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Molecular Iodine: An Efficient Catalyst for the One-Pot Synthesis of Primary 1-Aminophosphonates

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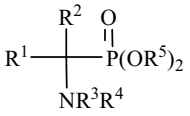
A new and convenient procedure has been developed for the one-pot synthesis of different types of primary 1-aminophosphonates from aldehydes/ketones, HMDS and diethyl phosphite using I_2 as an inexpensive, non-toxic, non-metallic and readily available catalyst. These reactions proceeded under solvent-free conditions and produced the desired products in high yields.

Keywords: 1-Aminophosphonates, Aldehydes, Ketones, Diethyl Phosphite, Iodine

INTRODUCTION

1-Functionalized phosphonates have found a wide range of applications 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]. Among 1-fuctionalized phosphonates, 1-aminophosphonates (Scheme 1) has stimulated extensive studies in the past decades because they serve as important surrogates for the corresponding 1-amino acids.



primary 1-aminophosphonates: R^3=H; R^4=H
secondary 1-aminophosphonates: R^3=alkyl, aryl; R^4=H
tertiary 1-aminophosphonates: R^3=alkyl, aryl; R^4=alkyl, aryl

Scheme 1

Indeed, a number of potent antibiotics [2], enzyme inhibitors [3] and pharmacological agents [4] are 1-aminophosphonates or peptide analogues. Moreover, aminophosphonates are found as constituents of natural products. There are several multi-step synthetic approaches to primary 1-aminophosphonates in the literature: a) addition of the P-H function to imines and nitriles [5,6], b) Hofmann rearrangement of substituted phosphonoacetic esters [7], c) alkylation of nucleophilic precursors such as Schiff bases [8], d) conversion of the corresponding 1-hydroxyphosphonates to 1-aminophosphonates [9,10] and e) reduction of 1-hydroxy-iminophosphonates [11].

In contrast to the widespread studies on the one-pot synthesis of secondary and tertiary 1-aminophosphonates [12-17], relatively few methods are reported for the one-pot synthesis of primary 1-aminophosphonates. The most typical procedure for the one-pot synthesis of primary 1-aminophosphonates is a Strecker-type reaction [18], which involves the treatment of an aldehyde with ammonia and diethyl phosphite. This method, however, is not high yielding and is unsuitable for large-scale production since the reaction is performed in a sealed vessel at 100 ºC. Recently, in this reaction, volatile ammonia has been substituted by ammonium salts or 1,1,1,3,3,3-hexamethyldisilazane (HMDS). These

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reactions are conducted by catalysts such as molecular sieve [19], $LiClO_4$ [20], tetra-*tert*-butyl-substituted phthalocyanine [21] and solid supports [22-26]. However, all the existing methods have drawbacks such as long reaction times [19,21] amenable only for aldehydes as carbonyl compounds [19,22-26] using nasty smelling trialkyl phosphite as the phosphorus nucleophile [20], requiring microwave activation [22-25], low yields of the products [19,21], formation of 1-hydroxyphosphonates or 1-trimethylsilyloxyphosphonates as side products [27] and using large amounts of solid supports or catalyst which eventually results in the generation of a large amount of toxic waste [17,22-25].

As part of our ongoing research to develop new synthetic routes for the preparation of 1-functionalized phosphonates [28-36], we herein introduce molecular iodine as an efficient catalyst for the one-pot synthesis of primary 1-aminophosphonates from coupling reaction of aldehydes/ketones, HMDS and diethyl phosphite under solvent-free conditions.

EXPERIMENTAL

Chemicals and Apparatus

Chemicals were purchased from Merck and Fluka Chemical Companies. All of the products were identified by their spectral data. IR spectra were run on a Perkin Elmer 780 instrument. NMR spectra were recorded on a Bruker Avance DPX-250. Mass spectra were recorded on a Shimadzu GCMS-QP5050A. The purity of the products and the progress of the reactions were accomplished by TLC on silica-gel polygram SILG/UV_{254} plates or by GC on a Shimadazu model GC-14A instrument.

General Procedure for the Preparation of Primary Diethyl 1-Aminophosphonates (2-29)

A mixture of carbonyl compound (2 mmol), HMDS (1 mmol), diethyl phosphite (1 mmol) and I_2 (0.01 mmol) was stirred at room temperature. The reaction was monitored by TLC or GC. After completion of the reaction, EtOAc (10 ml) and finely powdered $Na_2S_2O_3$ (≈0.3 g, in portion) were added to the reaction mixture. The resulting mixture was stirred for additional 30 min and filtered. The filtered cake was washed with EtOAc (10 ml) and the solvent was evaporated under reduced pressure. The resulting mixture was acidified to pH 1 by addition of HCl (aq) and the solution was washed with EtOAc (2 × 10 ml) to remove neutral materials. The aqueous phase was then made alkaline with NaOH (aq). The product was extracted with EtOAc (2 × 10 ml). The organic phases were combined, dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to give diethyl 1-aminophosphonates (**2-29**) with high purity.

Spectral Data for Selected Diethyl 1-Aminophosphonates

2. ^{1}H NMR ($CDCl_3$): δ 1.16 (t, 3 H, $^2J_{H,H}$ = 7.0 Hz, OCH_2CH_3), 1.26 (t, 3 H, $^2J_{H,H}$ = 7.0 Hz, OCH_2CH_3), 2.37 (bs, NH_2), 3.82-4.09 (m, 4 H, OCH_2CH_3), 4.24 (d, 1 H, $^2J_{P,H}$ = 17.2 Hz, CH), 7.21-7.46 (m, 5 H, C_6H_5); ^{13}C NMR ($CDCl_3$): δ 16.3 (d, $^3J_{C,P}$ = 5.7 Hz, OCH_2CH_3), 16.4 (d, $^3J_{C,P}$ = 5.7 Hz, OCH_2CH_3), 54.0 (d, $^1J_{C,P}$ = 149.5 Hz, CH), 62.7 (d, $^2J_{C,P}$ = 7.7 Hz, OCH_2CH_3), 62.8 (d, $^2J_{C,P}$ = 7.7 Hz, OCH_2CH_3), 127.5, 127.8, 128.2, 128.5 (C_6H_5); IR (Neat): 3385, 3298 (NH_2) cm^{-1}; MS (70 eV), *m/z* (%): 243 (M^+), 106 [M-P(O)$(OEt)_2$].

5. ^{1}H NMR ($CDCl_3$, TMS): δ 1.16 (t, 3 H, $^2J_{H,H}$ = 7.0 Hz, OCH_2CH_3), 1.26 (t, 3 H, $^2J_{H,H}$ = 7.0 Hz, OCH_2CH_3), 1.88 (bs, NH_2), 3.78 (s, 3H, OCH_3), 3.82-4.08 (m, 4H, OCH_2CH_3), 4.18 (d, 1 H, $^1J_{P,H}$ = 16.2 Hz, CH), 6.85-6.88 (m, 2H, C_6H_4), 7.33-7.45 (m, 2H, C_6H_4); ^{13}C NMR ($CDCl_3$, TMS): δ 16.3 (d, $^3J_{C,P}$ = 6.3 Hz, OCH_2CH_3), 16.4 (d, $^3J_{C,P}$ = 6.3 Hz, OCH_2CH_3), 53.4 (d, $^1J_{C,P}$ = 150.9 Hz, CH), 55.2 (s, OCH_3), 62.6 (d, $^2J_{C,P}$ = 6.9 Hz, OCH_2CH_3), 62.7 (d, $^2J_{C,P}$ = 6.9 Hz, OCH_2CH_3), 128.7, 128.8 (C_6H_5), 113.8 (d, $^3J_{C,P}$ = 2.5 Hz , C_6H_5), 159.2 (d, $^2J_{C,P}$ = 3.1 Hz, C_6H_5); IR: 3371, 3300 (NH_2) cm^{-1}; MS (70 eV), m/e: 273 (M^+), 136 [M-P(O)$(OEt)_2$].

10. ^{1}H NMR ($CDCl_3$, TMS): δ 1.15 (t, 3 H, $^2J_{H,H}$ = 7.0 Hz, OCH_2CH_3), 1.25 (t, 3 H, $^2J_{H,H}$ = 7.0 Hz, OCH_2CH_3), 2.19 (bs, NH_2), 3.78-4.10 (m, 4H, OCH_2CH_3), 4.43 (d, 1H, $^1J_{P,H}$ = 17.5 Hz, CH), 7.44-7.48 (m, 2H, $C_{10}H_7$), 7.56-7.60 (m, 1H, $C_{10}H_7$), 7.80-7.90 (m, 4H, $C_{10}H_7$); ^{13}C NMR ($CDCl_3$, TMS): δ 16.3 (d, $^3J_{C,P}$ = 5.7 Hz, OCH_2CH_3), 16.4 (d, $^3J_{C,P}$ = 5.7 Hz, OCH_2CH_3), 54.2 (d, $^1J_{C,P}$ = 149.7 Hz, CH), 62.8 (d, $^2J_{C,P}$ = 6.3 Hz, OCH_2CH_3), 62.9 (d, $^2J_{C,P}$ = 6.3 Hz, OCH_2CH_3), 125.7-126.6 (m, $C_{10}H_7$), 127.6-128.1 (m, $C_{10}H_7$), 132.9-133.2 (m, $C_{10}H_7$), 135.1 (d, $^2J_{C,P}$ = 3.8 Hz, $C_{10}H_7$); IR: 3371, 3292 (NH_2) cm^{-1}; MS (70 eV), m/e: 293 (M^+), 156 [M-P(O)$(OEt)_2$].

12. ^{1}H NMR ($CDCl_3$, TMS): δ 1.11-1.20 (t, 6H,

OCH_2CH_3), 2.51 (bs, NH_2), 3.82-4.03 (m, 4H, OCH_2CH_3), 4.42 (d, 1H, $^1J_{P,H}$ = 16.7 Hz, CH), 6.87 (t, $^2J_{H,H}$ = 4.0 Hz, 1H, C_4H_3S), 7.03 (s, 1H, C_4H_3S), 7.14 (d, $^2J_{H,H}$ = 5.0 Hz, 1H, C_4H_3S); ^{13}C NMR ($CDCl_3$, TMS): δ 16.3 (d, $^3J_{C,P}$ = 3.8 Hz, OCH_2CH_3), 16.4 (d, $^3J_{C,P}$ = 3.8 Hz, OCH_2CH_3), 49.9 (d, $^1J_{C,P}$ = 156.2 Hz, CH), 62.9 (d, $^2J_{C,P}$ = 7.6 Hz, OCH_2CH_3), 124.9, 125.5, 126.8 (C_4H_3S), 141 (d, $^2J_{C,P}$ = 3.8 Hz, C_4H_3S); IR: 3374, 3302 (NH_2) cm^{-1}; MS (70 eV), m/e: 249 (M^+), 112 [M-P(O)$(OEt)_2$].

13. ^{1}H NMR ($CDCl_3$, TMS): δ 1.07 (t, 3H, $^2J_{H,H}$ = 6.5 Hz, OCH_2CH_3), 1.26 (t, 3 H, $^2J_{H,H}$ = 6.5 Hz, OCH_2CH_3), 3.03 (bs, NH_2), 3.85-4.15 (m, 4H, OCH_2CH_3), 4.63 (d, 1H, $^1J_{P,H}$ = 15.0 Hz, CH), 6.95-7.70 (m, 4H, C_8H_6N), 9.33 (bs, NH, C_8H_6N); ^{13}C NMR ($CDCl_3$, TMS): δ 16.3 (OCH_2CH_3), 45.9 (d, $^1J_{C,P}$ = 158.7 Hz, CH), 63.1 (OCH_2CH_3), 110.7, 111.6, 118.8, 119.5, 122, 124.3 (C_8H_6N), 126.1 (1H, $^2J_{C,P}$ = 5.7 Hz, C_8H_6N), 136.1 (C_8H_6N); IR: 3396, 3252 (NH_2) cm^{-1}; MS (70 eV), m/e: 282 (M^+), 145 [M-P(O)$(OEt)_2$].

16. ^{1}H NMR ($CDCl_3$, TMS): δ 0.80-0.85 (m, 3H, CH_3), 1.23-1.75 (m, 14H, OCH_2CH_3, CH_2, NH_2), 2.80-2.91 (m, 1H, CH), 4.04-4.10 (m, 4H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, TMS): δ 18.8 (CH_3), 16.5 (d, $^3J_{C,P}$ = 5.5 Hz, OCH_2CH_3), 22.4, 28.2 (d, $^2J_{C,P}$ = 12.6 Hz, CH_2), 30.83 (CH_2), 48.6 (d, $^1J_{C,P}$ = 148.9 Hz, CH), 61.9, 62.0 (OC_2H_5); MS (70 eV), m/e: 223 (M^+), 86 [M-P(O)$(OEt)_2$].

19. ^{1}H NMR ($CDCl_3$, TMS): δ 0.80-0.87 (m, 3H, CH_3), 1.25-1.77 (m, 16H, OCH_2CH_3, CH_2), 2.34 (bs, NH_2), 2.85-2.93 (m, 1H, CH), 4.08-4.13 (m, 4H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, TMS): δ 14.0 (CH_3), 16.5 (d, $^3J_{C,P}$ = 5.7 Hz, OCH_2CH_3), 22.6, 26.15 (d, $^2J_{C,P}$ = 12.6 Hz, CH_2), 29.1, 29.3, 31.1, 31.7 (CH_2), 48.5 (d, $^1J_{C,P}$ = 148.7 Hz, CH), 61.9, 62.0 (OC_2H_5); MS (70 eV), m/e: 265 (M^+), 128 [M-P(O)$(OEt)_2$].

20. ^{1}H NMR ($CDCl_3$, TMS): δ 1.29 (t, 6H, $^2J_{H,H}$ = 7.2 Hz, OCH_2CH_3), 1.54-1.69 (m, 4H, C_5H_8), 1.87-2.04 (m, 6H, C_5H_8, NH_2), 4.08-4.20 (m, 4H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, TMS): δ 16.6 (d, $^3J_{C,P}$ = 5.7 Hz, OCH_2CH_3), 24.6 (d, $^2J_{C,P}$ = 11.3 Hz, C_5H_8), 36.3 (d, $^3J_{C,P}$ = 6.9 Hz, C_5H_8) 58.7 (d, $^1J_{C,P}$ = 154.7 Hz, C_5H_8), 62.2 (d, $^2J_{C,P}$ = 6.9 Hz, OCH_2CH_3); IR: 3368, 3294 (NH_2) cm^{-1}; MS (70 eV), m/e: 221 (M^+), 84 [M-P(O)$(OEt)_2$].

21. ^{1}H NMR ($CDCl_3$, TMS): δ 1.29 (t, 6H, $^2J_{H,H}$ = 7.2 Hz, OCH_2CH_3), 1.52-1.72 (m, 12H, C_6H_{10}, NH_2), 4.04-4.15 (m, 4 H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, TMS): δ 16.5 (d, $^3J_{C,P}$ = 5.7 Hz, OCH_2CH_3), 19.8 (d, $^3J_{C,P}$ = 11.3 Hz, C_6H_{10}), 25.5, 31.3 (C_6H_{10}) 51.6 (d, $^1J_{C,P}$ = 151 Hz, C_6H_{10}), 62.1 (d, $^2J_{C,P}$ = 8.2 Hz, OCH_2CH_3); IR: 3385, 3290 (NH_2) cm^{-1}; MS (70 eV), m/e: 235 (M^+), 98 [M-P(O)$(OEt)_2$].

22. ^{1}H NMR ($CDCl_3$, TMS): δ 1.21 (t, 6H, $^2J_{H,H}$ = 7 Hz, OCH_2CH_3), 1.42-1.52 (m, 12H, C_7H_{12}), 1.90 (bs, NH_2), 3.96-4.08 (m, 4H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, TMS): δ 16.5 (d, $^3J_{C,P}$ = 5.7 Hz, OCH_2CH_3), 21.9 (d, $^2J_{C,P}$ = 9.4 Hz, C_7H_{12}), 30.3 (s, C_7H_{12}), 35.5 (d, $^3J_{C,P}$ = 3.1 Hz, C_7H_{12}) 54.5 (d, $^1J_{C,P}$ = 144 Hz, C_7H_{12}), 62.1 (d, $^2J_{C,P}$ = 7.5 Hz, OCH_2CH_3); IR: 3369, 3300 (NH_2) cm^{-1}; MS (70 eV), m/e: 249 (M^+), 112 [M-P(O)$(OEt)_2$].

24. ^{1}H NMR ($CDCl_3$, TMS): δ 0.98 (t, 3H, $^2J_{H,H}$ = 7.5 Hz, CH_3), 1.24 (d, 3H, $^2J_{P,H}$ = 16 Hz, CH_3), 1.32 (t, 6H, $^2J_{H,H}$ = 7 Hz, OCH_2CH_3), 1.59-1.73 (m, 4H, CH_2, NH_2); 4.07-4.19 (m, 4H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, TMS): δ 7.3 (d, $^3J_{C,P}$ = 7.6 Hz, CH_3), 16.6 (d, $^3J_{C,P}$ = 5.7 Hz, OCH_2CH_3), 21.7 (d, $^2J_{C,P}$ = 21.7 Hz, CH_3), 30.0 (d, $^2J_{C,P}$ = 3.8 Hz, CH_2), 52.0 (d, $^1J_{C,P}$ = 147.4 Hz, C), 62.2 (d, $^2J_{C,P}$ = 7.6 Hz, OCH_2CH_3); IR: 3378, 3307 (NH_2) cm^{-1}; MS (70 eV), m/e: 209 (M^+), 72 [M-P(O)$(OEt)_2$].

25. ^{1}H NMR ($CDCl_3$, TMS): δ 0.95 (t, 6H, $^2J_{H,H}$ = 6.7 Hz, OCH_2CH_3), 1.23-1.33 (m, 9H, CH_3), 1.46-1.63 (m, 6H, CH_2, NH_2), 1.89-1.99 (m, 1H, CH), 4.05-4.17 (m, 4H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, TMS): δ 16.6 (d, $^3J_{C,P}$ = 5 Hz, OCH_2CH_3), 22.1 (d, $^3J_{C,P}$ = 1.9 Hz, CH_3), 23.2 (d, $^2J_{C,P}$ = 10.1 Hz, CH_2), 25.2 (s, CH_3), 45.5 (d, $^3J_{C,P}$ = 3.1, CH), 52.5 (d, $^1J_{C,P}$ = 145.3 Hz,), 62.2 (d, $^2J_{C,P}$ = 7.5 Hz, OCH_2CH_3); IR: 3390, 3302 (NH_2) cm^{-1}; MS (70 eV), m/e: 251 (M^+), 114 [M-P(O)$(OEt)_2$].

26. ^{1}H NMR ($CDCl_3$, TMS): δ 1.33 (t, 6H, $^2J_{H,H}$ = 7.0 Hz, OCH_2CH_3), 1.58 (d, 3H, $^3J_{P,H}$ = 16.2 Hz, CH_3), 2.11 (bs, NH_2), 3.78 (s, 3H, CO_2CH_3), 4.06-4.23 (m, 4H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, TMS): δ 16.5 (d, $^3J_{C,P}$ = 5.0 Hz, OCH_2CH_3), 21.9 (s, CH_3), 52.9 (s, CH_3), 58.4 (d, $^1J_{C,P}$ = 145.5 Hz, C), 63.4 (d, $^2J_{C,P}$ = 3.2 Hz, OCH_2CH_3), 63.5 (d, $^2J_{C,P}$ = 3.2 Hz, OCH_2CH_3), 172.2 [d, $^2J_{C,P}$ = 3.8 Hz, C(O)]; IR: 3394, 3316 (NH_2) cm^{-1}; MS (70 eV), m/e: 239 (M^+), 102 [M-P(O)$(OEt)_2$].

28. ^{1}H NMR ($CDCl_3$, TMS): δ 0.91 (t, 6 H, $^2J_{H,H}$ = 7.5 Hz, OCH_2CH_3), 1.28 (d, 3 H, $^2J_{P,H}$ = 17.1 Hz, CH_3), 1.64 (bs, NH_2), 4.19-4.23 (m, 4H, OCH_2CH_3), 7.50-7.54 (m, 2H, C_5H_4N), 7.68-7.72 (m, 2H, C_5H_4N); IR: 3377, 3299 (NH_2) cm^{-1}; MS (70 eV), m/e: 258 (M^+), 121 [M-P(O)$(OEt)_2$].

RESULTS AND DISSCUSION

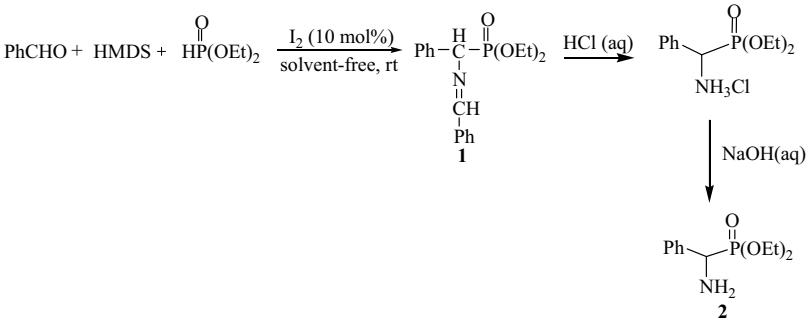
Recently, we have found iodine as an efficient catalyst for

the preparation of 1-trimethylsilyloxyphosphonates by silylation of 1-hydroxyphosphonates with HMDS [28]. This observation prompted us to examine the efficiency of iodine as a catalyst in the one-pot three-component reaction of carbonyl compounds, diethyl phosphite and HMDS for the preparation of 1-trimethylsilyloxyphosphonates. At first, a reaction of benzaldehyde, HMDS and diethyl phosphite was chosen as a model and the feasibility of the reaction was studied in the presence of I_2 (10 mol %) as the catalyst at ambient temperature under solvent-free conditions. Surprisingly, after 10 min, diethyl *N*-(phenylmethylene)-1-aminophenylmethyl phosphonate (**1**) was obtained in 96% yield without any formation of 1-trimethylsilyloxyphosphonate (Scheme 2). The ^{1}H NMR spectrum of **1** exhibited a doublet at 8.40 ppm which is indicative of the coupling of HC-P ($^1J_{HP}$ = 5 Hz) moiety in the molecule. Hydrolysis of **1** with HCl and neutralization of the chloride salt gave diethyl 1-aminophenylmethylphosphonate (**2**) (Scheme 2).

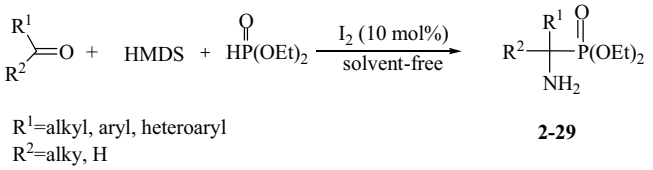
To show the generality and scope of this method, the reaction was examined with various structurally diverse aldehydes and ketones (Scheme 3) at ambient temperature under solvent-free conditions. The results are compiled in Table 1.

As shown in Table 1, different substituted benzaldehydes were successfully converted to their corresponding primary 1-aminophosphonates in good to high yields (Entries 1-8). The catalyst was compatible with functional groups such as Cl and O-Me. No competitive nucleophilic methyl ether cleavage was observed for substrate having an aryl-O-Me group (Entries 2-4), in spite of good nucleophilic property of phosphites. The reaction also proceeded well when naphthalene-2-carbaldehyde was employed as a polynuclear aldehyde (Entry 9). Difunctional aminophosphonate **11** was also prepared in 95% yield from terephthaldehyde by the present method (Entry 10). Thiophene-2-carbaldehyde and indole-3-carbaldehyde as heterocyclic aldehydes underwent smooth reactions under the present reaction conditions and produced the corresponding diethyl 1-aminophosphonates in excellent yields (Entries 11 and 12). This catalytic system was also effective for the preparation of primary 1-aminophosphonates from aliphatic aldehydes in 80-95% yields (Entries 13-18). In addition to aldehydes, some ketones were screened to carry out the coupling reaction by I_2 under solvent-free conditions. The results showed that the reactions involved cyclic ketones (Entries 19-22), acyclic dialkyl ketones (Entries 23-25) and alkyl aryl ketones (Entries 26-28) which worked well and the expected products were easily obtained in 70-96% yields.

In all of the reactions we have studied, primary 1-aminophosphonates were exclusively formed without any formation of the side products such as diethyl 1-tri-methyl-

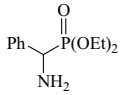
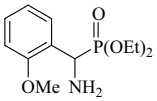
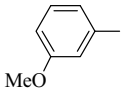
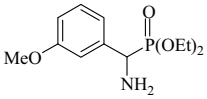
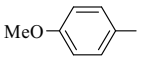
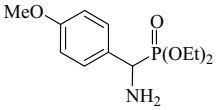
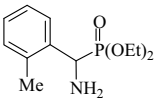
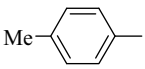
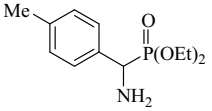
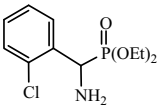
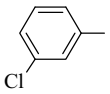
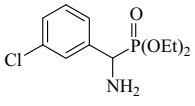
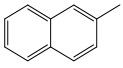
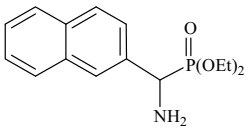


Scheme 2



Scheme 3

Table1. One-Pot Synthesis of Primary 1-Aminophosphonates from Aldehydes/ketones, HMDS and Diethylphosphite in the Presence of I_2 (10 mol%) at Ambient Temperature under Solvent-Free Conditions

Entry	R^1	R^2	Product	Time (min)	Yield (%)[a]
1		H	 **2**	10	93
2		H	 **3**	30	90
3		H	 **4**	30	95
4		H	 **5**	15	92
5		H	 **6**	15	95
6		H	 **7**	30	90
7		H	 **8**	15	95
8		H	 **9**	15	86
9		H	 **10**	15	88

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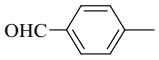
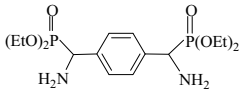
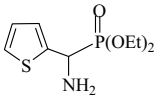
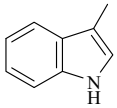
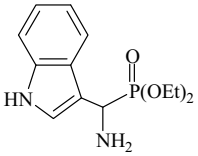
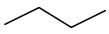
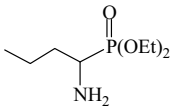
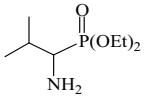
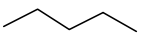
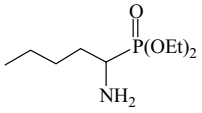
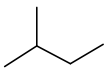
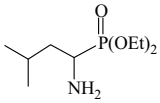
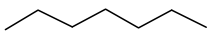
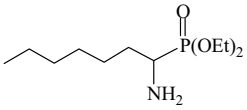
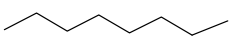
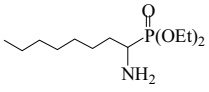
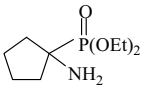
10		H	 **11**	3.5 h	95[b]
11		H	 **12**	2 h	93
12		H	 **13**	30	95
13		H	 **14**	1 h	85
14		H	 **15**	20	93
15		H	 **16**	30	87
16		H	 **17**	25	95
17		H	 **18**	1 h	90
18		H	 **19**	30	80
19			 **20**	5	88

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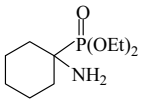
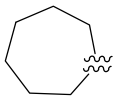
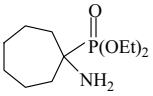
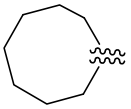
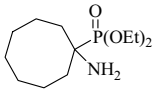
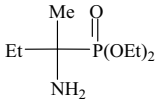
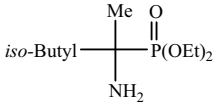
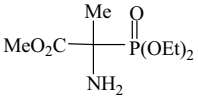
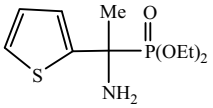
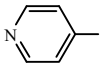
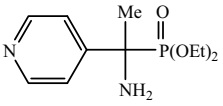
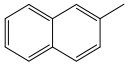
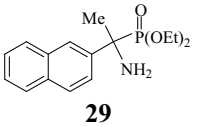
20			 **21**	5	80
21			 **22**	25	87
22			 **23**	30	83
23	Et	Me	 **24**	35	92
24	*iso*-Butyl	Et	 **25**	30	96
25	Me	CO_2Me	 **26**	15	95
26		Me	 **27**	4 h	70[c]
27		Me	 **28**	45	83
28		Me	 **29**	2.5h	82[c]

[a]Isolated yield. [b]Conditions:diethyl phosphite (4 mmol), HMDS (4 mmol). [c]Reaction temperature = 80 °C.

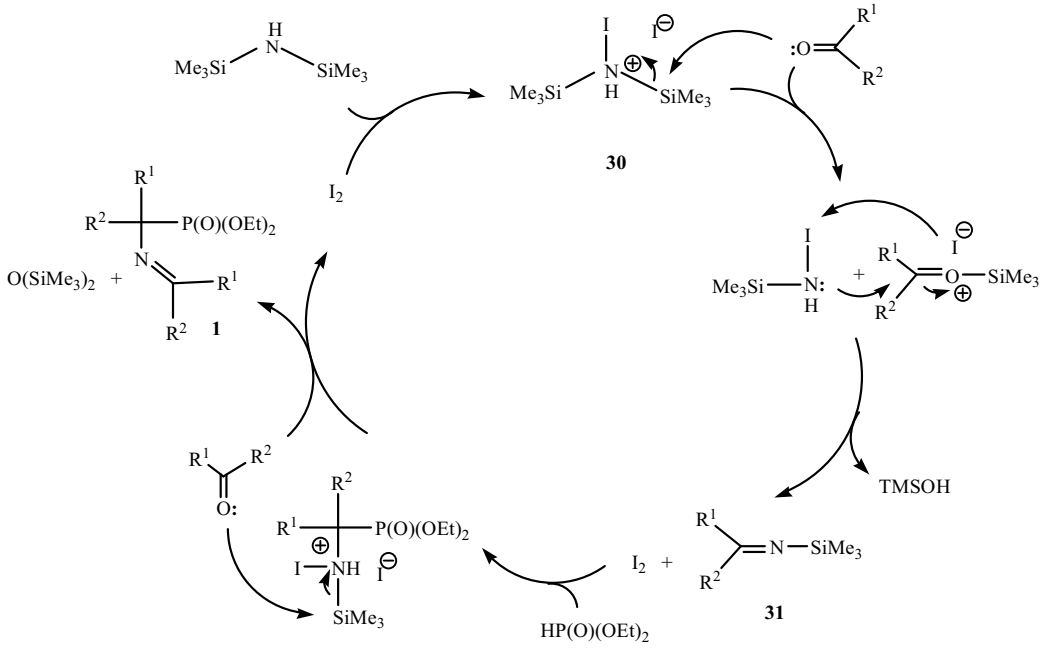
silyloxyphosphonate and diethyl 1-hydroxyphosphonate. These observations indicate excellent selectivity of this method for the synthesis of a variety of different types of primary diethyl 1-aminophosphonates. Release of ammonia gas was not detected in any of these transformations. It is worthy of mention that no evolution of ammonia gas was observed when a mixture of HMDS and iodine was stirred under similar reaction conditions. With these results in hand, we suggest a plausible mechanism for these transformations (Scheme 4). In this mechanism, I_2 polarized Si-N bond in HMDS and produced a reactive silylating agent (**30**). The reaction of **30** with carbonyl compound then led to the formation of imine **31** as an intermediate. Imine **31** was converted to **1** after the reaction with diethyl phosphite and carbonyl compound. I_2 is released during this process and reenters the same catalytic cycle (Scheme 4). Finally, primary diethyl 1-aminophosphonate (**2-29**) is obtained by hydrolysis of **1** under acidic conditions.

As the last step in our studies, in Table 2, we have compared the present method, using I_2, with the previously known procedures for the one-pot synthesis of diethyl 1-aminophenylmethylphosphonate (**2**) from benzaldehyde, HMDS and diethyl phosphite. A comparison of the present method, with respect to the product yield, with those of the literature reports in the presence of alumina (acidic, basic and neutral) and magnesia reveals the high efficiency of this newly developed method. The desired product (**2**) was obtained in

Table 2. Comparison of Catalytic Efficiency of I_2 with the Reported Promoters for the One-Pot Synthesis of **2** from the Reaction of Benzaldehyde, HMDS and Diethyl Phosphite

Entry	Catalyst	Time (min)	Yield (%)[a]
1	I_2	10	93
2	Al_2O_3 (acidic)[b]	60	5 [26]
3	MgO	15	0[c] [27]
4	$LiClO_4$[d]	15	88 [20]

[a]Isolated yield. [b]A mixture of **1** and diethyl-1-hydroxy-1-phenylmethylphosphonate (1:1 ratio) obtained in the presence of basic or neutral alumina [26]. [c]Diethyl-1-hydroxy-1-phenylmethylphosphonate was obtained as the major product in 95% yield. [d]200 mol% of $LiClO_4$ was used.



Scheme 4

low yields, when the reaction was carried out on the surface of alumina due to the formation of diethyl 1-hydroxyphenyl-methylphosphonate as a side product (Entry 2) [26]. No formation of the desired product (**2**) was observed in the presence of magnesia and diethyl 1-hydroxyphenyl-methylphosphonate was isolated as the major product (Entry 3) [27]. Although $LiClO_4$ can catalyze the same reaction to produce the desired product in high yield, the requirement of stoichiometric amount of the catalyst (200 mol%) indicates the lower catalytic activity of $LiClO_4$ in comparison with I_2 (Entry 4) [20].

CONCLUSIONS

In summary, the present method provides a new and facile procedure for the one-pot synthesis of different types of primary diethyl 1-aminophosphonates from aldehydes/ ketones, HMDS and diethyl phosphite using I_2 as an inexpensive, non-toxic, non-metallic and readily available catalyst. High yields, solvent-free conditions, using diethyl phosphite instead of nasty smelling trialkyl phosphite, no by-product formation, applicability to ketones as well as aldehydes, using a catalytic amount of I_2 without requiring a promoter, all make this protocol a useful contribution to the existing methodologies.

ACKNOWLEDGMENTS

We are thankful to Birjand University Research Council for their support of this work.

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