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Highly efficient metal-free one-pot synthesis of α-aminophosphonates through reduction followed by Kabachnik–fields reaction using three-component system

Murali Krishna Kolli[a,b], Palani Elamathi[a], Govindasamy Chandrasekar[a], Vishweshwar Rao Katta[b], and Gajendrasinh Balvantsinh Raolji[b]

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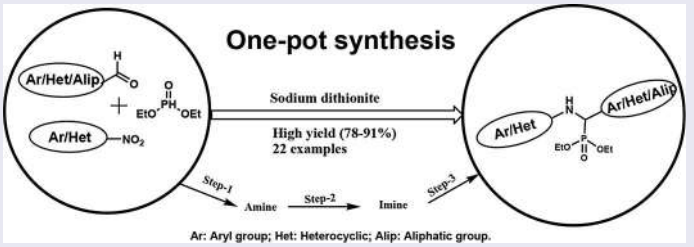
ABSTRACT

One-pot synthesis of α-aminophosphonates directly from aryl nitro compounds, aldehydes/ketones, and diethyl phosphite using sodium dithionite through reduction and followed by Kabachnik–Fields reaction under metal-free conditions is reported. The major advantages are excellent yield, high chemoselectivity, neutral reaction medium, and simple experimental procedure. This methodology consists of the following steps: 1) amine formation from nitro compound, 2) imine formation from amine and aldehyde/ketone, 3) phosphate addition to imine.

GRAPHICAL ABSTRACT



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KEYWORDS
α-Aminophosphonate; aldehydes; diethyl phosphite; ketones; nitro compounds; sodium dithionite

Introduction

α-Aminophosphonates are playing an important role in the medicinal chemistry as their moiety can be tailored to produce anti-HIV,[1] anticancer,[2a–e] anti-proliferative and apoptosis-inducing,[3a-b] antitumor,[4a–i] anti-inflammatory,[5a–c] Inhibitors to various microorganisms such as plant virus,[6a] *Streptococcus pneumonia* MetAP,[6b] protein tyrosine,[6c] topoisomerase II,[6d] and serine proteases,[6e] antibacterial,[7a–c] fungicidal activity,[8a,b] herbicidal activity,[9a,b] and antibiotic[10a,b] drugs. Literature reports revealed that they are also used as enzyme inhibitors,[11a–c] fungicides,[12] insecticides.[13a–c] The Kabachnik–Fields and Pudovik reactions are the most general, straightforward and widely

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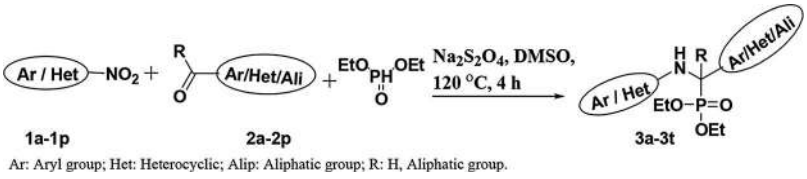
applied methods for construction of C–P bonds.[14a–d] In the last two decades, several reports are published describing the synthesis of α-aminophosphonates from imines/amines and aldehydes/ketones through Kabachnik–Fields reaction using Lewis acids, Brønsted acids, heterogeneous catalysts, metal triflates, and nanocatalysts.[15a–q] Also there are some reports published under catalyst and solvent-free conditions for the synthesis of α-aminophosphonates[16a–f]. But, these have following disadvantages of critical reaction conditions, air sensitive, toxic, expensive reagents or catalysts, low product yield, long reaction time, and tedious separation procedures.

The direct synthesis of α-aminophosphonates from aryl nitro compound is limited. The importance of direct synthesis of α-aminophosphonates from aryl nitro compounds is three steps process is reduced to a single step. Yang et al. used sodium dithionite to synthesis derivatives of *N*-aryl benzimidazoles[17] and arylquinazolin-4(3*H*)-ones[18] by reduction of nitro compounds under metal-free condition. This inspired to use sodium dithionite for the synthesis of α-aminophosphonates directly from aryl nitro compounds. However, in 2009 Das et al.[19] reported the direct synthesis of α-aminophosphonates from aryl nitro compounds using Indium/HCl. Since the reaction medium is highly acidic, this method is not feasible when the molecules containing acid sensitive groups, such as lactams, acetals, N-Boc, O-TMS, O-TBDMS, N-SEM,[20] (HCl present in the reaction medium), and metal labile groups, such as halides.[21] Hence it is necessary to find an efficient and economical alternative process to overcome these difficulties.

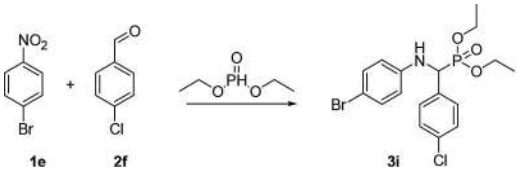
One-pot synthetic methodologies are attractive because they produce highly functionalized products in a single synthetic procedure. Furthermore, one-pot strategies are much desirable due to their advantages. 1) avoiding reaction work-up process at each stage, 2) environmental friendly and economical by avoiding the reagents and solvents, 3) purification of the intermediate chemical compounds would save time and resources while increasing reaction yield. Development of inexpensive and environmentally acceptable method for the synthesis of α-aminophosphonates is therefore highly desirable.

Here, our interest is to develop a new and highly efficient metal-free one-pot synthesis of α-aminophosphonates through reduction followed by Kabachnik–Fields reaction using three-component system. Hence a remarkable challenge is faced for one-pot synthesis of α-aminophosphonates directly from aryl nitro compounds. In the present contribution, to the best of our knowledge, we report for the first time, the one-pot synthesis of α-aminophosphonates directly from nitro compounds, aldehydes/ketones and diethyl phosphite (DEP) using sodium dithionite through reduction followed by Kabachnik–Fields reaction (Scheme 1). The reaction conditions were optimized by varying temperature, solvent and reactants molar ratio. The results are listed in Tables 1–2.



Scheme 1. One-pot synthesis of α-aminophosphonate. Reaction conditions: aryl nitro compound (1.0 mmol), aldehyde/ketone (1.0 mmol), diethyl phosphite (1.0 mmol) and sodium dithionate (1.0 mmol) in DMSO (1 mL) stirred at 120 °C for 4 h.

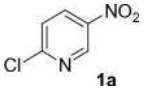
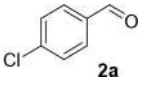
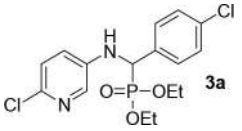
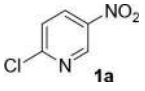
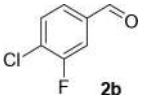
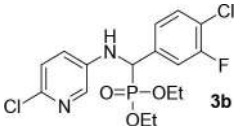
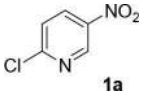
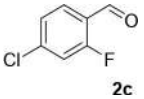
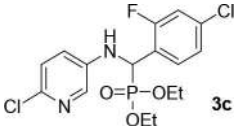
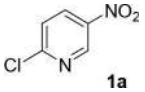
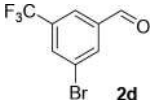
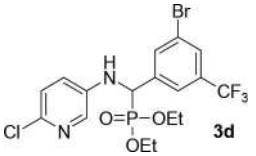
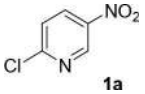
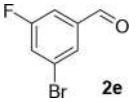
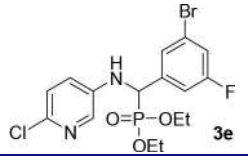
Table 1. Optimization of reaction parameters for α-aminophosphonate synthesis.



	Molar equiv.						
Entry	1a	2a	DEP	$Na_2S_2O_4$	Solvent/temp. (°C)	Time (h)	Yield (%)[a]
1	1	1	1	1	DMSO/25	12	–
2	1	1	1	1	DMSO/80	12	40
3	1	1	1	1	DMSO/100	3	85
4	1	1	1	1	DMSO/120	4	91
5	1	1	2	2	DMSO/120	4	91
6	1	1	1	1	Dioxane/120	4	32
7	1	1	1	1	EtOH/80	6	65
8	1	1	1	1	EtOH/100	6	71
9	1	1	1	1	DMF/120	3	13
10	1	1	2	2	DMF/120	6	29
11	1	1	1	1	Toluene/120	6	22
12	1	1	1	1	DMSO/120	0.1	85[b]
13	1	1	1	1	DMSO/120	3	79[c]

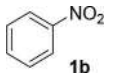
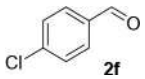
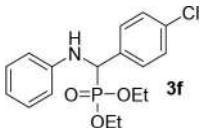
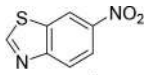
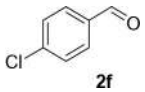
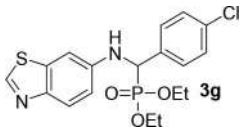
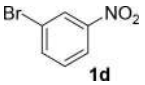
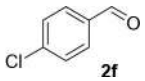
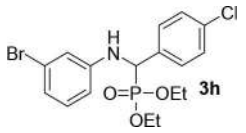
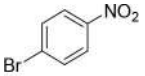
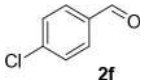
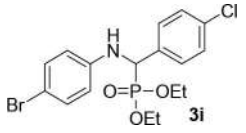
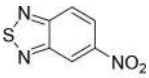
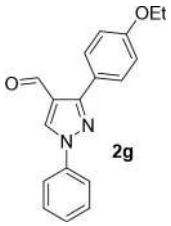
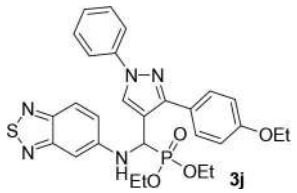
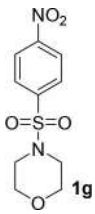
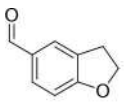
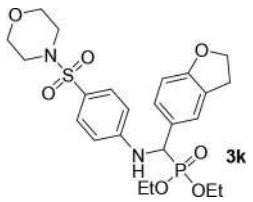
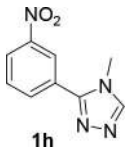
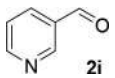
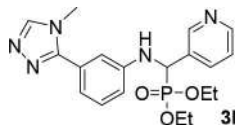
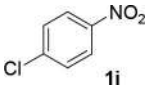
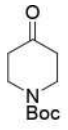
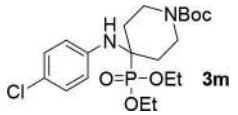
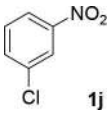
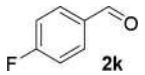
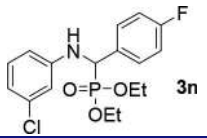
[a]Yields of isolated compounds. [b]Reaction performed in microwave apparatus. [c]Reaction performed in a sealed tube. DEP, diethyl phosphite.

Table 2. Various α-aminophosphonates synthesis from various arylnitro compounds.

Entry	Nitro compound	Aldehyde/ketone	Product/number	Yield[a] (%)
1	 1a	 2a	 3a	91
2	 1a	 2b	 3b	89
3	 1a	 2c	 3c	87
4	 1a	 2d	 3d	86
5	 1a	 2e	 3e	90

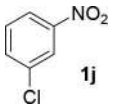
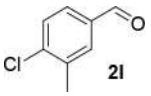
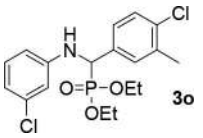
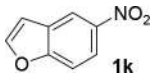
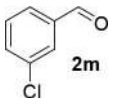
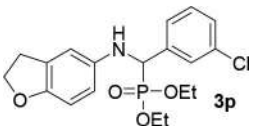
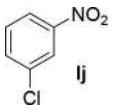
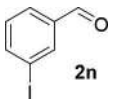
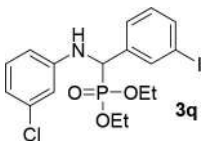
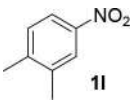
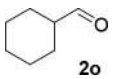
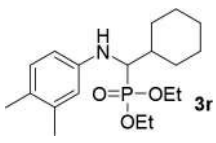
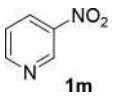
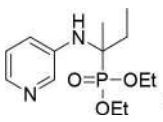
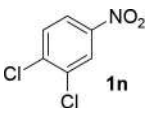
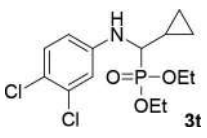
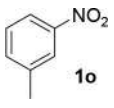
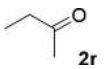
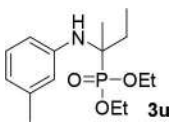
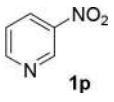
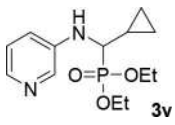
(*Continued*)

Table 2. Continued.

Entry	Nitro compound	Aldehyde/ketone	Product/number	Yield[a] (%)
6	 **1b**	 **2f**	 **3f**	91
7	 **1c**	 **2f**	 **3g**	84
8	 **1d**	 **2f**	 **3h**	86
9	 **1e**	 **2f**	 **3i**	91
10	 **1f**	 **2g**	 **3j**	91
11	 **1g**	 **2h**	 **3k**	91
12	 **1h**	 **2i**	 **3l**	89
13	 **1i**	 **2j**	 **3m**	78
14	 **1j**	 **2k**	 **3n**	91

(*Continued*)

Table 2. Continued.

Entry	Nitro compound	Aldehyde/ketone	Product/number	Yield[a] (%)
15	 **1j**	 **2l**	 **3o**	90
16	 **1k**	 **2m**	 **3p**	88
17	 **1j**	 **2n**	 **3q**	86
18	 **1l**	 **2o**	 **3r**	82
19	 **1m**	 **2p**	 **3s**	79
20	 **1n**	 **2q**	 **3t**	82
21	 **1o**	 **2r**	 **3u**	78
22	 **1p**	 **2s**	 **3v**	86

Reaction conditions: aryl nitro compound (1.0 mmol), aldehyde/ketone (1.0 mmol), diethyl phosphite (1.0 mmol), and sodium dithionate (1.0 mmol) in DMSO (1.0 mL) were stirred at 120 °C for the appropriate time (3–4 h).
[a]Isolated yield. [b]The spectral data (^{1}H, ^{13}C NMR) of known compounds (6, 9, and 14) were found to be identical with those reported in the literature.

Results and discussion

Initially, 1-bromo-4-nitrobenzene (**1e**), 4-chloro benzaldehyde (**2f**), and DEP were chosen as the model substrates to optimize the reaction conditions including solvents, molar ratios and reaction temperatures.

As shown in Table 1, most of the reactions were performed in aprotic solvents such as toluene, DMSO, DMF, and 1,4-dioaxane except ethanol. The product yield of **3i** was very

low even at the reflux condition and it was 32 and 22% in dioxane and toluene solvent medium, respectively (Table 1, entries 6 and 11). Whereas in ethanol medium (Table 1, entries 7 and 8) the product yield of **3i** was only 65 and 71% at 80 and 100 °C, respectively. But in the case of DMSO solvent medium (Table 1, entries 2, 3, and 4) the product yield of **3i** was 40, 85, and 91% at 80, 100, and 120 °C, respectively. When we altered the molar ratio of DEP and $Na_2S_2O_4$ (Table 1, entry 4 and entry 5) from 1:1 to 2:2, we could not find any changes in the in the product yield. Product yield compared by performing the reaction in the microwave apparatus (Anton paar, monowave 300 model) as well as in the sealed tube (Table 1, entries 12 and 13) preceded in good yield (85 and 79%). There was no product formation at room temperature (Table 1, entry 1).

After performing various reactions with different parameters, we found that the optimum reaction conditions: 1-bromo-4-nitrobenzene (1 equiv.), 4-chlorobenzaldehyde (1 equiv.), DEP (1 equiv.), and sodium dithionite (1 equiv.) in DMSO at 120 °C for 4 h (Table 1, entry 4). In the optimized reaction condition, the sodium dithionite promotes the reduction of various nitroarene to amine and followed by corresponding imine formation. Then DEP addition was taking place to the imine and is leading to the formation of α-aminophosphonates. Most of the reactions were completed within 4 h with reasonable yield of α-aminophosphonates. The results are summarized in Table 2. We have concluded that the aldehyde/ketone compounds were not reduced by sodium dithionite. This selective reduction enable us to synthesis of various α-aminophosphonates directly from arylnitro compounds in one-pot.

Scope and limitations of this reaction methodology were studied using various electron-donating and electron-withdrawing groups substituted in nitroaryl as well as in aryl/aliphatic aldehydes/ketone with DEP in the presence of $Na_2S_2O_4$. The methodology developed for the α-aminophosphonates synthesis was found to be more compatible with various functional groups, such as Cl, Br, F, I, Me, Et, and Boc, with excellent yield than other methods developed so far. Further this methodology were applied on various nitroaryl compounds containing electron-donating/electron-withdrawing groups with different aldehydes/ketones and the results of this investigation showed not much difference in their respective α-aminophosphonates yield. The bulky aldehyde (Table 2, entry 10) formed α-aminophosphonate with the very good yield of 94%, which indicates that this method used for the synthesis of even bulky α-aminophosphonates (Table 2, entry 10 and 11). There is no significant reaction time difference was observed in the reactions shown in Table 2 with respect to the product formation. Optimized conditions in hand, we applied on compounds (**1a–1p)** and compounds (**2a–2s**) yielded the (**3a–3v)** at variable yields.

We studied the possibility of scale-up process to synthesis α-aminophosphonates (Table 2, entry 1) on 10 g scale and 25 g scale and we found 91% of product yield in each batch size. This study clearly indicates that this methodology is convenient for a scale-up process and there is no difference in product yield between R&D scale (Table 2, entry 1) and scale up. We also analyzed the enantiomeric ratio formation for compounds **1** and **10** (Table 2, entry 1 and 10) using chiral HPLC and we observed the formation of enatiomeric ratio of 1:1.

To clarify the reaction pathway and rate of the reaction in one-pot synthesis, we analyzed the crude samples obtained at various time intervals of 1, 2, 3, and 4 h using ^{31}P and ^{1}H NMR (DMSO-d_6, 500 MHz) and the spectra are shown in Figures 1 and 2, respectively. The ^{31}P NMR spectrum (Figure 1a) showed that conversion of DEP to desired

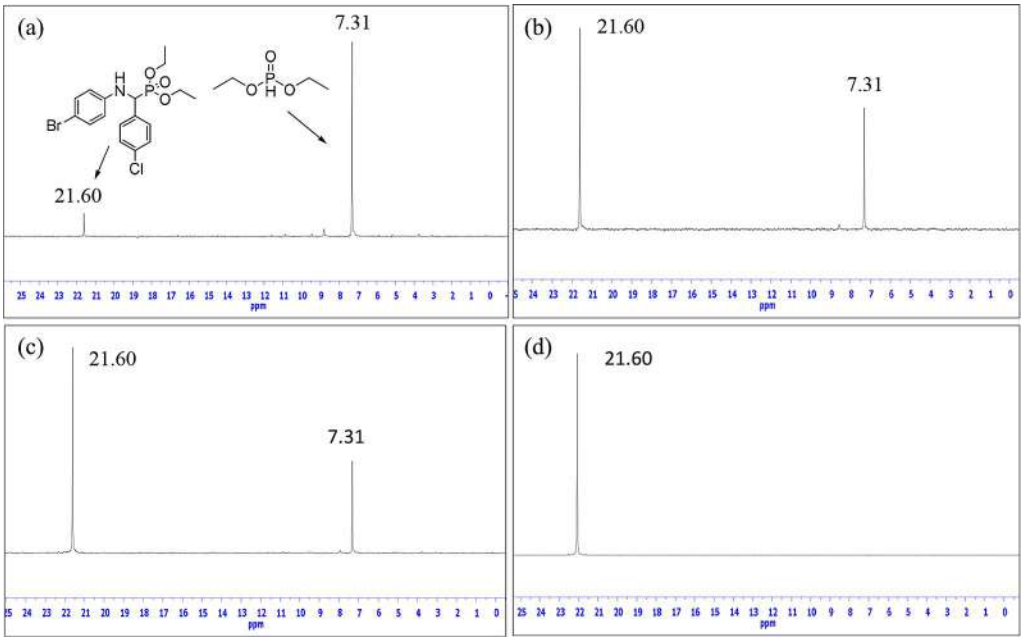


Figure 1. ^{31}P NMR (crude) tracing experiment for the synthesis of compound (**3i**) at varies time intervals of (a) 1 h, (b) 2 h, (c) 3 h, and (d) 4 h.

compound (**3i**) is initiated and corresponding peaks due to DEP and compound (**3i**) were observed at 7.31 and 21.60 ppm, respectively. The ^{31}P NMR spectra (Figure 1b,c) of crude obtained at 2 and 3 h showed a decrease in peak intensity at 7.31 ppm and corresponding

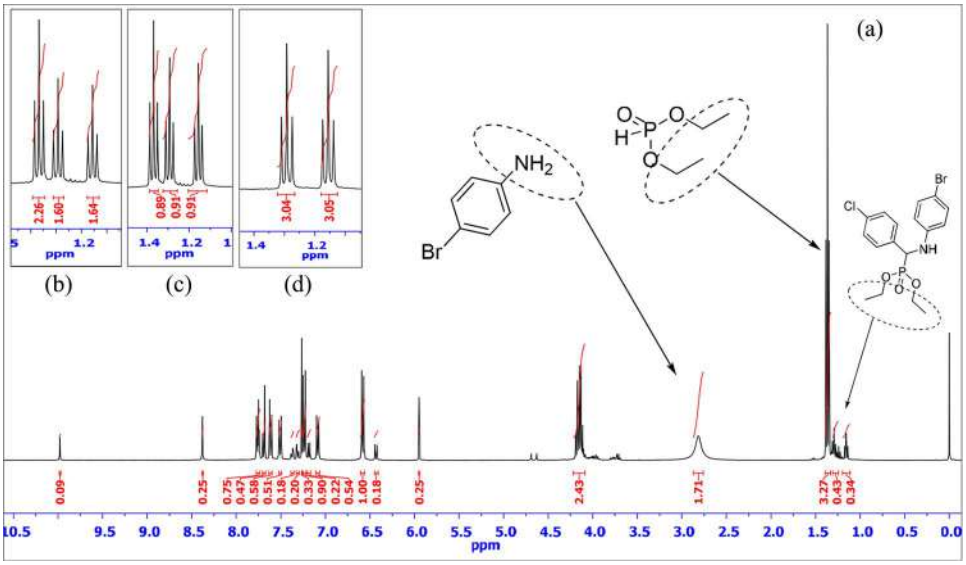


Figure 2. ^{1}H NMR (crude) tracing experiment for the synthesis of compound (**3i**) at varies time intervals of (a) 1 h, (b) 2 h, (c) 3 h, and (d) 4 h.

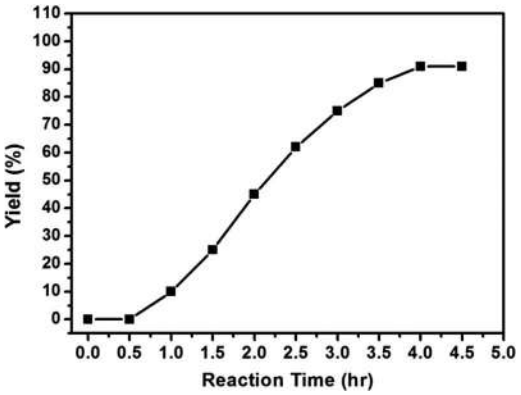


Figure 3. Product yield of compound 3a[a] with varies reaction time. Reaction conditions: 1-bromo-4-nitrobenzene (1 mmol), 4-chloro benzaldehyde (1 mmol), diethyl phosphite (1 mmol), and sodium dithionate (1 mmol) in DMSO (1 mL) stirred at 120 °C for the 4 h. *Note*: [a]Isolated yield.

increase in peak intensity at 21.60 ppm with increase in reaction time. The ^{31}P NMR spectrum (Figure 1d) is showing the complete transformation and formation of compound (**3i**) after 4 h.

The ^{1}H NMR spectrum (Figure 2a) indicating that the transformation of aryl nitro compound to aryl amine compound by $Na_2S_2O_4$ and corresponding peaks due to amine compound is observed at 2.81 ppm. The triplet signals at 1.15 and 1.27 ppm is indicating the compound (**3i**) formation is initiated. The ^{1}H NMR spectra (Figure 2b,c) of crude obtained at 2 and 3 h showed a decrease in peak intensity at 1.34 ppm and corresponding increase in peak intensity at 1.15 and 1.27 ppm due to the conversion of DEP to compound (**3i**). The ^{31}P NMR spectrum (Figure 2d) is showing the complete conversion and formation of compound (**3i**).

The kinetic study on the α-aminophosphonate formation is shown in Figure 3 and it clearly indicates that there is no product formation till 0.5 h and only 5%[a] of product is formed at 1 h gradually increased the yield over time and reached the 91%[b] yield at 4 h. There after no further yield increasing is observed.

The structures of the prepared α-aminophosphonates were determined and described in the supporting information from their spectral (^{1}H, ^{1}H-D_2O exchange, ^{13}C & ^{31}P NMR,

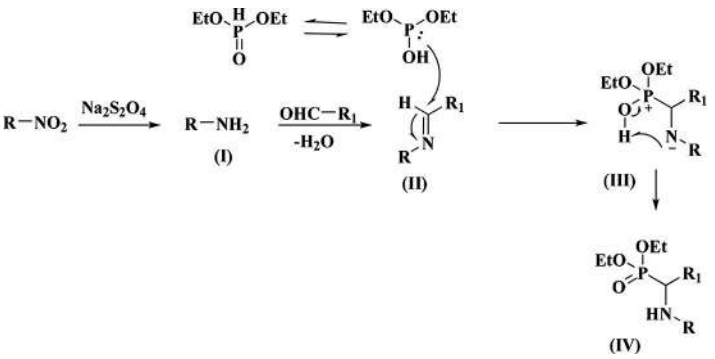


Figure 4. Plausible mechanistic pathway for the one-pot synthesis of α-aminophosphonate.

LCMS, HRMS, and IR) data. For known compounds, the recorded spectral data were found to be identical with the literature data (compounds 3f, 3i, and 3n)[22a–c]. The NH protons were confirmed by D_2O exchange experiments. It is of quite interest to observe the NH proton resonating at 5.00–4.8 ppm as quartet as seen in proton NMR spectrums and its disappearance was found in D_2O exchange experiments.

The proposed mechanism of synthesis is shown in Figure 4. First nitro compound reduced to corresponding amine compound (I) on reacting with $Na_2S_2O_4$. Amine compound which is formed reacts with aldehydes/ketones to form the corresponding imines (II). The addition of phosphate to this imine resulting in the formation of intermediate (III) which upon rearranged to give the corresponding α-aminophosphonates (IV).

Conclusion

In this work, we report for the first time an efficient protocol for the one-pot synthesis of α-aminophosphonates through reduction followed by Kabachnik–Fields reaction directly from nitroaryl compounds using commercially available sodium dithionite as an efficient and selective reducing agent and with an isolated product yield between 78 and 91%. The advantages of this method are 1) excellent yields, 2) high chemo selectivity, 3) easy isolation/purification, and 4) three steps process reduced to a single step in one-pot which is an economical and efficient method.

Experimental part

Materials and measurements

Most of the chemical reagents were purchased from Aldrich and all cases, were used without further purification. Thin layer chromatography (TLC) was performed using Merck 60 F_{254} precoated silica gel plate (0.2 mm thickness). Subsequent to elution, plates were visualized using UV radiation (254 nm). Further visualization was performed by staining with an ethanolic solution of ninhydrin. Flash-column chromatography was performed using silica gel (100–200 mesh) with commercially available solvents. ^{1}H NMR, ^{13}C NMR, ^{31}P NMR spectra were recorded on ing apparat Bruker avance III, 400 and 500 MHz spectrophotometers using TMS as an internal standard. Chemical shifts for ^{1}H NMR spectra are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (d 0.0) and relative to the signal of chloroform-d (d 7.2600, s). Multiplicities were given as: s (singlet), d (doublet), t (triplet), q (quartet), or m (multiplet). Coupling constants are reported as a *J* value in hertz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (d 0.0) and relative to the signal of chloroform-d (d 77.03, *t*). FTIR spectra were recorded on a SHIMADZU FTIR spectrometer. LCMS spectrums were recorded using the follows, Description: Agilent 1290 series, Mass 6150 quadru pole LCMS, Software: Chemistation; and LCMS run method specifications are column: Acquity UPLC BEH C18 (50 × 2.1 mm, 1.7 µm), Mobile Phase: B: 0.1% formic acid in water, A: 0.1% formic acid in acetonitrile, Gradient: Time (min)/% A: 0/2, 0.2/2, 1.5/98, 2.6/98, 2.61/2,3.2/2, Column Temp: 45 °C, Flow rate: 0.8 mL min^{-1}. HRMS analysis: The compound was dissolved in a solution of 50% (v/v) HPLC grade acetonitrile (Ranchem), 50% (v/v) deionized water and 0.1% formic acid. The solution was auto injected simultaneously with reference sample to ESI source at a flow rate of 500 µL min^{-1}. ESI(+)-MS was acquired using a hybrid high-resolution and high accuracy (5 µL L^{-1})

microTof (Q-TOF) mass spectrometer (Waters Q-Tofmicro) under the following conditions: capillary and cone voltages were set to +2960 and +142 V, respectively, with a desolvation temperature of 244 °C. For data acquisition and processing in QTOF-control data analysis software (Mass Lynx) was used. The data were collected in the *m/z* range of 100–1000 at the speed of two scans per second.

General procedure

Typical procedure for one-pot synthesis of α-aminophosphonates: A mixture of nitro compound (1.0 mmol), aldehyde (1.0 mmol), DEP (1.0 mmol), and sodium dithionite (1.0 mmol) in DMSO (1.0 mL) were stirred at 120 °C for the appropriate amount of time (3–4 h). After completion of the reaction as indicated by the TLC and LCMS, the reaction mixture was poured into water (5 mL), and then extracted with ethyl acetate (2 × 10 mL). The combined organic extracts were washed with saturated brine solution, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by recrystallization from diethyl ether (solid products) or purified by column chromatography using silica gel (100–200 mesh size) and eluting with hexane/ethyl acetate of increasing polarity to obtain the pure compound. When the above reaction was performed with 5-nitrobenzofuran (entry 16 in Table 2), the double bond between 2 and 3 carbons gets reduced by the sodium dithionite.

Diethyl (4-chlorophenyl) (6-chloropyridin-3-ylamino) methylphosphonate (3a)

Yield: 91%, Colourless solid, m. p.115–117 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.75 (d, J = 3.2 Hz, 1H, Ar–H), 7.26–7.38 (m, 4H, Ar–H), 7.02 (d, J = 8.4 Hz, 1H, Ar–H), 6.79 (dd, J = 3.2 Hz, J = 3.2 Hz, 1H, Ar–H), 4.90 (t, J = 8.4 Hz, 1H, Ar–NH–), 4.64 (dd, J = 7.2 Hz, J = 7.2 Hz, 1H, –CH(N)–), 4.07–4.18 (m, 2H, –O–CH_2–), 3.92–4.02 (m, 1H, –O–CH–), 3.70–3.76 (m, 1H, –O–CH–), 1.31 (t, J = 6.8 Hz, 3H, –C–CH_3), 1.15 (*t*, J = 7.2 Hz, 3H, –C–CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 141.73 (Ar–C), 141.58 (Ar–C), 140.16 (Ar–C), 135.82 (Ar–C), 134.25 (Ar–C), 133.53 (Ar–C), 129.21 (Ar–C), 124.0 (Ar–C), 123.3 (Ar–C), 63.77 (–CH(N)–), 56.06 (–O–CH_2–), 54.54 (–O–CH_2–), 16.54 (CH_2–CH_3), 16.27 (CH_2–CH_3); ^{31}P NMR (162 MHz, $CDCl_3$): δ 20.96 ppm; IR (KBr, cm^{-1}): 3302 (Ar–NH–), 2987 (Ar–C–H), 1230 (P = O), 942 (P–O–), 818 (P–C–); HRMS (ESI +): *m/z* calculated for $C_{16}H_{19}Cl_2N_2O_3P$ was 389.2189 and found $[M + H]^+$ 389.2187

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