[Chem. Pharm. Bull. 36(3)1139—1142(1988)]

Improved Synthesis of Methyl 2,6-Dimethyl-4-(2-nitrophenyl)-5-(2-oxo-1,3,2-dioxaphosphorinan-2-yl)-1,4-dihydropyridine-3-carboxylate (DHP-218)

IWAO MORITA,* MASAMI TSUDA, MASAHIRO KISE, and MAKOTO SUGIYAMA

Research Laboratories, Nippon Shinyaku Co., Ltd., Nishiohji-Hachijo, Minami-ku, Kyoto 601, Japan

(Received July 22, 1987)

Attempts were made to improve the synthesis of methyl 2,6-dimethyl-4-(2-nitrophenyl)-5-(2-oxo-1,3,2-dioxaphosphorinan-2-yl)-1,4-dihydropyridine-3-carboxylate (DHP-218), a new calcium antagonist. 2-Acetonyl-2-oxo-1,3,2-dioxaphosphorinane (**5a**), the key intermediate, was prepared from the allenylphosphonate (**2**) *via* the enaminophosphonate (**4**) in a good yield. Subsequently, the Knoevenagel condensation using **5a** and the imine (**6a**) gave the benzylideneacetonylphosphonate (**7a**) in a good yield without the use of the Horner–Emons reaction. This condensation also gave good results for other acetonylphopshonates. The final step gave DHP-218 in a good yield through a modified Hantzsch synthesis with the use of a dehydrating agent. The overall yield was increased from 1.7% to 22%.

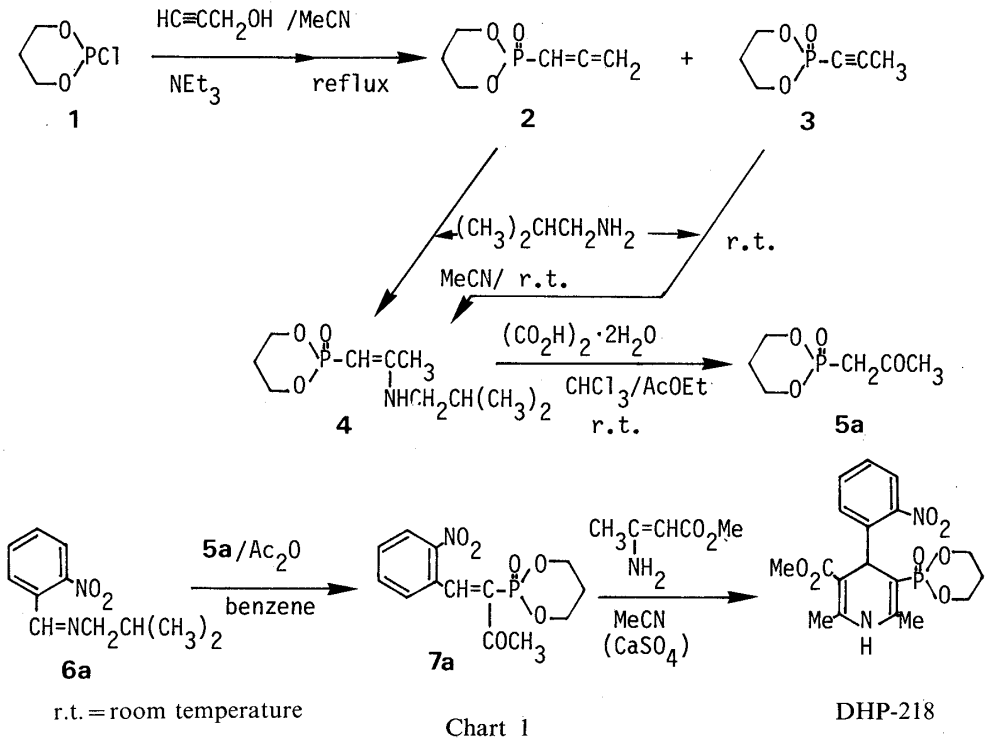
Keywords——DHP-218; calcium antagonist; improved synthesis; acetonylphosphonate; allenylphosphonate; benzylideneacetonylphosphonate; enaminophosphonate; Knoevenagel condensation; Schiff base; modified Hantzsch synthesis

Previously we reported the synthesis and antihypertensive activities of 1,4-dihydropyridine-5-phosphonate derivatives.[1] After examining the pharmacological and toxicological properties of these compounds, we selected methyl 2,6-dimethyl-4-(2-nitrophenyl)-5-(2-oxo-1,3,2-dioxaphosphorinan-2-yl)-1,4-dihydropyridine-3-carboxylate (DHP-218) at the most promising compound,[2] and it is now undergoing clinical trials. DHP-218 can be synthesized in four steps starting from trimethylene glycohol *via* 2-acetonyl-2-oxo-1,3,2-dioxaphosphorinane (**5a**). However, this method gives a very low overall yield (1.7%) because of the low yields at each step so it is not suitable for use on an industrial scale. In our previous paper,[3] we described the synthesis of the cyclic acetonylphosphonate (**5**) from the cyclic silyl phosphite with iodoacetone, but this method also gave an inadequate yield. Therefore, we looked for a technically simple and high-yield modification for the preparation of DHP-218. Here we describe the synthesis of **5a** *via* the allene intermediate (**2**) and the benzylideneacetonylphosphonate (**7a**) by the Knoevenagel condensation technique with the imine (**6a**).

Results and Discussion

Synthesis of 5a

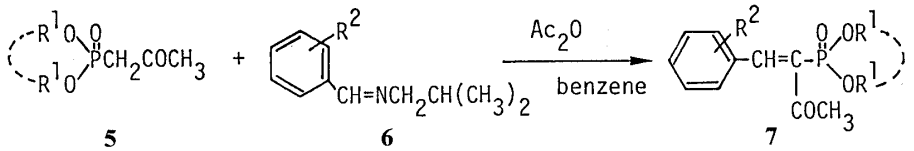
The authors have recently reported that dipropargyl acetonylphosphonate can be prepared by the reaction of ammonia with the allene intermediate obtained by the thermal rearrangement of tripropargyl phosphite.[4] First, we attempted to improve this method. The allene intermediate (**2**) is a known compound, but its preparation and characteristics have not yet been described.[5] It was prepared from 2-chloro-1,3,2-dioxaphosphorinane (**1**) with propargyl alcohol, followed by thermal rearrangement in MeCN in 71% yield. In this



r.t. = room temperature

Chart 1

TABLE I. Reaction of Acetonylphosphonates (**5**) with Imines (**6**)



Run	Product (7) R^1	R^2	Yield[a] (%)	mp (°C)	Ratio of (E/Z)[b]	Reported[c] yield (%)	(E/Z)
1	$CH_2CH_2CH_2$	2-NO_2	68	140—146	45/55	34	91/9
2	$CH_2CH_2CH_2$	3-NO_2	88	125—129	89/11	19	100/0
3	$CH_2C(CH_3)_2CH_2$	2-NO_2	66	142—145	41/59	29	56/44
4	$CH_2C(CH_3)_2CH_2$	3-NO_2	91	136—140	84/16	24	100/0
5	$CH_2C(CH_3)_2CH_2$	2-CF_3	64	75—78	62/38	28	83/17
6	$CH_2C(CH_3)_2CH_2$	2,3-Cl_2	58	113—119	100/0	25	100/0
7	Me	3-NO_2	51	Oil	91/9	43	91/9

a) Isolated yield. *b*) The (E/Z) ratio of **7** was calculated by NMR analysis. *c*) Reaction of **5** with benzaldehydes in the presence of piperidine–AcOH.[1]

reaction, the propynylphosphonate (**3**) was also produced in 1.4% yield.

Merour *et al.* have reported that the reaction of **2** with a primary or secondary amine gives enaminophosphonates.[5] Isobutylamine was selected as the amine part of enaminophosphonates from a consideration of the boiling point of the amine and the crystallizability of the enaminophosphonate and amine salt, as mentioned below. The reaction of **2** with isobutylamine in MeCN at room temperature gave the enaminophosphonate (**4**) as crystals in 91% yield. The **3** also gave **4** in 70% yield in the neat reaction with isobutylamine.

The enaminophosphonate (**4**) was hydrolyzed by an acid catalyst to give the acetonylphosphonate (**5a**), but **5a** has a high water solubility and is unstable in acid media. Therefore,

this hydrolysis was carried out with oxalic acid dihydrate (commercially available) in $CHCl_3$–AcOEt at room temperature, followed by collection of isobutylamine oxalate, which precipitated from the reaction mixture, to give **5a** in a quantitative yield.

When propylamine or diethylamine was used as the amine part, the enaminophosphonate was obtained in good yield as an oil which was used directly in the next reaction without purification, followed by hydrolysis with oxalic acid dihydrate to give **5a** in 76% or 73% yield, respectively.

Synthesis of Benzylideneacetonylphosphonate (7)

We recently reported that the preparation of **7** by the usual Knoevenagel condensation, using **5** and benzaldehydes, gives a low yield because of the simultaneously occurring Horner–Emons reaction. Therefore, in our improved method we tried to depress the formation of the by-product. The Horner–Emons reaction proceeds through an intermediate (>PO–C–C–O^-), which is produced from an aldehyde with a carbanion, to give benzalacetone. Therefore, the (C–O^-) functional group in this intermediate must be transformed to another functional group which has less affinity for phosphorus than oxygen. For this purpose, the Schiff base (**6a**) of 2-nitrobenzaldehyde was used. The Knoevenagel condensation with the imine has been reported by Franckowiak and Goldmann.[6] In the same manner, the reaction of **5a** with the imine (**6a**) (1.3 eq) using acetic anhydride (2 eq) in benzene at reflux gave **7a** in 68% yield without the Horner–Emons product, but the starting material (**5a**) was recovered in 17% yield. With this method, the reaction of acetonylphosphonates (**5**) with the imines (**6**) gave the benzylideneacetonylphosphonates (**7**) in good yields (Table I). The yields of **7** were twice the previously reported yield.[1] The (*E*/*Z*) ratio of **7** was higher than in the previous method because of the steric effect of the isobutyl group in **6**. This ratio had little influence on the subsequent Hantzsch synthesis.

Synthesis of DHP-218

The yield of the final step was 54%.[1] The cause of the low yield was assumed to be the decomposition of **7a** to the aldehyde and **5a** by simultaneously formed water. Therefore, a dehydrating agent (activated $CaSO_4$) was added to the reaction mixture and the refluxing solution was dried. With this method, the reaction of **7a** with methyl 3-aminocrotonate gave DHP-218 in 81% yield. The use of molecular sieves or $MgSO_4$ as a dehydrating agent gave inferior results (73% and 70% yields, respectively) as compared with $CaSO_4$.

Therefore, DHP-218 was synthesized from trimethyleneglycohol in an overall yield of 22%.

Experimental

All melting and boiling points are uncorrected. Infrared (IR) spectra were measured with a Shimadzu IR-435 spectrometer. Nuclear magnetic resonance (NMR) spectra were taken on a Varian YX-200 spectrometer. Chemical shifts are given in δ (ppm) with tetramethylsilane as the internal standard. Flash chromatography was performed on silica gel (Merck, Kiesel gel 60H).

2-Allenyl-2-oxo-1,3,2-dioxaphosphorinane (2)——2-Chloro-1,3,2-dioxaphosphorinane (**1**, 46.5 g, 0.33 mol), which was prepared from trimethyleneglycohol with phosphorus trichloride in 68% yield,[7] was added to a stirred solution of propargyl alcohol (18.5 g, 0.33 mol) and triethylamine (33.5 g, 0.33 mol) in MeCN (400 ml) at −10 °C over a period of 30 min. After the addition, the mixture was warmed to room temperature and stirred for 16 h. The reaction mixture was filtered and the filtrate was refluxed for 1 h. The solvent was removed *in vacuo*. The residue was subjected to chromatography on silica gel with hexane–AcOEt (2 : 1, v/v) as eluent to give, in order of elution, the propynylphosphonate (**3**, 0.75 g, 1.4%) as crystals and the allene (**2**, 37.65 g, 72%) as crystals.

2: mp 40—42 °C (from ether). *Anal.* Calcd for $C_6H_9O_3P$: C, 45,01; H, 5.67. Found: C, 44.76; H, 5.66. IR (KBr): 1970, 1950 (C=C=C), 1280 cm^{-1}. NMR ($CDCl_3$) δ: 1.78—1.98 (1H, m, >CH), 2.04—2.38 (1H, m, >CH), 4.24—4.64 (4H, m, 2 × OCH_2), 5.05 (1H, d, J = 7 Hz, =C=CH), 5.12 (1H, d, J = 7 Hz, =C=CH), 5.40 (1H, t, J = 7 Hz, –CH=).

2-(1-Propynyl)-2-oxo-1,3,2-dioxaphosphorinane (3)——mp 63—66 °C (ether). *Anal.* Calcd for $C_6H_9O_3P$: C,

45.01; H, 5.67. Found: C, 44.84; H, 5.82. IR (KBr): 2220 (C≡C), 1295, 1280 cm^{-1}. NMR ($CDCl_3$) δ: 1.64—1.83 (1H, m, >CH), 2.07 (3H, d, J=5 Hz, CH_3), 2.18—2.44 (1H, m, >CH), 4.30—4.55 (4H, m, 2×OCH_2).

2-(2-Isobutylamino-1-propenyl)-2-oxo-1,3,2-dioxaphosphorinane (4)——Isobutylamine (8.05 g, 0.11 mol) was added to a stirred solution of **2** (8.8 g, 0.055 mol) in MeCN (40 ml) at 10 °C. After the addition, the mixture was stirred for 16 h at room temperature, then warmed at 60 °C for 1 h. The solvent was removed *in vacuo* and the residue was crystallized from ether–AcOEt to give the enamine (**4**, 11.6 g, 91%) as an (*E*/*Z*) mixture, mp 95—97 °C (from ether–AcOEt). *Anal.* Calcd for $C_{10}H_{20}NO_3P$: C, 51.49; H, 8.57; N, 6.01. Found: C, 51.17; H, 8.41; N, 5.98. IR (KBr): 3250, 3080, 1590, 1555, 1220 cm^{-1}. NMR ($CDCl_3$) δ: 0.94 (6H, d, J=7 Hz, 2×CH_3), 1.64—1.98, 2.00—2.20 (each of 1H, m, >CH_2), 1.93, 2.20 [total 3H (4:3), d, J=1 Hz, =CCH_3], 2.81, 2.91 [total 2H (4:3), t, J=7 Hz, NCH_2), 3.56, 3.86 [total 1H (4:3), d, J=12.5, 10 Hz, PCH=], 4.06—4.35 (2.6H, m, OCH_2 and NH), 4.46—4.66 (2H, m, OCH_2), 7.65 (0.4H, br, NH).

The reaction of **2** (1.60 g, 0.01 mol) with propylamine (0.80 g, 0.011 mol) or diethylamine (0.60 g, 0.011 mol) was also carried out by the above method to give the enaminophosphonate in a good yield as an oil, which was used directly in the next reaction without purification.

Compound **4** was also prepared from **3** (0.01 mol) and isobutylamine (0.35 mol) at room temperature in 70% yield.

2-Acetonyl-2-oxo-1,3,2-dioxaphosphorinane (5a)——Oxalic acid dihydrate (7.2 g, 0.0575 mol) was added to a stirred solution of **4** (11.66 g, 0.05 mol) in $CHCl_3$–AcOEt (100 ml, 3:1) at room temperature (the salt immediately precipitated), then stirred for 18 h. The precipitated isobutylamine oxalate was filtered off, and the filtrate was concentrated *in vacuo* to give the acetonylphosphonate (**5a**, 8.9 g, quantitative yield) as a single spot on thin layer chromatography (TLC) (Merck silica gel No. 5554, AcOEt), bp 163—165 °C (1 mmHg, 8.1 g, 91%). Compound **5a** was identified by NMR and IR comparisons with an authentic sample.

The hydrolysis of the crude enaminophosphonate obtained from propylamine or diethylamine was carried out by the above method in AcOEt (30 ml) to give pure **5a** in 76% or 73% yield, respectively.

Synthesis of Benzylideneacetonylphosphonates (7)——2-[1-(2-Nitrobenzylidene)acetonyl]-2-oxo-1,3,2-dioxaphosphorinane (**7a**): A solution of 2-nitrobenzaldehyde (5.89 g, 0.039 mol) and isobutylamine (3.42 g, 0.0468 mol) in CH_2Cl_2 (20 ml) was stirred for 15 h at room temperature, then a dehydrating agent ($MgSO_4$) was added. The solvent was removed to give the crude imine (**6a**, 5.9 g) as an oil. A solution of **5a** (5.34 g, 0.03 mol), **6a** (5.9 g) and acetic anhydride (6.1 g, 0.06 mol) in benzene (50 ml) was refluxed with stirring for 4 h. The reaction mixture was concentrated *in vacuo* and the residue was subjected to chromatography on silica gel with hexane–AcOEt (2:1, v/v) as the eluent to afford an oil (7.57 g). The oil was diluted with ether, then the precipitated crystals were collected to give **7a** (6.34 g, 68%) as pure crystals, mp 140—146 °C. The filtrate was concentrated to give *N*-acetylisobutylamine (1.17 g) as an oil. The final eluate contained **5a** (0.91 g, recovery of 17%). Compound **7a** was identified by NMR and IR comparison with an authentic sample.

The other reactions (**7**) were carried out in the same manner. The results are listed in Table I.

Synthesis of DHP-218——A solution of **7a** (80 g), methyl 3-aminocrotonate (32.5 g, 1.1 eq) and activated $CaSO_4$ (90 g) in MeCN (600 ml) was refluxed with stirring for 10 h by the use of a Soxhlet extractor with activated $CaSO_4$. During the reaction, the solvent was continuously removed. The residue was dissolved in hot $CHCl_3$ (2.5 l), the solution was filtered, and the filtrate was concentrated *in vacuo*. The residue was triturated with AcOEt (500 ml) and the precipitated solid was collected to give crude DHP-218 (92.1 g, 88%). Recrystallization from $CHCl_3$–AcOEt gave pure DHP-218 (85.2 g, 81%), mp 246—248 °C (dec.).

The use of molecular sieves or $MgSO_4$ as a dehydrating agent on the 0.01 mol scale gave pure DHP-218 in 73% or 70% yield, respectively.

References

1) I. Morita, K. Kunimoto, M. Tsuda, S. Tada, K. Kise, and K. Kimura, *Chem. Pharm. Bull.*, **35**, 4144 (1987).
2) Y. Kimura, H. Fukui, M. Tanaka, M. Okamoto, A. Morino, A. Miura, K. Kimura, and H. Enomoto, *Arzneim.-Forsch.*, **36**(II), 1329 (1986); Y. Kimura, H. Fukui, M. Tanaka, M. Okamoto, A. Miura, K. Kimura, and H. Enomoto, *ibid.*, **36**(II), 1336 (1986).
3) I. Morita, M. Tsuda, M. Kise, and M. Sugiyama, *Chem. Pharm. Bull.*, **35**, 4711 (1987).
4) I. Morita, S. Tada, K. Kunimoto, M. Tsuda, M. Kise, and K. Kimura, *Chem. Pharm. Bull.*, **35**, 3898 (1987).
5) J.-Y. Merour, N. T. Thuong, and P. Chalrier, *C. R. Acad. Sci. Paris*, **t. 280**, 473 (1975).
6) G. Franckowiak and S. Goldmann, Ger. Offen. DE 3517950 (1986) [*Chem. Abstr.*, **106**, 84397*c* (1987)].
7) H. J. Lucas, F. W. Mitchell, Jr., and C. N. Glycols, *J. Am. Chem. Soc.*, **72**, 5491 (1950).