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Ultrasound-assisted one-pot synthesis of α-oxycarbanilinophosphonates via a three-component condensation of an aldehyde, diethyl phosphite and an isocyanate under solvent-free conditions

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ABSTRACT

An efficient one-pot method has been developed for the synthesis of α-oxycarbanilinophosphonates via a one-pot reaction of an aldehyde with diethyl phosphite in the presence of magnesium oxide followed by reaction with an isocyanate under solvent-free conditions using ultrasonic irradiation. This method is simple, rapid and good yielding.

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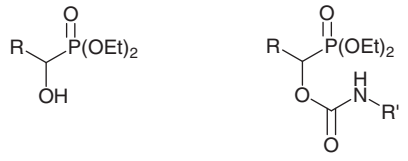
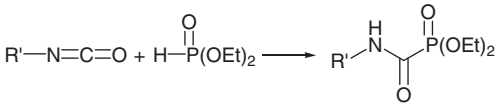
Organophosphorus compounds have found a wide range of application in the areas of industrial, agricultural and medicinal chemistry owing to their biological and physical properties, as well as their utility as synthetic intermediates.[1] α-Functionalized phosphonic acids are valuable intermediates for the preparation of medicinal compounds and synthetic intermediates,[2–4] with α-oxycarbanilinophosphonates and α-hydroxyphosphonates being important examples that exhibit a variety of interesting and useful properties. In recent years, the preparation of α-oxycarbanilino- and α-hydroxyphosphonates has attracted significant attention, due to their potential biological activities and broad applications as enzyme inhibitors or as dinucleotide analogues having antiviral properties (Scheme 1).[5]

In contrast to the widely studied α-hydroxyphosphonic acid derivatives,[1,6,7] relatively few papers have reported on the chemistry of α-oxycarbanilinophosphonates.[8] Many effective methods for the preparation of α-hydroxyphosphonates have been developed, but, to the best of our knowledge, only one synthetic route to α-oxycarbanilinophosphonates has been reported. The method involves prolonged heating (3 days) of α-hydroxyphosphonates with phenyl isocyanate at 50 °C in the presence of tin octanoate as a catalyst.[8] However, the method has drawbacks, including harsh reaction conditions, low yields, long reaction times, use of Lewis acid and yields side products. In the absence of tin octanoate as catalyst, isocyanurate was obtained as the major product. The key step in the one-pot synthesis of α-oxycarbanilinophosphonate is the nucleophilic addition of diethyl phosphite to an aldehyde followed by reaction of the isocyanate with the resulting α-hydroxyphosphonate. Therefore, formation of a carbamoylphosphonate frequently accompanies the synthesis (Scheme 2).



α-hydroxyphosphonates α–oxycarbanilinophosphonates

Scheme 1. Structures of α-oxycarbanilinophosphonates and α-hydroxyphosphonates.



Scheme 2. Reaction of the isocyanate with diethyl phosphite.

The development of simple and general synthetic routes for widely used organic compounds from readily available reagents is a major challenge in organic synthesis. Surface-mediated solid phase reactions are of growing interest[9] because of their advantages including 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 ultrasound energy to accelerate organic reactions is of increasing interest and offers several advantages over conventional techniques.[10] Syntheses which normally require long reaction times can be achieved conveniently and very rapidly under ultrasonic irradiation. As part of our efforts to explore the utility of solid phase reactions for the synthesis of organophosphorus compounds,[11] we report a new method for the one-pot synthesis of α-oxycarbanilinophosphonates from

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Table 1
Reaction of aldehydes with diethyl phosphite in the presence of magnesium oxide followed by reaction with isocyanates under solvent-free conditions using ultrasound

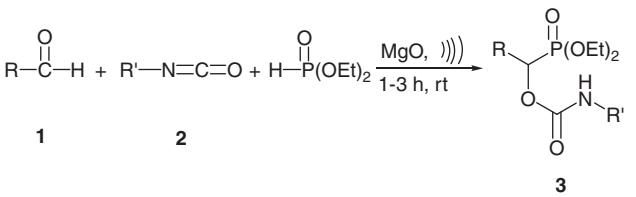
Entry	R **1**	R′ **2**	Product **3**	Reaction time (h)	Yield%[a] **3**
1	C_6H_5	C_6H_5	**3a**	1	62
2	*p*-FC_6H_4	C_6H_5	**3b**	1	56
3	*p*-MeC_6H_4	C_6H_5	**3c**	2	80
4	*p*-$MeSC_6H_4$	C_6H_5	**3d**	3	60
5	*p*-$MeOC_6H_4$	C_6H_5	**3e**	2	60
6	*o*-$O_2NC_6H_4$–CH=CH	C_6H_5	**3f**	2	77
7	2-Thienyl	C_6H_5	**3g**	2	74
8	2,4-$Cl_2C_6H_3$	3-Cl,4-MeC_6H_3	**3h**	1	60
9	*p*-$O_2NC_6H_4$	3-Cl,4-MeC_6H_3	**3i**	1	50
10	C_6H_5	Cyclohexyl	**3j**	2	63
11	C_6H_5–CH=CH	Cyclohexyl	**3k**	3	62
12	α-Naphthyl	$PhCH_2$	**3l**	2	60

[a] Yield (over two steps, based on aldehyde) refers to total isolated yield after column chromatography.

the reaction of diethyl phosphite with aldehydes followed by reaction with isocyanates in the presence of magnesium oxide under solvent-free conditions and ultrasonic irradiation, producing good yields of α-oxycarbanilinophosphonates.

We have previously reported the synthesis of α-hydroxyphosphonates by the reaction of aldehydes with diethyl phosphite in the presence of magnesium oxide.[12] Initially, we carried out the reaction of benzaldehyde (**1a**) with diethyl phosphite in the presence of magnesium oxide to afford a solid mixture after 30 min. When phenyl isocyanate (**2a**) was added to the solid mixture, the reaction failed to give the desired product and only the corresponding α-hydroxyphosphonate was obtained in 90% yield. Surprisingly, we found that, when the first step was carried out under ultrasonic irradiation for 30 min, the reaction mixture did not solidify. Following addition phenyl isocyanate (**2a**) to the reaction mixture, the corresponding α-oxycarbanilinophosphonate **3a** was obtained in 62% isolated yield under ultrasonic irradiation for 1 h. The reaction of benzaldehyde with diethyl phosphite and phenyl isocyanate without magnesium oxide under solvent-free conditions using ultrasonic irradiation, gave only the corresponding α-hydroxyphosphonate in 25% yield after 5 h.

These results prompted us to extend this process to other aldehydes and isocyanates (Table 1 and Scheme 3). Various substituted benzaldehydes reacted with diethyl phosphite in the presence of magnesium oxide followed by reaction with phenyl isocyanate to give the desired compounds **3b–e** in good yields. Treatment of 2-nitrocinnamaldehyde, as an example of an α,β-unsaturated aldehyde, with a mixture of diethyl phosphite and phenylisocyanate gave the desired compound **3f** in 77% yield. The reaction of thienyl-2-carbaldehyde with diethyl phosphite followed by reaction with phenyl isocyanate gave 74% yield of product **3g**. The reaction of substituted phenyl isocyanate with a mixture of aldehyde and diethyl phosphite gave the corresponding α-oxycarbanilinophosphonates **3h** and **i** in moderate yields. The reaction of cyclohexyl isocyanate, as an aliphatic isocyanate, with benzaldehyde and cinnamaldehyde in the presence of diethyl phosphite gave the desired products **3j** and **k** in 63% and 62% yield, respectively. 1-Naphthalenecarbaldehyde, polynuclear aldehyde, reacted with a mixture of benzyl isocyanate and diethyl phosphite in the presence of magnesium oxide, to give compound **3l** in 60% isolated yield. Thus, the three-component condensation reaction reported herein tolerates a wide variety of aldehydes and isocyanates for the synthesis of α-oxycarbanilinophosphonates.



Scheme 3. One-pot synthesis of α-oxycarbanilinophosphonates.

In summary, we have developed a simple and practical method for the synthesis of α-oxycarbanilinophosphonates via a three-component one-pot reaction of aldehydes, diethyl phosphite and isocyanates using ultrasonic irradiation in the presence of magnesium oxide in moderate to good yields. The simple work-up, mild conditions and clean reactions with no tar formation are advantages of this method.[13]

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.06.057.

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13. Aldehyde (10 mmol) was added to a mixture of diethyl phosphite (10 mmol) and MgO (0.2 g). The reaction mixture was irradiated with ultrasound for 30 min. The isocyanate (10 mmol) was then added and the mixture irradiated for 1–3 h (a BANDELN-SONOREX ultrasonic bath with intense frequency of 35 KHz was used in all experiments). The mixture was chromatographed on silica gel (*n*-hexane:EtOAc = 40/60) to give the pure product in 50–80% yield. All products gave satisfactory spectral data in accord with the assigned structures. Spectral data for the representative examples: *Diethyl[(3-chloro-4-methylanilinocarbonyl)oxy](2,4-dichlorophenyl)methyl phosphonate* (**3h**): mp 146–148 °C (*n*-hexane-EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.24 (3H, t, J = 7.2 Hz), 1.39 (3H, t, J = 7.2 Hz) 2.31 (3H, S), 3.90–4.25 (4H, m), 6.59 (1H, d, J_{HP} = 14.4 Hz), 7.11 (1H, d, J = 8.0 Hz), 7.22 (1H, d, J = 8.0 Hz), 7.28 (1H, d, J = 7.6 Hz), 7.46 (s, 2H), 7.71 (1H, d, J = 7.6 Hz), 8.54 (1H, br s, NH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 16.3, 16.5, 19.3, 63.7 (d, J_{PC} = 6.9 Hz), 63.9 (d, J_{PC} = 6.9 Hz), 66.8 (d, J_{PC} = 174.9 Hz), 116.8, 119.2, 127.6 (d, J = 2.0 Hz), 129.4 (d, J = 2.0 Hz), 130.5, 130.6, 130.7, 130.9, 134.3, 134.4, 135.4 (d, J = 3.0 Hz), 136.7, 151.7 (d, J_{PC} = 13.0 Hz) 117.6, 118.7, 129.5, 130.4, 131.5, 131.7, 133.6, 137.6, 152.3; ^{31}P NMR ($CDCl_3$/H_3PO_4, 162 MHz): δ = 16.94. Anal. Calcd for $C_{19}H_{21}NCl_3O_5P$: C, 47.60; H, 4.42; N, 2.92. Found: C, 47.48; H, 4.28; N, 2.81. *Diethyl[(cyclohexylaminocarbonyl)oxy]-3-phenylallyl phosphonate* (**3k**): mp 108–110 °C (*n*-hexane-EtOAc). ^{1}H NMR (DMSO-d_6, 250 MHz): δ = 0.84–1.92 (16H, m), 3.74 (1H, s), 4.14–4.21 (4H, m), 4.15 (1H, br s, NH), 5.73 (1H, m), 6.26 (1H, m), 6.74 (1H, m), 7.27–7.37 (5H, m); ^{13}C NMR (DMSO-d_6, 62.9 MHz): δ = 16.4, 16.4, 24.7, 25.4, 33.2, 48.83, 63.1 (d, J_{PC} = 6.9 Hz), 63.3 (d, J_{PC} = 6.9 Hz), 69.5 (d, J_{PC} = 170.5 Hz), 120.7, 126.8, 128.2, 128.6, 134.7, 134.8, 135.9; ^{31}P NMR ($CDCl_3$/H_3PO_4, 101 MHz): δ = 17.90. Anal. Calcd for $C_{20}H_{32}NO_5P$: C, 60.42; H, 8.12; N, 3.52. Found: C, 60.35; H, 8.00; N, 5.42.