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Organic Reactions in Water: A Distinct Novel Approach for an Efficient Synthesis of α-Amino Phosphonates Starting Directly from Nitro Compounds†

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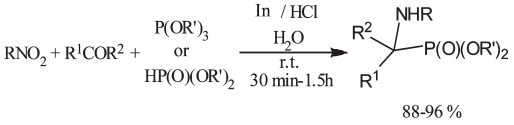

A distinct approach for high-yielding synthesis of α-amino phosphonates has been discovered through three-component reaction of nitro compounds, aldehydes, or ketones and dialkyl or trialkyl phosphites using indium in dilute aqueous HCl at room temperature. This one-pot conversion consists of the following steps: (i) reduction of nitro compounds to amines, (ii) formation of imines from amines and carbonyl compounds, and (iii) hydrophosphonylation of imines.

α-Amino phosphonates are biologically and industrially important compounds. They possess anticancer,[1a] anti-HIV,[1b] antithrombotic,[1c] and antibacterial properties.[1d] They are also employed as enzyme inhibitors[2] and peptide mimics.[3] Additionally, they are utilized as insecticides,[4a] herbicides,[4b] and fungicides.[4c] They are also applied as fire retardants for cotton.[5] Several methods have been developed for the synthesis of these useful compounds both in racemic and in optically active forms.[6] In general, α-amino phosphonates are prepared from amines and carbonyl compounds or directly from the imines. However, expensive reagents, long reaction times, and high temperatures are the problems in many of these methods. Herein we report a distinct approach for the synthesis of α-amino phosphonates starting directly from the nitro compounds.

SCHEME 1. Synthesis of α-Amino Phosphonates Directly Starting from Nitro Compounds

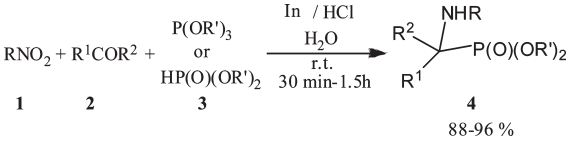

TABLE 1. Synthesis of α-Amino Phosphonates Using Different Metals[a]

entry	metal	time (h)	yield (%)[b]
1	Zn	5	62
2	Sn	6	68
3	Fe	4	61
4	In	0.5	96

[a]Reaction conditions: nitrobenzene (1 mmol), 1 N aqueous HCl (1 mL), benzaldehyde (1 mmol), triethyl phosphite (1.3 mmol), and 5 mL of water at room temperature. [b]Yields of isolated pure compound after column chromatography.

In continuation of our work[7] on the development of useful synthesis methodologies, we have discovered that α-amino phosphonates can be synthesized efficiently through the three-component reaction of nitro compounds, aldehydes, or ketones and dialkyl or trialkyl phosphites using indium in dilute aqueous HCl at room temperature (Scheme 1).

Initially, the reaction of nitrobenzene, benzaldehyde, and triethyl phosphite was conducted using different metals such as Zn, Fe, Sn, and In in aqueous HCl at room temperature (Table 1). Indium was found to be most effective in respect to the reaction time and yield at room temperature. Recently, indium has been utilized efficiently in various organic syntheses.[8] The advantage with this metal is that it generally does not affect oxygen- and nitrogen-containing functionalities.

Considering all of the benefits of using indium, subsequently, it was applied to prepare a series of α-amino phosphonates from different nitro compounds, aldehydes, or ketones and phosphites (Table 2). The conversion required only 30 min to 1.5 h to form the desired products in excellent yields (88−96%). Various derivatives of

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(6) (a) Allen, J. G.; Atherton, F. R.; Hall, M. J.; Hassal, C. H.; Holmes, S. W.; Lambert, R. W.; Nisbet, L. J.; Ringrose, P. S. *Nature* **1978**, *272*, 56–58. (b) Changtao, Q.; Taishing, H. *J. Org. Chem.* **1998**, *63*, 4125–4128. (c) Ramu, B.; Hajra, A.; Jana, H. *Org. Lett.* **1999**, *1*, 1141–1143. (d) Manabe, K.; Kobayashi, S. *Chem. Commun.* **2000**, 669–670. (e) Lee, S.; Park, J. K.; Lee, J. K. *Chem. Commun.* **2001**, 1698–1699. (f) Yadav, J. S.; Reddy, B. V. S.; Sreedhar, P. *Green Chem.* **2002**, *4*, 436–438. (g) Joly, G. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 4102–4103. (h) Kaboudin, B.; Moradi, K. *Tetrahedron Lett.* **2005**, *46*, 2989–2991. (i) Pawar, V. D.; Bettigeri, S.; Wang, S.-S.; Kan, J.-Q.; Chen, C.-T. *J. Am. Chem. Soc.* **2006**, *128*, 6308–6309. (j) Bhagat, S.; Chakraborti, A. K. *J. Org. Chem.* **2007**, *72*, 1263–1270. (k) Saito, B.; Egami, H.; Katsuki, T. *J. Am. Chem. Soc.* **2007**, *129*, 1978–1986. (l) Bhanushali, M. J.; Nandurkar, N. S; Jagtap, S. P.; Bhanage, B. M. *Synth. Commun.* **2009**, *39*, 845–859. (m) Hosseini-Sarvari, M. *Tetrahedron* **2008**, *64*, 5459–5466.

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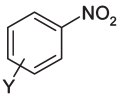
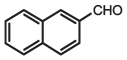
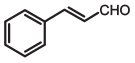
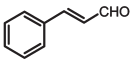
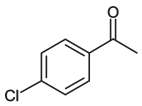
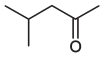
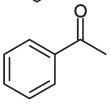
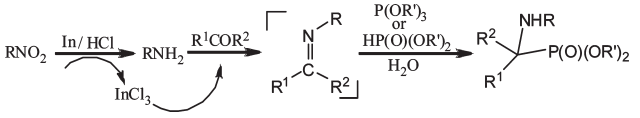
TABLE 2. Synthesis of α-Amino Phosphonates Using Indium in Dilute Aqueous HCl at Room Temperature[a]

Entry	Aldehyde/ Ketone	Nitro compound	Phosphite	Time (min)	Yield[b] (%)
					
1	Z=H	Y=H	TEP[c]	30	96
2	Z=CH_3	Y=H	TEP	35	94
3	Z=2,4-di-Cl	Y=H	TEP	40	92
4	Z=3,4-di-OMe	Y=H	TEP	50	88
5	Z=isopropyl	Y=H	TEP	40	90
6	Z=4-OEt	Y=3-NO_2	TEP	55	91
7	Z=3-F,4-Cl	Y=4-CH_3	TEP	50	92
8	Z=4-NO_2	Y=4-OH	TEP	45	94
9	Z=4-NMe_2	Y=4-CH_3	TEP	40	94
10	Z=4-Cl	Y=4-OMe	TEP	40	95
11	Z=4-NMe_2	Y=H	DEP[d]	50	92
12	Z=4-CH_3	Y=H	TMP[e]	40	93
13	Z=4-Cl	Y=4-OMe	DEP	50	91
14		Y=H	TEP	50	88
15		Y=H	TEP	45	90
16		Y=H	TEP	45	90
17		Y=H	TEP	55	88
18		Y=H	TEP	60	90
19		Y=4-CH_3	TEP	60	89
20		Y=H	DMP[f]	60	89
21		Y=4-CH_3	TMP	60	90
22		Y=4-CH_3	TMP	80	94
23		Y=H	TEP	90	93
24		Y=4-F	TMP	75	92
25		Y=H	DEP	80	89
26		Y=4-F	DEP	90	90

[a]The structures of the products were settled from their spectral (IR, ^{1}H, ^{13}C NMR, and MS) data. [b]Yields of isolated pure compounds after column chromatography. [c]Triethyl phosphite. [d]Diethyl phosphite. [e]Trimethyl phosphite. [f]Dimethyl phosphite.

nitrobenzene were applied to prepare α-amino phosphonates. Different functional groups including hydroxyl, ether, amine, and halogen remained intact. The reaction with a dinitrobenzene produced only a mono-α-amino phosphonate containing an unchanged nitro group. However, with an alkyl nitrate, a mixture of products was obtained. It was difficult to identify the desired product in this mixture by ^{1}H NMR spectrum though ESIMS indicated the presence of this product. The present conversion was found to be general for aldehydes and ketones. Both aliphatic and aromatic carbonyl compounds afforded the corresponding α-amino phosphonates smoothly. The aromatic carbonyl compounds contained electron-donating as well as electron-withdrawing groups. An acid-sensitive aldehyde such as cinnamaldehyde or furfuraldehyde and a sterically hindered aldehyde such as 2-naphthaldehyde furnished the desired products in impressive yields. Even with ketones, the reaction was accomplished at room temperature. The methods for the preparation of α-amino phosphonates from both aldehydes and ketones are limited.[6c,j] Moreover, with ketones, the reaction was generally conducted under reflux.[6c] In some methods, only aromatic aldehydes have been used.[6e,h] The present conversion also proceeded equally with dialkyl and trialkyl phosphites. In some earlier methods, the formation of α-amino phosphonates required much longer reaction times when dialkyl phosphites were used instead of trialkyl phosphites.[6e] Even in some cases, the conversions scarcely proceeded with dialkyl phosphites.[6d] Following our present method, 26 α-amino phosphonates have been successfully prepared using both dialkyl and trialkyl phosphites. The structures of the products were settled from their spectral (IR, ^{1}H, ^{13}C NMR, and MS) data.

SCHEME 2. Derived Mechanism for Synthesis of α-Amino Phosphonates Directly Starting from Nitro Compounds



The present synthesis of α-amino phosphonates consists of three steps in one pot. Initially, the nitro compounds on treatment with In/HCl reduce to amines,[9] which then react with carbonyl compounds to produce the corresponding imines. Finally, the imines undergo hydrophosphorylation with phosphites to form the α-amino phosphonates (Scheme 2). When the conversion was conducted with an amine, a carbonyl compound, and phosphite under the present reaction conditions, the corresponding α-amino phosphonate was also obtained in high yield and in short reaction time.

In conclusion, we have developed a novel efficient method for the one-pot synthesis of α-amino phosphonates through a distinct approach involving the reaction of nitro compounds, aldehydes, or ketones and phosphites using indium in dilute aqueous HCl at room temperature. The direct application of nitro compounds, reaction in water, mild experimental conditions, rapid conversion, and impressive yields are the advantages of the present method. The method is general for aliphatic and aromatic aldehydes and ketones and for dialkyl and trialkyl phosphites.

Experimental Section

General Experimental Procedure: To a mixture of nitro compound **1** (1.0 mmol) were added indium powder (325 mesh,

(9) Lee, J. C.; Choi, K. II; Koh, H. Y.; Kang, Y.; Kim, Y.; Kang, Y.; Cho, Y. S. *Synthesis* **2001**, 81–84.

2 mmol), 1 N aqueous HCl (1 mL), aldehyde **2** (1.0 mmol), alkyl phosphite **3** (1.3 mmol), and water (5 mL). The mixture was stirred at room temperature, and the reaction was monitored by TLC. After completion, the reaction mixture was washed with saturated $NaHCO_3$ solution (3 × 5 mL) and water (3 × 5 mL) and extracted with EtOAc (3 × 5 mL). The extract was concentrated, and the residue was subjected to column chromatography (silica gel, hexane/EtOAc) to obtain pure α-amino phosphonate.

Diethyl(2,4-dichlorophenyl)(phenylamino)methyl phosphonate (Table 2, entry 3): IR ν_{max} 3309, 1607, 1508, 1247 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.51 (1H, d, J = 8.0 Hz), 7.40 (1H, d, J = 2.0 Hz), 7.22 (1H, dd, J = 8.0, 2.0 Hz), 7.06 (2H, t, J = 8.0 Hz), 6.64 (1H, t, J = 8.0 Hz), 6.48 (2H, d, J = 8.0 Hz), 5.23 (1H, dd, J = 24.0, 10.0 Hz), 4.82 (1H, t, J = 10.0 Hz), 4.25−4.12 (2H, m), 3.91 (1H, m), 3.67 (1H, m), 1.35 (3H, t, J = 7.0 Hz), 1.11 (3H, t, J = 2.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 146.2 (d, J = 14.0 Hz), 130.2, 129.8, 128.2, 119.1, 113.5, 96.2, 63.4 (d, J = 6.5 Hz), 63.2 (d, J = 6.5 Hz), 51.6 (d, J = 155.2 Hz), 16.6 (d, J = 6.5 Hz), 16.2 (d, J = 6.5 Hz); ESIMS m/z 387 $[M]^+$, 388, 390, 392 $[M + H]^+$; HRMS (ESI) m/z 410.0459 $[M + Na]^+$ (calcd for $C_{17}H_{20}Cl_2NO_3PNa$ m/z 410.0455).

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Supporting Information Available: General information, general experimental procedure, the spectral (IR, ^1H, and ^{13}C NMR, ESIMS and ESIHRMS) data and copies of NMR (^1H and ^{13}C) and HRMS (ESI) spectra of the new α-amino phosphonates (entries 3−10 and 21−24 in Table 2). This material is available free of charge via the Internet at http://pubs.acs.org.