN bond fission, it might be useful for the synthesis of biologically interesting phosphonates such as α,β-unsaturated α-aminophosphonates[10] and heterocyclic phosphonates.[11] However, there are only a few reports of such reactions so far, *i.e.*, the cycloaddition of the lithium salt of trimethylsilyldiazomethane[12] and nitrile oxides[13] to the cyano group of DEPC to produce the 1,2,3-triazole- and 1,2,4-oxadiazole-4-phosphonates, respectively. Previously, we investigated the Lewis acid-promoted addition of carbon nucleophiles to the cyano group of ethyl cyanoformate.[14] We then examined the reaction of active methylene compounds with DEPC in the presence of Lewis acid, and here we describe a novel nucleophilic addition of active methylene compounds (**1**) to the cyano group of DEPC to yield α,β-unsaturated α-aminophosphonates (**2**), and the conversion of **2** to uracil-6-phosphates (**6**).

Initially we examined the reaction of DEPC with dimethyl malonate (**1a**) in the presence of triethylamine and a Lewis acid such as $ZnCl_2$, $FeCl_3$, $AlCl_3$, $TiCl_4$, or $SbCl_5$, which is expected to increase the electrophilicity of the cyano carbon atom.[15] Among them, $ZnCl_2$ gave the best result. Thus, $ZnCl_2$ was gradually dissolved in a methylene chloride solution of DEPC at room temperature. The resulting solution was allowed to react with dimethyl malonate (**1a**) and triethylamine to give α,β-unsaturated α-aminophosphonate (**2a**) in 22% yield together with recovered malonate (**1a**). The yield of **2a** (66%) could be improved by adding molecular sieves 4A (MS4A) to the above reaction mixture. Since the reaction in the absence of $ZnCl_2$ did not occur at all, $ZnCl_2$ presumably promotes this reaction by coordination to the cyano nitrogen atom in DEPC.

Similar treatment of DEPC with methyl cyanoacetate (**1b**) afforded a single isomer of α,β-unsaturated α-aminophosphonate (**2b**) in 43% yield. In this case, the low yield seemed to be due to the coordination of $ZnCl_2$ to both of the nitrile groups of DEPC and **1b**. When a three-fold excess of $ZnCl_2$ was used, the yield of **2b** was not appreciably improved (49%). The stereochemistry of **2b** was confirmed by comparison of the C–C=C–P coupling constants of the ester and nitrile carbons in the ^{13}C-NMR spectrum. The C–C=C–P coupling constant (20—22 Hz) in *E* geometry is generally larger than that (5—8 Hz) in *Z* geometry.[16] The signals due to the ester and nitrile carbons of **2b** appeared as doublets ($J_{C-C=C-P}$ 19.1 and 5.3 Hz) at 167.8 and 116.3 ppm, respectively, that is, the ester group is situated *E* to the phosphoryl group. The stereoselectivity can be interpreted as follows; after C–C bond formation, the intermediate (**3**) is fixed by chelation of zinc metal with the ester carbonyl oxygen atom, rather than the nitrile nitrogen atom, followed by proton shift

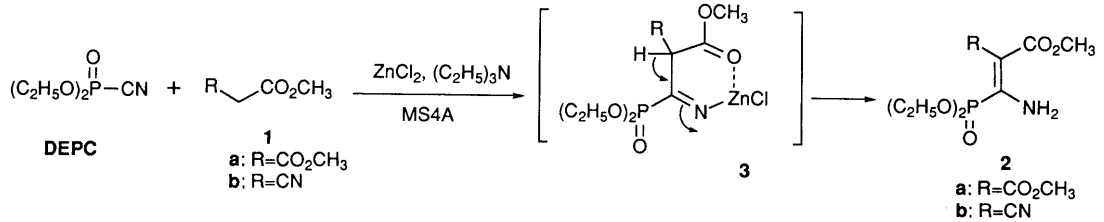

Chart 1

This paper is dedicated to Professor Yoshifumi Maki on the occasion of his retirement from Gifu Pharmaceutical University in March 1994.

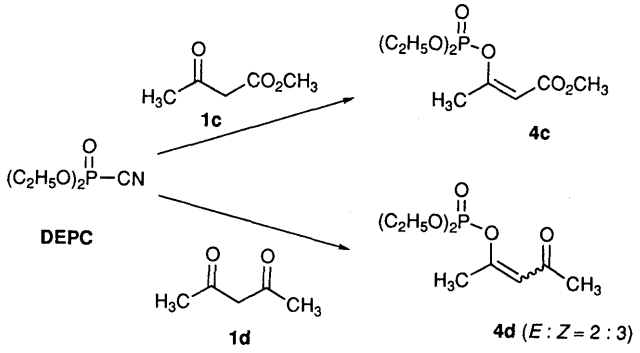

Chart 2

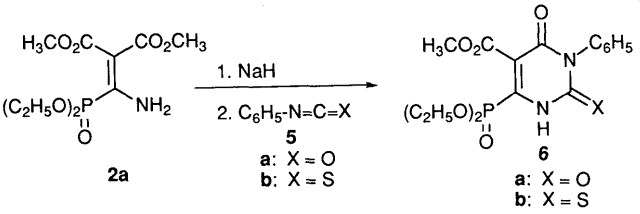

Chart 3

to afford the product (**2b**). The reaction with malononitrile did not occur under the same conditions.

The reaction of enolizable active methylene compounds such as methyl acetoacetate (**1c**) and acetylacetone (**1d**) with DEPC under the same conditions proceeded not *via* the desired attack on the cyano carbon of DEPC but *via* nucleophilic attack on the phosphorus atom to give the corresponding enolphosphates (**4c,d**). The stereochemistry of **4c** was confirmed by an nuclear Overhauser effect (NOE) experiment; positive NOE (5%) was detected between the Me (δ 2.18) and vinyl protons (δ 5.33). The stereochemistry of **4d** was assigned by comparison with the chemical shifts of Me and vinyl protons; δ 2.36 and 6.25 for *E*-**4d**, δ 2.32 and 5.50 for *Z*-**4d**, and δ 2.18 and 5.33 for *Z*-**4c**.

Next we examined the conversion of **2a** to uracil-6-phosphonates (**6**). Thus, treatment of **2a** with sodium hydride followed by reaction with phenyl isocyanate (**5a**) gave uracil-6-phosphonate (**6a**) in 71% yield. Similarly, the thioderivative (**6b**) (22%) was obtained by the reaction of **2a** with isothiocyanate (**5b**).

In conclusion, the present results suggest that DEPC can be utilized as a new building block for phosphonic acid derivatives.

Experimental

All melting points are uncorrected and were measured on a Yanagimoto micromelting point apparatus. IR spectra were recorded with a Hitachi 270-30 spectrophotometer. NMR spectra were determined with a JEOL JNM-GX 270 or GX-400 spectrometer with tetramethylsilane as an internal standard. The *J*-values are given in Hz. Mass spectra were obtained with a JEOL JMS-DX302 instrument with a direct inlet system operating at 70 eV. Elemental analyses were obtained by using a Perkin-Elmer Model 240B elemental analyzer. Column chromatography was carried out on silica gel (Kanto Chemical Co., Inc., 100—200 mesh and Merck, 400 mesh).

Diethyl 1-Amino-2,2-dimethoxycarbonylethenylphosphonate (2a) a) Without Molecular Sieves (MS4A): DEPC (0.75 g, 4.6 mmol) was added to a suspension of $ZnCl_2$ (0.98 g, 7.2 mmol) in dry CH_2Cl_2 (5 ml) at 0 °C, and the mixture was stirred at room temperature until the $ZnCl_2$ dissolved (about 12 h). Et_3N (0.56 g, 5.5 mmol) was added to the mixture under ice cooling, and then dimethyl malonate (**1a**) (0.66 g, 5 mmol) was added dropwise. The mixture was stirred at room temperature overnight. To the resulting mixture, 150 ml of $CHCl_3$ and 100 ml of water were added. After adjustment to pH 4 with 10% aqueous HCl, the mixture was extracted with $CHCl_3$, and the extract was washed with saturated aqueous Na_2CO_3 (80 ml), dried over $MgSO_4$, and concentrated under reduced pressure to give an oily residue. The residue was chromatographed on silica gel using $CHCl_3$–EtOAc (5 : 1) as an eluent to give the phosphonate (**2a**) (0.30 g, 22%), mp 60—61 °C (from Et_2O–hexane). IR (Nujol): 3450, 3320, 1730, 1680 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.37 (6H, t, J=7.0, O–$CH_2C\underline{H}_3$), 3.74 (3H, s, OMe), 3.76 (3H, s, OMe), 4.18 (4H, m, P–O–CH_2), 6.02 (1H, br s, NH), 8.69 (1H, br s, NH). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 16.1 (J_{CP}=6.9, P–O–C–$\underline{C}$), 51.6 (s, OCH_3), 52.3 (s, OCH_3), 63.9 (J_{CP}=5.3, P–O–C), 99.3 (J_{CP}=13.7, P–C=$\underline{C}$), 151.3 (J_{CP}=179.3, P–$\underline{C}$=C), 166.9 (J_{CP}=6.1, C=O), 163.7 (J_{CP}=22.1, C=O). MS *m/z* (%): 295 (M^+, 33), 264 (43), 192 (96), 158 (35), 126 (89), 111 (100), 82 (68). *Anal.* Calcd for $C_{10}H_{18}NO_7P$: C, 40.68; H, 6.15; N, 4.74. Found: C, 40.46; H, 6.40; N, 4.76.

b) With Molecular Sieves: DEPC (0.75 g, 4.6 mmol) was added to a suspension of $ZnCl_2$ (0.98 g, 7.2 mmol) and MS4A (1.5 g) in dry CH_2Cl_2 (5 ml) at 0 °C, and the mixture was treated in the same manner as described above to give **2a** (0.89 g, 66%).

Diethyl (*E*)-1-Amino-2-cyano-2-methoxycarbonylethenylphosphonate (2b) Using a procedure similar to that described above for the reaction of DEPC with **1a**, DEPC (0.75 g, 4.6 mmol) was treated with $ZnCl_2$ (0.98 g, 7.2 mmol), Et_3N (0.56 g, 5.5 mmol), MS4A (1.5 g), and methyl cyanoacetate (**1b**) (0.49 g, 5 mmol) to give the phosphonate (**2b**) (0.52 g, 43%). mp 100—101 °C (from CH_2Cl_2). IR (Nujol): 3370, 3220, 2215, 1700 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.43 (6H, t, J=7.0, O–$CH_2C\underline{H}_3$), 3.82 (3H, s, OMe), 4.29 (4H, m, P–O–CH_2), 7.17 (1H, br d, J=1.1, NH), 9.33 (1H, dr d, J=3.2, NH). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 16.1 (J_{CP}=6.1, P–O–C–$\underline{C}$), 52.2 (s, OCH_3), 65.1 (J_{CP}=6.9, P–O–C), 75.9 (J_{CP}=9.2, P–C=$\underline{C}$), 116.3 (J_{CP}=5.3, CN), 167.8 (J_{CP}= 177.8, P–$\underline{C}$=C), 167.8 (J_{CP}=19.1, C=O). MS *m/z* (%): 262 (M^+, 50), 203 (35), 175 (50), 183 (77), 125 (76), 111 (84), 82 (100), 65 (43). *Anal.* Calcd for $C_9H_{15}N_2O_5P$: C, 41.23; H, 5.77; N, 10.68. Found: C, 41.41; H, 5.92; N, 10.78.

Methyl (*Z*)-3-Diethoxyphosphoryloxycrotonate (4c) Using a procedure similar to that described above for the reaction of DEPC with **1a**, the phosphate (**4c**) (0.88 g, 70%) was obtained from DEPC (0.90 g, 5.5 mmol), $ZnCl_2$ (0.82 g, 6 mmol), Et_3N (0.56 g, 5.5 mmol), and methyl acetoacetate (**1c**) (0.58 g, 5 mmol). bp 175 °C (3 mmHg) (bath temperature). IR ($CHCl_3$): 1724, 1674 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz) δ: 1.38 (6H, dt, J=1.0, 6.9, O–$CH_2C\underline{H}_3$), 2.18 (3H, dd, J=1.0, 1.7, =C–Me), 3.68 (3H, s, CO_2Me), 4.27 (4H, dq, J=6.9, 7.3, P–O–CH_2), 5.33 (1H, br s, –CH=). MS *m/z* (%): 252 (M^+, 12), 220 (49), 192 (40), 164 (55), 155 (60), 127 (65), 99 (100). HR-MS: Calcd for $C_9H_{17}O_6P$: 252.0763. Found: 252.0742.

(*E*)- and (*Z*)-4-Diethoxyphosphoryloxy-3-penten-2-one (4d) Using a procedure similar to that described above for the reaction of DEPC with **1a**, a mixture of *E*- and *Z*-isomers (2 : 3) of the phosphate (**4d**) (1.31 g, 56%) was obtained from DEPC (1.96 g, 12 mmol), $ZnCl_2$ (1.64 g, 12 mmol), triethylamine (1.11 g, 11 mmol), and methyl acetoacetate (**1d**) (0.98 g, 9.8 mmol). bp 155 °C (3 mmHg) (bath temperature). IR ($CHCl_3$): 1680, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz) δ: 1.38 (3/5 × 3H, dt, J=1.2, 7.3, O–$CH_2C\underline{H}_3$), 1.39 (2/5 × 3H, dt, J=0.9, 7.0, O–$CH_2C\underline{H}_3$), 2.205 (3/5 × 3H, s, COMe), 2.21 (2/5 × 3H, s, COMe), 2.32 (3/5 × 3H, br s, =C–Me), 2.36 (2/5 × 3H, d, J=0.6, =C–Me), 4.22 (2/5 × 2H, dq, J=6.1, 7.0, P–O–CH_2), 4.26 (3/5 × 2H, dq, J=6.6, 7.3, P–O–CH_2), 5.50 (3/5 × 1H, s, =CH–), 6.25 (2/5 × 1H, s, =CH–). MS *m/z* (%): 236 (M^+, 36), 193 (10), 165 (19), 155 (100). HR-MS: Calcd for $C_9H_{17}O_5P$: 236.0813. Found: 236.0797.

Diethyl 5-Methoxycarbonyl-3-phenyluracil-6-phosphonate (6a) A solution of the phosphonate (**2a**) (1.48 g, 5 mmol) in dry tetrahydrofuran (THF) (10 ml) was treated with NaH (60% dispersion in oil, 0.24 g, 6 mmol) at room temperature with stirring for 15 min and then at 50 °C until the evolution of hydrogen ceased. Phenyl isocyanate (**5a**) (0.60 g, 5.1 mmol) was gradually added to the mixture at 0 °C. The mixture was stirred at room temperature for 6 h, and concentrated. The residue was poured into water (5 ml), and neutralized with AcOH to give crystalline precipitates, which were collected, washed with Et_2O, and recrystallized from EtOAc to give the phosphonate (**6a**) (1.35 g, 71%). mp 196–197 °C. IR (Nujol): 1725, 1665, 1615 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.35 (6H, t, J=7.0, $CH_2C\underline{H}_3$), 3.87 (3H, s, OMe), 4.20 (4H, dq, J=6.4,

7.0, P–OCH$_2$), 7.23 (2H, d, J=7.0, PhH), 7.44 (1H, d, J=7.0, PhH), 7.49 (2H, t, J=7.0, PhH), 9.34 (1H, br d, J=8.5, NH). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 16.2 (J_{CP}=6.1, P–O–C–C), 53.2 (s, OMe), 65.0 (J_{CP}=6.0, P–O–C), 114.9 (J_{CP}=9.2, P–C=C), 128.1 (s, Ph–C), 129.2 (s, Ph–C), 129.4 (s, Ph–C), 133.6 (s, Ph–C), 140.5 (J_{CP}=190.7, P–C=C), 150.1 (J_{CP}=13.6, C-2), 159.9 (J_{CP}= 17.5, O–C=O), 163.1 (J_{CP}=5.3, C-4). MS m/z (%): 382 (M^+, 64), 323 (61), 290 (69), 191 (37), 138 (100), 119 (99), 82 (52). *Anal.* Calcd for $C_{16}H_{19}N_2O_7P$: C, 50.27; H, 5.01; N, 7.33. Found: C, 50.27; H, 5.03; N, 7.35.

Diethyl 5-Methoxycarbonyl-3-phenyl-2-thiouracil-6-phosphonate (6b) Using a procedure similar to that described above for the preparation of **6a**, the thiouracil (**6b**) (0.086 g, 22%) was obtained from **1a** (0.295 g, 1 mmol), NaH (60% in oil, 0.04 g, 1 mmol), and phenyl isothiocyanate (**5b**) (0.135 g, 1 mmol). mp 158—159 °C (from EtOAc). IR (Nujol): 3150, 3100, 1750, 1680 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.43 (6H, t, J=7.0, CH_2CH_3), 3.88 (3H, s, OMe), 4.33 (4H, dq, J=7.0, 7.9, P–O–CH_2), 7.44 (2H, d, J=7.0, PhH), 7.46 (1H, d, J=7.0, PhH), 7.52 (2H, t, J=7.0, PhH), 9.84 (1H, br s, NH). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 16.5 (J_{CP}=6.0, P–O–C–C), 53.2 (s, OMe), 65.3 (J_{CP}=5.3, P–O–C), 116.9 (J_{CP}=8.4, P–C=C), 127.8 (s, Ph–C), 129.3 (s, Ph–C), 129.8 (s, Ph–C), 137.7 (s, Ph–C), 140.6 (J_{CP}=188.5, P–C=C), 157.4 (J_{CP}=16.0, C-4), 162.6 (J_{CP}=6.3, O–C=O), 176.9 (J_{CP}=10.7, C-2). MS m/z (%): 398 (M^+, 67), 365 (100), 337 (42), 309 (55), 161 (30), 111 (28), 77 (66). *Anal.* Calcd for $C_{16}H_{19}N_2O_6PS$: C, 48.24; H, 4.81; N, 7.03. Found: C, 48.43; H, 4.89; N, 6.98.

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References and Notes

1) Part VI: M. Sakamoto, M. Abe, K. Ishii, *Chem. Pharm. Bull.*, **39**, 277 (1991).
2) For a review, see: T. Shioiri, *Yuki Gosei Kagaku Kyokai Shi*, **37**, 856 (1979).
3) *a*) For a review, see: T. Shioiri, Y. Hamada, *Yakugaku Zasshi*, **108**, 1115 (1988); *b*) K. Hayashi, Y. Hamada, T. Shioiri, *Tetrahedron Lett.*, **33**, 5075 (1992).
4) T. Shioiri, Y. Hamada, *J. Org. Chem.*, **43**, 3631 (1978), and references cited therein.
5) *a*) For a review, see: T. Kurihara, S. Harusawa, R. Yoneda, *Yuki Gosei Kagaku Kyokai Shi*, **46**, 1164 (1988); *b*) R. Yoneda, S. Harusawa, T. Kurihara, *J. Org. Chem.*, **56**, 1827 (1991), and references cited therein.
6) S. Harusawa, Y. Hamada, T. Shioiri, *Synthesis*, **1979**, 716.
7) B. S. Nagra, G. Shaw, D. H. Robinson, *J. Chem. Soc., Chem. Commun.*, **1985**, 459.
8) S. Harusawa, T. Shioiri, *Tetrahedron Lett.*, **23**, 447 (1982).
9) This behavior is based on the high electrophilicity of the phosphorus atom and the high eliminability of the cyano group in DEPC; R. Greenhalgh, R. M. Heggie, M. A. Weinberger, *Can. J. Chem.*, **48**, 1351 (1970).
10) J.-M. Campagne, J. Coste, P. Jouin, *Tetrahedron Lett.*, **34**, 6743 (1993); S. Hanessian, Y. L. Bennani, Y. Hervé, *Synlett*, **1993**, 35.
11) R. Neidlein, T. Eichinger, *Helv. Chim. Acta*, **75**, 124 (1992); C. Yuan, W. Huang, *Synthesis*, **1993**, 473.
12) T. Aoyama, K. Sudo, T. Shioiri, *Chem. Pharm. Bull.*, **30**, 3849 (1982).
13) S. K. Das, S. N. Balasubrahmanyam, *J. Org. Chem.*, **48**, 4232 (1983).
14) Y. Akiyama, S. Takebayashi, T. Kawasaki, M. Sakamoto, *Chem. Pharm. Bull.*, **32**, 1800 (1984).
15) F. C. Schaefer, "The Chemistry of the Cyano Group," ed. by Z. Rappoport, John Wiley & Sons, London, 1970, chapter 6.
16) E. Öhler, S. Kotzinger, *Synthesis*, **1993**, 497; *idem*, *Justus Liebigs Ann. Chem.*, **1993**, 269; E. Öhler, E. Zbiral, *Chem. Ber.*, **124**, 175 (1991).