Microwave-assisted One-pot Synthesis of α-Amino Phosphonates via Three Component Coupling on a Silica Gel Support

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(Received April 19, 2005; CL-050537)

A fast, highly efficient, general procedure under microwave irradiation, using silica gel-supported reagents for the synthesis of α-aminophosphonates is developed through a one-pot reaction of aldehydes and ketones with amines.

Recently, solvent-free reactions using either organic or inorganic solid supports have received increasing attention.[1] There are several advantages to perform synthesis in dry media: (i) short reaction times, (ii) increased safety, (iii) economic advantages due to the absence of solvent. Silica gel is effective because the end products can easily be separated. Moreover, silica gel can function as a convenient medium and also act as a mild acidic catalyst.[2]

The application of microwave (MW) irradiation as a nonconventional energy source for activation of reactions, in general and on inorganic solid supports in particular, have gained popularity over the usual homogeneous and heterogeneous reactions, as they can be performed rapidly to give pure products in high yields under solvent-free conditions with several eco-friendly advantages in the context of green chemistry.[3,4]

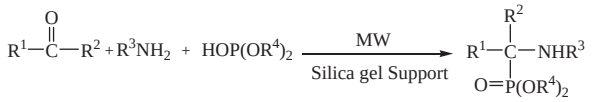
α-Aminophosphonates are an important class of compounds in modern pharmaceutical chemistry. The potential of α-aminophosphonates as peptide mimetics,[5] haptens of catalytic antibodies,[6] enzyme inhibitors,[7] and antibiotics and pharmacologic agents[8] has been established. Thus, how to efficiently synthesize α-aminophosphonates has been explored. Of the methods available, the nucleophilic addition of phosphites to imines is most convenient. These reactions are usually promoted by a base or an acid.[9] Lewis acids such as $SnCl_2$, $SnCl_4$, $BF_3{\cdot}OEt_2$, $ZnCl_2$, and $MgBr_2$ have been found to be effective.[10] However, these reactions cannot be carried out in a one-pot operation with carbonyl compound, amine and phosphite, because amine and water produced during imine formation can decompose or deactivate these Lewis acids. Recently, it has been reported that using lanthanide triflate,[11] samarium diiodide,[12] scandium tris(dodecyl sulfate),[13] indium(III) chloride,[14] $TaCl_5$-SiO_2,[15] and (Bromodimethyl)sulfonium bromide[16] as catalysts, one-pot reactions can proceed smoothly. However, these catalysts have some drawbacks: For instance, reactions require a long time,[11,12,14,15] when carbonyl compounds are ketones, many of these catalysts proved to be less effective,[11–13,16] and when starting materials contain aliphatic amines, reactions gave noncharacterizable products.[15] In addition, some of these catalysts are either expensive or somewhat difficult to prepare. Of late, Kaboudin reported that microwave-assisted one-pot synthesis of α-aminophosphonates using alumina-supported reagents.[17] However, although this approach is satisfactory for reactions with aromatic aldehydes, the reaction of ketones has not been reported. In addition, aminophosphonates from aliphatic aldehydes are obtained in moderate yields. Thus, a fast, efficient, and general method is desirable for the synthesis of α-aminophosphonates from both aldehydes and ketones with aromatic as well as aliphatic amines.

Herein we report an efficient and rapid microwave-assisted one-pot synthesis of α-aminophosphonates from both aldehydes and ketones on a silica gel support.

In a typical procedure, a mixture of carbonyl compound, an amine, and a dialkyl phosphite absorbed on silica gel was irradiated in a microwave oven for a certain period of time as required to complete the reaction (TLC). A wide range of structurally varied carbonyl compounds were used as substrates and converted to the corresponding α-aminophosphonates in good to excellent yields. The results are reported in Table 1.

Not only benzaldehydes but also electron rich aromatic aldehydes, electron deficient aromatic aldehydes and aliphatic

Table 1. Synthesis of α-aminophosphonates from aldehydes/ketones and amines using silica gel-supported reagents under MW



1 **2** **3** **4**

Entry	R^1	R^2	R^3	R^4	Time	4[a]/%[b]
1	Ph	H	Ph	Et	15 min	4a/94
2	Ph	H	Ph	Me	15 min	4b/92
3	Ph	H	Ph	*i*-Pr	15 min	4c/80
4	*p*-MeO-Ph	H	Ph	Et	15 min	4d/95
5	*o*-MeO-Ph	H	Ph	Et	15 min	4e/93
6	2,4-Dichloro-C_6H_4	H	Ph	Et	10 min	4f/85
7	*p*-MeO-Ph	H	*n*-Pr	Et	10 min	4g/91
8	*o*-HO-Ph	H	Ph	Et	15 min	4h/83
9	*p*-NO_2-Ph	H	Ph	Me	10 min	4i/81
10	Cyclohexyl	H	Ph	Et	15 min	4j/88
11	Ph	H	$PhCH_2$	Et	15 min	4k/95
12	Ph	H	$PhCH_2$	Me	10 min	4l/91
13	PhCH=CH (trans)	H	$PhCH_2$	Et	10 min	4m/88
14	Cyclohexanone		$PhCH_2$	Et	5 min	4n/88
15	Cyclohexanone		*n*-Pr	Et	5 min	4o/87
16	CH_3	CH_3	$PhCH_2$	Et	5 min	4p/87
17	Cyclopentanone		*n*-Pr	Et	3 min	4q/83
18	CH_3	isobutyl	$PhCH_2$	Et	10 min	4r/85

[a]All products gave satisfactory spectral and analytical data. For a general procedure, see Ref. 18 [b]Isolated yields after column chromatography.

aldehydes react with aromatic as well as aliphatic amines to give the α-aminophosphonates in high yields. This procedure is equally effective for conversion of ketone to the respective dialkyl phosphonates. The reaction from ketones gave a high yield of the desired product in 3–10 min and a prolonged reaction time will lead to the decomposition of the product. Several sensitive functionalities such as NO_2, OMe, OH, and Cl and the C–C double bond are unaffected in the reaction. It should be noted that silica gel was easily recovered by filtration, washed with methanol, and reused after activation at 100 °C for 1 h.

Microwave assisted rapid synthesis of a variety of organic compounds because of the selective absorption of microwave energy by polar molecules.[19] We envisioned that our three-component coupling was accelerated by microwave energy because of reactants' polar nature. The role of silica gel may be two-fold: (1) Physisorption of reactants on the silica surface leading to an increase in local concentration, which in turn enhances the rate of the reaction. (2) The acidic nature of the silica surface promotes our three-component coupling.

In conclusion, the present procedure provides an efficient one-pot synthesis of α-aminophosphonates from the reaction of a carbonyl compound, amine and dialkyl phosphite. The notable advantages of this procedure are (1) general applicability to aldehydes and ketones, (2) high yields of products, (3) very short reaction times, (4) operational simplicity, (5) solvent-free conditions, (6) silica gel is cheap and can be reused. We believe that all these advantages make this method an attractive and a useful contribution to present methodologies.

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18 A typical experimental procedure for the synthesis of α-aminophosphonate **4d** is as follows: A mixture of *p*-anisaldehyde (136 mg, 1 mmol), aniline (93 mg, 1 mmol), and diethyl phosphite (138 mg, 1 mmol) absorbed on 0.25 g silica gel (99% SiO_2, 300–400 mesh, Surface area 300–400 m^2/g) was mixed thoroughly by grinding into a fine, homogeneous powder. Then the mixture was taken in a 5 mL conical flask and was placed in a microwave oven (cooking type, Galanz WP 700P 21-6) and irradiated for 15 min at 680 W. After completion of the reaction indicated by TLC, the reaction mixture was diluted with EtOAc and followed by filtration. The filtrate was evaporated under reduced pressure and the residue was purified by column chromatography to afford the pure α-aminophosphonate **4d** (331 mg, 95%). IR (film) ν_{max}: 3301, 1603, 1510, 1245, 1025, 751 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.14 (t, $J = 7.0$ Hz, 3H, $OCH_2C\underline{H}_3$), 1.28 (t, $J = 7.0$ Hz, 3H, $OCH_2C\underline{H}_3$), 3.66–3.73 (m, 1H, $OC\underline{H}_2$), 3.77 (s, 3H, $OC\underline{H}_3$), 3.92–3.98 (m, 1H, $OC\underline{H}_2$), 4.06–4.17 (m, 2H, $OC\underline{H}_2$), 4.72 (d, $^2J_{PH} = 24.0$ Hz, 1H, $PC\underline{H}$), 6.58–6.60 (m, 2H, $Ar\underline{H}$), 6.67–6.71 (m, 1H, $Ar\underline{H}$), 6.85–6.88 (m, 2H, $Ar\underline{H}$), 7.08–7.12 (m, 2H, $Ar\underline{H}$), 7.37–7.40 (m, 2H, $Ar\underline{H}$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 16.15 (d, $^3J_{PC} = 5.5$ Hz, $OCH_2\underline{C}H_3$), 16.33 (d, $^3J_{PC} = 5.5$ Hz, $OCH_2\underline{C}H_3$), 55.10, 55.26 (d, $^1J_{PC} = 151.3$ Hz, $P\underline{C}H$), 63.07 (d, $^2J_{PC} = 7.4$ Hz, $O\underline{C}H_2$), 63.13 (d, $^2J_{PC} = 7.4$ Hz, $O\underline{C}H_2$), 113.79, 113.94, 118.23, 127.58, 128.86 (d, $^2J_{PC} = 5.5$ Hz, $CH\underline{C}_{Ar}$), 129.03, 146.28 (d, $^3J_{PC} = 14.9$ Hz, $NH\underline{C}_{Ar}$), 159.21. ESI-MS: m/z (%) = 350 (100) [$M + H^+$]. Anal. Calcd for $C_{18}H_{24}NO_4P$: C, 61.88; H, 6.92; N, 4.01%. Found: C, 62.12; H, 6.90; N, 4.09%.

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Published on the web (Advance View) June 18, 2005; DOI 10.1246/cl.2005.1042