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Mandelic acid catalyzed one-pot three-component synthesis of α-aminonitriles and α-aminophosphonates under solvent-free conditions at room temperature

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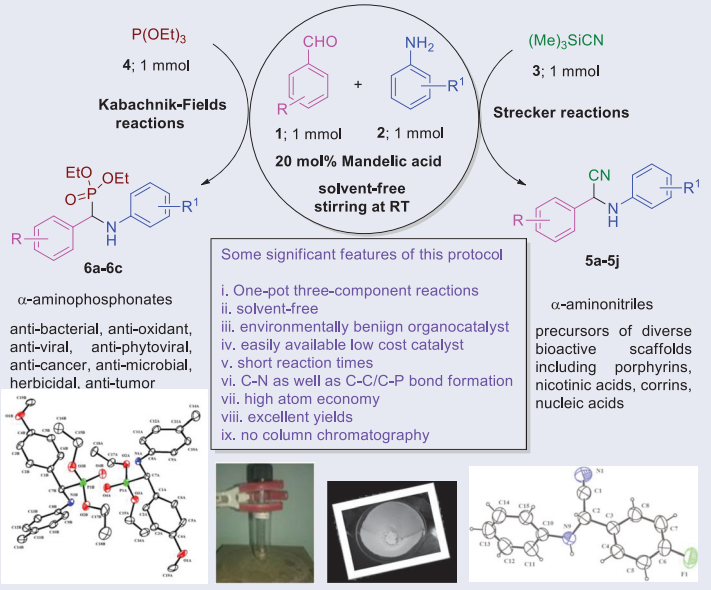
ABSTRACT

A simple, mild, straightforward, efficient and eco-friendly protocol has been developed for the synthesis of a series of α-aminonitriles *via* the one-pot three-component Strecker reactions between various aldehydes, amines and trimethylsilyl cyanide using a catalytic amount of mandelic acid as a naturally occurring, low-cost, efficient organo-catalyst under solvent-free conditions at room temperature. Under the same optimized conditions synthesis of α-aminophosphonates were also achieved *via* the one-pot three-component Kabachnik-Fields reactions of aldehydes, amines and triethyl phosphate.

GRAPHICAL ABSTRACT



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KEYWORDS

α-Aminonitriles; α-aminophosphonates; mandelic acid; room temperature; organocatalysis

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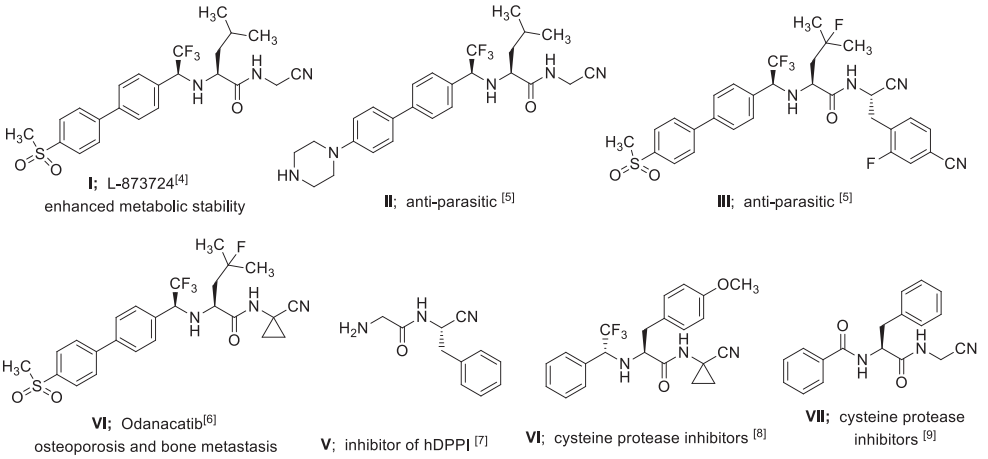


Figure 1. Glimpse of bioactive scaffolds containing α-aminonitrile as a structural subunit.

Introduction

α-Aminonitriles are recognized as versatile precursors of diverse bioactive scaffolds including porphyrins, nicotinic acids, corrins, nucleic acids etc.[1,2] In many occasions, α-aminonitriles are found as important intermediates for the synthesis of various nitrogen- and sulfur-containing heterocycles that include imidazoles and thiadiazoles.[3] Moreover, many bioactive molecules contain α-aminonitrile as an important structural subunit (Figure 1).[4–9] On the other hand, α-aminophosphonate bearing molecules in many occasions showed significant biological efficacies including anti-bacterial, anti-oxidant, herbicidal, anti-viral, anti-phytoviral, anti-cancer, anti-microbial, anti-tumor etc activities (Figure 2).[10–23] After realizing the importance of α-aminonitrile as well as α-aminophosphonate derivatives, scientists were motivated to synthesize these important scaffolds under various reaction conditions. As a result, number methods are available in the literature for the synthesis of α-aminonitriles *via* one-pot three-component Strecker reaction between aldehydes, amines and trimethylsilyl cyanide using various homogeneous as well as heterogeneous catalysts (Table 1).[24–52] Similarly, syntheses of α-aminophosphonates were also achieved *via* the one-pot three-component Kabachnik-Fields reaction between aldehydes, amines and triethyl phosphite under various catalytic conditions (Table 2).[23,53–71] Although these methods reported by others possess certain merits, still under *Green Chemistry* perspective they are suffering from few drawbacks which include in most of the cases they used either metal containing catalysts ($Bi(NO_3)_3$, $La(NO_3)_3{\cdot}6H_2O$, $NiCl_2$, $ZrOCl_2.8H_2O$, $FeCl_3$ etc.) or expensive catalysts ($Ga(OTf)_3$, $GdCl_3{\cdot}6H_2O$, $RuCl_3$, Fe_3O_4@PVA-SO_3H, Fe_3O_4@DHAA, $RhI_3.H_2O$, $Cu(OTf)_2$ etc.), some of them utilized organic solvents (MeCN, EtOH, MeOH, toluene, THF), involvement of ionic liquids ($[EtNH_3]NO_3$, [Sipim]HSO_4, [bmim]BF_4/[bmim]PF_6, [bmim]ClO_4, [hmim]HSO_4), reflux conditions *etc*. In some reported methods α-aminonitriles were synthesized under microwave or ultrasound irradiated conditions. De[35] synthesized α-aminonitriles using nickel(II)chloride as catalyst in acetonitrile which took 6–18 h at room temperature. Moreover, all these reported methods focused only

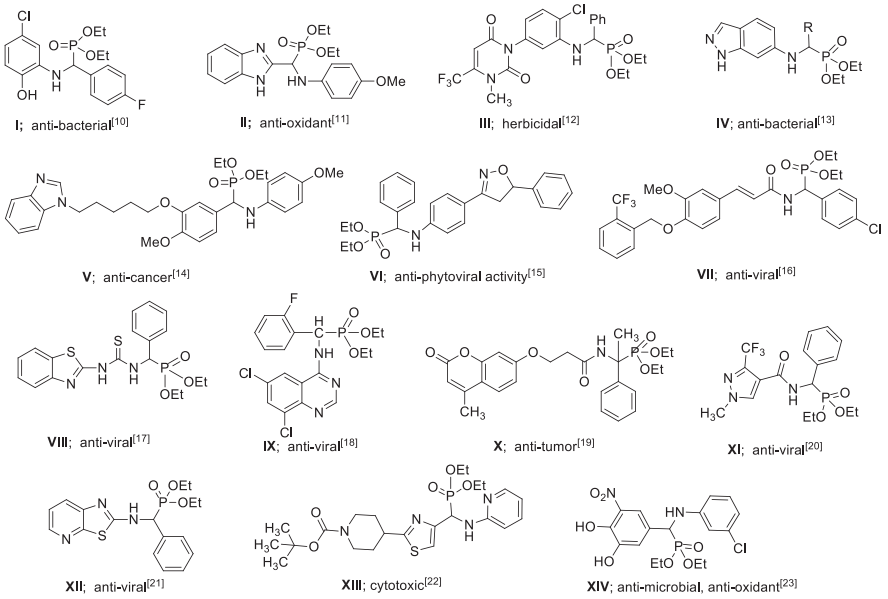


Figure 2. Glimpse of bioactive synthetic scaffolds containing α-aminophosphonates.

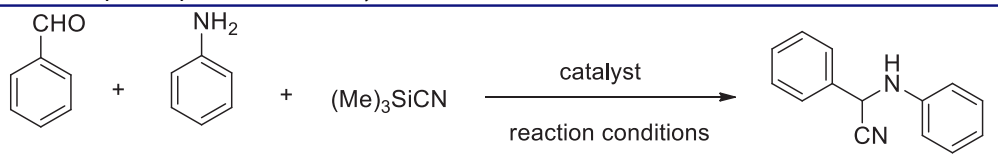
on the synthesis of either α-aminonitriles or α-aminophosphonates. Therefore, search for a common, efficient, environmentally benign and high yielding route for the synthesis of α-aminonitriles as well as α-aminophosphonates remains a valid exercise.

In these environmental conscious days, metal-free organo-catalyzed reactions are in high demand.[72–74] In recent times, among many others, mandelic acid is also regarded as an efficient organo-catalyst. The catalytic efficiency of mandelic acid was first explored by our group.[75,76] To the best of our knowledge, this is the third report where mandelic acid acts as an efficient catalyst in organic synthesis. On the other hand, in many circumstances, it was noticed that the best solvent to carry out organic transformation is 'no solvent'.[77] Under this purview, in continuation of our strong research interest toward organo-catalyzed reactions,[78–81] in this communication we wish to report the synthesis of both α-aminonitriles as well as α-aminophosphonates under solvent-free conditions at room temperature using a catalytic amount of mandelic acid as an efficient, commercially available, low cost, environmentally benign organo-catalyst.

Results and discussion

To optimize the protocol, we carried out a series of trial reactions between benzaldehyde (1 mmol), aniline (1 mmol) and trimethylsilyl cyanide (1 mmol) under various conditions. Initially, we performed the above mentioned reaction without using any catalyst in aqueous medium at room temperature which produced only 20% of 2-phenyl-2-(phenylamino)acetonitrile (**5a**) after two hours (Table 3, entry 1). The same reaction yielded 73% of **5a** after one hour in the presence of a catalytic amount of mandelic acid (20 mol%) in water at room temperature (Table 3, entry 2). Using the same amount of

Table 1. Reported protocols for the synthesis of α-aminonitriles.



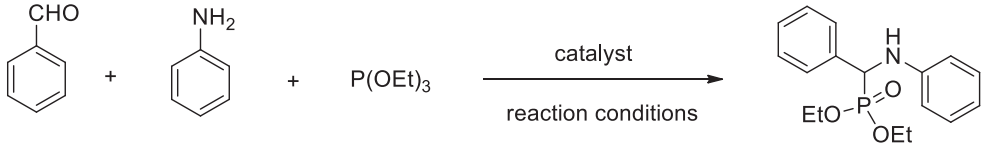
1 **2** **3** **5a**

Entry	Catalyst	Solvent	Temp.	Time (min)	Yield (%)[REF]
1	$Pr(OTf)_3$	CH_3CN	RT	600	89[24]
2	H_3BO_3	H_2O	RT	10	88[25]
3	$La(NO_3)_3{\cdot}6H_2O$/ $GdCl_3{\cdot}6H_2O$	CH_3CN	RT	60/180	96/94[26]
4	$Bi(NO_3)_3$	CH_3CN	RT	60	94[27]
5	$Ga(OTf)_3$	CH_2Cl_2	RT	180	90[28]
6	$RuCl_3$	CH_3CN	RT	20	74[29]
7	Anhy. $CeCl_2$	CH_3CN	RT	60	95[30]
8	$ZrOCl_2.8H_2O$	neat	RT	5	95[31]
9	Ph_3P/DEAD	neat	RT	20	85[32]
10	Fe_3O_4@PVA-SO_3H	EtOH	RT	5	96[33]
11	Fe_3O_4@DHAA[a]	EtOH	RT	15	90[34]
12	$NiCl_2$	CH_3CN	RT	720	92[35]
13	Sulfated Polyborate	neat	RT	2	99[36]
14	$RhI_3.H_2O$	CH_3CN	RT	10	97[37]
15	NH_4Cl	neat	MW, 90 °C	3	87[38]
16	Na_2SO_4	$ClCH_2CH_2Cl$	−20 °C	600	99[39]
17	$LiClO_4$	diethylether	RT	5	92[40]
18	$BiCl_3$	CH_3CN	RT	10 h	84[41]
19	SBPPSA[b]	EtOH	RT	5	85[42]
20	[c][bmim]BF_4/[bmim]PF_6	neat	RT	300	92[43]
21	[d][Sipim]HSO_4	EtOH	RT	75	90[44]
22	[bmim]ClO_4	neat	RT	15	86[45]
23	Choline chloride. $ZnCl_2$	neat	RT	3	87[46]
24	[e][hmim]HSO_4	neat	RT	15	93[47]
25	Co/SBA-15	neat	MW, 45 °C	30	80[48]
26	Nafion-Fe	CH_2Cl_2	60 °C	240	95[49]
27	$Cu(OTf)_2$	CH_2CN	RT	360	89[50]
28	nano-$CuFe_2O_4$	aq. AcOH	RT	50	93[51]
29	*L*-proline	CH_2CN	RT	120	95[52]
30	mandelic acid	neat	RT	3	93[this work]

[a]DHAA: dehydroascorbic acid; [b]SBPPSA: silica-bonded *N*-propylpiperazine sulfamic acid; [c][bmim]: 1-butyl-3-methylimidazolium; [d][Sipim]: N-(3-silicapropyl) imidazolium; [e][hmim]: methyl imidazolium

catalyst, comparable yields (67–75%) of **5a** were recorded in other organic solvents such as ethanol, methanol, acetonitrile and chloroform (Table 3, entry 3–6). An excellent yield (93%) of **5a** was obtained within just three minutes when the same reaction carried out using 20 mol% of mandelic acid as catalyst under solvent-free conditions at room temperature (Table 3, entry 7). This may be due to the greater interaction between the reactant molecules and catalyst in solid phase. We tried to optimize the required catalyst amount keeping the other parameters remain same. Lesser amount of **5a** (81% & 86%) was isolated using 10 mol% and 15 mol% of mandelic acid respectively (Table 3, entry 8-9). No significant improvement was observed in the reaction rate even by increasing the catalyst amount to 25 mol% (Table 3, entry 10). On the basis of these above experimental outcomes, it was came out that 20 mol% of mandelic acid is an efficient organo-catalyst for the synthesis of 2-phenyl-2-(phenylamino)acetonitrile (**5a**) under solvent-free conditions at room temperature. To check the generality as well as

Table 2. Reported protocols for the synthesis of α-aminophosphonates.

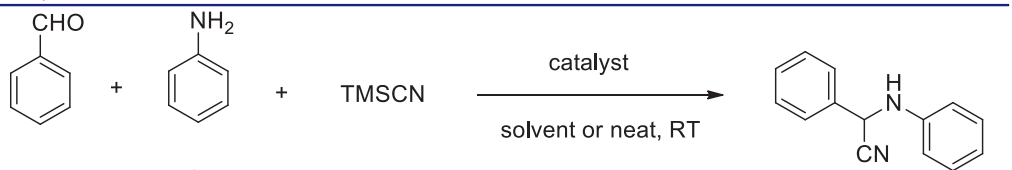


1 2 4 6

Entry	Catalyst	Solvent	Temp.	Time	Yield (%)[REF]
1	$FeCl_3$	THF	RT	90 min	73[53]
2	Amberlyst-IRC 748	toluene	RT	30 min	92[23]
3	$[EtNH_3]NO_3$	neat	RT	120 min	95[54]
4	$BiCl_3$	CH_3CN	reflux	360 min	92[55]
5	$FeCl_3$	THF	RT	45 min	95[56]
6	$YbCl_2$	CH_3CN	RT	24 h	93[57]
7	$In(OTf)_3 + MgSO_4$	THF	reflux	21 h	79[58]
8	$Al(OTf)_3$	neat	RT	30 min	96[59]
9	$TaCl_5$-SiO_2	CH_2Cl_2	RT	24 h	92[60]
10	PPh_3	neat	60 °C	60 min	87[61]
11	Amberlite-IR 120	neat	MW	2 min	90[62]
12	$NbCl_5$	neat	50 °C	30 min	95[63]
13	$[bmim]BF_4$/$[bmim]PF_6$	neat	RT	5/8 h	90/84[64]
14	$InCl_3$	THF	RT	90 min	92[65]
15	[a][bnmim][HSO_4]	neat	RT	1 min	96[66]
16	$Yb(OTf)_3$	CH_2Cl_2	RT	240 min	89[67]
17	$Mg(ClO_4)_2$	neat	RT	2 min	98[68]
18	$Al(H_2PO_4)_3$	neat	100 °C	90 min	93[69]
19	$ZrOCl_2{\cdot}8H_2O$	neat	RT	5 min	95[70]
20	[b]Cu(3,4-tmtppa)($MeSO_4$)$_4$	H_2O	80°C	0.5 h	96[71]
2 [c]	mandelic acid	neat	RT	7 min	87 [this work]

[a][bnmim]: 1-Benzyl-3-methyl imidazolium; [b]Cu(3,4-tmtppa)($MeSO_4$)$_4$: tetramethyl-tetra-3,4-pyridinoporphyrazinato copper (II) methyl sulfate; [c]4-bromoaniline was used instead of aniline

Table 3. Optimization of reaction conditions for the synthesis of 2-phenyl-2-(phenylamino)acetonitrile.

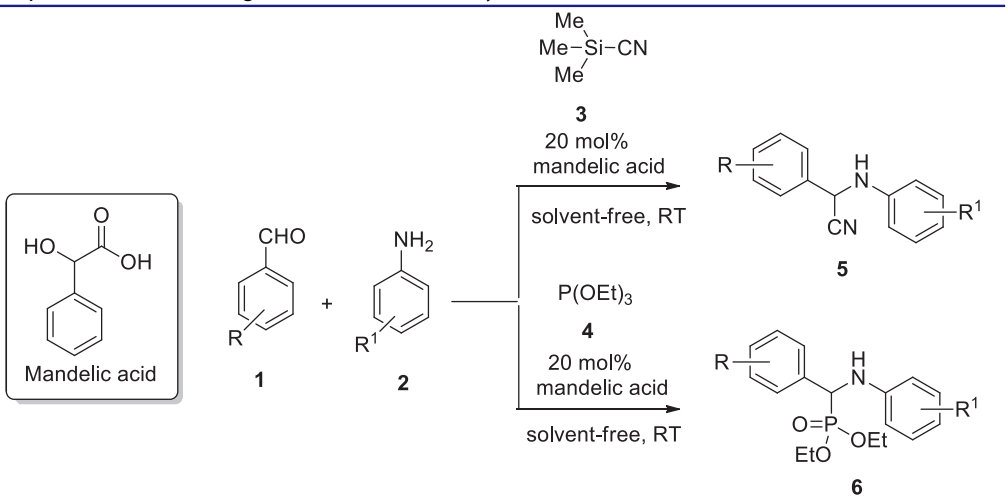


1 2 3 5

Entry	Catalyst (mol%)	Condition	Time (min)	Yield (%)[a,b]
1.	Catalyst-free	H_2O	120	20
2	Mandelic acid (20)	H_2O	60	73
3	Mandelic acid (20)	EtOH	60	70
4	Mandelic acid (20)	MeOH	60	67
5	Mandelic acid (20)	MeCN	60	72
6	Mandelic acid (20)	$CHCl_3$	60	75
7	**Mandelic acid (20)**	**solvent-free**	**3**	**93**
8	Mandelic acid (10)	solvent-free	10	81
9	Mandelic acid (15)	solvent-free	5	86
10	Mandelic acid (25)	solvent-free	3	94

[a]Reaction conditions: benzaldehyde (**1**; 1 mmol), aniline (**2**; 1 mmol) and TMSCN (**3**; 1 mmol) in the absence or presence of a catalytic amount of naturally occurring mandelic acid in neat/4 mL of water/ethanol/methanol/aqueous ethanol at 20–25 °C. [b]Isolated yields.

Table 4. Synthesis of 2-aryl-2-(arylamino)acetonitrile (**5a–5j**) and diethyl (aryl(arylamino) methyl)-phosphonate (**6a–6c**) using mandelic acid as catalyst under solvent-free conditions.



Sl No.	R	R^1	Product	Time (min)	Yield (%)
1	H	H	**5a**	3	93
2	4-Cl	H	**5b**	3	94
3	4-F	H	**5c**	3	91
4	H	4-Br	**5d**	3	89
5	4-OMe	4-Br	**5e**	3	84
6	4-OMe	4-Me	**5f**	3	86
7	4-Me	4-Br	**5g**	3	88
8	3,4-OCH_2-	3-Me	**5h**	5	90
9	3,4-OCH_2-	4-F	**5i**	5	94
10	3,4-OCH_2-	3-Cl	**5j**	5	92
11	H	4-Br	**6a**	7	87
12	4-OMe	4-Br	**6b**	8	86
13	4-OMe	4-Me	**6c**	8	89

[a]Reaction conditions: aldehydes (**1**; 1 mmol), amines (**2**; 1 mmol) and TMSCN (**3**; 1 mmol) or triethyl phosphite (**4**; 1 mmol) in the presence of mandelic acid (20 mol%) as catalyst under solvent-free conditions at 28–32 °C.
[b]Isolated yields.

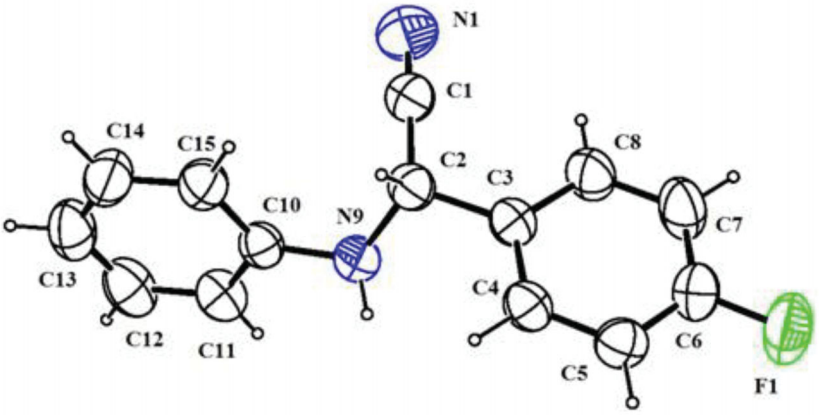


Figure 3. ORTEP view of the molecule **5c** with displacement ellipsoids drawn at 50% (CCDC 1975998).

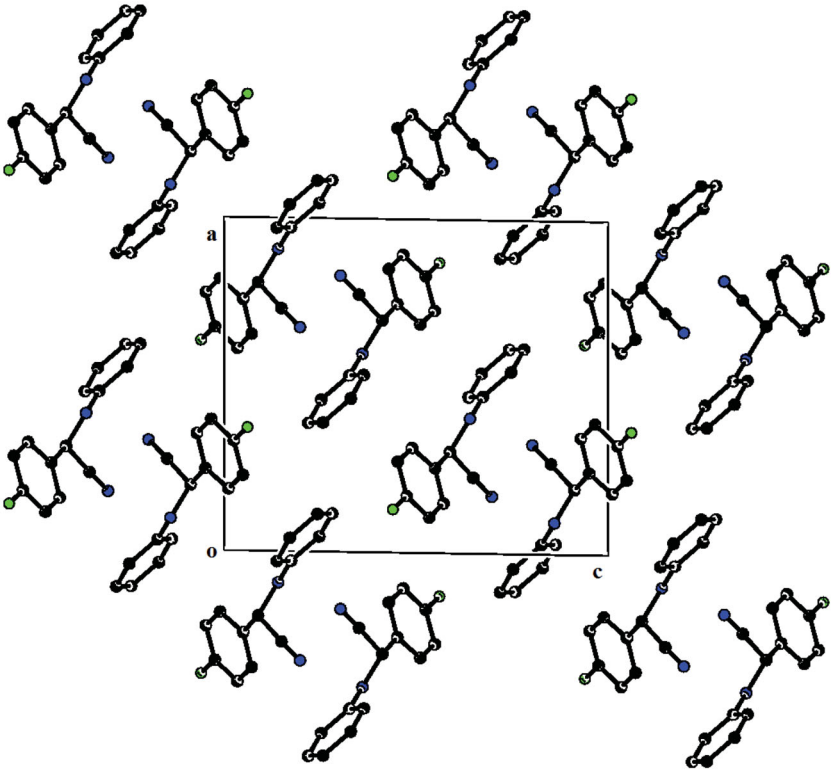


Figure 4. Packing view of molecules down b-axis within the unit cell of compound **5c**.

effectiveness of this optimized reaction conditions, we were then motivated to synthesize some other derivatives of 2-aryl-2-(arylamino)acetonitrile *via* one-pot three-component Strecker reaction. Therefore, we carried out the reactions between various benzaldehyde derivatives (**1**; 1 mmol) substituted anilines (**2**; 1 mmol) and TMSCN (**3**; 1 mmol) in the presence of 20 mol% mandelic acid as catalyst under solvent-free conditions at room temperature which afforded excellent yields (84–94%) of the desired 2-aryl-2-(arylamino)acetonitriles (**5b–5j**) (Table 4; entry 2–10). As expected, aldehydes with electron donating substituent like methoxy produced lower yields of the desired products. To extend the scope of our developed protocol, one-pot three component Kabachnik-Fields reactions between benzaldehydes (**1**; 1 mmol) anilines (**2**; 1 mmol) and triethyl phosphite (**4**; 1 mmol) were also carried out under the same optimized reaction conditions which afforded the corresponding diethyl (aryl(arylamino)methyl)phosphonate (**6a–6c**) with 87–89% yields (Table 4; entry 11 & 13).

No column chromatographic purification was required as all the products were isolated pure just by simple filtration and subsequent washing with aqueous ethanol. Under the same optimized reaction conditions, gram scale production (1.83 g; 88%) of 2-phenyl-2-(phenylamino)acetonitrile (**5a**) was also achieved from the reactions of 10 mmol benzaldehyde, 10 mmol aniline and 11 mmol trimethylsilyl cyanide within 30 min. All the synthesized compounds were well characterized by the detail spectroscopic analyses including FT-IR, ^{1}H NMR, ^{13}C NMR and HRMS. It is also note worthy to mention that we were able to form single crystal of two compounds *i.e.,* compound

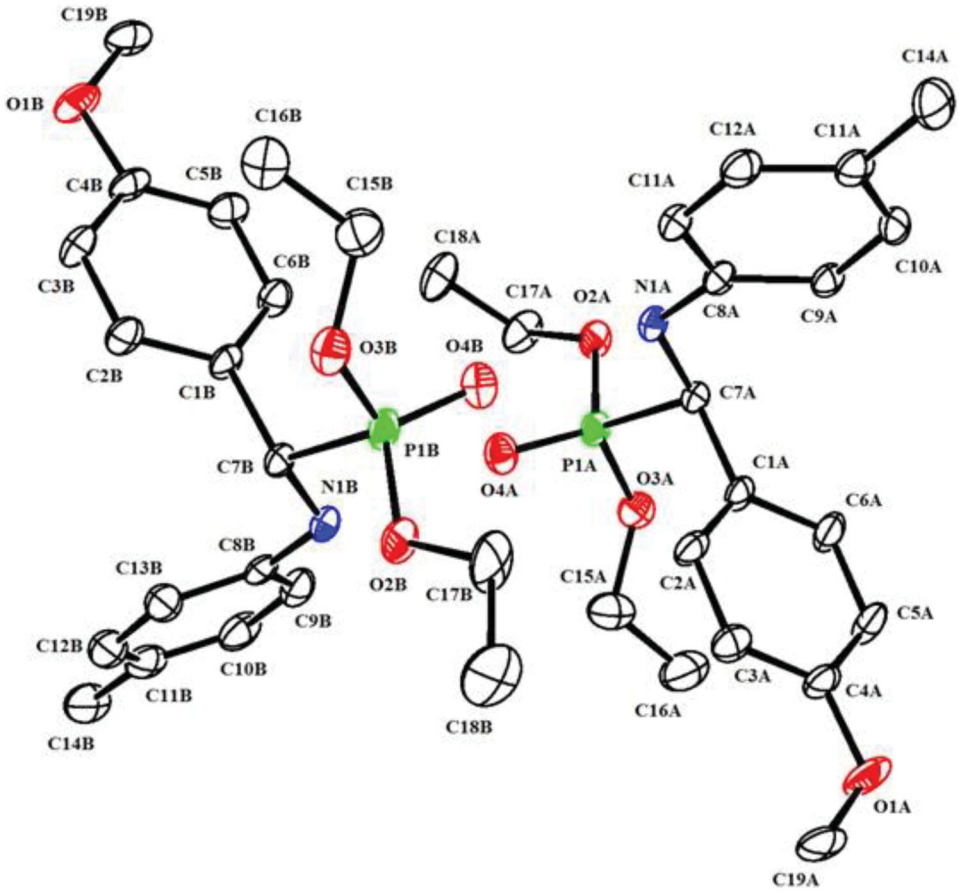


Figure 5. ORTEP view of the molecules **6c** with displacement ellipsoids drawn at 40% probability level. (CCDC 1976000).

5c and **6c**. ORTEP view of compound **5c** is shown in Figure 3. In this ORTEP small spheres of arbitrary radii represent H atoms. Figure 4 shows the packing view of molecules down b-axis within the unit cell of compound **5c**. ORTEP diagram of compound **6c** is shown in Figure 5 which indicates that the structure contains two crystallographically independent molecules, A and B, in the asymmetric unit. In this ORTEP, H-atoms have been excluded for better clarity. Figure 6 represents the packing view of molecules **6c** down a-axis within the unit cell.

Experimental section

General

Melting points were recorded on a Digital Melting Point Apparatus (Model No. MT-934) and are uncorrected. TLC was performed on silica gel 60 F254 (Merck) plates. Infrared spectra were recorded on Agilent (Cary 660) FT-IR spectrophotometer on KBr disks. ^{1}H and ^{13}C NMR spectra were obtained at 500 MHz Jeol (JNM ECX-500) NMR

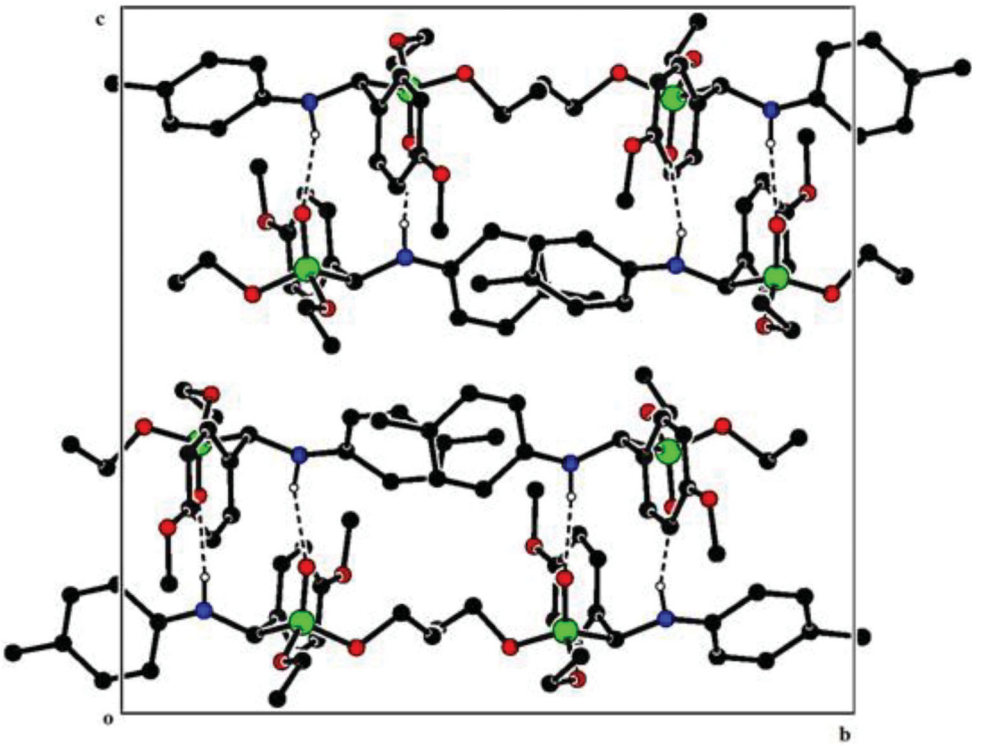


Figure 6. Packing view of molecules down a-axis within the unit cell of compound **6c**.

machines with $CDCl_3$ as the solvent. Mass spectra (TOF-MS ES^+) were measured on a Bruker Impact HD QTOF Micro mass spectrometer.

General procedure for the synthesis of 2-phenyl-2-(phenylamino)acetonitrile (5a)

In an oven-dried screw-cap test tube a magnetic stir bar, benzaldehyde (**1**; 1 mmol), aniline (**2**; 1 mmol), trimethyl silylcyanide (**3**; 1 mmol) and a catalytic amount of mandelic acid (20 mol%) were taken sequentially. The reaction mixture was then stirred vigorously at room temperature under solvent-free conditions. The reaction was monitored by TLC. After completion of the reaction, 10 mL of water was added in the reaction vessel and the mixture was allowed to stir for 5 min. 2-Phenyl-2-(phenylamino)acetonitrile (**5a**) was isolated pure with 93% yield just by simple filtration and subsequent washing with aqueous ethanol (H_2O:EtOH = 4:1).

General procedure for the synthesis of diethyl (((4-bromophenyl)amino)(phenyl)methyl)phosphonate (6a)

By repeating the above mentioned procedure, diethyl (((4-bromophenyl)amino)(phenyl)methyl)phosphonate (**6a**) was also synthesized with 87% yield from the reactions of benzaldehydes (**1**; 1 mmol), 4-bromoaniline (**2**; 1 mmol) and triethyl phosphite (**4**; 1 mmol) by using 20 mol% of mandelic acid as catalyst under the same optimized

conditions. The structures of the synthesized compounds were determined by the detail spectral analysis including FT-IR, ^{1}H NMR, ^{13}C NMR and HRMS.

Characterization data of some representative entries

2-Phenyl-2-(phenylamino)acetonitrile (**5a**): White solid; mp 81–83 °C; IR (KBr) ν_{max}/cm^{-1}: 3335, 335, 2359, 1599, 1496, 1450, 1284, 1244, 1196, 1115, 1066, 1029, 925, 879, 751; ^{1}H NMR (500 MHz, $CDCl_3$) δ/ppm: 7.60 (2H, dd, J = 7.37 & 1.85 Hz, aromatic H), 7.47–7.44 (2H, m, aromatic H), 7.29–7.25 (2H, m, aromatic H), 6.91 (1H, t, J = 7.45 & 7.00 Hz, aromatic H), 6.78 (2H, d, J = 8.05 Hz, aromatic H), 5.43 (1H, d, J = 8.20 Hz), 4.04 (1H, d, J = 8.00 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ/ppm: 144.75, 134.00, 129.69 (2 C), 129.46 (2 C), 127.38 (2 C), 120.39 (2 C), 118.29, 114.23 (2 C), 50.31; HRMS (ESI-TOF) m/z: For $C_{14}H_{12}N_2$ Calcd. $[M + Na]^+$ 231.0898; Found $[M + Na]^+$ 231.0988.

Diethyl (((4-bromophenyl)amino)(phenyl)methyl)phosphonate (**6a**): Grayish solid; mp 99–101 °C; IR (KBr) ν_{max}/cm^{-1}: 3286, 2980, 2904, 1591, 1514, 1488, 1449, 1391, 1292, 1233, 1199, 1071, 963, 878, 732; ^{1}H NMR (500 MHz, $CDCl_3$) δ/ppm: 7.43 (2H, d, J = 7.60 Hz, aromatic H), 7.34 (2H, t, J = 7.55 & 6.85 Hz, aromatic H), 7.29–7.26 (1H, m, aromatic H), 7.17 (2H, d, J = 8.95 Hz, aromatic H), 6.46 (2H, d, J = 8.95 Hz, aromatic H), 4.87 (1H, t, J = 8.90 & 8.25 Hz), 4.69 (1H, dd, J = 24.08 & 7.55 Hz), 4.16–4.06 (2H, m), 3.64–3.89 (1H, m), 3.67–3.62 (1H, m), 1.29 (3H, t, J = 6.90 & 6.85 Hz. -OCH_2CH_3), 1.10 (3H, t, J = 7.55 & 6.85 Hz, -OCH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ/ppm: 145.29, 145.18, 135.29, 131.86 (2 C), 128.66, 128.11, 127.75, 127.71, 115.42 (2 C), 110.14, 63.43 (d, J_{PC} = 7.16 Hz, OCH_2CH_3), 63.26 (d, J_{PC} = 7.15 Hz, OCH_2CH_3), 56.48 (d, J_{PC} = 150.22 Hz, *C*HP), 16.41 (d, J_{PC} = 5.96 Hz, OCH_2CH_3), 16.16 (d, J_{PC} = 5.95 Hz, OCH_2CH_3); HRMS (ESI-TOF) m/z: For $C_{17}H_{21}BrNO_3P$ Calcd. $[M + Na]^+$; 420.0340 Found $[M + Na]^+$ 420.0613.

Supporting information

General procedure, characterization data including scanned spectra of FTIR, ^{1}H-NMR, ^{13}C-NMR and HRMS for all entries are supplemented in Supporting information.

Conclusions

We have developed a simple, facile and general pathway for the synthesis of both α-aminonitriles as well as α-aminophosphonates *via* one-pot three-component reactions of aldehydes, amines and trimethylsilyl cyanide or triethyl phosphate using a catalytic amount of mandelic acid as an efficient, low cost, easily available naturally occurring organo-catalyst under solvent-free conditions at room temperature. Mild, general, energy efficiency, high atom economy, one-pot three component strategy, use of cheap and efficient organo-catalyst, column-free easy isolation procedure, solvent-free reaction conditions are some of the salient features of this developed protocols.

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Disclosure statement

The authors declare no conflict of interest.

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