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Lewis Acid-catalyzed Nucleophilic Addition of Dialkylphosphite to Hydrazones Derived from Benzoylhydrazine and aliphatic ketones

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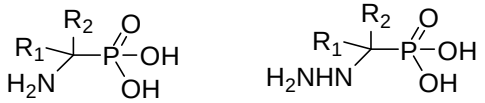
Abstract: The synthesis of new derivatives **2** of α-hydrazino-(disubstituted)- alkylphosphonic acids by the Lewis acid mediated addition of dialkylphosphite to hydrazones, derived from benzoylhydrazine and aliphatic ketones, is described. Reactions were successfully and catalytically promoted by BF_3 etherate under mild condition in methylene chloride at room temperature.

Keywords: Lewis acid; Nucleophilic addition; dialkylphosphite; α-hydrazinoalkylphosphonic acids; ketone hydrazones; benzoic acid hydrazides.

1. Introduction

It has been recognized that the phosphonate group is an important pharmacophore in both agricultural and pharmaceutical chemistries [1-4]. For example, α-aminoalkylphosphonic acids 1 and related derivatives represent a class of compounds with strong biological activities including antibiotics [5], herbicides [6], insecticides, fungicides [7], and anti-viral agents [8]. Although numerous synthetic methods, including the synthesis of chiral α-aminoalkylphosphonic acids, have been reported; the synthesis of corresponding α-hydrazinoalkylphosphonic acids 2 and their derivatives has received much less attention.

With a very few examples available in the literature, the synthesis of α-hydrazinoalkylphosphonic acids, in general, involved with the addition of dialkyl phosphite to compounds bearing with a hydrozono group (C=N-N), followed by a subsequent treatment leading to the final products. Thus, Rachon reported that the preparation of α-hydrazinoalkylphosphonic acids 5 was based on the addition of diethyl phosphite on aldazine 3 catalyzed by abase, followed by acid hydrolysis of intermediate 4 [9].



1 2

Figure 1. Structures of α-aminoalkylphosphonic acids 1 and α-hydrazinoalkylphosphonic acids 2

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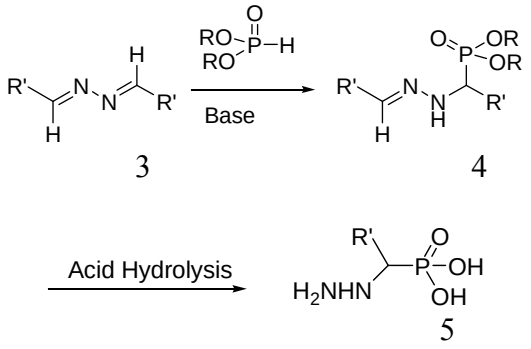
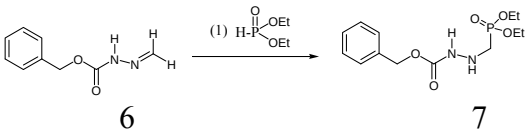
Scheme 1: Rachon's method



Maier described a method to prepareα- hydrazinomethylphosphonic acid derivatives **7** by the addition of dialkylphophite to hydrazone **6,** the latter was prepared by the condensation of formaldehyde with a hydrazine, in which one of the amino functions was protected by benzyloxycarbonyl group which can be later removed smoothly bycatalytic hydrogenation [10].

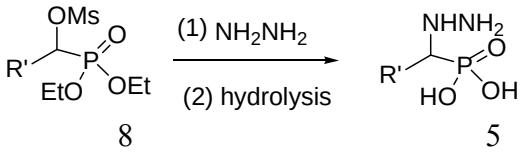
Scheme 2: Maier's method:



Unfortunately, this method does not apply to hydrazones which 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 [11-12].

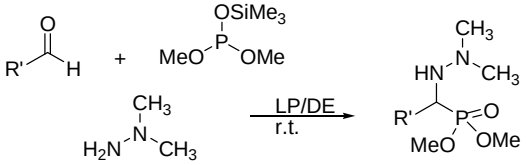
Alternatively, Yuan and Maier reported that nucleophilic substitution of diethyl α -sulfonyloxyalkylphosphonates 8 by hydrazine followed by acid hydrolysis resulted in the synthesis of α- hydrazinoalkylphosphonic acids 5 [11].

Scheme 3: Yuan and Maier's method



Recently, the synthesis of α - hydrazinomethylphosphonic derivatives was reported by Heydari and co-workers, in which a one pot reaction of a three-component reaction (aldehydes, N,N-dimethylhydrazine and dimethyl(trimethylsilyl)phosphite) was catalyzed by lithium perchlorate/diethyl ether (LP/DE), as shown in the following Scheme 4 [13]:

Scheme 4: Heydari's synthesis



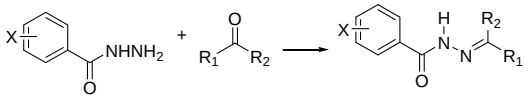
All the above mentioned methods, however, involved with the preparations of (monosub -stituted) alkyl, namely (monosubstituted) methyl, analogs of α-hydrazinoalkylphosp -honic acids or their derivatives. To the best of our Knowledge, no α -hydrazino- (disubstituted) methylphosphonic acids or their derivatives have been reported in the literature.

2. Results and discussion

Herein, we wish to report a convenient method for the synthesis of the derivatives of α-hydrazino- (disubstituted) methylphospho -nic acids via Lewis acid promoted nucleophilic addition of dimethylphosphite on several ketone hydazones 11 which were readily prepared by the conventional method in which benzolyhydrazide 9 is condensed with ketone **10** with or without solvent. Table 1 lists the compounds 11a to 11e discussed in

this report.

Scheme 5: Synthesis of hydrazone intermediates



9 10 11

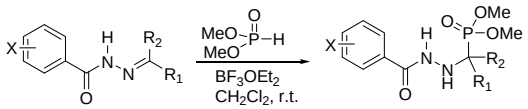
Table 1. A list of hydrazone intermediate

Entry	X	R_1	R_2	Yield
11a	H	Me	Me	99%
11b	4-Cl	Me	Me	82%
11c	4-NO_2	Me	Me	98%
11d	H	-$(CH_2)_4$-		95%
11e	H	Me	Et	93%

Hydrazones 11 was originally reacted with dimethylphosphite without adding Lewis acid as a catalyst resulting with no reaction, either at room temperature or at refluxing temperature of the solvent used. Inspired by the work of Martens et al., in which various phosphites were successfully added on heterocyclic imines mediated by Lewis acid, such as boron trifluoride etherate [14], we decided to investigate the BF_3-mediated hydrophosphonylation on our hydrazone system. In the beginning of this process, we used one equivalent of BF_3 for the hydrophosphonylation of hydrazones 11 as demonstrated in Martens experiments of preparing α-aminoalkylphosp -honic derivatives. After several attempts, we found out that a catalytic amount (~ 0.5 equivalents) of BF_3 is enough for the nucleophilic addition of dimethylphosphite on the hydrazones in our exeperiments with reasonable yields. Table 2 shows a list of compounds, 12a to 12e, we selected to prepare.

It must be pointed out that the role of BF_3 as a catalyst for this reaction seems to be unique, because when other Lewis acids, such as $SnCl_4$ and $TiCl_4$, were utilized using similar reaction conditions to that of BF_3, no anticipated reaction was observed.

Scheme 6: Lewis acid catalyzed nucleophilic addition



11 12

Table 2. List of synthesized α-hydra- zino-(disubs -tituted)methylphosphonic acids

Entry	X	R_1	R_2	Yield[a]
12a	H	Me	Me	44%
12b	4-Cl	Me	Me	28%
12c	4-NO_2	Me	Me	14%
12d	H	-$(CH_2)_4$-		13%
12e	H	Me	Et	44%

a: purified yields by column chromatography

3. Conclusion

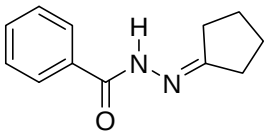
We have successfully prepared deriva- tives of α-hydrazino-(disubstituted) methylphosphonic acids via Lewis acid catalyzed nucleophilic addition of dimethylphosphite to several ketone hydazones. This method represents the first synthesis of this class of compounds under a mild reaction condition. Preliminarily, the three species of Lewis acids under investigation were BF_3, $SnCl_4$, and $TiCl_4$; however only BF_3 being able to promote the reaction catalytically.

Experimental

NMR spectra were obtained by 200 MHz in $CDCl_3$ solvent (unless otherwise noted) and chemical shifts were reported in δ ppm. Melting points were uncorrected. IR spectra were obtained by Perkin Elmer Paragon 500 and reported in wave number. All the reagents were used as received from the commercial sources, unless otherwise noted. Mass spectra and HRMS data were obtained from the Instruments Center, National Chung Hsing University.

General procedure for the preparation of hydrazones from various ketones:

A typical reaction for the preparation of **cyclopentanone benzoylhydrazone 11d**:



Procedure:

The mixture of benzoylhydrazine (0.50 g, 3.7 mmol) and cyclopentanone (0.93 g, 11 mmole) with magnetic stirring was refluxed for 12 h. Cooled to room temperature to give a white precipitate and washed with some hexane to give a white solid, 0.70 g (yield: 95 %). mp 150-152 ^{o}C (lit.[15] mp 150-152 ^{o}C) IR (film) cm^{-1}: 3225, 1728, 1652, 1539, 1495; ^{1}HNMR ($CDCl_3$) δ: 1.78-1.99 (4H, m), 2.30-2.60 (4H, m), 7.42-7.54 (3H, m),7.78-7.82(2H, m), 8.45 (1H, br s).

Acetone benzoylhydrazone 11a: Compound appears as a white solid, mp 142~143.3 ℃ (lit [16] mp 127-129 ^{o}C IR (film) cm^{-1}: 3457, 1729, 1650, 1580, 1488; ^{1}H NMR ($CDCl_3$) δ : 1.97 (2H, s), 2.16 (4H, s), 7.27~7.54 (3H, m), 7.81 (2H, d, J = 6.8 Hz), 8.62 (1H, s).

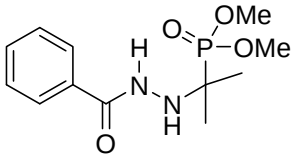
Acetone 4-chlorobenzolyhydrazone 11b: Compound appears as a white solid, mp 186-187℃ (lit [17] mp 188~189℃). IR (film) cm^{-1}: 3303, 1733, 1653, 1558, 1460; ^{1}H NMR ($CDCl_3$) δ : 1.97 (3H, s), 2.12 (3H, s), 7.41 (2H, d, J = 8.6 Hz), 7.76 (2H, d, J = 6.6Hz), 8.68 (1H, s);

Acetone 4-nitrobenzoylhydrazone 11c: Compound appears as a pale yellow solid, mp 162.5~167.2℃.IR (film) cm^{-1}: 3435, 1733, 1543, 1490, 1349; ^{1}H NMR ($CDCl_3$) δ : 2.01 (4H, s), 2.20 (2H, s), 7.80 (2H, d, J = 7.6 Hz), 8.31 (2H, d, J = 7.6 Hz), 8.69 (1H, s).

Methylethyl ketone benzoylhydrazone 11e: Compound appears as a white solid, mp 110.5-111℃. IR (film) cm^{-1}: 3231, 1733, 1652, 1636, 1578; ^{1}H NMR ($CDCl_3$) δ : 1.17 (3H, t, J = 5.6 Hz), 1.95(3H, s), 2.44~2.48 (2H, m), 7.26~7.54 (3H, m), 7.81 (2H, d, J = 4.8Hz), 8.6 (1H, s).

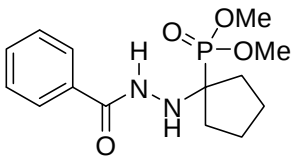
General Procedure for the Nucleophilic addition of dimethyl phosphite on various hydrazones:

Example 1: The preparation of **2-[(dimethoxyphosphinyl)dimethylmethyl] benzoic acid hydrazide 12a**:



Procedure: To a solution of acetone benzoylhydazone (0.65g, 3.6 mmol) in methylene chloride (10 mL) at room temperature with magnetic stirring was added dimethylphosphite (0.44 g, 4 mmol) followed by boron trifluoride etherate (0.65 g, 1.8 mmol). The mixture was stirred for further 24 h. Water (80 mL) and methylene chloride (80 mL) were added and the aqueous layer was extracted by methylene chloride (2 x 80 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and filtered. The volatiles were evaporated on a rotary evaporator to give a white solid, 0.68 g (64% yield). A pure compound was obtained by column chromatography eluted with actone/methylene chloride (1:3) to give a white solid, mp 134.2-135.3 ^{o}C. IR (film) cm^{-1}: 3435, 1734, 1559, 1508; ^{1}H NMR ($CDCl_3$) δ : 1.40 (6H, d, J = 15.6 Hz), 3.87 (6H, d, J = 13 Hz), 7.26~7.52 (3H, m), 7.79~7.84 (m, 2H), 8.56 (1H, d, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ : 21.11, 53.52, 53.66, 55.74, 58.96, 126.77, 128.60, 131.64, 132.44, 165.59; HRMS(EI): Calculated for $C_{12}H_{19}N_2O_4P$: 286.1082, Found: 286.1086; MS-EI: 178(31), 177(100), 105(60), 77(36), 56(50).

Example 2: The preparation of **2-[(dimethoxyphosphinyl)cyclopentylmethyl] benzoic acid hydrazide 12d:**



Procedure: To a solution of cyclopentanone benzoylhydrozone (1.0 g, 4.9 mmol) in methylene chloride (10 mL) at room temperature with magnetic stirring was added dimethylphosphite (0.60 g, 5.4 mmol) followed by boron trifluoride etherate (0.73 g, 2.4 mmol). The mixture was stirred for further 24 h. Water (100 mL) and methylene chloride (25 mL) were added and the aqueous layer was extracted by methylene chloride (2 x 25 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and filtered. The volatiles were evaporated on a rotary evaporator to give a residue, 0.54 g (70 % crude yield). A pure product was obtained by column chromatography eluted with actone/methylene chloride (1:3) as a thick oil. IR (film) cm^{-1}: 3274, 1729, 1540, 1480; ^1H NMR ($CDCl_3$) δ : 1.26(1H, b), 1.70 ~2.01 (8H, m), 3.86 (3H, d, J = 10.4), 7.39~7.51 (3H, m), 7.78~7.83 (2H, m), 8.79 (1H, s); ^{13}C NMR ($CDCl_3$) δ : 24.36, 24.57, 32.15, 32,23, 53.50, 53.64, 65.55, 68.89, 126.76, 128.59, 131.63, 132.40, 165.33; HRMS(EI): Calculated for $C_{14}H_{21}N_2O_4P$: 312.1239, Found: 312.1238; MS-EI: 204(25), 203(100), 173(17), 105(62), 77(31).

2-[(dimethoxyphosphinyl)dimethylmethyl] 4-chlorobenzoic acid hydrazide 12b:

Compound appears as a white solid, mp 94-96℃. IR (film) cm^{-1}: 3435, 1733, 1596, 1476; ^1H NMR ($CDCl_3$) δ : 1.38 (6H, d, J = 15.6 Hz), 3.85 (6H, d, J = 10.4 Hz), 7.40 (2H, d, J = 11 Hz), 7.77 (2H, d, J = 11 Hz), 8.78 (1H, s); ^{13}C NMR ($CDCl_3$) δ : 21.10, 53.53, 55.69, 58.90, 128.25, 128.81, 130.80, 137.84, 164.62; HRMS(EI): Calculated for $C_{12}H_{18}ClN_2O_4P$: 320.0693, Found: 320.0686; MS-EI: 213(35), 211(100), 195(24), 139(56), 56(34).

2-[(dimethoxyphosphinyl)dimethylmethyl] benzoic acid hydrazide 12e

Pure Compound appears as a pale yellow solid, mp 134.5~136℃ IR (film) cm^{-1}: 3365, 1733, 1558, 1507, 1347; ^1H NMR ($CDCl_3$) δ : 1.40 (6H, d, J = 15.4 Hz), 3.87 (6H, d, J = 10.2 Hz), 7.80 (2H, d, J = 8.8 Hz), 8.30 (2H, d, J = 8.8 Hz), 9.01 (1H, s); ^{13}C NMR ($CDCl_3$) δ : 21.21, 53.67, 53.82, 55.68, 58.90, 132.84, 128.06, 138.05, 149.68, 163.25; HRMS(EI): Calculated for $C_{12}H_{18}N_3O_6P$: 331.0933, Found: 331.0940; MS-EI: 222(100), 206(60), 150(46), 104(26), 79(29), 56(31).

2-[(dimethoxyphosphinyl)ethylmethylmethyl] benzoic acid hydrazide 12e

Pure compound appears as a thick oil.
IR (film) cm^{-1}: 3425, 1733, 1558, 1501; ^1H NMR ($CDCl_3$) δ : 1.00(3H, t, J = 7.5 Hz), 1.32 (3H, d, J = 16.2 Hz), 1.71~1.89 (2H, m), 3.86 (6H, dd, J = 10.2 Hz), 7.39 ~7.51 (3H, m), 7.78~7.83 (2H, m), 8.76 (1H, d, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ : 6.97, 7.15, 17.23, 26.21, 53.76, 53.85, 53.90, 53.99, 58.86, 62.07, 127.01, 128.89, 131.88, 132.73, 165.16; HRMS(EI): Calculated for $C_{13}H_{21}N_2O_4P$: 300.1239, Found: 300.1244; MS-EI: 192(11), 191(100), 161(23), 105(53), 77(18).

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