An Efficient Procedure for the Synthesis of Substituted Pyridines Using $KF{\cdot}Al_2O_3$

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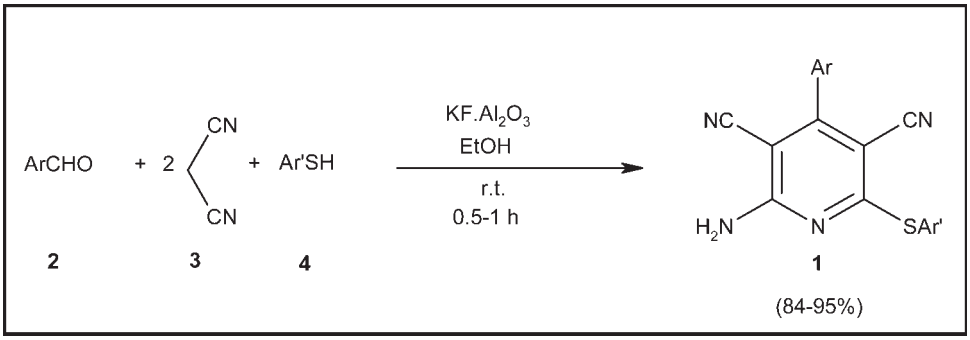

Three-component coupling of aldehydes, malononitrile, and thiophenols has efficiently been carried out at room temperature using potassium fluoride on alumina ($KF{\cdot}Al_2O_3$) as a catalyst to furnish highly substituted pyridines in high yields.

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INTRODUCTION

Pyridine moiety in highly substituted form is frequently observed in various bioactive compounds [1–3]. This ring exists in both naturally occurring and synthetic drugs. The substituted pyridines of the common structure **1** possess significant antibacterial and anti-infective properties [4] and are useful for the development of other bioactive agents [5]. Thus, a number of methods for the synthesis of substituted pyridines have been reported [6–14]. One of the convenient methods involving three-component coupling of aldehydes, malononitrile, and thiols using bases, such as 1,4-diaza bicyclo [2,2,2,] octane and Et_3N, in ethanol under reflux led to the direct formation of **1** [8]. However, the yields of the products are unsatisfactory (20–48%), and the reactions are conducted at high temperature. The yields were improved by performing the reaction in the presence of an oxidizing agent [9]. Very recently, the similar method using ionic liquid has also been reported [12].

RESULTS AND DISCUSSION

In continuation of our work [15–17] on the development of useful synthetic methodologies, we have observed that the condensation of aldehydes, malononitrile, and thiols can efficiently be accomplished using potassium fluoride on alumina ($KF{\cdot}Al_2O_3$) to produce the substituted pyridines at room temperature. (Scheme 1).

A series of 2-amino-4-aryl-3,5-dicyano-6-sulfanyl pyridines have been prepared from various aromatic aldehydes following the aforementioned procedure (Table 1). The aldehydes containing both electron-donating and electron-withdrawing groups underwent the conversion smoothly. Different functionalities, such as hydroxyl, ether, halogen, and nitro, remained unchanged. The conversion was complete within 0.5–1 h and the substituted pyridines were formed in high yields (84–95%). However, with aliphatic aldehydes and thiols, the reaction was not successful. The structures of the products were established from their spectral (^{1}H NMR, IR, and MS) data.

$KF{\cdot}Al_2O_3$ has recently emerged as a valuable solid-phase catalyst for various organic transformations [18,19]. It possesses interesting catalytic activity. It can easily be handled and removed from the reaction mixture. It has been used here for the first time for the

Scheme 1

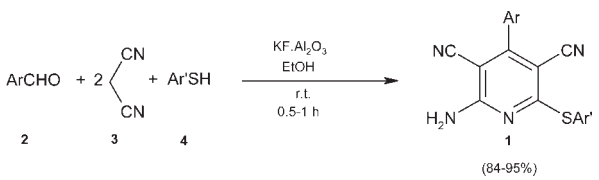


Table 1

Synthesis of substituted pyridines using $KF{\cdot}Al_2O_3$.[a]

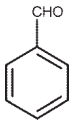
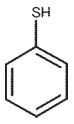
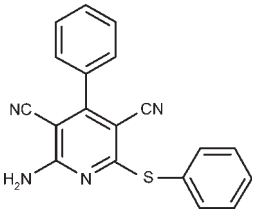
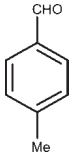
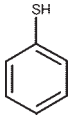
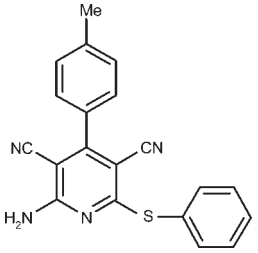
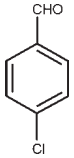
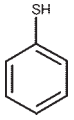
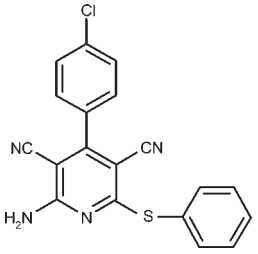
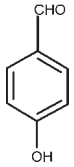
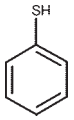
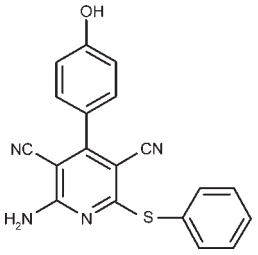
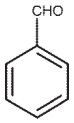
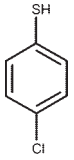
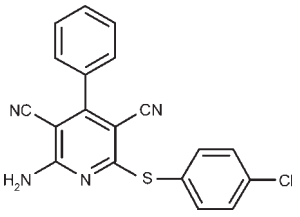
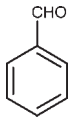
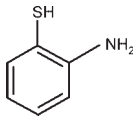
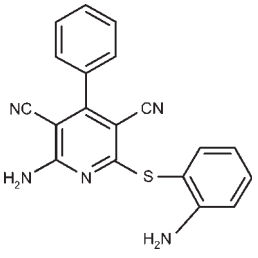
Entry	Aldehyde (**2**)	Thiol (**3**)	Product (**1**)	Time (min)	Isolated yield (%)	Mp (°C) [reference]
a				30	87	216–218 [11]
b				40	90	208–211 [11]
c				35	92	222–224 [11]
d				40	88	315–316 [11]
e				30	90	228–230 [11]
f				35	85	224–225 [11]

Table 1
(*Continued*)

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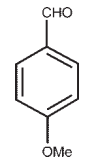
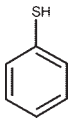
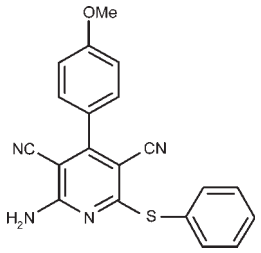
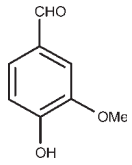
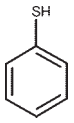
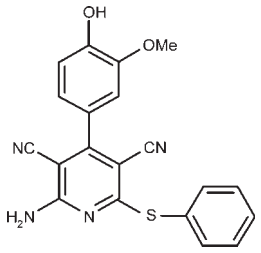
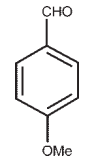
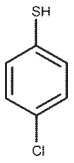
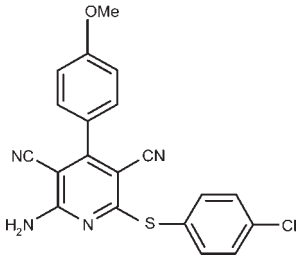
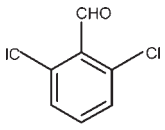
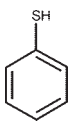
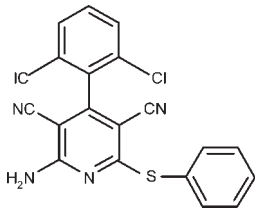
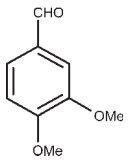
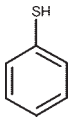
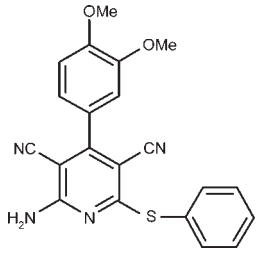
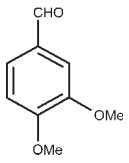
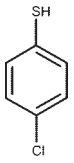
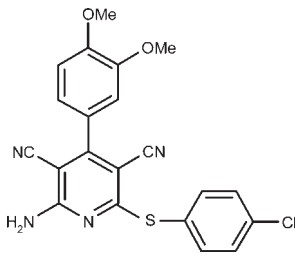
g				50	89	238–240 [11]
h				30	92	218–220 [11]
i				40	87	252–254
j				30	95	319–320 [11]
k				35	91	261–263 [10]
l				40	95	273–275

Table 1
(*Continued*)

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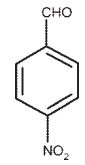
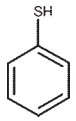
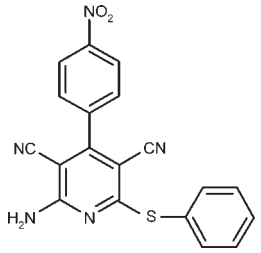
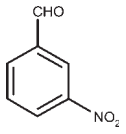
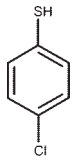
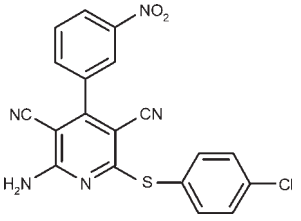
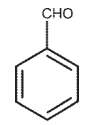
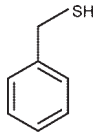
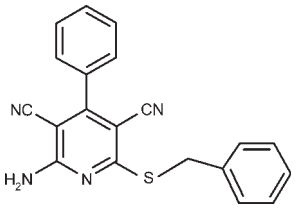
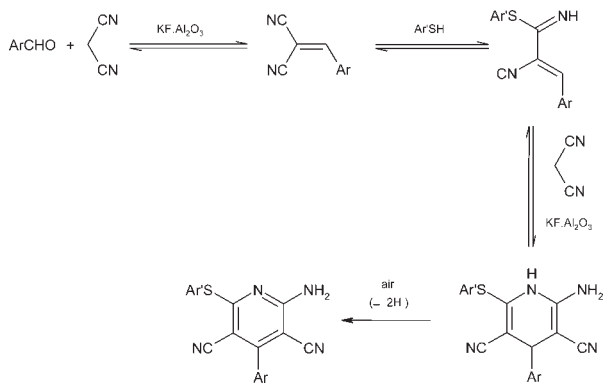
m				55	84	287–289 [11]
n				60	85	279–281
o				45	90	193–195 [11]

[a] The structures of the products were settled from their spectral (^{1}H NMR, IR, and MS) values.

preparation of substituted pyridines. In the absence of this catalyst, the reaction did not proceed.

The formation of substituted pyridines in impressive yields in the present reaction can be explained by a mechanism (Scheme 2) related to that described by Ranu *et al*. [12] for their high-yielding synthesis of pyridines through a similar reaction in the presence of a basic ionic liquid. In both the cases, air played the role of an oxidant under the reaction conditions, and no additional oxidant was required [9,11,12].

Scheme 2



In conclusion, we have improved the process of synthesis of the substituted pyridines from aldehydes, malononitrile, and thiols using $KF{\cdot}Al_2O_3$ at room temperature. The use of (i) inexpensive solid-phase catalyst, (ii) mild reaction conditions, (iii) impressive yields, and (iv) operational simplicity are the notable advantages of the present procedure.

General Procedure for the Synthesis of Substituted Pyridines. To a mixture of an aldehyde (0.5 mmol), malononitrile (1 mmol) and thiophenol (0.5 mmol) dissolved in EtOH (5 mL) $KF{\cdot}Al_2O_3$ (prepared by reported method [15]) (10 mol%) was added, and the mixture was stirred at room temperature. The reaction was monitored by thin layer chromatography. After completion, the mixture was filtered, and the filtrate was concentrated. The residue was purified by column chromatography (silica gel, hexane-EtOAc) to obtain pure pyridine derivative.

The spectral (IR, ^{1}H NMR, and MS) data of the unknown products are given.

1i: IR (KBr): 3427, 2209, 1614, 1543 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ 7.60–7.41 (6H, m), 7.04 (2H, d, J = 8.0 Hz), 6.89 (2H, brs), 3.90 (3H, s); FABMS: m/z 415, 417 $[M+Na]^+$. Anal. Calcd. for $C_{20}H_{13}ClN_4OS$: C 61.14, H 3.31, N 14.26; Found: C 61.82, H 3.43, N 14.38.

1l: IR (KBr): 3425, 2212, 1621, 1546 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ 7.56 (2H, d, J = 8.0 Hz), 7.42 (2H, d, J = 8.0 Hz), 7.15 (1H, dd, J = 8.0, 2.0 Hz), 7.06 (1H, d, J = 2.0 Hz), 7.02 (1H, d, J = 8.0 Hz), 6.79 (2H, brs), 3.96 (3H, s); 3.92 (3H, s); FABMS: m/z 445, 447 $[M+Na]^+$. Anal. Calcd. for $C_{21}H_{15}ClN_4O_2S$: C 59.64, H 3.55, N 13.25; Found: C 59.84, H 3.67, N 13.13.

1n: IR (KBr): 3417, 2214, 1638, 1551 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ 8.50–8.36 (2H, m), 7.95–7.80 (2H, m), 7.54 (2H, d, J = 8.0 Hz), 7.45 (2H, d, J = 8.0 Hz), 7.28 (2H, brs); FABMS: m/z 430, 432 $[M+Na.]^+$. Anal. Calcd. for $C_{19}H_{10}ClN_5O_2S$: C 55.95, H 2.45, N 17.17; Found: C 56.32, H 2.57, N 17.28.

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