Studies on the Synthesis of 1-Aminoalkylphosphonates from Aldehydes Using Silica-Supported Ammonium Hydrogen Carbonate

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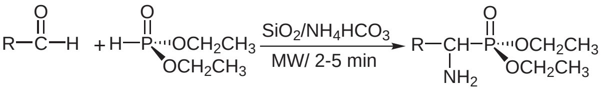
Abstract: Studies on the use of silica-supported ammonium hydrogen carbonate as an efficient reagent for the synthesis of 1-aminophosphonates under microwave irradiation in solvent-free conditions is reported. Investigations showed that this reaction proceeds by the formation of methanediamine as an intermediate. The reaction in the absence of diethyl phosphite gave *cis*-imidazolines as the major products.

Key words: 1-aminophosphonates, silica, ammonium hydrogen carbonate, methanediamines, imidazolines

In recent years, considerable interest has been focused on the synthesis of phosphonic acids, particularly the α-substituted analogs that are an important class of compounds with applications as antibiotics, antiviral agents and enzyme inhibitors. Among the α-functionalized phosphonic acids, α-aminophosphonic acid derivatives are gaining interest in medicinal chemistry. α-Aminophosphonic acids are analogues of naturally occurring α-amino acids in biological systems. Extensive investigations over the last twenty years have shown that they are of particular importance in biological and medicinal research.[1–4] In this respect, the uses of α-amino alkyl phosphonates as enzyme inhibitors,[5] antibiotics and pharmacological agents,[6] herbicides,[7] and haptens of catalytic antibodies[8] are well documented. Although there are many classical methods for synthesizing α-aminophosphonic acids,[9–14] these involve either long reaction times, expensive reagents, or the use of conditions which are amenable to aliphatic aminophosphonic acids rather than aromatic aminophosphonic acids.[15] The most typical procedure is a Strecker-type reaction[16] which involves the treatment of an aldehyde with ammonia and dialkyl phosphite. This method, however, is not high yielding nor is it suitable for large-scale production since the reaction is performed in a sealed vessel with heating at 100 °C.

Surface-mediated solid phase reactions are of growing interest[17] because of their advantages of ease of set up, mild conditions, rapid reactions, selectivity, increased yields of the products and low cost compared with their homogeneous counterparts. The application of microwave energy to accelerate organic reactions is of increasing interest and offers several advantages over conventional techniques.[18]

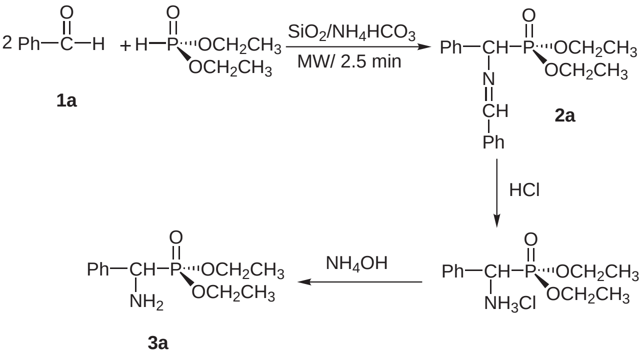
As part of our studies on the solvent-free reactions for the synthesis of organophosphorus compounds using immobilized reagents on inorganic solid phases,[19–23] we recently found that silica-supported ammonium hydrogen carbonate is a suitable and efficient reagent for the one-pot synthesis of 1-aminophosphonates from aldehydes (Scheme 1).[24]



Scheme 1

We decided to analyze this reaction and report further investigations on the synthesis of 1-aminophosphonates using silica-supported ammonium hydrogen carbonate under microwave irradiation. Thus, the reaction of benzaldehyde, chosen as a model compound, was studied in the presence of silica-supported ammonium hydrogen carbonate under microwave irradiation. As described below, treatment of benzaldehyde (**1a**) with diethyl phosphite in the presence of silica-supported ammonium hydrogen carbonate gave diethyl-*N*-(phenylmethylene)-1-aminophenyl methylphosphonate (**2a**) in 92% yield (Scheme 1). The ^{1}H NMR spectrum of **2a** exhibits a doublet at δ = 8.42 indicative of the HC–P coupling ($^4J_{HP}$ = 4.7 Hz). The hydrolyses of **2a** with hydrochloric acid (5%), followed by neutralization of the chloride salt, gave 1-(aminophenylmethyl)phosphonate **3a** (Scheme 2).

The question arises here as to how it is possible to obtain diethyl-*N*-(phenylmethylene)-1-aminophenylmethylphosphonate (**2a**) in the reaction of benzaldehyde (**1a**) with diethyl phosphite in the presence of silica-supported



Scheme 2

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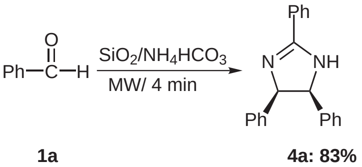
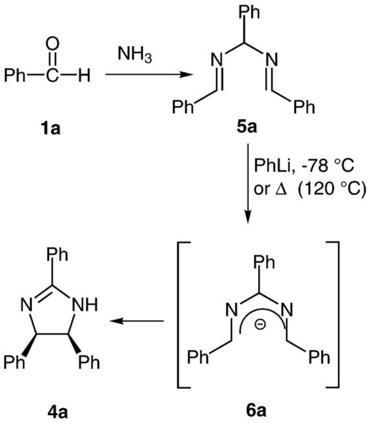
ammonium hydrogen carbonate under microwave irradiation. We therefore decided to study the reaction of benzaldehyde (**1a**) with silica-supported ammonium hydrogen carbonate in the absence of diethylphosphite. We found that the reaction gave *cis*-2,4,5-triphenylimidazoline (**4a**) as the major product (Scheme 3). The addition of diethyl phosphite to the reaction mixture did not give **2a** under microwave irradiation.



Scheme 3

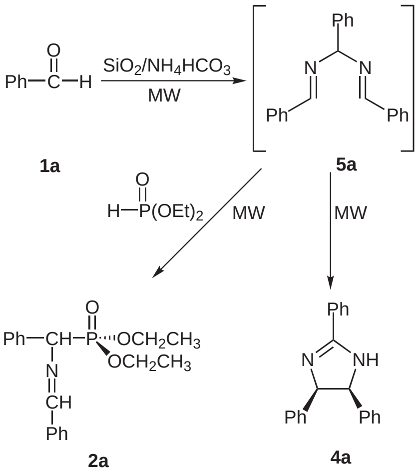
The reaction of benzaldehyde with ammonia leads to the long-known substance '*N*,*N*′-bis(phenylmethylidene)phenylmethanediamine'.[25] Deprotonation of *N*,*N*′-bis(arylmethylidene) arylmethanediamines (**5a**) with a strong base (PhLi) or under thermal conditions results in formation of the transient 2,4-diazapentadienyl anion (**6a**) which cyclises in a disrotatory fashion to furnish the *cis*-2,4,5-triphenylimidazoline (**4a**) (Scheme 4).[26]



Scheme 4

The reaction of benzaldehyde (**1a**) in the presence of silica-supported ammonium hydrogen carbonate gave *N*,*N*′-bis(phenylmethylidene)phenylmethanediamine (**5a**). Deprotonation of **5a** under microwave irradiation gave *cis*-2,4,5-triphenylimidazoline (**4a**) as the major product in 83% yield (Scheme 3).

Thus *N*,*N*′-bis(phenylmethylidene)phenylmethanediamine reacts with diethylphosphite, before cyclization, to give diethyl-*N*-(phenylmethylene)-1-aminophenylmethylphosphonate (**2a**), which can be easily hydrolysed to diethyl-1-amino-1-phenylmethylphosphonate (**3a**). We found that the reaction of *N*,*N*′-bis(phenylmethylidene)phenylmethanediamine with diethyl phosphite under microwave irradiation gave diethyl-*N*-(phenylmethylene)-1-aminophenylmethylphosphonate (**2a**, Scheme 5).[27]



Scheme 5

In conclusion, we have found that the reaction of benzaldehyde with silica-supported ammonium hydrogen carbonate gave *N*,*N*′-bis(phenylmethylidene)phenylmethanediamine that cyclises under microwave irradiation to form cis-2,4,5-triphenylimidazoline. Triphenylimidazolines are good precursors for the synthesis of imidazoles and diphenylethylenediamines that can be used as chiral ligands in asymmetric synthesis.[28] Herein, we introduced a new method for the synthesis of imidazolines of aldehydes using silica-supported ammonium carbonate under microwave irradiation. *N*,*N*′-Bis(phenylmethylidene)phenylmethanediamine reacts with diethylphosphite, before cyclisation, to give diethyl *N*-(phenylmethylene)-1-aminophenyl methylphosphonate (**2a**), which can be easily hydrolysed to diethyl-1-amino-1-phenylmethylphosphonate (**3a**). Thus, one-pot reaction of diethylphosphite with aldehydes in the presence of silica-supported ammonium carbonate is important for the preparation of 1-aminophosphonates under microwave irradiation. Further investigations of the reaction of diethyl phosphite with *cis*-2,4,5-triphenylimidazoline are now in progress.

All chemicals were commercial products and distilled or recrystallised before use. A commercially available kitchen-type pulse microwave at 2450 MHz (600 W) was used in all experiments. The IR spectra were determined using a FT-IR Brucker-Vector 22. NMR spectra were taken with a DMX-500 Bruker Avance instrument with the chemical shifts reported as δ and couplings expressed in Hertz. 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.

cis-2,4,5-Triphenylimidazoline (4a) from Benzaldehyde (1a) using Silica-Supported Ammonium Hydrogen Carbonate under Microwave Irradiation

This solvent-free reaction is operationally simple. The reagent (6 mmol) was prepared by grinding together ammonium hydrogen carbonate (6 mmol, finely ground) and silica (2 g) with mortar and pestle until a fine, homogeneous, powder was obtained (5–10 min). Benzaldehyde (6 mmol) was added to the powder and the mixture was irradiated in a microwave for 4 min using 600 W power. The mixture was then washed with EtOAc (200 mL). Chromatography

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through a plug of silica gel with EtOAc–*n*-hexane (1:9–5:5) as eluent yielded the pure product *cis*-2,4,5-triphenylimidazoline (**4a**) in 83% yield; mp 126–127 °C (washed with *n*-hexane–EtOAc) (Lit.[29] mp 127–128 °C, Lit.[30] mp 129–130 °C).

One-Pot Synthesis of Diethyl-*N*-(Phenylmethylene)-1-aminophenylmethylphosphonate (2a) under Microwave Irradiation

This solvent-free reaction method is operationally simple. The reagent (6 mmol) was prepared as described above and benzaldehyde (10 mmol) was added to the powder. Diethyl phosphite (6 mmol) was added and the mixture was irradiated by microwave for 2.5 min using 600 W power. The reaction mixture was washed with EtOAc (100 mL) and evaporation of solvent yielded the crude product in nearly quantitative yield (92%).

Diethyl-*N*-(Phenylmethylene)-1-aminophenylmethylphosphonate(2a)[27]

Colourless oil.

IR (neat): 1639 (CH=N), 1260 (P=O), 1050–950 (P-O-Et) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$/TMS): δ = 1.20 (t, *J* = 7.1 Hz, 3 H), 1.23 (t, *J* = 7.1 Hz, 3H), 3.99–4.11 (m, 4 H), 4.93 (d, *J* = 18.4 Hz, 1 H), 7.30–7.84 (m, 10 H), 8.42 (d, *J* = 4.7 Hz, 1 H; doublet is converted to singlet in phosphorus-decoupled ^{1}H NMR).

^{31}P NMR (202.4 MHz, $CDCl_3$/H_3PO_4): δ = 25.05.

Reaction of *N,N′*-Bis(phenylmethylidene) phenylmethanediamine with Diethyl Phosphite under Microwave Irradiation

Diethyl phosphite (6 mmol) was added to *N,N′*-bis(phenylmethylidene)phenylmethanediamine (4 mmol, prepared according to literature procedure[30]) in the presence of silica (2 g). The mixture was irradiated by microwave for 2 min using 600 W power. The reaction mixture was washed with EtOAc (100 mL) and chromatography through a plug of silica gel with EtOAc–*n*-hexane (1:9–5:5) yielded the pure product **2a** in 93% yield.

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