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$KHSO_4$-mediated synthesis of α-amino phosphonates under a neat condition and their ^{31}P NMR chemical shift assignments

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ABSTRACT

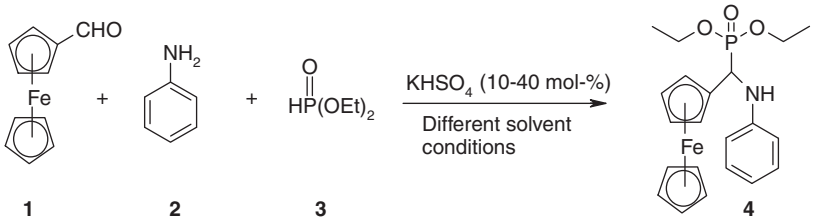
A simple and efficient method for the synthesis of α-amino phosphonates has been accomplished from aromatic aldehydes, diethyl phosphite, and aromatic (or) aliphatic amines using potassium hydrogen sulfate as a catalyst under solvent free condition at ambient temperature and these compounds are characterized by ^{31}P NMR with reference to H_3PO_4.

In recent years, the synthesis of α-amino phosphonates has received an increasing amount of attention due to their structural analogs of the corresponding α-amino acids and transition state mimics of peptide hydrolysis.[1] α-Amino phosphonates are an important class of compounds in pharmaceutical chemistry[2] with potential biological effects and medicinal importance such as enzyme inhibitors,[2] HIV protease,[3] antibiotics,[4] herbicides, fungicides, insecticides,[5] plant growth regulators,[6] antithrombotic agents,[7] peptidases, and proteases.[8]

The available methods for the synthesis of α-amino phosphonates are based on the synthesis of imines followed by a Lewis acid-catalyzed nucleophilic addition of phosphates to imines. Lewis acids such as $SnCl_2$, SmI_2,[9] $BF_3{\cdot}Et_2O$,[10] $ZnCl_2$, $MgBr_2$, metal triflates (M = Mg, Al, Cu, Ce),[11] and $InCl_3$[12] have been used. However, most of these Lewis acids are moisture sensitive and hence difficult to handle. Also their cost is of concern especially for the scale up of the reaction. These reactions cannot be performed in one-pot because the amines and water that are present during imine formation can decompose or deactivate these Lewis acids. Although a number of different methods have been reported for the preparation of α-amino phosphonates,[13] there is still a need to search for better catalysts with regards to their handling and economic viability.

Recently the commonly available $KHSO_4$ is used as a catalyst instead of Lewis acids by us.[14] This catalyst is inexpensive, mild, and does not require the maintenance of anhydrous conditions. To the best of our knowledge, there have been no reports for the synthesis of α-amino phosphonates using $KHSO_4$ as catalyst. In continuation of our interest to develop synthetic routes for biologically active heterocyclic compounds and the use of green chemical techniques in organic synthesis,[15] herein we successfully endeavor yet another application of $KHSO_4$ as a catalyst for the synthesis of α-amino phosphonates under a neat condition.

In an initial endeavor, we carried out the reaction of ferrrocene-1-carboxaldehyde (**1**), aniline (**2**), and diethyl phosphite (**3**) in the presence of $KHSO_4$ with various catalytic amounts (10–40 mol %) using various solvents at ambient temperature (Scheme 1, Table 1). Excellent results were obtained, when the reaction was carried with 20 mol % of $KHSO_4$ under a neat condition. It was found that the amount of $KHSO_4$ also affects the yield of the product. The substrate scope of the reaction under the optimized condition was investigated and the results are summarized in Table 2. The reaction was amenable to a wide variety of arylamines bearing various substituents such as hydroxyl, ether, bromo, chloro, and heterocycles[16,17] (Scheme 2).



Scheme 1. Synthesis of α-amino phosphonates.

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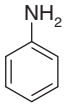
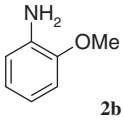
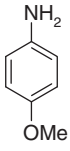
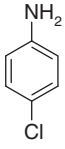
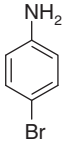
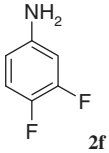
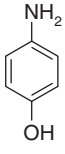
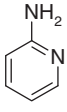
Table 1
Screening of solvents and catalyst

Entry	Solvents	$KHSO_4$ (mol %)	Yield[a,b] (%)
1	MeOH	40	50[c]
2	EtOH	40	55[c]
3	Water	40	0[c]
4	CH_3CN	40	65
5	CH_2Cl_2	40	63
6	Neat	40	83
7	Neat	30	83
8	Neat	20	83
9	Neat	10	65

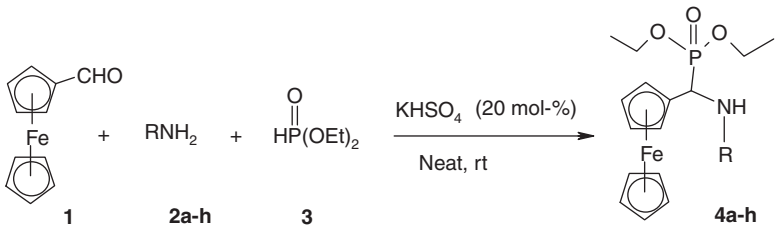
[a] Isolated yield.
[b] All reactions were carried out for 10 h at ambient temperature condition.
[c] Starting materials remain unconsumed.

The structure of α-amino phosphonate derivatives (**4a–h**) was thoroughly characterized with spectral and elemental analysis. IR spectrum of compound **4f** (Table 2, entry 6) showed stretching frequencies at 3412 cm^{-1} for –NH functional groups. The ^1H NMR spectrum showed three apparent singlets at δ 4.06, 4.17, and 4.22 for ferrocenyl ring protons and a broad singlet at δ 4.37 (D_2O exchangeable) for –NH proton. In ^{13}C NMR spectra, peaks in the range of δ 102.2–144.8 correspond to aromatic carbons and the three distinguishing singlet at δ 67.9, 68.6, and 70.4 for ferrocenyl carbon. The ^{31}P NMR showed distinguishable singlet at δ 21.2 ppm for the phosphorous atom. The mass spectrum displayed the distinct $[M+H]^+$ peak at *m/z*: 464.33. Finally the structure of compound **4f** was confirmed by single crystal X-ray diffraction analysis. The ORTEP diagram of compound **4f** is shown in Figure 1.[19]

Table 2
Synthesis of α-amino phosphonates from ferrocene-1-carboxaldehyde

Entry	Amine	Product (**4**)[a]	Time (h)	Yield[b] (%)	^{31}P NMR chemical shift[c] (ppm)
1	 **2a**	**4a**	9	83	21.5
2	 **2b**	**4b**	12	71	22.2
3	 **2c**	**4c**	11	79	22.5
4	 **2d**	**4d**	9	81	20.9
5	 **2e**	**4e**	8	82	21.1
6	 **2f**	**4f**	8	79	21.2
7	 **2g**	**4g**	10	81	20.8
8	 **2h**	**4h**	11	77	21.1

[a] The products were characterized by NMR, IR, mass and elemental analysis.
[b] Isolated yield.
[c] Chemical shift with reference to H_3PO_4.



Scheme 2. Synthesis of α-amino phosphonates from ferrrocene-1-carboxaldehyde.

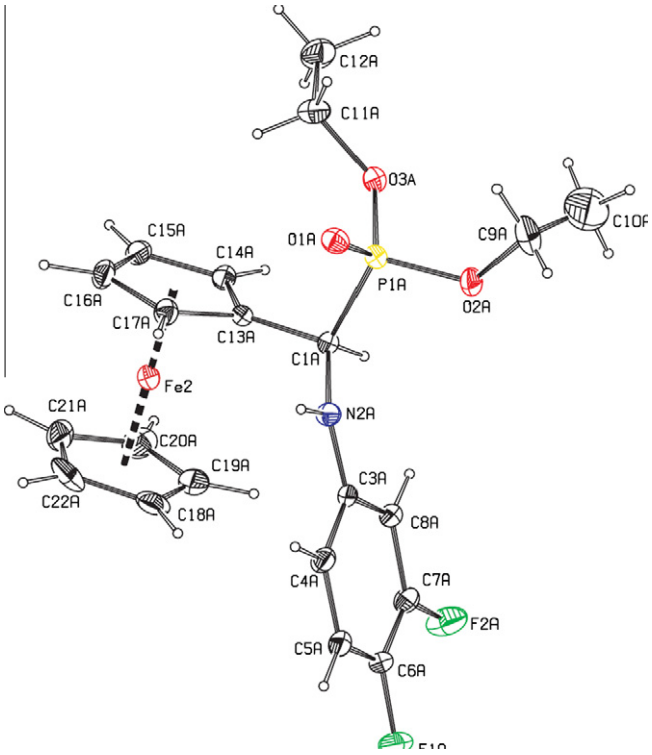
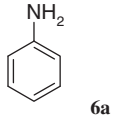
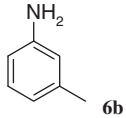
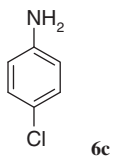
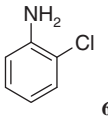
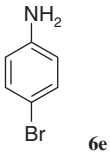
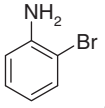
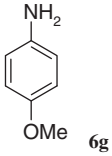
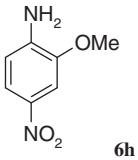
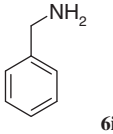
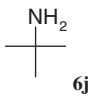


Figure 1. ORTEP diagram of compound **4f**.

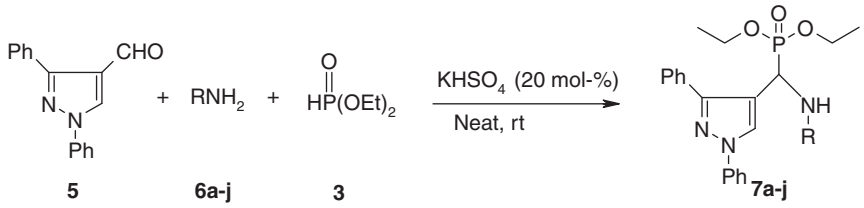
Table 3
Synthesis of α-amino phosphonates from pyrazole aldehyde

Entry	Amine	Product (**7**)[a]	Time (h)	Yield[b] (%)	^{31}P NMR chemical shift[c] (ppm)
1	 **6a**	**7a**	8	79	24.1
2	 **6b**	**7b**	8.5	78	24.2
3	 **6c**	**7c**	7.5	79	23.8
4	 **6d**	**7d**	8	73	23.3
5	 **6e**	**7e**	7.5	80	23.8
6	 **6f**	**7f**	8	72	23.2
7	 **6g**	**7g**	7.5	81	23.3
8	 **6h**	**7h**	9	77	22.6
9	 **6i**	**7i**	9	75	24.9
10	 **6j**	**7j**	9	73	25.3

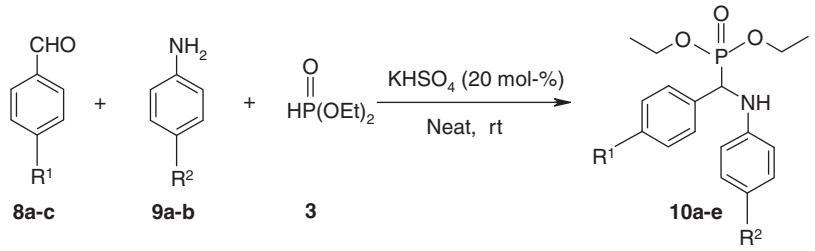
[a] The products were characterized by NMR, IR, mass and elemental analysis.
[b] Isolated yield.
[c] Chemical shift with reference to H_3PO_4.

Based on the above results, we extended our protocol to the synthesis α-amino phosphonate derivatives using various substituted amines, pyrazole aldehyde, and diethyl phosphite under optimized conditions. The reaction proceeded very smoothly and gave a high yield of the product without the formation of any side products. The substrate scope of the reaction under the optimized conditions was investigated, and the reaction was found to be amenable to a variety of aromatic and aliphatic amines[18] (Table 3 & Scheme 3).

The structures of the compounds **7a–j** were investigated with spectral studies and elemental analysis as demonstrated for com-



Scheme 3. Synthesis of α-amino phosphonates from pyrazole aldehyde.



Scheme 4. Synthesis of α-amino phosphonates from various aromatic aldehydes.

Table 4
Synthesis of α-amino phosphonates from various aromatic aldehydes

Entry	R^1 (**8**)	R^2 (**9**)	Product (**10**)[a]	Time (h)	Yield[b] (%)	^{31}P NMR chemical shift[c] (ppm)
1	H	H	**10a**	5.5	75	23.5
2	H	Br	**10b**	5	78	23.2
3	CH_3	H	**10c**	5.5	79	23.6
4	CH_3	Br	**10d**	5	81	23.2
5	Br	Br	**10e**	5	80	23.1

[a] The products were characterized by NMR, IR, mass, and elemental analysis.
[b] Isolated yield.
[c] Chemical shift with reference to H_3PO_4.

pound **7d** (Table 3, entry 4) as given below. In the IR spectrum, the –NH-stretching frequency appeared at 3298 cm^{-1}. In the ^{1}H NMR spectra, there are two doublet of doublets in the region of δ 4.95 (J = 8.4 and 20.6 Hz) and 5.07 (J = 6.1 and 8.4 Hz) ppm with the integral value of one assigned as –CH and –NH protons, respectively. The latter was confirmed by D_2O experiment. The former one became doublet with the coupling constant (J): 20.65 Hz on D_2O experiment. Based on above results, the coupling constants J = 20.6 (on –*CH* proton) and 6.1 Hz (on –N*H* proton) were due to the presence of phosphorous atom (one bond and three bonds coupling, respectively). In ^{13}C NMR spectrum, the peak at δ 46.8 ppm doublet with coupling constant $J^1_{c-p} = 639.1$ Hz ascertained the presence of a methine group (Ar-*C*H–P). A distinguishable singlet at δ 23.3 ppm in the ^{31}P NMR showed the presence of phosphorous atom. The mass spectrum displayed the molecular ion $[M]^+$ peak at *m/z:* 495.13.

To explore the scope and limitations of this reaction, we extended our studies to various aromatic aldehydes with substituted aromatic amines under optimized conditions (Scheme 4). As indicated in Table 4, the reactions proceeded efficiently with both substituted aldehydes and amine derivatives.

In summary we have demonstrated a simple and environmental friendly protocol for the synthesis of α-amino phosphonate using $KHSO_4$ as a catalyst under a neat condition. The method employs inexpensive, non-toxic, and an easily available salt catalyst and eliminates the use of hazardous organic solvents. Further studies to delineate the scope and limitations of the present methodology are underway.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.08.066.

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16. *General procedure for the synthesis of α-amino phosphonate derivatives*: A mixture of aldehyde (1 mmol), substituted aromatic or aliphatic amine (1 mmol), diethyl phosphate (1.5 mmol), and potassium hydrogen sulfate (20 mol %) under a neat condition was stirred at room temperature. After completion of the reaction as indicated by TLC, it was poured into water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated under vacuum. The crude product was chromatographed and the appropriate isolated yield is shown in Tables 2 and 3.
17. *Spectral data of compound* **4f** (Table 2, *entry 6) as follows*: Deep red color semisolid; R_f 0.42 (40% AcOEt/petroleum ether); IR (KBr): 1252, 1362, 1556, 1639, 2962, 3412 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.16–1.20 (m, 6H, $-CH_3$), 3.92–3.95 (m, 1H, –C*H*), 3.97–4.02 (m, 4H, $-CH_2$), 4.06 (s, 5H, -fc-*H*), 4.17 (s, 2H, -fc-*H*), 4.22 (s, 2H, -fc-*H*), 4.37 (br s, 1H, –N*H*), 6.46–6.48 (m, 1H, -Ar-*H*), 6.63-6.65 (m, 1H, -Ar-*H*), 6.97–7.03 (m, 1H, -Ar-*H*); ^{13}C NMR (125 MHz, $CDCl_3$): 16.4, 16.5, 51.8 (d, $J^1_{c-p} = 161.0$ Hz), 62.9 (d, $J^2_{c-p} = 7.2$ Hz), 63.2 (d, $J^2_{c-p} = 161.0$ Hz), 67.9, 68.8, 70.4, 84.9 (d, $J^3_{c-p} = 5.9$ Hz), 102.2, 102.3, 108.8, 117.7, 117.8, 144.8; MS (EI): $m/z = 464.33$ $[M+H]^+$; Anal. Calcd for $C_{21}H_{24}F_2FeNO_3P$: C, 54.45; H, 5.22; N, 3.02. Found: C, 54.37; H, 5.24; N, 3.01.
18. *Spectral data of compound* **7d** (Table 3, *entry 3*) *as follows*: Colorless solid; mp 158–160 °C; R_f 0.53 (40% AcOEt/petroleum ether); IR (KBr): 1023, 1052, 1232, 1491, 1597, 1737, 2980, 3298 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.18 (t, $J = 6.9$ Hz, 3H, $-CH_3$), 1.27 (t, $J = 7.7$ Hz, 3H, $-CH_3$), 3.93–3.98 (m, 1H, $-CH_2$), 4.07–4.15 (m, 2H, $-CH_2$), 4.21–4.24 (m, 1H, $-CH_2$), 4.95 (dd, $J = 8.4$ Hz, $J = 20.6$ Hz, 1H, –C*H*), 5.07 (dd, $J = 6.1$ Hz, $J = 8.4$ Hz, 1H, –N*H*), 6.36 (d, $J = 8.4$ Hz, 1H, Ar-*H*), 6.61 (t, $J = 7.6$ Hz, 1H, Ar-*H*), 6.92 (t, $J = 7.7$ Hz, 1H, Ar-*H*), 7.21 (d, $J = 6.9$ Hz, 1H, Ar-*H*), 7.25–7.27 (m, 1H, Ar-*H*), 7.42–7.47 (m, 5H, Ar-*H*), 7.70 (d, $J = 6.9$ Hz, 2H, Ar-*H*), 7.76 (d, $J = 7.7$ Hz, 2H, Ar-*H*), 8.29 (s, 1H, Ar-*H*); ^{13}C NMR (125 MHz, DMSO-d_6): δ 16.4, 16.6, 46.8 (d, $J^1_{c-p} = 639.1$ Hz), 63.6 (d, $J^2_{c-p} = 23.8$ Hz), 63.8 (d, $J^2_{c-p} = 28.6$ Hz), 112.7, 116.7, 118.8, 119.1, 120.1, 126.6, 127.7, 128.5, 128.7, 128.9, 129.3, 129.5, 132.7, 139.8, 141.9, 152.6, 163.1; MS (EI): m/z 495.13 $[M]^+$; Anal. Calcd for $C_{26}H_{27}ClN_3O_3P$: C, 62.97; H, 5.49; N, 8.47. Found: C, 62.73; H, 5.45; N, 8.50.
19. Crystallographic data of compound **4f** in this Letter have been deposited with the Cambridge Crystallographic Data centre as supplemental publication no. CCDC 775941. Copies of the data can be obtained, free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 01223 336033 or email: deposit@ccdc.cam.ac.uk).