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Microwave-Assisted Synthesis of 1-Hydrazinophosphonates via the Reaction of Aldazines with Dialkyl Phosphite

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ABSTRACT: *A simple, efficient, and novel method has been developed for the synthesis of 1-hydrazinophosphonic acids from aldazines. As described below, treatment of aldazines with diethyl phosphite gives the corresponding 1-hydrazinophosphonic acids in good yields. The reaction proceeds under microwave irradiation at 110°C and neutral condition without any additives such as base, acid, or catalyst. This method is easy, rapid, and gives good yields for the 1-hydrazinophosphonic acids.* © 2012 Wiley Periodicals, Inc. Heteroatom Chem 23:304–308, 2012; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.21019

INTRODUCTION

The organic chemistry of phosphorus compounds has become increasingly useful and important in organic synthesis [1–3]. Aminophosphonic acids, the phosphonic acid analogues of 1-amino carboxylic acids, are an important class of compounds that exhibit a variety of interesting and useful properties. 1-Aminophosphonic acids are valuable intermediates for the preparation of medicinal compounds and synthetic intermediates [4]. 1-Hydrazinophosphonic acids and their derivatives, as an analog of 1-aminophosphonic acids, are an important class of the compounds that exhibit a variety of interesting and useful properties. Some of these compounds show a good effect against the phytotoxic action of chloroacetanilide herbicides [5]. In contrast to the widely studied aminophosphonic acid derivatives [6–9], relatively few papers have reported on the chemistry of 1-hydrazinophosphonic acids. Synthetic routes to 1-hydrazinophosphonic acids involve base-catalyst condensation of diethyl phosphite with aromatic aldazines [10], nucleophilic substitution of 1-mesylated phosphonates with hydrazine [11], and reduction of 1-hydrazinophosphonates, prepared from diethyl oxophosphonates, with sodium borohydride or $BH_3 \cdot THF$ [12]. However, these methods have problems, including the use of chlorinated solvents and strong bases, low yields, and side reactions. In addition, some of the starting materials have to be synthesized and cleavage of a Et—O—P bond of the product occurred in the reaction process using strong bases [13].

Aldazines serve as a good precursor for the synthesis of numerous organic compounds, especially heterocyclic compounds [14, 15]. Recently, aldazines have received significant attention due to their utility in a number of interesting reactions, their biological properties, and their potential applications in bond formation, liquid crystals, and nonlinear optical materials [16]. These easily accessible precursors can be produced by the condensation of aldehydes or ketones with hydrazine in ethanol solution under reflux conditions [17].

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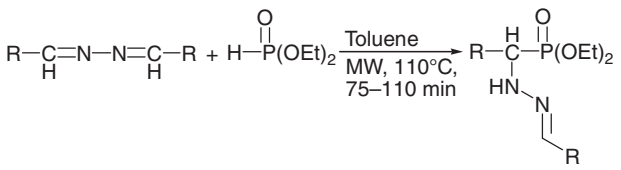


SCHEME 1 Treatment of aldazines with diethyl phosphite under microwave condition.

The application of microwave energy to accelerate organic reactions is of increasing interest and offers several advantages over conventional techniques [18]. Syntheses that normally require for periods can be achieved conveniently and very rapidly in a microwave reactor. As part of our efforts to introduce novel methods for the synthesis of organophosphorus compounds (for example, see Ref. [19]), herein we report a new method for the synthesis of 1-hydrazinophosphonates. We have found that the microwave-assisted reaction of aldazines, prepared by a novel solvent-free solid phase procedure, with diethyl phosphite in toluene at 110°C gives 1-hydrazinophosphonates in good yields (Scheme 1).

TABLE 1 Addition Reaction of Diethyl Phosphite to Aldazines in Toluene at 110°C under Microwave Irradiation

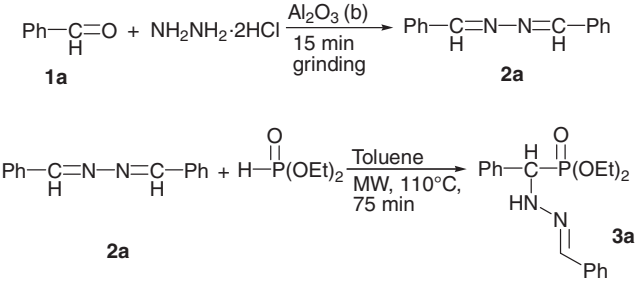
Entry	R	Product	Time (min)	Yield (%)[a]
1	C_6H_5-	**3a**	12[b]	–[c]
2	C_6H_5-	**3a**	75	75
3	*p*-MeC_6H_4-	**3b**	90	78
4	*p*-$MeOC_6H_4$-	**3c**	80	83
5	*p*-ClC_6H_4-	**3d**	90	76
6	*p*-BrC_6H_4-	**3e**	105	68
7	*p*-FC_6H_4-	**3f**	85	73
8	*p*-$NO_2C_6H_4$-	**3g**	110	62
9	*m*-MeC_6H_4-	–[d]	110	–
10	*m*-$MeOC_6H_4$-	–[d]	110	–
11	*m*-$NO_2C_6H_4$-	–[d]	110	–
12	*o*-ClC_6H_4-	–[d]	110	–
13	*o*-MeC_6H_4-	–[d]	110	–
14	β-naphthyl	–[d]	110	–
15	2-Thienyl	–[d]	110	–
16	$PhCH_2CH_2$-	–[e]	110	–

[a]Yields refer to the isolated pure products.
[b]Reaction carried out at reflux in toluene.
[c]Mixture of unknown compounds.
[d]Product is very unstable in the column chromatography, and a mixture of unknown compounds was obtained after purification.
[e]The method used basic alumina as a solid but failed to give the corresponding aliphatic diazine.

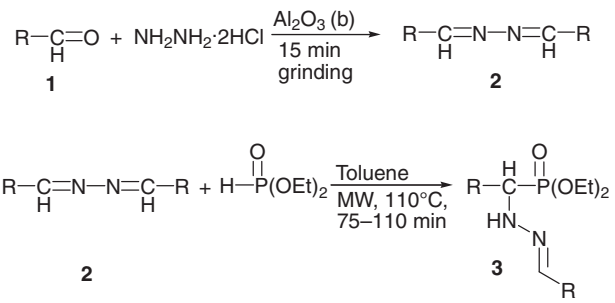
RESULTS AND DISCUSSION

The reaction of benzaldehyde (**1a**), chosen as a model compound, with hydrazine dihydrochloride followed by treatment with diethyl phosphite was studied under the various reaction conditions (Scheme 2). The progress of the reaction was monitored by TLC, and the experimental data for the screening conditions are listed in Table 1. In recent years, the use of reagents and catalysts immobilized on solid supports has received considerable attention. Such reagents not only simplify purification processes but also help in preventing release of reaction residues into the environment. Treatment of benzaldehyde with hydrazine dihydrochloride on the surface of basic alumina gave corresponding aldazine **2a** in almost quantitative yields. The reaction of aldazine **2a** with diethyl phosphite in toluene at reflux for 12 h gave a mixture of unknown products (Table 1, entry 1). The ^{31}P NMR spectrum of the reaction mixture exhibited a mixture of the unknown products. The reaction, when conducted under microwave irradiation for 75 min at 110°C (Table 1, entry 2), gave **3a**, with a simple crystallization of the reaction mixture from ethanol, in 75% isolated yield. The ^{31}P NMR spectrum of the product exhibited one peak at δ 22.23 ppm for the compound **3a** (Scheme 2). The ^{1}H NMR spectrum exhibited one doublet peak at δ 4.91 ppm indicative of HC–P coupling (J_{HP} = 21.5 Hz). The ^{13}C NMR spectrum exhibited a doublet peak at δ63.4 (J_{CP} = 149 Hz). The structure was supported by elemental analysis.

To determine the scope and limitations of the present protocol, under the above optimized conditions, aldazines were employed in the addition reaction with diethyl phosphite. The obtained results are summarized in Table 1 (Scheme 3). Treatment of different *p*-substituted aldazines with diethyl phosphite under microwave irradiation in toluene at 110°C gave corresponding 1-hydrazinophosphonates in good isolated yield (Table 1, entries 3–8). In the case of other substituted aldazines, we could not obtain any crystal, through crystallization from ethanol or



SCHEME 2 Reaction of aldazine **2a** with diethyl phosphite under microwave condition.



SCHEME 3 Reaction of aldazines with diethyl phosphite under microwave condition.

other solvents, for more identification analysis. The ^{31}P NMR data of the reaction mixture showed that compound **3** was obtained, and the product is very unstable in the column chromatography. A mixture of unknown compounds was obtained after purification using silica or alumina as an adsorbent in the column chromatography (Table 1, entries 9–13).

1-Naphthylcarbaldehyde and 2-thiophenecarbaldehyde, as a polynuclear and heteroaryl aldehyde, gave the corresponding aldazine in quantitative yield in the presence of alumina. In these cases, we could not obtain any crystal, via crystallization from ethanol or other solvents, for more identification analysis (Table 1, entries 14 and 15).

We also examined the reaction of aliphatic aldehyde (Table 1, entry 16) in the presence of a mixture of hydrazine dihydrochloride and basic alumina. The reaction failed to give the corresponding aldazine after 1 h of grinding.

In summary, we have developed a simple and practical method for the preparation of aldazines and 1-hydrazinophosphonates via the addition reaction of diethyl phosphite to aldazines. Through the condensation reaction of aldehydes with hydrazine dihydrochloride in the presence of basic alumina, aldazines can be synthesized in quantitative yields. This method is quite useful, in comparison with previously reported methods, because it allows the use of a readily available inexpensive reagent. In addition, by carrying out the addition reaction of diethyl phosphite with aromatic aldazines (phenyl- and para-substituted aromatic aldazines) under microwave irradiation at 110°C, we achieved 1-hydrazinophosphonates without any additives such as base or acid or catalyst. Other advantages of this environmentally benign and safe protocol include a simple reaction setup and good yields of 1-hydrazinophosphonates. In the case of other substituted aldazines, the ^{31}P NMR data of the reaction mixture showed that the compound **3** was obtained and the product is very unstable during the column chromatography. We could not obtain any crystal, via crystallization from ethanol or other solvents, for more identification analysis.

EXPERIMENTAL

All chemicals were commercial products and distilled or recrystallized before use. NMR spectra were taken with a 250 and 400 Brucker Avance instrument with the chemical shifts being reported as δ ppm and couplings expressed in hertz. The chemical shift data for each signal on ^1H NMR are given in units of δ relative to $CHCl_3$ ($\delta = 7.26$) for $CDCl_3$ solution. For ^{13}C NMR spectra, the chemical shifts in $CDCl_3$ are recorded relative to the $CDCl_3$ resonance ($\delta = 77.0$). The chemical shifts of ^{31}P are recorded relative to external 85% H_3PO_4 ($\delta = 0$) with broadband ^1H decoupling. Silica gel column chromatography was carried out with Silica gel 100 (Merck no. 10184). Merck silica-gel 60 F254 plates (no. 5744) were used for the preparative TLC.

*General Procedure for the Preparation of Aldazines Using Basic Alumina (**2**)*

This solvent-free reaction method is operationally simple. Five mmol of hydrazine dihydrochloride was added to a mixture of basic alumina (Al_2O_3, 2 g) and aldehyde (10 mmol) in a mortar and pestle by grinding them together until a fine, homogeneous powder was obtained (15 min). The mixture was extracted with chloroform (3×50 mL); evaporation of solvent gave the pure product as solid in almost quantitative yields. All products gave satisfactory spectral data in accordance with the assigned structures and literature reports [17].

*General Procedure for the Addition of Diethyl Phosphite to Aldazines under Microwave Irradiation (**3**)*

Diethyl phosphite (15 mmol) was added to a mixture of aldazine (5 mmol) and toluene (25 mL), and the solution was stirred for 75–110 min at 110°C at ambient pressure in a microwave reactor (a Milestone Micro Synth (Italy) microwave labstation for synthesis; a microwave reactor was used for all experiments). The solvent was evaporated under reduced pressure, ethanol (10 mL) was added to a crude mixture, and the solution was then left in the refrigerator for 1 h. The solid was collected, and the pure product could be obtained after the solid was further washed by hexane and ethanol, and vacuum dried. All products gave satisfactory spectral data in accordance

with the assigned structures and literature reports [11].

*Diethyl [(2E)-2-benzylidenehydazino](phenyl) methyl phosphonate (**3a**)*. White solid, mp = 97–99°C; ^{1}H-NMR ($CDCl_3$–TMS, 250 MHz), δ: 1.11 (t, 3H, J = 7.2 Hz), 1.29 (t, 3H, J = 7.2 Hz), 3.72–4.16 (m, 4H), 4.92 (d, 1H, J_{HP} = 21.5 Hz), 6.05 (s, 1H, NH), 7.24–7.47 (m, 10H), 7.63 (s, 1H); ^{31}P NMR ($CDCl_3$-H_3PO_4, 101.25 MHz), δ: 22.23; ^{13}C NMR ($CDCl_3$–TMS, 62.9 MHz), δ: 18.6 (d, J_{PC} = 6.3 Hz), 18.8 (d, J_{PC} = 6.3 Hz), 63.4 (d, J_{PC} = 149.0 Hz), 65.5 (d, J_{PC} = 3.8 Hz), 65.6 (d, J_{PC} = 3.8 Hz), 128.5, 130.4, 130.5 (d, J_{PC} = 6.3 Hz), 130.8, 130.9, 131.0, 137.5, 137.8, 142.7.

*Diethyl [(2E)-2-(4-methylbenzylidene)hydazino](4-methylphenyl)methyl phosphonate (**3b**)*. White solid, mp = 98–99°C; ^{1}H NMR ($CDCl_3$-TMS, 400 MHz), δ: 1.15 (t, 3H, J = 6.8 Hz), 1.32 (t, 3H, J = 6.8 Hz), 2.38 (s, 6H), 3.79–4.21 (m, 4H), 4.95 (d, 1H, J_{HP} = 21.0 Hz), 6.68 (s, 1H, NH), 7.25–7.30 (m, 4H), 7.47–7.51 (m, 4H), 7.69 (s, 1H); ^{31}P NMR ($CDCl_3$–H_3PO_4, 162 MHz), δ: 21.90; ^{13}C NMR ($CDCl_3$–TMS, 100.6 MHz), δ: 16.2 (d, J_{PC} = 6.8 Hz), 16.4 (d, J_{PC} = 6.8 Hz), 22.2, 22.3, 61.3 (d, J_{PC} = 150.0 Hz), 63.2 (d, J_{PC} = 7.0 Hz), 63.3 (d, J_{PC} = 7.0 Hz), 127.6, 127.9, 128.1, 128.5, 128.6, 130.1, 135.3, 135.8, 140.3.

*Diethyl [(2E)-2-(4-methoxybenzylidene)hydazino](4-methoxyphenyl) methyl phosphonate (**3c**)*. White solid, mp = 110–112°C; ^{1}H NMR ($CDCl_3$–TMS, 250 MHz), δ: 1.10 (t, 3H, J = 7.5 Hz), 1.29 (t, 3H, J = 7.5 Hz), 3.74 (s, 6H), 3.78–4.17 (m, 4H), 4.86 (d, 1H, J_{HP} = 22.5 Hz), 5.72 (s, 1H, NH), 6.93–7.07 (m, 4H), 7.40–7.46 (m, 4H), 7.62 (s, 1H); ^{31}P NMR ($CDCl_3$–H_3PO_4, 101.25 MHz), δ: 22.23; ^{13}C NMR ($CDCl_3$–TMS, 62.9 MHz), δ: 16.3 (d, J_{PC} = 6.9 Hz), 16.4 (d, J_{PC} = 6.9 Hz), 55.4, 56.5, 60.9 (d, J_{PC} = 149.0 Hz), 63.1 (d, J_{PC} = 4.4 Hz), 63.5 (d, J_{PC} = 4.4 Hz), 126.1–128.7 (m, Ar), 135.1, 135.4, 140.2, 153.0, 153.9.

*Diethyl [(2E)-2-(4-chlorobenzylidene)hydazino](4-chlorophenyl) methyl phosphonate (**3d**)*. White solid, mp = 151–153°C; ^{1}H NMR ($CDCl_3$–TMS, 400 MHz), δ: 1.25 (t, 3H, J = 8.0 Hz), 1.30 (t, 3H, J = 8.0 Hz), 4.02–4.14 (m, 4H), 5.05 (d, 1H, J_{HP} = 23.0 Hz), 5.99 (s, 1H, NH), 7.25–7.41 (m, 8H), 7.73 (s, 1H); ^{31}P NMR ($CDCl_3$–H_3PO_4, 162 MHz), δ: 20.74; ^{13}C NMR ($CDCl_3$–TMS, 100.6 MHz), δ: 16.0 (d, J_{PC} = 7.0 Hz), 16.3 (d, J_{PC} = 7.0 Hz), 62.6 (d, J_{PC} = 7.0 Hz), 63.3 (d, J_{PC} = 149.0 Hz), 63.7 (d, J_{PC} = 7.0 Hz), 128.3, 128.4, 128.5, 128.7, 128.9, 130.0, 130.4, 131.1, 143.

*Diethyl [(2E)-2-(4-bromobenzylidene)hydazino](4-bromophenyl) methyl phosphonate (**3d**)*. White solid, mp = 132–134°C; ^{1}H NMR ($CDCl_3$–TMS, 400 MHz), δ: 1.15 (t, 3H, J = 6.8 Hz), 1.32 (t, 3H, J = 6.8 Hz), 3.75–4.20 (m, 4H), 4.96 (d, 1H, J_{HP} = 20.0 Hz), 6.67 (s, 1H, NH), 7.25–7.28 (m, 4H), 7.48–7.50 (m, 4H), 7.69 (s, 1H); ^{31}P NMR ($CDCl_3$–H_3PO_4, 162 MHz), δ: 21.68; ^{13}C NMR ($CDCl_3$–TMS, 100.6 MHz), δ: 16.2 (d, J_{PC} = 6.0 Hz), 16.4 (d, J_{PC} = 6.0 Hz), 61.2 (d, J_{PC} = 150.0 Hz), 63.2 (d, J_{PC} = 7.0 Hz), 63.3 (d, J_{PC} = 7.0 Hz), 127.5, 127.9, 128.0, 128.4, 128.6, 130.0, 135.2, 135.5, 140.3.

*Diethyl [(2E)-2-(4-flourobenzylidene)hydazino](4-flourophenyl) methyl phosphonate (**3f**)*. White solid, mp = 112–114°C; ^{1}H NMR ($CDCl_3$–TMS, 250 MHz), δ: 1.14 (t, 3H, J = 7.0 Hz), 1.29 (t, 3H, J = 7.0 Hz) 3.78–4.17 (m, 4H), 4.87 (d, 1H, J_{HP} = 21.2 Hz), 5.72 (s, 1H, NH), 6.93–7.07 (m, 4H), 7.40–7.46 (m, 4H), 7.62 (s, 1H); ^{31}P NMR ($CDCl_3$–H_3PO_4, 101.25 MHz), δ: 21.77 (d, J_{FP} = 5.1); ^{13}C NMR ($CDCl_3$–TMS, 62.9 MHz), δ: 16.2 (d, J_{PC} = 5.6 Hz), 16.4 (d, J_{PC} = 5.6 Hz), 60.3 (d, J_{PC} = 150.3 Hz), 63.1 (d, J_{PC} = 6.3 Hz), 63.2 (d, J_{PC} = 6.3 Hz), 115.3, 115.7, 127.7, 127.8, 129.7 (d, J_{FC} = 6.3 Hz), 129.8 (d, J_{FC} = 6.3 Hz), 131.2, 139.5, 162.8 (d, J_{FC} = 252 Hz).

*Diethyl [(2E)-2-(4-nitrobenzylidene)hydazino](4-nitrophenyl) methyl phosphonate (**3g**)*. White solid, mp = 165–167°C; ^{1}H NMR ($CDCl_3$–TMS, 400 MHz), δ: 1.18 (t, 3H, J = 7.2 Hz), 1.32 (t, 3H, J = 7.2 Hz), 3.83–4.18 (m, 4H), 4.89 (d, 1H, J_{HP} = 21.2 Hz), 5.55 (s, 1H, NH), 6.98–7.09 (m, 4H), 7.44–7.48 (m, 4H), 7.64 (s, 1H); ^{31}P NMR ($CDCl_3$–H_3PO_4, 162 MHz), δ: 21.24; ^{13}C NMR ($CDCl_3$–TMS, 100.6 MHz), δ: 16.3 (d, J_{PC} = 6.0 Hz), 16.4 (d, J_{PC} = 6.0 Hz), 60.5 (d, J_{PC} = 149.0 Hz), 63.2 (d, J_{PC} = 7.0 Hz), 63.3 (d, J_{PC} = 7.0 Hz), 115.4, 115.6, 127.8, 129.8, 129.9, 131.2, 139.4, 161.7, 164.1.

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