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A concise and versatile synthesis of 2-amino-3-cyanopyridine derivatives in 2,2,2-trifluoroethanol

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ABSTRACT

Trifluoroethanol (TFE) is found to be an efficient and recyclable medium in promoting one-pot, four-component coupling reactions of aldehydes, ketones, malononitrile, and ammonium acetate to afford the corresponding 2-amino-3-cyanopyridine derivatives in high yields. The solvent (TFE) can be readily separated from reaction products and recovered in excellent purity for direct reuse.

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1. Introduction

The pyridine substructure is one of the most prevalent heterocycles found in natural products, pharmaceuticals, and functional materials [1–4]. Among these compounds, 2-amino-3-cyanopyridine derivatives have been reported to possess antiviral, antibacterial, and fungicidal activities [5–8]. 2-Amino-3-cyanopyridine derivatives were also reported as novel IKK-b inhibitors [9], A_{2A} adenosine receptor antagonists [10], potent inhibitor of HIV-1 integrase [11], and so on. 2-Amino-3-cyanopyridines are important and useful intermediates in preparing variety of heterocyclic compounds [12,13]. Therefore, the synthesis of these compounds is of great significance. A number of reports on this topic have appeared in the literature [14–17]. However, some of these procedures have certain limitations such as harsh reaction conditions, long reaction time, toxic benzene as solvent, high temperature or microwave assistance, tedious work-up, and low yields. Murata et al. have reported the synthesis of 2-amino-6-aryl-3-cyano-4-piperidinylpyridine derivatives through four-component coupling reaction of acetophenone, *N*-Boc-formylpiperidine, malononitrile and ammonium acetate in conventional heating mode [18]. Nevertheless, the protocol gives comparatively lower yields and longer reaction time. Very recently, Wang et al. reported a one-pot synthesis of 2-amino-3-cyanopyridines using ytterbium perfluorooctanoate in ethanol under reflux condition [19]. However, the development of novel methods for the synthesis of 2-amino-3-cyanopyridines is of great importance because of their potential biological and pharmaceutical activities. Over the last years, fluorinated alcohols have received recognition as green media in organic synthesis, because they display many advantages over common organic solvents, such as high hydrogen bonding donor ability, nonvolatility, nonflammability, polarity, high ionizing power, and low nucleophilicity [20]. A more attractive feature of fluorinated alcohols is the possibility to recycle them and to easily recover the product (by simple distillation). Fluorinated alcohols are attracting increasing attention as alternative solvents for a wide range of catalytic and organic reactions [21–34]. In continuation of our interest using of fluorinated solvents as efficient medium in various organic transformations [35–40], we turned our attention toward the four-component condensation of aldehydes, ketones, malononitrile, and ammonium acetate in TFE as solvent. Herein, we describe a novel, efficient, and green procedure for the synthesis of 2-amino-3-cyanopyridine derivatives **5** via the four-component condensation (Scheme 1).

2. Results and discussion

Initially, we carried out the four-component condensation of benzaldehyde (1 mmol), acetophenone (1 mmol), malononitrile (1 mmol), and ammonium acetate (1.5 mmol) in trifluoroethanol (2 mL) at refluxing temperature for 6 h. At the beginning of the reaction, the reagents itself were dissolved completely in the medium to form a homogeneous mixture (Fig. 1a), but near the completion of the reaction, the system became a suspension, and the product precipitated at the end of the reaction (Fig. 1b).

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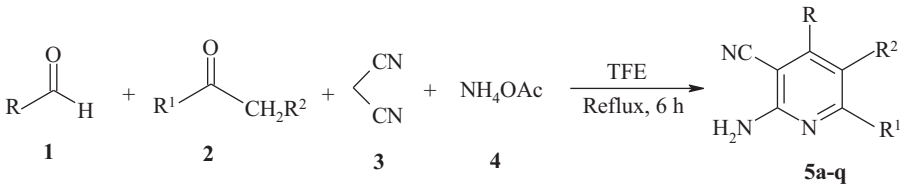


Scheme 1. One-pot four component condensation of aldehydes, ketones, malononitrile, and ammonium acetate in TFE.

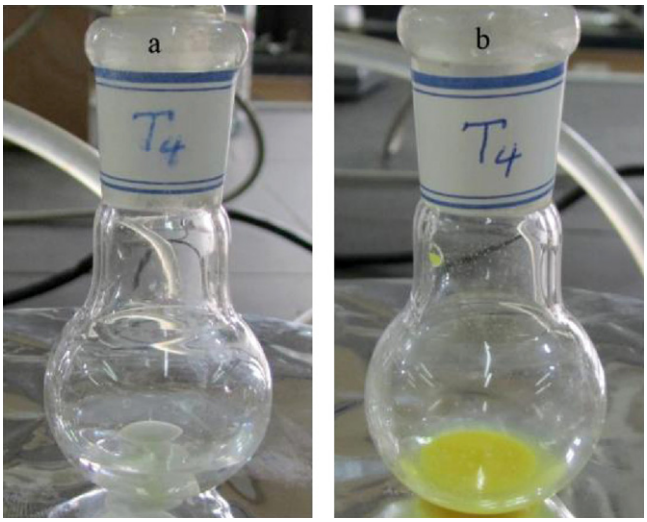
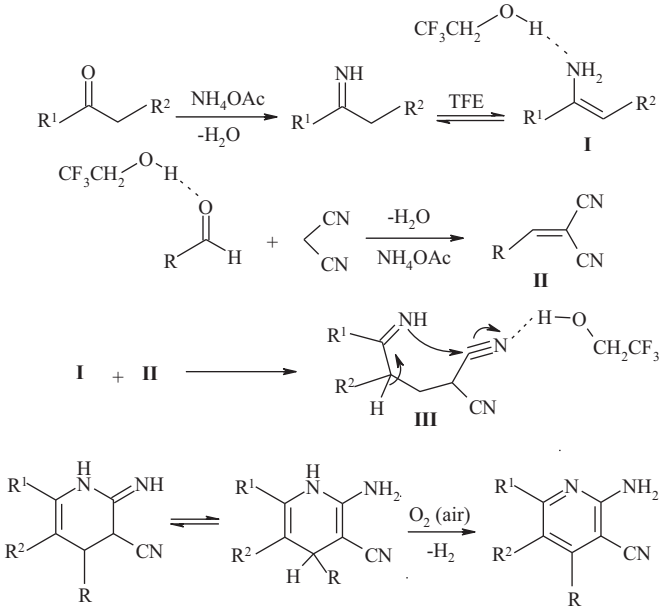


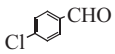
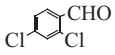
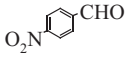
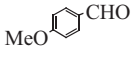
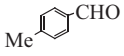
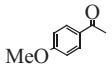
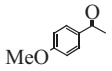
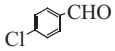
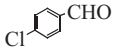
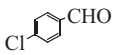
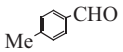
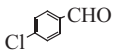
Fig. 1. (a) Homogeneous mixture during the reaction, and (b) at the end of the reaction; the product has precipitated.

The products were isolated after selective evaporation of the TFE and were purified by recrystallization from tetrahydrofuran to afford the pure product. The products 2-amino-3-cyanopyridine derivatives **5a**, shown in Scheme 1 and confirmed by NMR measurements, were obtained in good yield (90%). The scope and generality of this four-component condensation was examined in more detail. Both the electron-rich and -deficient aldehydes worked well leading to good yields of products **5**. Aromatic aldehydes with several functionalities such as Cl, Me, OMe, and NO_2 were found to be compatible under the optimized reaction condition. The electronic effect seemed to have a slight influence on the reaction since either the electron-withdrawing or the electron-donating groups on the different aromatic ring resulted in the hardly discriminate yields. We also examined this four-component condensation with 2-substituted benzaldehyde, finding that the reaction time was longer and yields were somewhat lower than other aldehydes which were probably attributed to the steric hindrance (Table 1, entries 3 and 4). To expand the scope of ketone substrates, aromatic ketones with substituents or not, as well as aliphatic and cyclic ketones, were applied to this protocol.



Scheme 2. Proposed mechanism for the synthesis of 2-amino-3-cyanopyridines.

Table 1
Synthesis of 2-amino-3-cyanopyridine in TFE.

Entry	Ketones	Aldehydes	Product	Yield %	Refs.
1			**5a**	90	[15]
2			**5b**	90	[19]
3			**5c**	80	[19]
4			**5d**	82	[17]
5			**5e**	88	[19]
6			**5f**	90	[17]
7			**5g**	90	[19]
8			**5h**	95	[19]
9			**5i**	95	[17]
10			**5j**	85	[14]
11			**5k**	85	[14]
12			**5l**	90	[19]
13			**5m**	95	[17]
14			**5n**	85	[17]
15			**5o**	80	[19]
16			**5p**	80	[19]
17			**5q**	85	[19]

In all cases, the desired reactions took place successfully to afford a series of 2-amino-3-cyanopyridine derivatives in moderate to good yields. The results are summarized in Table 1.

Satisfactorily, the reactions displayed high functional group tolerance and afforded the corresponding pyridines with great efficiency. The structure of the products (**5a–q**) was established from their IR spectral data and comparison of their melting points with those of authentic samples. Also, the structure of some products was confirmed by ^{1}H NMR and ^{13}C NMR spectral data. Interestingly, the reaction did not proceed to completion when either ethanol or water alone was used as solvent, even at reflux conditions. After the reaction, TFE can be easily separated (by distillation) and reused without decrease in its activity. For example, the reaction of benzaldehyde, acetophenone, malononitrile, and ammonium acetate (Table 1, entry 1) afforded the corresponding 2-amino-3-cyanopyridine derivative in 90%, 90%, 88%, 88% and 85% isolated yield over five cycles. When we carried out the reaction in TFE at room temperature, the reaction proceeded very slowly to give very poor yields. A plausible mechanism for the formation of 2-amino-3-cyanopyridine is shown in Scheme 2.

In this process, TFE act as Bronsted acid [41] and plays a significant role in increasing the electrophilic character of the electrophiles. The hydrogen bond donor ability might not be important in this case. Actually the hydrogen bond donating ability of these solvents drops as temperature rises owing to the fact that hydrogen-bond formation is exothermic [42,43]. The polar transition state of the reaction could be stabilized well by the high ionizing solvent TFE. The reaction may proceed via enamine **I**, which formed from ketone and ammonium acetate, and then activated by TFE, reacts with alkylidene malononitrile **II** (from condensation of aldehyde with malononitrile) to give intermediate **III**, followed by cycloaddition, isomerization, and aromatization to afford the final product. It may be assumed that the water-exclusion of TFE may favor both imine and alkylidene malononitrile formation.

3. Conclusion

In conclusion, an extremely efficient and green process has been developed for the synthesis of 2-amino-3-cyanopyridine derivatives via one-pot condensation of aldehydes, ketones, malononitrile, and ammonium acetate in TFE without using any catalyst or additives. This method is bestowed with merits like avoiding the use of any base, metal or Lewis acid catalyst, ease of product isolation/purification by non-aqueous work-up, high chemoselectivity, no side reaction, low costs and simplicity in process and handling and environmentally benign nature. These advantages of TFE made this process very useful for the synthesis of 2-amino-3-cyanopyridine derivatives. Further exploration of the scope of fluorinated solvent to other type of reactions is underway.

4. Experimental

Typical experimental procedure. A mixture of aldehyde (1 mmol), ketone (1 mmol), malononitrile (1 mmol), and ammonium acetate (1.5 mmol) were stirred in one-pot in TFE (2 mL) at refluxing temperature for the stipulated time. The progress of the reaction is monitored by TLC. After completion of the reaction, the corresponding solid product **5** was obtained through simple filtering, and recrystallized from tetrahydrofuran affording the highly pure 2-amino-3-cyanopyridine derivatives. The physical data (mp, IR, NMR) of known compounds were found to be identical with those reported in the literature. Spectroscopic data for selected examples are shown below.

2-Amino-4,6-diphenyl-nicotinonitrile (**5a**). mp: 186–187 °C. IR (KBr): 3461, 3301, 3176, 2202, 1637, 1546, 1257 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.35 (br s, 2H, NH_2), 7.21 (s, 1H), 7.46–7.52 (m, 6H), 7.64 (d, J = 8.0 Hz, 2H), 8.00 (d, J = 4.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 91.2, 116.5, 121.3, 125.2, 127.1, 128.1, 129.3, 130.1, 131.2, 133.3, 157.5, 165.5, 164.7, 166.2.

2-Amino-4-(4-chlorophenyl)-6-phenylnicotinonitrile (**5b**). mp: 233–235 °C. IR (KBr): 3496, 3305, 3183, 2204, 1641, 1606, 1257 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.37 (br s, 2H, NH_2), 7.18 (s, 1H), 7.48–7.60 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 93.2, 116.3, 119.3, 125.2, 126.3, 127.5, 127.8, 132.2, 133.4, 134.5, 135.4, 154.3, 164.5, 166.2.

2-Amino-4-(2-chlorophenyl)-6-phenylnicotinonitrile (**5c**). mp: 193–196 °C. IR (KBr): 3480, 3336, 3180, 2221, 1621, 1562, 1241 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.48 (br s, 2H, NH_2), 7.07 (s, 1H), 7.48–7.60 (m, 7H), 7.92–7.94 (m, 2H). ^{13}C NMR

(100 MHz, $CDCl_3$): δ = 92.1, 115.6, 120.1, 124.3, 125.6, 126.1, 128.1, 129.8, 133.8, 134.1, 135.6, 136.5, 138.5, 155.3, 160.2, 166.1.

*2-Amino-6-phenyl-4-p-tolylnicotinonitrile (***5g***).* mp: 175–176 °C. IR (KBr): 3463, 3293, 3168, 2202, 1631, 1575, 1257 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.43 (s, 3H), 5.35 (br s, 2H, NH_2), 7.21 (s, 1H), 7.32–7.99 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.3, 91.2, 116.5, 120.1, 125.2, 125.7, 128.1, 129.2, 133.5, 133.8, 134.5, 136.5, 156.8, 162.3, 166.5.

*2-Amino-4-(4-chlorophenyl)-6-methylnicotinonitrile (***5m***).* mp: 255–256 °C. IR (KBr): 3479, 3401, 3318, 3168, 2210, 1645, 1573, 1251 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.46 (s, 3H), 5.29 (br s, 2H, NH_2), 6.63 (s, 1H), 7.47 (d, J = 8.5 Hz, 2H), 7.50 (d, J = 8.5 Hz, 2H). ^1H NMR (400 MHz, $CDCl_3$): δ = 21.2, 91.3, 116.2, 120.4, 126.8, 130.1, 133.2, 141.3, 157.6, 164.2, 166.2.

*2-Amino-4-phenyl-5,6,7,8-tetrahydroquinoline-3-carbonitrile (***5p***).* mp: 230–233 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.65–1.69 (m, 2H), 1.82–1.88 (m, 2H), 2.35 (t, J = 6.4 HZ, 2H), 2.82 (t, J = 6.4 Hz, 2H), 5.20 (br s, 2H, NH_2), 7.28–7.50 (m, 5H). ^1H NMR (400 MHz, $CDCl_3$): δ = 22.5, 22.8, 26.5, 33.2, 90.4, 116.7, 120.7, 128.5, 128.8, 136.5, 154.5, 157.1, 161.43.

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