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Solventless convenient synthesis of new cyano-2-aminopyridine derivatives from enaminonitriles

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ABSTRACT

A synthesis of novel 4-substituted-3-cyano-2-aminopyridines using enaminonitriles and various primary amines was established under microwave irradiation and solvent-free conditions. Structures of the new compounds were characterized by IR, MS, ^{1}H and ^{13}C NMR data and the structure of 2-aminopyridine of the products was confirmed by X-ray analysis.

1. Introduction

2-Aminopyridines and analogues constitute an important class of compounds in organic chemistry.[1] They have applications in different fields: they present a wide spectrum of biological activities including inhibition of nitric oxide synthases (NOS),[2] they could be used as intermediate in the manufacture of pharmaceuticals[3] like Piroxicam[4] and moreover, because of their chelating abilities, they can be used as ligands in organic and inorganic chemistry.[5] Among 2-aminopyridine derivatives, substituted-3-cyano-2-aminopyridines are compounds which display also many attractive properties (see Fig. 1). They could be valuable intermediates in organic synthesis to obtain more complex nitrogen heterocycles.[6] They could show various biological properties[7] like antifungal, anti-inflammatory, analgesic, antipyretic and antimicrobial. To a certain extent, they could present interesting photophysical properties as NLO compounds.[8]

In the literature, many syntheses of substituted-3-cyano-2-aminopyridines have been reported.[9] Among them, one of the most widely used is the derivatization of the pyridine moiety including amination method in which a substitution of 2-halo-3-cyanopyridines and analogues with ammonia or an equivalent is

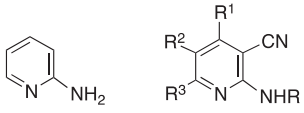
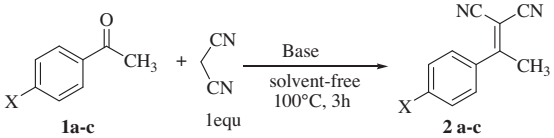


Figure 1. Structures of 2-aminopyridine and substituted-3-cyano-2-aminopyridines.

Table 1
Synthesis of arylethylidenemalononitrile derivatives **2a–c**[17]



1a-c 1equ

1equ

2 a-c
2a : X=H
2b: X=CH_3
2c: X=OMe

Entry	Acetophenone	X	Product	Yield[a,b] (%)	
1	**1a**	H	**2a**	77	73
2	**1b**	Me	**2b**	85	83
3	**1c**	OMe	**2c**	81	80

[a] Isolated yield using ammonium acetate as a base.
[b] Isolated yield using ammonium carbonate as a base.

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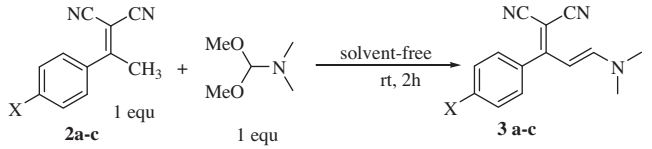
Table 2
Synthesis of enaminonitriles **3a–c**[20]



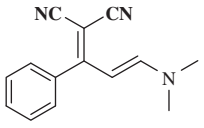
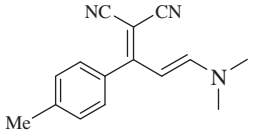
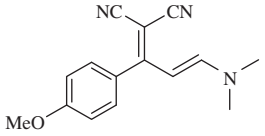
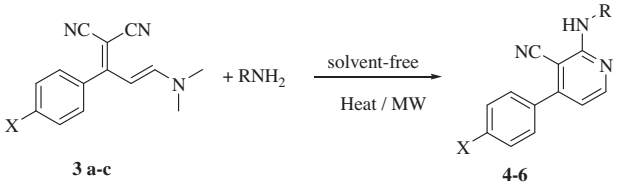
Entry	2	X	Product	Yield (%)
1	**2a**	H	 **3a**	71
2	**2b**	Me	 **3b**	89
3	**2c**	OMe	 **3c**	80

Table 3
Synthesis of 4-substituted-3-cyano-2-aminopyridines **4–6**[21]



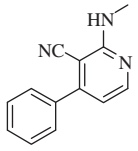
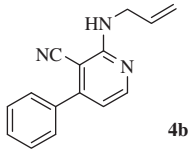
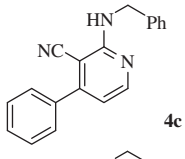
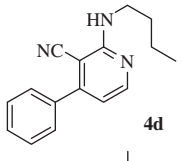
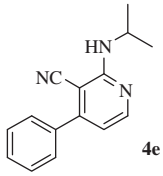
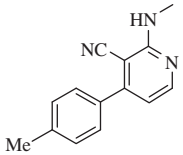
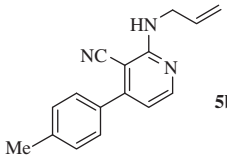
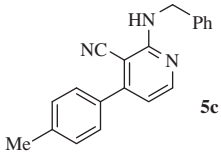
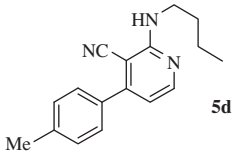
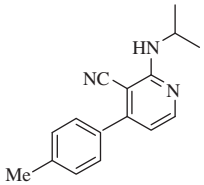
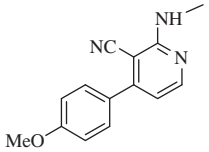
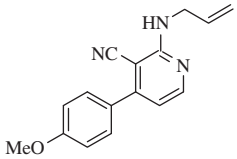
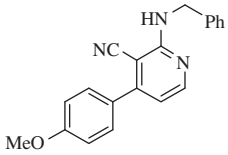
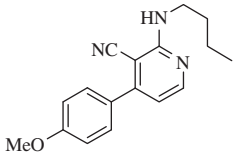
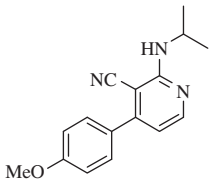
Entry	3	R	Product	Yield[a,b] (%)	
1		Methyl	 **4a**	66	70
2		Allyl	 **4b**	70	75
3	**3a**	Benzyl	 **4c**	73	82
4		*n*-Butyl	 **4d**	64	80
5		Isopropyl	 **4e**	48	50

Table 3 (*continued*)

Entry	3	R	Product	Yield[a,b] (%)	
6		Methyl	 **5a**	71	76
7		Allyl	 **5b**	75	80
8	**3b**	Benzyl	 **5c**	79	83
9		*n*-Butyl	 **5d**	63	70
10		Isopropyl	 **5e**	54	65
11		Methyl	 **6a**	69	72
12		Allyl	 **6b**	73	79
13	**3c**	Benzyl	 **6c**	78	84
14		*n*-Butyl	 **6d**	61	69
15		Isopropyl	 **6e**	52	63

[a] Isolated yield of the reactions carried out under solvent-free conditions with conventional heating.
[b] Isolated yield of reactions carried out under solvent-free conditions under microwave activation.

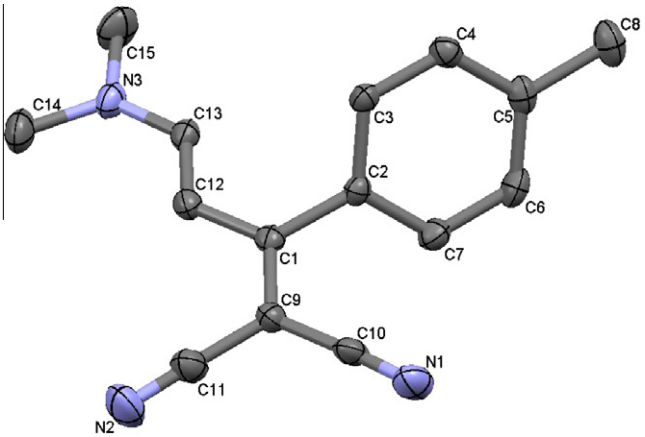


Figure 2. Crystal structure of compound **3b**.

performed.[10] A variation is an azidolysis followed by a reduction in a one pot procedure.[11] Another recent possibility is the use of a variety of substituted formamides.[12] The second very useful pathway involves the building of the pyridine ring via a Michael reaction of a chalcone with malonodinitrile, followed by an addition of amine, cyclization and aromatization.[13] Other neighbouring syntheses have been developed that furnish fused 3-cyano-2-aminopyridines.[7a,c]

In the continuation of our extensive research programme towards performing new approaches to a wide variety of heterocyclic compounds under green conditions,[14,15] we have developed a new synthesis of 2-aminopyridines via enaminonitrile intermediates. These latter are versatile synthetic intermediates in organic chemistry and they have recently received a considerable attention as precursors in the synthesis of heterocycles.[16]

One of the key areas of Green Chemistry is the elimination of solvents in chemical processes or the replacement of hazardous solvents by environmentally benign solvents. In this work we have prepared 4-substituted-3-cyano-2-aminopyridines under solvent-free conditions from different enaminonitriles and primary amines under microwave activation.

2. Results and discussion

2.1. Synthesis of arylethylidenemalononitriles

The starting point of our new synthetic method is the synthesis of arylethylidenemalononitriles **2a–c**. The first step of this synthesis is the Knoevenagel condensation of substituted acetophenones **1a–c** with malononitrile in the presence of ammonium acetate (NH_4OAc) or ammonium carbonate $(NH_4)_2CO_3$ under solvent free conditions (Table 1).

2.2. Synthesis of enaminonitriles

Since Meerwein has discovered *N,N*-dimethylformamide diethylacetal (DMFDEA) in 1961,[18a] formamide acetals have become

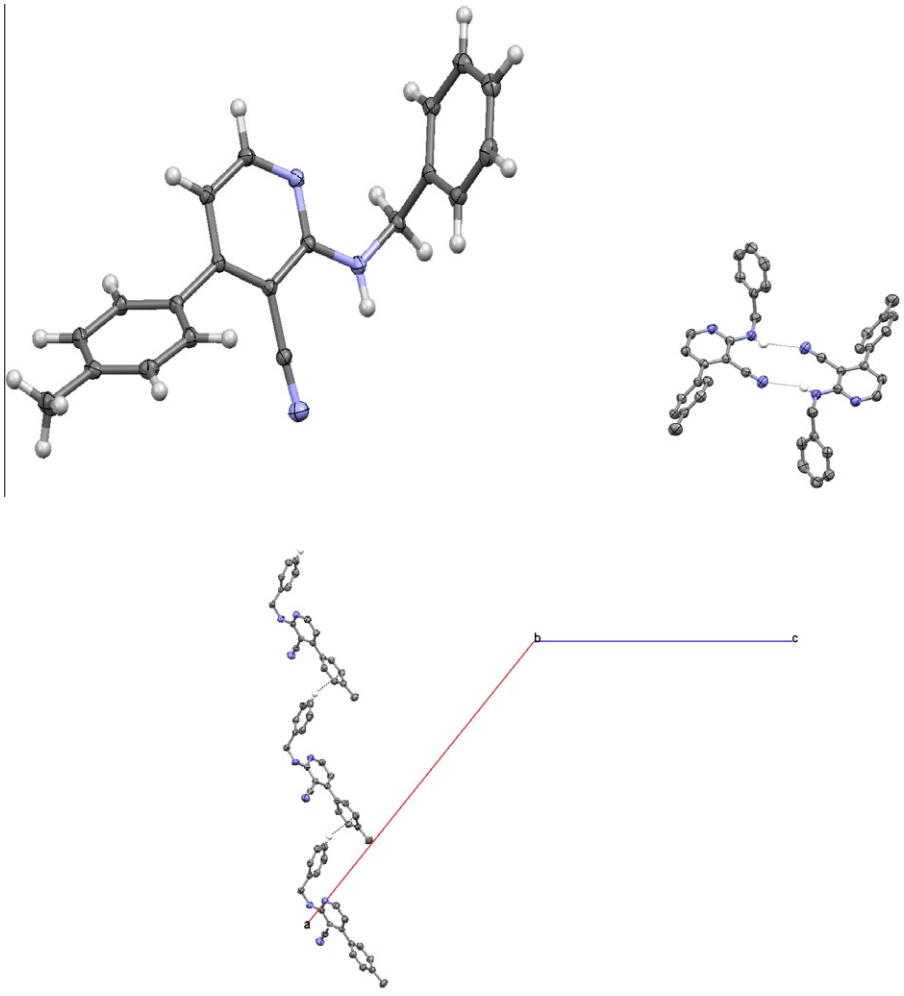


Figure 3. Crystal structure of compound **5c** and crystal packing.

established intermediates in synthetic organic methodology as formylating agents for the preparation of enamines.[18] DMFDMA is a potentially valuable reagent in heterocyclic synthesis[19] and we have used it for the preparation of enaminonitriles. The compounds **3a–c** were prepared by the reaction of arylethylidenemalononitrile derivatives with an equimolar amount of DMFDMA at room temperature for 2 h under solvent free conditions (Table 2).

The structure of the compounds **3a–c** was confirmed by spectral analysis. The IR spectra showed the appearance of a new band near 1600 cm^{-1} of C=C group. For all the compounds, the mass spectra displayed molecular ion peaks in agreement with the expected structures. NMR spectra of **3a–c** were in accordance with the expected structure. Finally the X-ray crystallography of compound **3b** has confirmed the structure of enaminonitrile that is completely planar.

The crystal packing of **3b** is governed by intermolecular C–H...N weak interactions (Fig. 2).

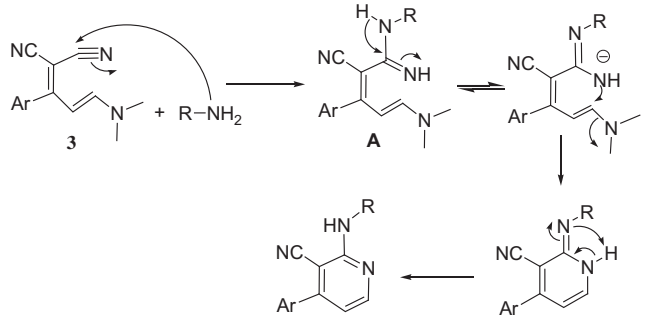
2.3. Synthesis of 2-aminopyridine derivatives

In continuation of our current studies on the chemistry of enaminonitriles and particularly in the application of solvent-free synthesis of nitrogen heterocycles, we have synthesized a new series of substituted 2-aminopyridines **4–6** via the reaction of enaminonitriles **3a–c** with various primary amines (Table 3). We report herein an extension of our investigation on the synthesis of 2-aminopyridines[15d] under solvent-free conditions using both thermal heating and MW irradiation methods and we have compared our results which demonstrate the advantage of MW irradiation method. Heating an equimolar mixture of precursors **3a–c** and different primary amines (methylamine, allylamine, butylamine, isopropylamine and benzylamine) for 3 h provided the compounds **4–6** in the yields of 48–79%[a] (Table 3). On the other hand, compounds **4–6** were obtained in high yields 50–84%[b] from precursors **3a–c** and different amines using MW irradiation for 2 min. It is clear here that both solvent-free methods using conventional heating and MW irradiation are efficient, but because of the short reaction times (few minutes) and higher yields, MW irradiation is preferred (Table 3). All structures are fully characterized by standard spectroscopic methods (^{1}H and ^{13}C NMR, IR MS data).

The 2-aminopyridine structure was confirmed by single crystal X-ray diffraction studies of the compound **5c** (Fig. 3).

Within the crystal, compound **5c** is stabilized by one H-bond between N2–H2...N3 to give a dimer and by a weak intermolecular C–H...π (arene) interaction to form infinite columns of molecules along the axis [101] (Fig. 3).

A possible mechanism for the formation of 4-substituted-3-cyano-2-aminopyridines was described in Scheme 1. First, intermediate **A** was obtained by a condensation reaction between primary amines and one of the nitrile groups of enaminonitrile **3**. **A** then underwent an intramolecular cyclization reaction between the imine anion and the double bond of the enamine. The reaction finished by an aromatization step.



Scheme 1. Formation of 4-substituted-3-cyano-2-aminopyridines **4–6**.

3. Conclusions

In conclusion, we have reported a convenient and green approach for the preparation of novel 4-substituted-3-cyano-2-aminopyridines under solvent-free conditions under heating or under MW activation. This methodology opens a new route for the synthesis of various substituted nitrogen heterocycles because of its ease in execution, rapid access and good yields.

Acknowledgement

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17. *General procedure **1** for the synthesis of arylethylidenemalononitriles **2a–c**:* A mixture of substituted acetophenones **1a–c** (10 mmol), malononitrile

(10 mmol) and ammonium acetate 10 mmol (or ammonium carbonate 10 mmol) was stirred and heated at 100 °C during 3 h. The reaction mixture was cooled down to room temperature, diluted with 30 mL of CH_2Cl_2. The organic layer obtained was washed with water (3 × 20 mL), then with solution of saturated NaCl (10 mL), dried on $MgSO_4$, filtered and evaporated under vacuum. The compounds **2a–c** were obtained as white solids. Compound **2b** 2-(1-*p*-tolylethylidene)malononitrile was obtained according to the procedure **1** using 4-methylacetophenone (10 mmol; 1.34 g), malononitrile (10 mmol; 0.66 g) and ammonium acetate (10 mmol; 0.77 g)[A] or ammonium carbonate (10 mmol, 0.96 g)[B] as a white solid, (1.55 g, 85%[A]), or (1.51 g, 83%[B]) mp 99 °C. NMR ^{1}H ($CDCl_3$) δ: 7.26–7.49 (4H, m, H_{arom}); 2.62 (3H, s, CH_3); 2.44 (3H, s, CH_3); NMR ^{13}C ($CDCl_3$): 175.3, 139.1, 133.0, 129.8, 127.6, 113.2, 113.1, 83.7, 24.1, 21.6. EIMS *m*/*z* (% relative abundance): 183 (M+H, 100), 130 (50), 102 (25). HRMS (ESI-QTOF) Calcd for $C_{12}H_{11}N_2$ M+H 183.0922 Found: 183.0926. IR (neat/cm^{-1}): 2218, 1554.

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20. *General procedure **2** for the synthesis of enaminonitriles **3a–c**:* A mixture of **2a–c** (10 mmol) and *N*,*N*-dimethylformamide dimethyl acetal (10 mmol) was stirred at room temperature without solvent during 2 h. A brown coloration more pronounced over time occurred. The purple solid obtained was washed several times with diethyl ether (3 × 20 mL) and recrystallized from absolute ethanol to provide products **3a–c**. Compound **3b** (*E*)2-(3-(dimethylamino)-1-*p*-tolylallylidene)malononitrile was obtained according to the procedure **2**, using **2b** (10 mmol; 1.82 g) and *N*,*N*-dimethylformamide dimethyl acetal (10 mmol; 1.19 g) as a green solid (2.12 g; 89%), mp 174 °C. NMR ^{1}H ($CDCl_3$) δ: 7.12–7.25 (4H, m, H_{arom}); 6.66 (1H, d, *J* = 12.0 Hz, CH=CH–N); 5.77 (1H, d, *J* = 12.0 Hz, CH=CH–N); 3.03 (6H, s, 2 CH_3); 2.37 (3H, s, CH_3). NMR ^{13}C ($CDCl_3$): 161.4, 156.2, 142.3, 129.4, 128.3, 117.1, 114.4, 114.3, 103.3, 55.4, 44.6, 31.1; EIMS *m*/*z* (% relative abundance): 238 (M+H, 100), 158 (12)). HRMS (ESI-QTOF) Calcd for $C_{15}H_{16}N_3$ M+H 238.1344; Found: 238.1351. IR (neat/cm^{-1}): 2201, 1602, 1504.
21. *General procedure **3** for the synthesis of 4-substituted-3-cyano-2-aminopyridines **4–6**: Method **A**:* A mixture of **3a–b** (10 mmol) and primary amine (10 mmol) was heated for 3 h. After the completion of the reaction (TLC) the residue was purified by column chromatography over silica gel using a mixture of *n*-hexane–EtOAc (8:1) as the eluent. *Method **B**:* A mixture of **3a–b** (2 mmol) and primary amine (2 mmol) was irradiated in a CEM Discover to 120 W during 5 min. After the completion of the reaction (TLC) the residue was purified by column chromatography on silica gel to afford desired compounds **4–6**. Compound **5c** 2-(benzylamino)-4-*p*-tolylnicotinonitrile was obtained according to the procedure **3** with Method **B**, using **3b** (10 mmol; 2.37 g) and benzylamine (10 mmol, 1.07 g) as a solid. (2.48 g; 83%). NMR ^{1}H ($CDCl_3$) δ ppm: 8.15 (1H, d, *J* = 4.6 Hz, CH=CH); 7.11–7.45 (9H, m, H_{arom}); 6.58 (1H, d, *J* = 4.6 Hz, CH=CH); 5.60 (1H, t, *J* = 5.4 Hz, NH); 4.66 (2H, d, *J* = 5.4 Hz, NH–CH_2); 2.34 (3H, s, CH_3). NMR ^{13}C ($CDCl_3$) δ ppm: 164.2; 153.3, 147.4, 139.3, 136.7, 129.2, 128.4, 127.3, 127.5, 126.5, 126.4, 116.3, 105.2, 86.3, 47.7, 24.3. EIMS *m*/*z* (% relative abundance): 300 (M+H, 100), 91 (12), HRMS (ESI-QTOF): Calcd for $C_{20}H_{18}N_3$ M+H 300.1501; Found: 300.1496. IR (neat/cm^{-1}): 3366, 2211, 1573, 1542. Crystal structure of **3b** and **5c**: CCDC 910868 and CCDC 910869.