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A convenient multi-component one-pot synthesis of highly substituted pyridines under solvent-free conditions

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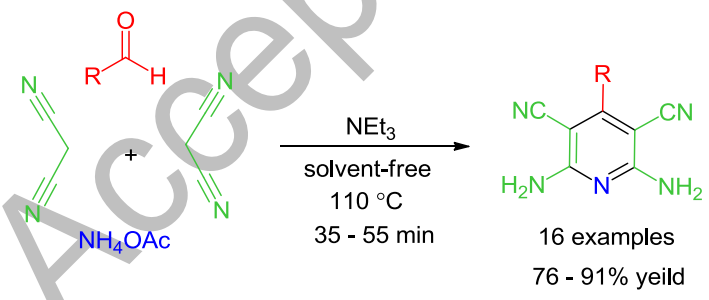
Abstract

Highly substituted pyridine derivatives have been accessed through an efficient one-pot multi-component reaction of aldehydes, malononitrile and ammonium acetate in the presence of triethylamine as a catalyst under solvent-free conditions. This procedure affords the desired products in high purity and has such advantages as short reaction time, excellent yields and simple workup procedure. This procedure affords the desired products in moderate to high yield and has such advantages as short reaction time and simple workup procedure.

Graphical Abstract



KEYWORDS: Pyridine derivatives, Multi-component reaction, One-pot reaction, Solvent-free condition

INTRODUCTION

The development of multi-component reactions (MCRs) has possessed much consideration due to their widely used in the synthesis of biologically active compounds in heterocyclic, medicinal and combinatorial chemistry.[1–3] The attractive heterocyclic scaffolds prepared by MCRs are specifically valuable for the diverse chemical library foundation of drug-like compounds, in which combination of small molecular building blocks in a one-step process would lead to a greater efficiency in generating diversity.[4,5] One-pot multi-component synthetic strategies provides substantial benefits over conventional linear-type preparing products by virtue of their environmental concerns, productivity, atom-economy, facile execution and high yields.[6–9] Production of functionalized nitrogen containing heterocyclic compounds using MCR technique has evolved as an efficient and powerful synthetic tool [10–12]. N-containing heterocycles are very abundant in several natural substances and numerous biologically active molecules. Polysubstituted pyridines have attracted great interest among the all heteroaromatic compounds and as well considered as "privileged medicinal scaffolds" since their structural motifs are found in many pharmaceuticals, synthetic and naturally occurring products.[13–17] In recent years, pyridine-3,5-dicarbonitriles have found several applications in medicinal fields. One of such example is 2-guanadino-3,5-dicyanopyridine derivatives that present cytotoxic property against A-549, P-388, HT-29, MEL-28 tumoral cell lines and also they are very strong inhibitors of histamine release (I in Fig. 1).[18] Some Highly substituted pyridine derivatives are used as electrical materials,[19] non-linear optical materials,[20] as fluorescent liquid crystals[21] and chelating agents in metal ligand chemistry.[22] On the other hand, 2-aminopyiridine

structural motif is existing in several significant biologically active compounds, such as the antitumoral 2-amino-4-aryl-6-dialkylamino-3,5-dicyanopyridines (II in Fig. 1),[23] the antiproliferative 2,6-dibenzylamino-3,5-dicyanopyridines (III in Fig. 1)[24] and the nitric oxide synthase (NOS) inhibitors bearing the 2-amino-4-methylpyridine nucleus (IV in Fig. 1).[25] Also, 2-Aminopyridine derivatives have been examined as suitable chelating ligands for organometallic and catalytic applications and also as starting materials in chemical synthesis.[26] To the best of our knowledge, the reaction of amines with 6-chloro substituent of 2-amino-4-phenyl-pyridine-3,5-dicarbonitrile, [27,28] usage of 3-amino-3-ethoxyacrylonitrile (ethyl 2-cyanoacetimidate)[29,30] and (trimethoxymethyl)benzene[27] with related compounds, and multi-component reaction of aldehydes, malononitrile and amines or ammonia[31–34] are the reported methods to access 2,6-diamino-4-arylpyridine-3,5-dicarbonitriles. Accordingly, discovery and development of an efficient process to obtain new derivatives of these compounds are still desirable for the purposes of drug discovery. With these precedents in mind, along with the understanding the 4*H*-thiopyrans formation mechanism through 2-arylpropane-1,1,3,3-tetracarbonitrile intermediates,[35] we wish to report the one-pot multi-component synthesis of 2,6-diamino-3,5-dicarbonitrile pyridine derivatives from reactions of aldehydes (**1**), malononitrile (**2**) and ammonium acetate (**3**) using triethylamine as a catalyst under solvent-free conditions (Scheme 1).

RESULTS AND DISCUSSION

We commenced our study with the reaction of benzaldehyde **1a** (1 mmol), malononitrile **2** (2 mmol), ammonium acetate **3** (1.5 mmol) and a catalytic amount of triethylamine in

refluxing dichloromethane. It was found that under the described reaction condition, the corresponding product was obtained in low yield (Table 1, entry 1). To find the optimized condition for the reaction process, we resorted to screening of different solvents and catalysts. As illustrated in Table 1, performing reaction in the protic and aprotic solvents did not result in any significant improvement in the product yield (Table 1, entries 1-5).

In recent years, the solvent-free synthesis holds a significant challenge in heterocyclic compounds preparation. In this vein, we next turn our attention to the solvent-free condition with different catalysts. It was evidence that this technique at 90 °C gave access to the pyridine derivatives with excellent yields and short reaction time. Elevating the reaction temperature to 110 °C further improved the reaction yield and shortened the reaction time (Table 1, entries 6-8). With this reaction conditions in hand, several other catalysts were tested and superior result was achieved in the presence of triethylamine as catalyst (Table 1, entries 9-12).

To demonstrate the generality of this reaction, we subjected a variety of aromatic and heteroaromatic aldehydes to the optimized reaction conditions. As presented in Table 2, both electron-rich and electron-deficient aromatic aldehydes resulted pyridine derivatives **4a-p** in good yields. The substituents on aromatic aldehydes have not distinct effect on products yields. The conversion of reaction is approximately 100% but the difference on isolated products yields take places on workup and separation step of completed reaction. The aliphatic aldehydes did not afford any products, may be due to absence of conjugation in their intermediates that cause rising the transition state energy. The

structures of these products (**4a-p**) as shown in Fig. 2, were characterized by ^{1}H-NMR, ^{13}C-NMR and FT-IR spectroscopy as well as melting point and elemental analysis.

We have surmised a possible mechanism for the formation of pyridine derivative **4a** in Scheme 2. Our proposed mechanism initiates with the standard Knoevenagel condensation of benzaldehyde **1a** and malononitrile **2** in the presence of triethylamine which would lead to formation of benzylidenemalononitrile **A** as an intermediate. Michael addition of the second equivalent of the malononitrile **2** would furnish the adduct **B** with tautomeric form **C**.[36] Next, a nucleophilic attack of ammonium acetate **3** on a cyanide group of **C** afford the intermediate **D**. Cycloaddition of **D** would yield to the structure **E** that is in equilibration with **F** tautomer, this tautomer would subsequently undergoes dehydrogenation to yield the product **4a**.

CONCLUSION

In summary, we have achieved an efficient synthesis of highly substituted pyridine derivatives by a one-pot, multi-component reaction of aromatic aldehydes, malononitrile and ammonium acetate in the presence of triethylamine as a catalyst under solvent-free conditions. This procedure offers several notable advantages, including the use of a low-cost and readily available catalyst, simple workup procedure, short reaction time and minimal environmental impact due to solvent-free conditions. These highly substituted pyridine molecules could serve as key chemotypes for molecular design based research.

EXPERIMENTAL

General Information

All commercially available chemicals were obtained from Merck and Fluka companies, and used without further purification. Melting points were measured on an Electrothermal 9100 apparatus without correction. FT-IR spectra were recorded on a Unicom Galaxy Series FT-IR 5000 spectrophotometer using KBr pellets and are expressed in cm^{-1}. $^{1}H/^{13}C$ NMR spectra were recorded on Bruker avance 400 MHz and Bruker AMX 400 MHz spectrometer at 400/100 MHz, respectively. Coupling constants, *J*, were reported in hertz unit (Hz). Elemental analyses were performed by Vario EL equipment at Arak University. Thin layer chromatography (TLC) on commercial aluminum-backed plates of silica gel, 60 F254 was used to monitor the progress of reactions.

General Procedure For Preparation Of Highly Substituted Pyridine Derivative (4a-P)

A mixture of aldehyde (1 mmol), malononitrile (2 mmol), ammonium acetate (1.5 mmol) and a catalytic amount of triethylamine were heated with stirring at 110 °C for appropriate times. The progress of the reaction was monitored by TLC (EtOAc/n-hexane, 2:1). The reaction mixture was allowed to cool to room temperature, EtOH (95%, 5 mL) and then water (5 mL) was added. The precipitate was filtered off, and the pure product was obtained by further recrystallization in ethanol. This procedure was followed for the synthesis of products **4a-p** (Table 2).

2,6-Diamino-4-(Thiophen-2-Yl)Pyridine-3,5-Dicarbonitrile (4p)

Light brown powder; m.p. > 300 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88-7.87 (m, 1H, ArH), 7.52-7.50 (m, 1H, ArH), 7.23 (m, 5H, 2 NH_2 and 1H, ArH) ppm; ^{13}C NMR (100

MHz, DMSO-d_6) δ 161.5, 159.8, 134.2, 130.8, 130.2, 128.2, 116.9, 80.1 ppm; Anal. Calcd. For $C_{11}H_7N_5S$ (241.27): C, 54.76; H, 2.92; N, 29.03; S, 13.29% found: C, 54.78; H, 2.85; N, 29.07; S, 13.26%. IR (KBr, cm^{-1}): 3481, 3425, 3364, 3215, 3151, 2926, 2204, 1676, 1624, 1568, 1539, 1450, 1248, 1035, 773, 707.

SUPPORTING INFORMATION

Experimental detail, ^{1}H NMR and ^{13}C NMR spectra. This material can be found via the "Supplementary Content" section of this article's webpage.

ACKNOWLEDGEMENT

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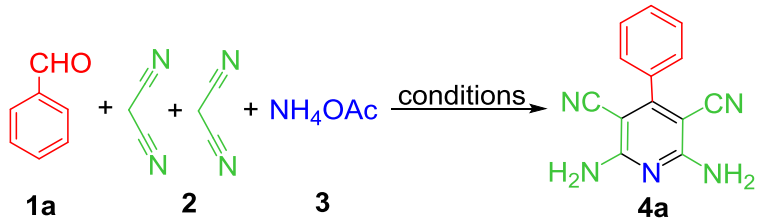
Table 1. Optimization of reaction conditions.



1a 2 3 4a

Entry	Solvent	Catalyst	Temp.	Time	Yield (%) [a]
1	CH_2Cl_2	NEt_3	reflux	4 h	38
2	CH_3CN	NEt_3	reflux	4 h	42
3	THF	NEt_3	reflux	4 h	37
4	EtOH	NEt_3	reflux	4 h	52
5	H_2O	NEt_3	reflux	4 h	45
6	solvent-free	NEt_3	90 °C	1 h	74
7	**solvent-free**	**NEt_3**	**110 °C**	**40 min**	**87**
8	solvent-free	NEt_3	130 °C	55 min	77
9	solvent-free	DABCO	110 °C	1 h	72
10	solvent-free	pyridine	110 °C	1 h	68
11	solvent-free	-	110 °C	1 h	66
12	solvent-free	p-TSA	110 °C	1 h	73

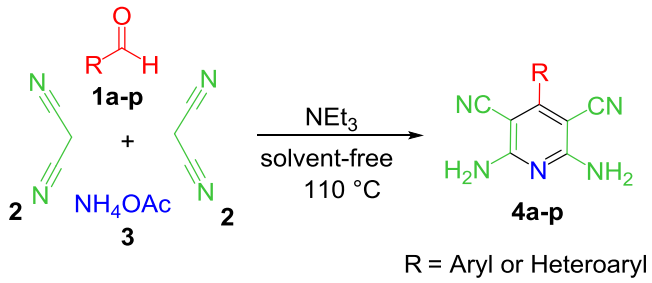
[a] isolated yields.

Table 2. Multi-component synthesis of pyridine derivatives **4a-p**.

Entry	**Aldehyde**	**Product**	**Time (min)**	**Yield (%)[a]**
1	Benzaldehyde	**4a**	40	87
2	4-Methylbenzaldehyde	**4b**	55	85
3	4-Hydroxybenzaldehyde	**4c**	45	84
4	4-Methoxylbenzaldehyde	**4d**	55	84
5	4-Fluorobenzaldehyde	**4e**	35	87
6	4-Chlorobenzaldehyde	**4f**	35	91
7	4-Bromobenzaldehyde	**4g**	40	88
8	3-Hydroxybenzaldehyde	**4h**	55	86
9	3-Nitrobenzaldehyde	**4i**	35	83
10	2,4-dichlorobenzaldehyde	**4j**	40	81
11	2-Chlorobenzaldehyde	**4k**	40	83
12	Terephthalaldehyde	**4l**	45	80
13	Isophthalaldehyde	**4m**	55	76
14	3-Pyridylaldehyde	**4n**	40	84
15	2-Pyridylaldehyde	**4o**	45	80
16	2-Thiophenealdehyde	**4p**	40	86

[a] Isolated yields

Scheme 1. Multi-component synthesis of pyridine derivatives.



Scheme 2. Suggested mechanism for the synthesis of compound **4a**.

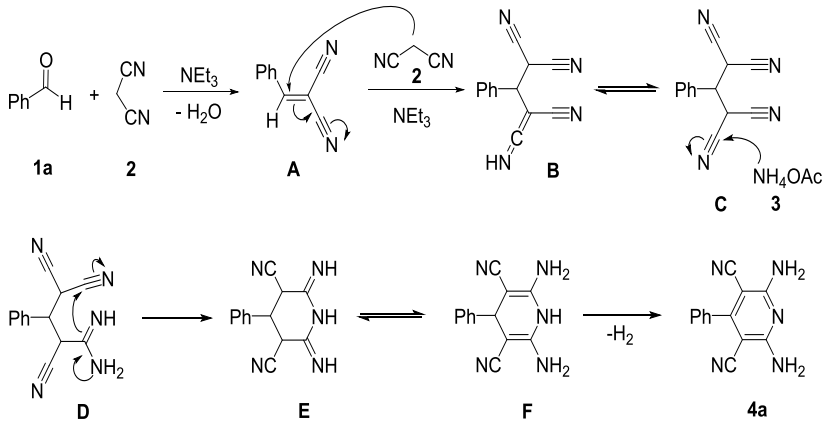


Figure 1. Examples of biologically active pyridine derivatives.

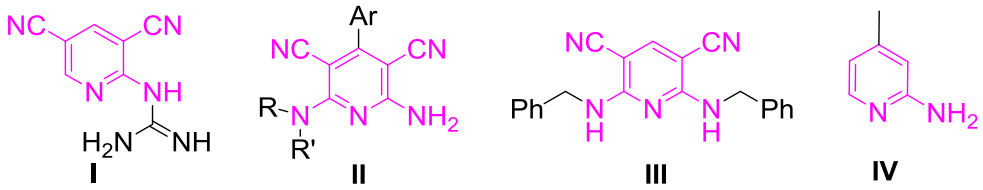


Figure 2. Products **4a-p**.