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ONE-POT THREE-COMPONENT SYNTHESIS OF α-AMINONITRILES USING SODIUM DIHYDROGEN PHOSPHATE AS A CATALYST AT ROOM TEMPERATURE

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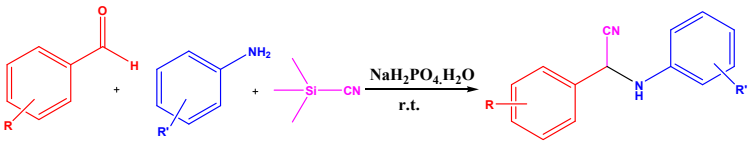
Sodium dihydrogen phosphate was applied as an efficient and inexpensive catalyst for the synthesis of biologically potent α-aminonitrile derivatives through a one-pot three-component reaction of aldehyde, amine and trimethylsilyl cyanide. The reactions were easily carried out under mild, green and eco-friendly conditions in ethanol at room temperature affording high yields of the products in short times.



INTRODUCTION

α-Aminonitriles are specific and interesting bifunctional compounds with wide applications in the fields of chemistry and biology, which are efficient precursors and valuable intermediates in the synthesis of α-amino acids, heterocycles and diamines.[1–2] Additionally, α-aminonitriles are structurally found in different biologically important alkaloids like saframycin-A, girgensohnine, anagliptin, and vildagliptin.[3–5]

Therefore, considerable attentions have been devoted for the synthesis of α-aminonitriles. One of the most popular and significant tool in the synthesis of α-aminonitriles is the Strecker reaction, nucleophilic addition of cyanide ion into imines. Several modifications of Strecker reaction have been studied using a variety of cyanide reagents.[5,6] However, multicomponent reaction of trimethylsilyl cyanide (TMSCN), amines and aldehydes or ketones is the most direct and viable method. In this context, several attempts have been made with different catalysts and media.[5,7–22] Although, the reported methods have some merits, they exhibit at least one of the imperfections like the harsh reaction conditions, expensive or unobtainable reagents, use of toxic organic solvents, sensitive catalyst, cumbersome catalyst preparation procedure, tedious workup conditions and long reaction times. Hence, there is further scope to develop milder, safer and more efficient catalyst for this reaction.

Considering the biomedical applications of α-aminonitrile derivatives and in the perpetuation of the development of practical, convenient and environmentally-friendly procedures for one-pot multi-component reactions,[23–27] we were prompted to exploit the catalytic potential of sodium dihydrogen phosphate for a facile and efficient three-component synthesis of functionalized α-aminonitriles through a multicomponent reaction of aldehyde, amine, and TMSCN (Scheme 1).

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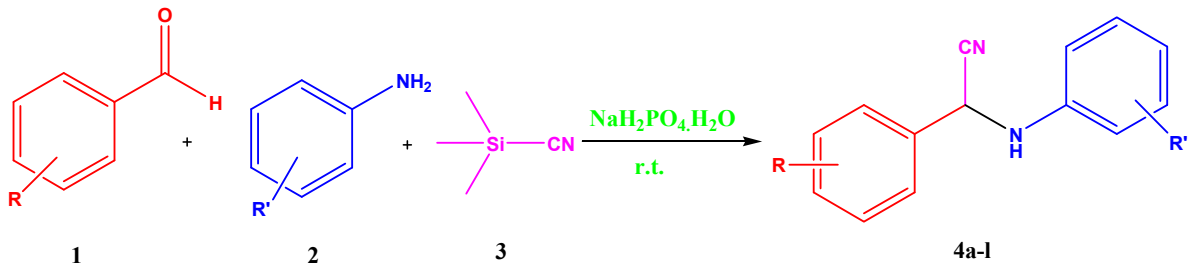


1 **2** **3** **4a-l**

Scheme 1 – Synthesis of α-aminonitriles.

Our literature survey at this stage revealed that sodium dihydrogen phosphate (NaH_2PO_4) has not been utilized for the synthesis of α-aminonitriles. However, NaH_2PO_4 has been successfully employed as an efficient and inexpensive catalyst in the synthesis α-aminophosphonates and 2-substituted-2,3-dihydro-4(1H)-quinazolinones by our group.[26,27]

RESULTS AND DISCUSSION

To find out the suitable conditions for the reaction, systematic investigations were performed with the reaction of 4-chlorobenzaldehyde, aniline, and TMSCN as a model reaction. The results are depicted in Table 1.

The optimum loading of the catalyst for completion of the reaction was demonstrated with different amounts of $NaH_2PO_4.H_2O$, i.e 20, 30, 40 and 50 mol% (Table 1). It is important to recall that α-aminonitrile could not be synthesized at room temperature in the absence of catalyst. In contrast, 40 mol% of $NaH_2PO_4.H_2O$ was sufficient to drive the reaction to completion in short time (20 min) at room temperature (Table 1, entry 5). However, higher amounts of phosphate catalyst did not show major effect on the product yield (Table 1, entry 6).

The reaction medium generally plays an important role in the condensation reactions. To identify the most suitable one, different solvents such as EtOH, H_2O, $CHCl_3$, CH_3CN, n-hexane and also under solvent-free conditions were screened (Table 1, entries 7–11). Based on the screening results, EtOH was chosen as the most suitable solvent for further study.

To investigate the efficacy and generality of $NaH_2PO_4.H_2O$ in the synthesis of α-aminonitrile derivatives, various arylaldehydes were reacted with aniline and TMSCN under optimized conditions to obtain the desired products. The results are displayed in Scheme 2 and Table 2.

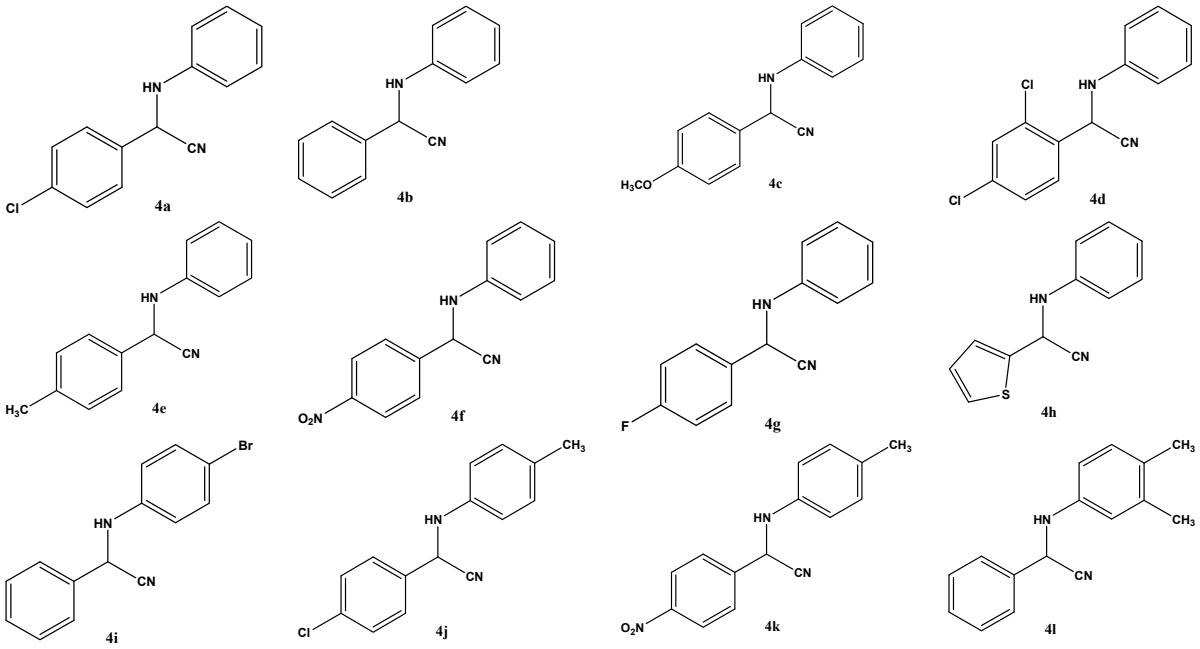
As it can be seen, the three-component reaction has been carried out with different arylaldehydes possessing electron-releasing substituents, electron-withdrawing substituents and halogens on their aromatic ring. Thus, the reaction proceeds efficiently under mild conditions and the corresponding α-aminonitrile products were obtained in excellent yields, regardless of the nature and position of the substituents. Moreover, the protocol was also amenable to aniline derivatives (Table 2, entries 9-12), affording the desired product in excellent yields and in reasonable reaction times at room temperature.

Table 1

Optimizing the reaction conditions[a] for the synthesis of **4a**

Entry	$NaH_2PO_4.H_2O$ (mol%)	Solvent	Time (min)	Yield (%)
1	0	Ethanol	300	0
3	20	Ethanol	60	75
4	30	Ethanol	60	80
5	**40**	**Ethanol**	**20**	**92**
6	50	Ethanol	20	92
7	40	H_2O	180	60
8	40	$CHCl_3$	180	50
9	40	CH_3CN	180	70
10	40	n-hexane	180	30
11	40	Solvent-free	180	80

[a] 4-chlorobenzaldehyde (1.0 mmol), aniline(1.0 mmol) and TMSCN (1.2 mmol), solvent (5.0 mL) at r.t.

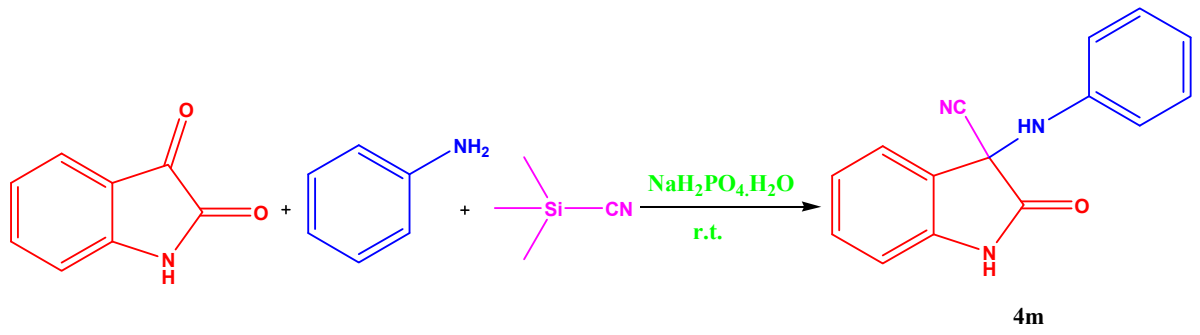


Scheme 2 – The structures of α-aminonitriles **4a-l**.

Table 2

Synthesis of α-aminonitriles in the presence of $NaH_2PO_4.H_2O$

Entry	aldehyde	amine	Product	Time (min)	Yield (%)	m.p. (°C)[ref.]
1	4-chlorobenzaldehyde	aniline	**4a**	20	92	110-112[23]
2	benzaldehyde	aniline	**4b**	30	90	80-82[9]
3	4-methoxybenzaldehyde	aniline	**4c**	40	85	91-92[17]
4	2,4-dichlorobenzaldehyde	aniline	**4d**	30	90	117-119[9]
5	4-methylbenzaldehyde	aniline	**4e**	30	88	73-75[22]
6	4-nitrobenzaldehyde	aniline	**4f**	20	95	114-116[17]
7	4-fluorobenzaldehyde	aniline	**4g**	20	93	98-100[23]
8	2-thiophene carboxaldehyde	aniline	**4h**	40	82	105-107[22]
9	benzaldehyde	4-bromoaniline	**4i**	40	85	90-93[9]
10	4-chlorobenzaldehyde	*p*-toluidine	**4j**	30	90	84-86[12]
11	4-nitrobenzaldehyde	*p*-toluidine	**4k**	20	92	83-85[17]
12	benzaldehyde	3,4-dimethylaniline	**4l**	40	85	92-94[23]



4m

Scheme 3 – Three-component reaction of isatin, aniline and TMSCN.

In addition, under the same conditions, one-pot three-component condensation reaction of isatin, aniline and trimethylsilyl cyanide afforded the corresponding α-aminonitrile **4m** bearing an indoline moiety of potential synthetic and pharmacological interest at 30 min with 90% yield (Scheme 3).

The formation of the products was confirmed by comparing their melting points with literature values,[7–22] while the structures of the selected α-

aminonitrile derivatives were established by IR, and NMR spectra. All the characterizations and interpretations are in good agreement with the expected structures of the α-aminonitriles.

EXPERIMENTAL

1. Materials

All starting materials and reagents were commercially available and used without further purification. Thin-layer chromatography (TLC) was performed on aluminum plates pre-coated with Merck silica gel. Melting points were measured by an electrothermal type 9100 melting point apparatus. The infrared (IR) spectra were recorded on a Bruker Tensor 27 FTIR spectrophotometer as KBr disks. NMR spectra were determined on a Bruker AC 300 MHz instrument as DMSO-d_6 solutions at room temperature.

2. General procedure for the one-pot synthesis of α-aminonitriles

A mixture of aldehyde (1 mmol), amine (1 mmol), trimethylsilyl cyanide (1.2 mmol), $NaH_2PO_4.H_2O$ (40 mol%), and ethanol (5 mL) was stirred at room temperature for the appropriate time indicated in Table 1. The progress of reactions was monitored by TLC (ethyl acetate/n-hexane=1/4). After completion of the reaction, the reaction mixture was concentrated, followed by crystallization from ethanol to afford pure products.

3. Product characterization data

2-(4-Chlorophenyl)-2-(phenylamino)acetonitrile **(4a).** IR (KBr): ν/cm^{-1} 3380, 2931, 2238, 1600, 1515, 1457, 1270, 1161, 1096, 789; ^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm 3.90 (brs, 1H), 5.34 (d, *J*=7.9 Hz, 1H), 6.74 (d, *J*=8.0 Hz, 2H), 6.88 (t, *J*=7.8 Hz, 1H), 7.24 (t, *J*=7.8 Hz, 2H), 7.37 (d, *J*=7.8 Hz, 2H), 7.59 (d, *J*=8.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ/ppm 49.8, 114.3, 117.9, 120.4, 128.5, 129.4, 129.8, 132.4, 135.4, 114.1

2-phenyl-2-(phenylamino)acetonitrile **(4b).** IR (KBr): ν/cm^{-1} 3337, 2954, 2242, 1600, 1516, 1450, 1244, 754; ^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm 4.05 (brs, 1H), 5.46 (s, 1H), 6.81 (dd, J_1= 8.5 Hz, J_2= 1.0 Hz, 2H), 6.93 (t, *J*= 7.35 Hz, 1H), 7.29-7.33 (m, 2H), 7.46-7.51 (m, 3H), 7.61-7.65 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ/ppm 50.3, 114.2, 118.2, 120.4, 127.3, 129.4, 129.6, 131.3, 134.0, 144.7.

2-(2,4-dichlorophenyl)-2-(phenylamino)acetonitrile **(4d).** IR (KBr): ν/cm^{-1} 3422, 3050, 2923, 2227, 1594, 1502, 1283, 825, 725; ^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm 4.05 (brs, 1H), 5.70 (s, 1H), 6.79 (dd, J_1= 8.6 Hz, J_2= 0.8 Hz, 2H), 6.94 (t, *J*= 7.4 Hz, 1H), 7.27-7.32 (m, 2H), 7.39 (dd, J_1= 8.3 Hz, J_2= 2. 1 Hz, 1H), 7.53 (d, *J*= 2.1 Hz, 1H), 7.70 (d, *J*= 8.3 Hz, 1H). ^{13}C NMR (75MHz, $CDCl_3$): δ/ppm 47.7, 114.4, 117.4, 120.8, 128.1, 129.7, 129.9, 130.4, 134.3, 136.5, 144.3.

2-(phenylamino)-2-(2-thienyl)acetonitrile **(4h).** IR (KBr): ν/cm^{-1} 3357, 3100, 2237, 1599, 1500, 1436, 1348, 1252, 1149, 1063, 884, 833, 751; ^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm 4.18 (brs, 1H), 5.56 (s, 1H), 6.73 (d, *J*= 7.6 Hz, 2H), 6.88 (t, *J*= 7.5 Hz, 1H), 6.90-7.03 (m, 1H), 7.21-7.33 (m, 4H); ^{13}C NMR (75MHz, $CDCl_3$): δ/ppm 46.1, 114.6, 117.4, 120.5, 127.0, 127.1, 127.2, 129.4, 136.8, 144.0.

2-(4-bromophenylamino)-2-phenylacetonitrile **(4i).** IR (KBr): ν/cm^{-1} 3400, 3080, 2915, 2220, 1595, 1500, 1280, 1069, 820, 720; ^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm 4.00 (brs, 1H), 5.31 (s, 1H), 6.56-6.60 (m, 2H), 7.29-7.31 (m, 2H), 7.36-7.42 (m, 3H), 7.49-7.53 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ/ppm 50.2, 112.4, 115.8, 117.8, 127.3, 129.5, 129.8, 132.4, 133.5, 143.7.

2-(4-toulyl)-2-phenylacetonitrile **(4j).** IR (KBr): ν/cm^{-1} 3331, 2960, 2220, 1600, 1510, 1280, 1245, 1100, 810; ^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm 2.31 (s, 3H), 3.97 (brs, 1H), 5.41 (s, 1H), 6.71 (d, *J*= 8.91 Hz, 2H), 7.11 (d, *J*= 7.91 Hz, 2H), 7.44 (d, *J*= 8.29 Hz, 2H), 7.56 (d, *J*= 8.29 Hz, 2H); ^{13}C NMR (75MHz, $CDCl_3$): δ/ppm 20.6, 50.2, 114.7, 118.0, 128.6, 130.1, 130.2, 132.7, 135.5, 142.1.

2-(3,4-dimethylphenylamino)-2-phenylacetonitrile **(4l).** IR (KBr): ν/cm^{-1} 3330, 2920, 2230, 1594, 1540, 1445, 1210, 1164, 925, 880, 690; ^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm 2.12 (s, 3H), 2.17 (s, 3H), 3.81 (brs, 1H), 5.32 (s, 1H), 6.48 (dd, J_1= 7.94 Hz, J_2= 2.4 Hz, 1H), 6.53 (s, 1H), 6.96 (d, 1H, J= 8.1 Hz), 7.34-7.41 (m, 3H), 7.50-7.54 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ/ppm 18.9, 20.1, 50.7, 111.7, 116.1, 118.5, 127.3, 128.6, 129.3, 129.5, 130.6, 134.2, 137.9, 142.8.

2-Oxo-3-(phenylamino)indoline-3-carbonitrile **(4m).** IR (KBr): ν/cm^{-1} 3400, 3320, 3050, 2960, 2230, 1670, 1603, 1468, 1347,1323, 1220, 1055, 744; ^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm 4.80 (brs, 1H), 6.85 (d, J = 7.6 Hz, 1H), 7.30–7.69 (m, 8H), 9.30 (s, 1H). (75MHz, $CDCl_3$): δ/ppm 71.0, 111.5, 120.0, 121.0, 125.3, 126.7, 129.0, 131.4, 132.8, 140.5, 150.0, 153.0, 176.0.

CONCLUSIONS

In conclusion, sodium dihydrogen phosphate has been utilized as a catalyst for the one-pot, three-component reaction of arylaldehydes, anilines and trimethylsilyl cyanide results in efficient formation of α-aminonitrile derivatives. The inexpensive $NaH_2PO_4.H_2O$ catalyst provides a green protocol through good to excellent yields, easy work-up procedure as well as mild reaction conditions at room temperature. Hence, our proposed method offers a better alternative to existing methods.

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