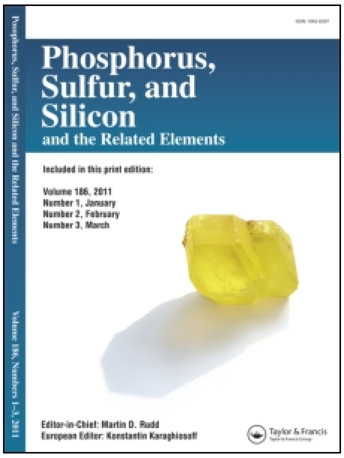

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Lewis Acid-Mediated Nucleophilic Addition of Dialkylphosphite to C=N Double Bond of Hydrazones

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Lewis Acid–Mediated Nucleophilic Addition of Dialkylphosphite to C=N Double Bond of Hydrazones

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*The synthesis of new phenyl substituted derivatives (**2**) of α-hydrazinoalkylphosphonic acids by Lewis acid–mediated addition of dialkylphosphite to hydrazones, derived from benzoylhydrazines and benzaldehydes, is described. Reactions were successfully promoted by boron trifluoride etherate under mild conditions in methylene chloride at room temperature.*

Keywords Dialkylphosphite; α-hydrazinoalkylphosphonic acids derivatives; hydrazones; Lewis acid; nucleophilic addition

INTRODUCTION

Hydrazinoalkylphosphonic acids and their derivatives, as analogs of more renowned aminoalkylphosphonic acids and their derivatives, have gradually gained some interest recently due to their potential biological activity.[1] With a very few examples available in the literature, the most efficient method to synthesize derivatives of α-hydrazinoalkylphosphonic acids involves the addition of dialkylphosphite to compounds bearing a hydrozono group (C=N-N). However, the reaction condition was either reported as a base-catalyzed nucleophilic addition or at a high reaction temperature, which dramatically decreases its scope and utility in the preparation of different derivatives of this class of compounds. Thus, Rachon and Wasielewski reported that the preparation of α-hydrazinoalkylphosphonic acids was based on the addition of diethyl phosphite on aliphatic aldazine catalyzed by a base.[2]

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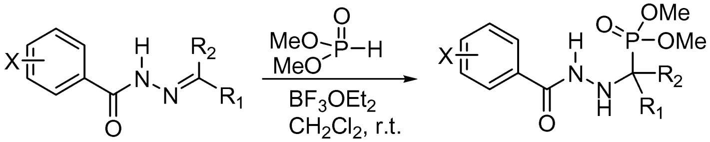
A similar reaction condition, in which diethyl phosphite was added to a bis-imines at 80–110 °C in the presence of triethylamine was recently reportedby Ali.[3] Diel and Maier described a method to prepare α- hydrazinomethylphosphonic acid derivatives using the addition of dialkylphophite to hydrazone at 120–130 °C, in which their hydazone was prepared by the condensation of formaldehyde with a hydrazine.[1] Unfortunately, this method does not apply to hydrazones that are derived from carbonyl compounds other than formaldehyde. As a matter of fact, it has been mentioned that other substituted hydrazones are inert to nucleophilic addition of dialkylphosphite.[4]

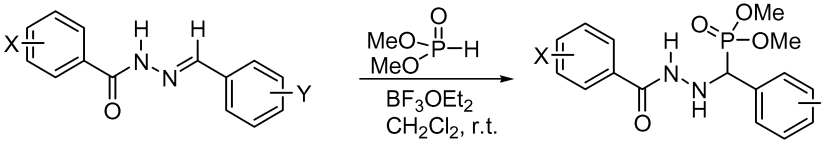


SCHEME 1

Recently, we have reported the preparation of α-hydrazino-(disubstituted)methyl-phosphonic acid derivatives as depicted in Scheme 1, in which the dialkylphosphite group was introduced, via a nucleophilic addition mediated by boron trifluoride etherate, to hydrazones prepared from benzoylhydrazine and various dialkyl ketones, representing a convenient method for the synthesis of new derivatives of α-hydrazino-disubstitutedalkylphosphonic acids.[5]

RESULTS AND DISCUSSION

As an extension of the new method we developed, we want to report here the synthesis of another series of new compounds, as shown in Scheme 2. As indicated in our previous report for the synthesis of derivatives of α-hydrazino-disubstitutedalkyl-phosphonic acids, the preparation of compounds **(2)** was also inspired by the work of Schlemminger et al., in which various phosphites were successfully added onto heterocyclic imines mediated by Lewis acid, such as boron trifluoride etherate.[6]



(1a)–(1g) **(2a)–(2g)**

SCHEME 2

TABLE I Hydrazone Intermediates (1a)–(1g)

Entry	X	Y	Yield	mp(°C)
(1a)	4-Cl	H	90%[a]	231–233[7]
(1b)	H	4-Cl	96%[a]	167–168[8]
(1c)	4-Cl	4-Cl	96%[a]	219–222[9]
(1d)	4-NO_2	4-Cl	96%[a]	256–257[10]
(1e)	H	4-CH_3	95%[a]	159–161[11]
(1f)	4-Cl	4-CH_3	96%[a]	212–213[12]
(1g)	H	H	90%[b]	209–211[13]

[a] Compounds were prepared by **Method A**: refluxing in ethanol.

[b] Compound was prepared by **Method B**: reaction in hexane at room temperature. All compounds were characterized by comparison of their spectroscopic and physical data with those reported in the literature indicated.

Hence, the desired compounds (**2**) have been synthesized successfully via BF_3-mediated nucleophilic addition of dialkylphosphite to various benzaldehyde hydrazones at room temperature in methylene chloride.

The required hydrazone intermediates (**1a**)–(**1g**) were prepared using the condensation of benzoylhydrazines and benzaldehydes either in refluxing ethanol (**Method A**) or in hexane with or without the presence of a drying agent at room temperature (**Method B**). The known compounds have been reported before, and yields are usually high as shown in Table I.

The prepared hydrazones were initially reacted with dimethylphosphite without adding Lewis acid as a catalyst. As expected, the reaction resulted in no reaction, either at room temperature or at refluxing temperature of the solvent used. On the other hand, when one equivalent of boron trifluoride etherate was added into the reaction mixture at room temperature, the hydrazone was converted into the desired product as anticipated. TLC indicated that all reactions showed only one major product with moderate yields ranging from 53–89%. Pure products can be obtained by column chromatography giving either a semisolid or a crystallizing compound as shown in Table II. All final compounds were demonstrated by IR, ^1H NMR, and mass spectroscopy. Several compounds, including (**2a**), (**2e**), and (**2f**), had also been identified by ^{31}P NMR spectroscopy.

EXPERIMENTAL

^1H NMR spectra were obtained by a Varian Mercury 200 MHz in $CDCl_3$ solvent (unless otherwise noted), and chemical shifts were reported in δ ppm. ^{31}P NMR spectra were determined on a Bruker Avance 500

TABLE II Hydrazinomethylphosphonates (2a)–(2g)

Entry	H	Y	Yield[a]	mp(°C) or Physical appearance
(2a)	4-Cl	H	33%	116–120
(2b)	H	4-Cl	21%	semisolid
(2c)	4-Cl	4-Cl	30%	semisolid
(2d)	-NO_2	4-Cl	18%	semisolid
(2e)	H	4-CH_3	42%	129–130
(2f)	4-Cl	4-CH_3	23%	154–155
(2g)	H	H	53%	pink oil

[a] All pure compounds were obtained by column chromatography on silica gel.

MHz spectrometer using 85% phosphoric acid as external standard. Melting points were uncorrected. IR spectra were obtained by a Perkin Elmer Paragon 500 and reported in wave number. Mass spectral (ESI) data were obtained from the Applied Chemistry Department, Chaoyang University of Technology, and HRMS data were obtained from the Instruments Center, National Chung Hsing University. All the reagents were used as received from the commercial sources, unless otherwise noted.

General Procedure for the Preparation of Hydrazones (1a) to (1g): Method A

2-(Phenylmethylene)-(4-chloro)benzoic acid hydrazide (1a)

To a solution of 4-chlorobenzhydrazide (1.00 g, 5.80 mmol) in ethanol (50 mL), benzaldehyde (0.62 g, 5.80 mmol) was added. The mixture was refluxed for 2.5 h. The mixture was cooled down to room temperature, and the solvent was evaporated by a rotary evaporator to give a residue. The residue was triturated by hexane, and the resulting precipitate was collected by suction-filtration and washed with a small amount of hexane to give a white solid, 1.36 g (90%), mp 231–233°C (Lit.[7], mp 229°C). ^{1}H NMR($CDCl_3$): δ 8.29 (s, 1H), 7.86 (d, J = 8.2 Hz, 4H), 7.78 (br s, 1H), 7.33–7.47 (m, 5H, Ar-H). The syntheses of (**1b**) to (**1f**) were conducted in a similar way as described in Method A. Their physical data (melting points) have been recorded in Table I.

Method B

2-(Phenylmethylene)benzoic acid hydrazide (1g)

To a solution of benzohydrazide (0.50 g, 3.7 mmol) in hexane (10 mL), benzaldehyde (1.16 g, 10.9 mmol) was added with magnetic stirring. The mixture was stirred at room temperature for 14 h. A resultant precipitate was obtained by suction-filtration, and washed with hexane to give a white solid, 0.72 g (88 %). mp 211–212°C (Lit.[13], mp 210–212°C).

General Procedures for the Syntheses of Dimethyl Hydrazino-Phenylsubstituted-Methyl-Phosphonates

2-[(Dimethoxyphosphinyl)phenylmethyl]–(4-chloro) benzoic acid hydrazide (2a)

To a solution of (**1a**) (0.50 g, 1.9 mmol) in THF (40 mL) at room temperature, dimethylphosphite (0.21 g, 2.1 mmol) was added followed by boron trifluoride diethyl etherate (0.68 g, 2.3 mmol). The mixture was stirred at room temperature for 14 h. The solvent was evaporated by a rotary evaporator, and the residue was dissolved in ethyl acetate (30 mL) and washed with water (30 mL) three times and with saturated NaCl solution one time. The organic layer was dried over anhydrous sodium sulfate and filtered. The solvent was evaporated to give a crude product, 0.63 g (89%). Pure product was obtained by column silica gel chromatography eluted with acetone/methylene chloride (1:3) giving 0.19 g (30%) as yellow solid, mp 116∼120 °C. IR(film) cm^{-1}: 3273, 2955, 2952, 2854, 1717, 1652, 1560, 1540; ^1H NMR ($CDCl_3$): δ 8.53 (s, 1H), 7.65∼7.28 (m, 9H), 4.63 (d, J = 13.2 Hz, 1H), 3.69 (dd, J = 3.6, 10.6 Hz, 6H); ^{31}P NMR: δp ($CDCl_3$, 202.46 MHZ): δ24.01 ppm; HRMS calculated for $C_{16}H_{18}ClN_2O_4P$: 368.0693, Found: 368.0690.

2-[(Dimethoxyphosphinyl)-4-chlorophenylmethyl]benzoic acid hydrazide (2b)

A similar reaction as described in (**2a**) was conducted at room temperature for 14 h to give a crude product, 0.63 g (89%), which was purified by column silica gel chromatography eluted with actone/methylene chloride (1:3) giving a white solid, (yield 30%). Mp 116–120 °C; IR (film) cm^{-1}: 3274, 2925, 2854, 1717, 1653, 1560, 1540; ^1H NMR($CDCl_3$): δ 8.24 (s, 1H), 7.69∼7.27 (m, 9H), 4.65 (d, J = 14.0 Hz, 1H), 3.73 (dd, J = 1.0, 10.6 Hz, 6H); HRMS calculated for $C_{16}H_{18}ClN_2O_4P$: 368.0693, Found: 368.0695.

2-[(Dimethoxyphosphinyl)-4-chlorophenylmethyl]-(4-chloro) benzoic acid hydrazide (2c)

A similar reaction as described in (**2a**) was conducted at room temperature for 12 h to give a crude product, 0.25 g (61%), which was purified by column silica gel chromatography eluted with ethyl acetate/

hexane (1:3), giving a pure semi-solid (yield 30%); IR (film) cm^{-1}: 3260, 2925, 2850, 1717, 1653, 1558, 1540; ^{1}H NMR (CDCl$_3$): δ 8.37 (s, 1H), 7.75~7.32 (m, 8H), 4.61 (d, J = 13.8 Hz, 1H), 3.70 (dd, J = 2.4, 10.6 Hz, 6H); HRMS calculated for $C_{16}H_{17}Cl_2N_2O_4P$: 402.0303, Found: 402.0298.

2-[(Dimethoxyphosphinyl)-4-chlorophenylmethyl]-(4-nitro) benzoic acid hydrazide (2d)

A similar reaction as described in (**2a**) was conducted at room temperature for 12 h to give a crude product, 0.26 g (64%), which was purified by column silica gel chromatography eluted with ethyl acetate/hexane (1:1), giving a pure semi-solid (17 %); IR(film) cm^{-1}: 3241, 2928, 2857, 1717, 1653, 1558, 1540; ^{1}H NMR(CDCl$_3$): δ 8.39~7.34 (m, 9H), 4.66 (d, J = 14.2 Hz, 1H), 3.46 (s, 3H), 3.11 (s, 3H); HRMS calculated for $C_{16}H_{17}ClN_3O_6P$: 413.0543, Found: 413.0540.

2-[(Dimethoxyphosphinyl)-4-methylphenylmethyl]benzoic acid hydrazide (2e)

A similar reaction as described in (**2a**) was conducted at room temperature for 24 h yielding a crude product 1.21 g (83%), which was purified by column silica gel chromatography eluted first with 100% ethyl acetate followed by methanol/methylene chloride (5:95). The collected material was further crystallized from ethyl acetate to give a white solid, 0.61 g (42%), mp 129–130 °C, ^{1}H NMR (CDCl$_3$): δ 7.98 (d, J = 6.6 Hz, 1H), 7.69~7.17 (m, 9H), 5.50 (dd, J = 5.4, 18.2 Hz, 1H), 4.58 (dd, J = 2.4, 12.6 Hz, 1H), 3.74 (dd, J = 3.8, 10.5 Hz, 6H), 2.36~2.35 (s, 3H); ^{31}P NMR: δp (CDCl$_3$, 202.46 MHZ): δ24.30 ppm; MS(ESI) m/z 349.060 [M+H]$^+$.

2-[(Dimethoxyphosphinyl)-4-methylphenylmethyl]-(4-chloro) benzoic acid hydrazide (2f)

A similar reaction as described in (**2a**) was conducted at room temperature for 50 h to give a crude product, 1.24 g (89%), which was purified by column silica chromatography eluted with acetone/methylene chloride (1:3). The collected material was further crystallized from methylene chloride to give 0.32 g (23%), mp 154–155 °C; ^{1}H NMR (CDCl$_3$): δ 8.12 (d, J = 7.2 Hz, 1H), 7.65–7.16 (m, 8H), 5.48 (dd, J = 7.6, 18.4 Hz, 1H), 4.55 (dd, J = 2.6, 12.4 Hz, 1H), 3.73 (dd, J = 4.2, 11.6 Hz, 6H), 2.36–2.35 (s, 3H); ^{31}P NMR: δp (CDCl$_3$, 202.46 MHZ): δ24.24 ppm; MS(ESI)m/z 383.036 [M+H]$^+$.

2-[(Dimethoxyphosphinyl)phenylmethyl]benzoic acid hydrazide (2g)

A similar reaction as described in (**2a**) was conducted at room temperature for 46 h to give a crude product. Pure product was obtained by column silica gel chromatography eluted with 100% ethyl acetate to give a pink oil, 0.79 g (53%); ^{1}H NMR ($CDCl_3$): δ 8.07 (d, 1H, J = 7.0 Hz, 1H), 7.68–7.28 (m, 10H), 5.52 (ddd, J = 2.2, 7.0, 17.6 Hz, 1H), 4.64 (dd, J = 2.2, 13.2 Hz, 1H), 3.73 (dd, J = 1.8, 10.6 Hz, 6H); MS(ESI) m/z 335.085 $[M+H]^+$.

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