Green, one-pot synthesis of α -aminophosphonates catalyzed by ZnI₂ at room temperature

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Abstract

An efficient, green and simple solvent-free method is described for the synthesis of α -aminophosphonates based on one-pot three-component condensation of trimethylphosphite, aldehydes and amines in the presence of zinc iodide. This method offers some advantages such as shorter reaction times, simple work-up and excellent yield at room temperature.

Keywords: α-aminophosphonates; room temperature; solvent-free; trimethylphosphite; zinc iodide.

1. Introduction

Phosphorus-carbon bond formation has been the focus of growing attention because of its application in organic synthesis and bioorganic chemistry [1]. As a type of natural amino acid analogs, \alpha-aminophosphonates constitute an important class of compounds with diverse biological activities. The activity of α -aminophosphonates as peptidomimetics [2], enzyme inhibitors [3], pharmacogenic agents [4], haptens of catalytic antibodies [5], herbicidals [6], inhibitors of serine hydrolases [7], inhibitors of UDP-galactopyranose mutase [8] and antitumor agents [9-11], and many other applications are well documented. However, one-pot synthesis of α-aminophosphonates remains a favorite due to its versatile route and high yielding reactions. Recently, three-component syntheses starting from aldehydes, amines and diethylphosphite or triethylphosphite have been reported by using Lewis and Bronsted acid catalysts [12-23]. However, many of these methods suffer from several drawbacks such as long reaction times, low yields of the products, harsh reaction conditions, expensive reagents and use of toxic organic solvents.

In previous reports, we have shown that catalysts such as boric acid [24], sodium dihydrogen phosphate [25] and cobalt (II) chloride [26] catalyzed synthesis of α -aminophosphonates. However, there is a need to develop one-pot syntheses of α -aminophosphonates using new methods. Herein, we describe a simple, general and efficient protocol for the synthesis of α -aminophosphonates based on three-component

reactions of aldehydes, amines and trimethylphosphite using catalytic amounts of zinc iodide (ZnI₂) under solvent-free conditions at room temperature.

2. Results and discussion

At the outset the three-component reaction of benzaldehyde, aniline and trimethylphosphite in the presence of a catalytic amount of zinc iodide as a solid heterogeneous catalyst was investigated. The optimized reactant ratios were found to be 1.0 equiv. benzaldehyde, 1.0 equiv. primary amine and 1.0 equiv. trimethylphosphite in the presence of 0.2 equiv. solid ZnI_2 . The reaction proceeded smoothly and gave the corresponding α -aminophosphonates 3a as the sole product in 96% yield after 15 min at room temperature without the use of any solvent (Scheme 1).

To evaluate the generality of the process, several examples illustrating the present method for the synthesis of α -aminophosphonates 3 was studied (Table 1). The reaction of trimethylphosphite with various aromatic aldehydes bearing electron withdrawing groups (such as nitro, halide), electron releasing groups (such as hydroxyl, methoxy groups) and anilines (aniline, 4-chlor- or 4-bromoaniline) was carried out in the presence of zinc iodide as a catalyst. In these cases, clean and complete conversion leading to the corresponding α -aminophosphonates was observed in shorter reaction times (5–20 min) at room temperature. The yields obtained were good to excellent without formation of any side products. The results are summarized in Table 1.

All products are known compounds and structures of them were confirmed by comparison with their known physical and spectral (NMR and IR) data.

A plausible mechanism involves the formation of an imine by the addition of aldehyde and amine. It is believed that zinc iodide coordinates with the imine nitrogen to accelerate a nucleophilic reaction of phosphite to give a phosphonium intermediate, which then undergoes reaction with the water generated during formation of the imine to give the α -aminophosphonate and methanol as shown in Scheme 2 [16, 25].

$$\begin{array}{c} O \\ R \end{array} \begin{array}{c} O \\ H \end{array} \begin{array}{c$$

Scheme 1 Synthesis of α -aminophosphonates.

Table 1 Synthesis of a animophospholates in the presence of Zini ₂ .					
Entry	R	R'	Product	Time (min)	Yield (%)
1	C ₆ H ₅	C ₆ H ₅	3a	15	96
2	$2-NO_2C_6H_4$	$C_6^0H_5^3$	3b	15	75
3	$4-\text{MeC}_{6}H_{4}$	$C_6^0H_5^3$	3c	5	80
4	4-MeOC ₆ H ₄	C_6H_5	3d	5	95

3e

3f

3g

3h

3i

3j

3k

31

C,H,

C,H,

C,H,

C,H,

C6H5

4-ClC₆H₄

4-ClC₆H₄

4-BrC₆H₄

Table 1 Synthesis of α-aminophosphonates in the presence of ZnI.

4-HOC, H,

4-ClC,H,

3-NO₂C₂H₄

3-MeOC, H,

4-MeC₆H₄

4-MeOC, H

4-HOC₆H₄

2,3-Cl₂C₆H₃

In conclusion, we have reported herein a zinc iodide catalyzed novel and eco-friendly method for the synthesis of α -aminophosphonates at room temperature under solvent-free conditions. The advantages of the present protocol are mild heterogeneous reaction conditions, shorter reaction times and easy work-up; inexpensive and ready availability of the catalyst makes the procedure an attractive alternative to the existing methods for the synthesis of α -aminophosphonates.

3. Experimental

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A mixture of aldehyde (1 mmol), amine (1 mmol), trimethylphosphite (1 mmol) and zinc iodide (20 mol%) was stirred at room temperature for the specified time (Table 1). After thin layer chromatography indicated the disappearance of starting materials, chloroform (10 ml) was added and the insoluble material was filtered to separate the catalyst. The filtrate was concentrated. The crude solid residue was purified by crystallization in ethanol, and in the case of the liquid product it was purified by chromatography on a short column of silica gel to afford pure α -aminophosphonates.

Compound **3a**: ¹H NMR (CDCl₃): δ 3.51 (d, 3H, J=10.5 Hz, OCH₃), 3.81 (d, 3H, J=10.6 Hz, OCH₃), 4.82 (d, 1H, J=24 Hz, CHP), 6.64 (d, 2H, J=8.0 Hz, ArH), 6.74 (t, 1H, J=7.2 Hz, ArH), 7.10 (t, 2H, J=7.7 Hz, ArH), 7.30 (t, 1H,

Scheme 2 Proposed mechanism.

J=7.5 Hz, ArH), 7.39 (t, 2H, J=7.4 Hz, ArH), 7.50 (d, 2H, J=7.3 Hz, ArH); 13 C NMR (CDCl₃): δ 54.1 (d, J=7.0 Hz), 54.2 (d, J=6.8 Hz), 56.2 (d, J=150 Hz), 114.3 (CH), 119.0, 128.2 (d, J=5.8 Hz), 128.4 (d, J=3.1 Hz), 129.1, 131.2, 136.0, 146.6 (d, J=14.5 Hz).

80

90

75

70

65

50

78

55

mp (°C) 87–89 155–158 113–115

130-135

60-62

60 - 62

130-135

Viscous oil

Viscous oil

Viscous oil

Viscous oil

154-156

References

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- [1] Quin LD, Quin GS. A Guide to Organophosphorus Chemistry, John Wiley & Sons Ltd.: New York, 2000, pp. 351–379.
- [2] Kafarski P, Lejczak B. Phosphor. Sulfur Silic. Relat. Elem. 1991, 63, 193–215.
- [3] Allen MC, Fuher W, Tuck B, Wade R, Wood JM. J. Med. Chem. 1989, 32, 1652–1661.
- [4] Baylis EK, Campbell CD, Dingwall JG. J. Chem. Soc. Perkin Trans. 1 1984, 2845–2853.
- [5] Bencovic SJ, Hirschman R. *Tetrahedron Lett.* 1994, 35, 6853–6856.
- [6] Hassal CH, Hahn EF. Antibiotics, Vol. VI, Springer: Berlin, 1983, pp. 1–11.
- [7] Makhavea GF, Malygin VV, Yu A. Dockl. Biochem. Biophys. 2005, 400, 92–95.
- [8] Pan W, Ansiaux C, Vincent SP. Tetrahedron Lett. 2007, 48, 4353–4356.
- [9] Bloemink MJ, Diederen JJH, Dorenbos JP, Heetebrij RJ, Keppler BK, Reedijk J. Eur. J. Inorg. Chem. 1999, 10, 1655–1657.
- [10] Jin L, Song B, Zhang G, Xu R, Zhang S, Gao X, Hu D, Yang S. Bioorg. Med. Chem. Lett. 2006, 16, 1537–1543.
- [11] Rao X, Song Z. Heteroatom. Chem. 2008, 19, 512–516.
- [12] Vahdat SM, Baharfar R, Tajbakhsh M, Heydari A, Baghbanian SM, Khaksar S. *Tetrahedron Lett.* 2008, 49, 6501–6504.
- [13] Kaboudin B, Sorbiun M. Tetrahedron Lett. 2007, 48, 9015–9017.
- [14] Wu J, Sun W, Xia H, Sun X. Org. Biomol. Chem. 2006, 4, 1663–1666.
- [15] Bhattacharya AK, Kaur T. Synlett 2007, 5, 745-748.
- [16] Akbari J. Tetrahedron Lett. 2009, 50, 4236–4238.
- [17] Hosseini-Sarvari M. Tetrahedron 2008, 64, 5459–5466.
- [18] Maghsoodlou M, Khorassani SMH, Hazeri N, Maleki N. Heteroatom Chem. 2009, 20, 316–318.
- [19] Banik A, Batta S, Bandyopadhyay D, Banik BK. *Molecules* 2010, 15, 8205–8213.
- [20] Dindulkar SD, Reddy MV, Jeong YT. Catal. Commun. 2012, 17, 114–117.

- [21] Gangwar N, Kasana VK. Synth. Commun. 2011, 41, 2800–2804.
- [22] Agawane SM, Nagarkar JM. Tetrahedron Lett. 2011, 52, 3499–3504.
- [23] Tang J, Wang L, Wang W, Zhang L, Wu S, Mao D. J. Fluorine Chem. 2011, 132, 102–106.
- [24] Karimi-Jaberi Z, Amiri M. Heteroatom Chem. 2010, 21,



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- [25] Karimi-Jaberi Z, Amiri M, Sadeghi N. Synth. Commun. 2010, 40, 2948–2953.
- [26] Karimi-Jaberi Z, Zare H, Amiri M, Sadeghi N. Chin. Chem. Lett. 2011, 22, 559–562.

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