Facile and Rapid Access to Poly Functionalized Pyridine Derivatives

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An efficient and greener protocol for the synthesis of poly functionalized pyridines using tetra-*n*-butyl ammonium fluoride (TBAF) in water is established. Remarkable advantages of the present synthetic strategy over the others are shorter reaction times, higher isolated yields, reuse of catalytic system, simple work-up procedure and more especially its applicability to heteryl and aliphatic aldehydes.

Keywords green chemistry, pyridines, tetra-*n*-butyl ammonium fluoride (TBAF), water chemistry

Introduction

For chemists, "water" is one of the sustainable gifts from nature, as it can be a surrogate for organic solvents. In recent times, reactions of water-insoluble organic compounds that take place in aqueous suspensions are gaining immense interest because of their high efficiency and straightforward synthetic protocols.[1] Innovative studies of organic reactions in aqueous media demonstrated that Diels-Alder reactions[1b,1f,2,3] and Claisen rearrangements[4] of hydrophobic reactants are accelerated in aqueous solutions. In addition to these findings, aqueous environments result in reactivity and selectivity that are unique from reactions in hazardous organic solvents, and this has been reflected in the development of many versatile and innocuous organic reactions.[5] Consequently, more efficient syntheses of biologically active compounds in aqueous media are highly desirable.

Pyridine and its derivatives are important motifs present in a great number of pharmaceuticals and natural products.[6-14] The unique structural array and highly pronounced biological and physiological activities[6-14] displayed by the class of pyridine moieties have made them attractive synthetic targets. Specifically, 2-amino-3,5-dicarbonitrile-6-thio-pyridines are considered to be an important medicinal scaffolds[7-14] as they are endowed with PrPSc accumulation in scrapie-infected mouse neuroblastoma cells (ScN2a),[7a] IKK-2 for treating HBV infection[7b] and modulate androgen receptor function.[7c] The current interest in the synthesis of polysubstituted pyridine derivatives, especially bearing nitrile functionality, arises from their potential applications as potassium channel openers in the treatment of urinary incontinence,[8] and their often use as anti-prion,[7a,9] anti-hepatitis B virus,[7b] anti-bacterial,[10] and anti-cancer agents.[11] Therefore, the interest of organic chemists in the synthesis or structure modifications of pyridine derivatives remains high.

The most common approach for the synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines involves the three component condensation of aldehyde, malononitrile and thiol. Various basic[9a,14] as well as acid[15] catalysts have been utilized for this cyclocondensation reaction. Moreover, silica nanoparticles,[16a] and nanocrystaline magnesium oxide[16b] were also found to catalyze the synthesis of polysubstituted pyridines. However, some of these protocols have significant drawbacks such as formation of inevitable side products, prolonged reaction times, lower yields, harsh reaction conditions, tedious work-up, and the use of expensive and environmentally toxic catalysts as well as solvents. Thus, organic chemists have challenge to overwhelm these shortcomings and develop efficient methods for this nucleus using milder, non-hazardous and inexpensive reagents. In this endeavor, we wish to disclose task specific role of TBAF in water for the synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines.

Quaternary ammonium fluorides, particularly tetraalkyl ammonium fluorides, have been widely recognized as a convenient, organic-soluble source of naked fluoride ion. Their utility in modern organic synthesis has been well documented for a range of fluoride-assisted reactions,[17] fluorination,[18] deprotection of silyl groups[19] and desilylation[20] reactions. Moreover, it is evident from the literature that fluoride ions have invoked enormous interest as a green and potential catalyst[21,22] to construct carbon-carbon and carbon-heteroatom bonds in various organic transformations such as Knoevenagel condensation, Michael addition and O, N, S-alkylation reactions. The potential ability of the fluoride ion to act as a base might be predicted on considering the strength of the H—F bond, solvent used for dissolution, amount of water that is present, and the

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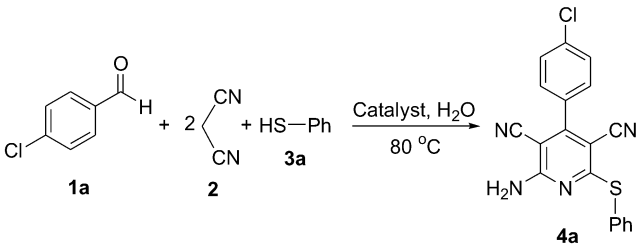
countercation. They react under essentially neutral conditions and are therefore often associated with clean reactions where side reactions are kept to a minimum.[21] Considering these sets of data and for exploitation of applications of TBAF in synthetic organic chemistry, attempt has been made for its use in pyridine synthesis.

Results and discussion

On preliminary basis, one-pot three-component condensation reaction of *p*-chlorobenzaldehyde (**1a**), malononitrile (**2**) and thiophenol (**3a**) at 80 ℃ was considered as a standard model reaction (Scheme 1). Keeping the significance of above discussed aspects and in the context of green chemistry, it has been decided to prefer water as a solvent in our initial study for optimizing catalyst. For establishing the effectiveness of the catalysts, reaction was carried out using different fluorides as well as their halide analogs such as chloride and bromide. Fluoride ion was found to be more active among the used halides (Table 1, Entries 1—5). The reactions carried out in the presence of tetra-*n*-butyl ammonium chloride (TBACl) and tetra-*n*-butyl ammonium bromide (TBAB) were sluggish and incomplete even after 6 h with 36% and 32% yields, respectively. KF and CsF afforded the desired products in 79% and 86% yields respectively, whereas in the presence of tetra-*n*-butyl ammonium fluoride (TBAF) the product was obtained in excellent yield (94%).

Scheme 1 Standard model reaction



During this experiment, it was observed that solid compound precipitates out after addition of catalytic amount of TBAF indicating the rapid Knoevenagel condensation of aldehyde and malononitrile. Afterward, heating the reaction mass at 80 ℃ started to convert the white solid intermediate into the yellow solid via subsequent Michael addition, which finally on *S*-alkylation, cyclization and air oxidation afforded the pale yellow coloured crude product.

Temperature of 80 ℃ was intentionally chosen as most of the fluorides are thermally unstable above 80 ℃.[22] For evaluation of temperature effect, this reaction was performed at room temperature, 60, 80 ℃ and reflux conditions (Table 1, Entries 5—8). Reaction at room temperature and 60 ℃ afforded product in good yields but it takes longer reaction period for completion, while at reflux condition the product was obtained in lower yield, since catalyst becomes unstable above 80 ℃. At 80 ℃, reaction proceeds smoothly towards completion in excellent yield (94%).

Table 1 Screening of catalysts and solvents[a]

Entry	Catalyst	Solvent	Temperature/℃	Time/h	Yield[b]/%
1	TBACl	Water	80	6	36
2	TBAB	Water	80	6	32
3	KF	Water	80	1	79
4	CsF	Water	80	1	86
5	TBAF	Water	80	1	94
6	TBAF	Water	r.t.	8	87
7	TBAF	Water	60	4	90
8	TBAF	Water	100	1	78
9	TBAF	—	80	1	52
10	TBAF	DMF	80	1	Trace
11	TBAF	THF	Reflux	1	28
12	TBAF	MeCN	80	1	39
13	TBAF	Ethanol	Reflux	1	60
14	TBAF	Methanol	Reflux	1	67
15	TBAF	Toluene	80	1	86

[a] Reaction conditions: **1a** (1 mmol), **2** (2 mmol), **3a** (1 mmol), catalyst (10 mol %), in solvent (5 mL); [b] isolated yields.

After finalizing the catalyst (TBAF) for this reaction, the next target was to choose proper solvent because of the variable basicity and solubility shown by ionic fluorides as well as the possibility of solvent participation in subsequent reactions. Various solvents like DMF, THF, acetonitrile, ethanol, methanol and toluene [Figure 1(A), Table 1, Entries 9—15] have been tested and compared their results with water mediated reaction. Prior to using solvents, reaction was examined under neat conditions, but reaction failed to afford more than 52% yield in 1 h. In DMF, reaction rate becomes lethargic after Knoevenagel condensation of aldehyde and malononitrile. In comparison, THF and acetonitrile carried out the subsequent reactions, but afforded lower yields. Ethanol and methanol were found to be compatible with the reaction conditions with moderate yields along with some side products. Reaction in toluene proceeded smoothly in agreement with water. But its tedious work up procedure, toxicity and hazardous nature confined its use for this reaction.

We were pleased to find that among the conditions screened [Figure 1(A)], the corresponding pyridine was obtained quantitatively with TBAF at 80 ℃ in water. It is known that TBAF in water produces an equilibrium in which tetra-*n*-butyl ammonium hydroxide (TBAOH) and HF_2^- are present,[20e] so one may speculate the possibility of catalysis of this reaction by TBAOH. But, this possibility has been ruled out considering the following points: (i) KF and CsF afford the products in good yields (79% and 86%, respectively) and reaction in toluene also proceeds smoothly confirming the assistance of fluoride ion to catalyze the reaction, where chances of TBAOH formation in reaction mixture are eliminated. (ii) Even it has been studied and proved that

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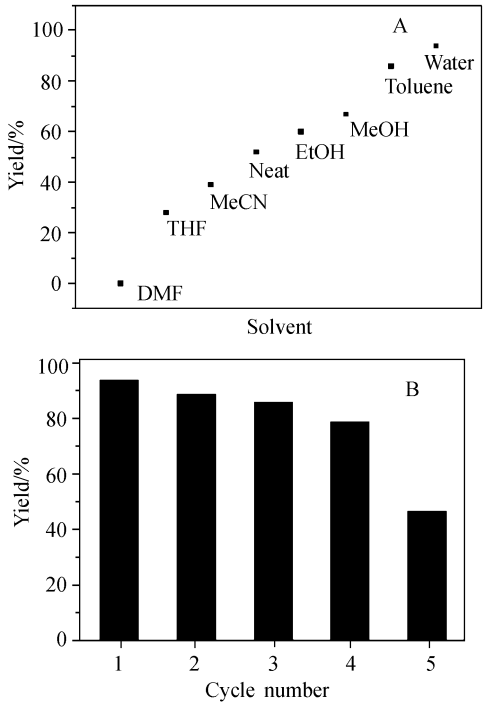


Figure 1 (A) Solvent effect on product yield, and (B) recycling and reuse of TBAF.

equilibrium generated due to addition of water to TBAF shifts towards the side of TBAF rather than TBAOH due to presence of HF_2^-.[20e] (iii) Literature reveals that TBAF does not react with water in the presence of organic substrates, since organic molecules act as more powerful H-bond e-acceptors than water.[21] This dramatic influence of water over the other solvents could be attributed to H-bonding which must have played important role in the basic behavior of fluoride anion. In the presence of powerful H-bond e-acceptors (organic substrates), fluoride ions bond with them and enhance their nucleophilicity, due to H-bonding between fluoride ion and organic molecule resulting in transfer of electron density from the anion to organic substrate. Water is only able to solvate and mask fluoride ion if more powerful H-bond e-acceptor than itself is absent. Increase in the thiols reactivity seems reasonable to assume the importance of H-bonding base like reactions of the anion.[21] One more aspect that could be helpful for bringing the reaction in favor of water is hydrophobic interactions which induce favorable aggregation of organic substrates in water.

In a simplified way, to understand the role of TBAF it should be noted that in water TBAF gets dissociated to afford tetra-*n*-butyl ammonium cation and fluoride anion. Cationic species bind with the organic substrates (electrophiles) to increase their electrophilicity and fluoride ion (which plays major role) behaves as a base in the presence of H-bond e-acceptors (organic substrates/nucleophiles), and enhances their nucleophilicity. In this manner, major role of fluoride ion as a base and assistance of tetra-*n*-butyl ammonium cation accelerates the rate of reaction. Plausible mechanism involved in the synthesis of highly substituted pyridines is depicted with the help of Figure 2.

To determine the appropriate concentration of the catalyst (TBAF), we investigated the model reaction at different concentrations of TBAF such as 0, 2.5, 5, 10 and 15 mol%. The product was formed in trace, 58%, 77%, 94%, and 94% yields, respectively (Table 2). This indicates that 10 mol% of TBAF is sufficient to carry out the reaction smoothly.

It is noteworthy to point out that, recently, recycling and reuse of TBAF in water[23] has been successfully achieved. Hence we carried out this experiment for the present reaction and it was observed that this catalytic system could be recovered and reused without any significant loss in its catalytic activity. Recovery process is very easy and convenient to carry out. On completion of reaction, filtrate obtained after simple filtration can be

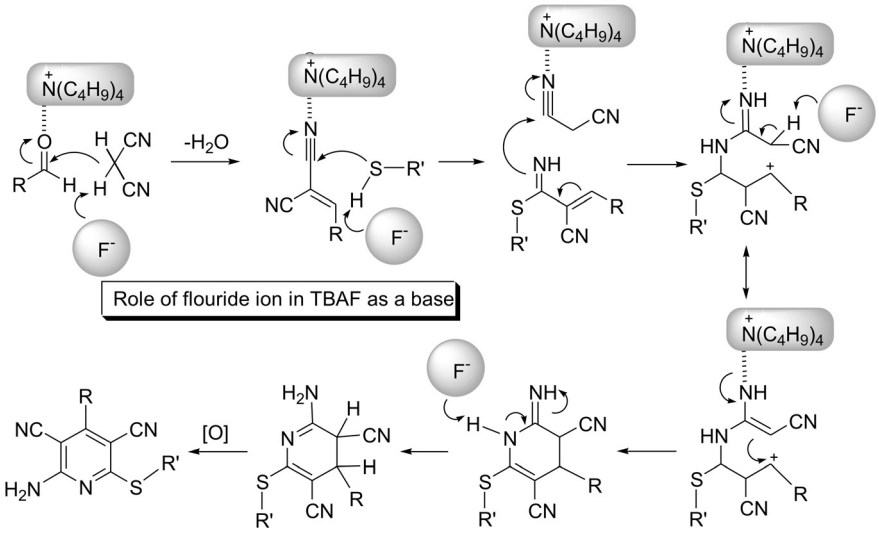


Figure 2 Plausible mechanism for the synthesis of pyridines.

Table 2 Concentration effect, recycling and reuse of TBAF[a]

Entry	TBAF/mol%	Yield[b]/%
1	0	Trace
2	2.5	58
3	5	77
4[c]	10	94, 89, 86, 79, 47
5	15	94

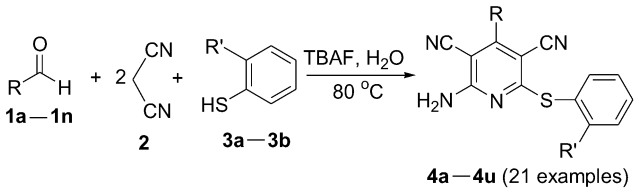
[a] Reaction conditions: **1a** (1 mmol), **2** (2 mmol), **3a** (1 mmol), in water (5 mL) at 80 ℃ for 60 min; [b] isolated yields; [c] catalyst was reused for four times.

reused directly for model reaction [Figure 1(B) and Table 2, Entry 4].

In order to extend the scope of the reaction and to generalize the procedure, variety of electronically divergent aldehydes with respect to thiophenol and *o*-aminothiophenol were examined. The reaction was straightforward for the wide range of aryl aldehydes. Various heteryl aldehydes were well tolerated to afford excellent yields. Interestingly, aliphatic aldehydes such as acetaldehyde and propionaldehyde also gave the desired product in moderate yields. All the results are compiled in Table 3. Formation of the desired product was confirmed with the help of IR, ^{1}H NMR, and mass spectroscopic data.

Comparative study of the developed protocol with the known methods reveals the following advantages: (i) This strategy is higher yielding under mild reaction conditions. (ii) All the reported methods have been performed in either organic solvents or ethanol except our previous one,[15b] in contrast, we have used greener aqueous medium. (iii) Most of the known strategies including our previous one fail for aliphatic aldehydes, whereas, developed method keeps the potential to utilize aliphatic aldehydes. (iv) In comparison to others, catalyst used in this route can be reused up to four runs without loss of significant reactivity.

Table 3 Synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines[a]



Entry	Compd.	R	R'	Time/min	Yield[b]/%	m.p.[c]/℃
1	**4a**	4-ClC_6H_4	H	60	94	221—222
2	**4b**	Ph	H	50	92	216—218
3	**4c**	4-FC_6H_4	H	50	90	226—228
4	**4d**	4-$MeOC_6H_4$	H	65	92	240—241
5	**4e**	4-HOC_6H_4	H	70	87	315—316
6	**4f**	4-$NO_2C_6H_4$	H	45	95	289—290
7	**4g**	4-MeC_6H_4	H	50	89	208—210
8	**4h**	4-HO-3-$MeOC_6H_3$	H	55	91	218—220
9	**4i**	3,4-$(MeO)_2C_6H_3$	H	65	90	225—227
10	**4j**	Piperonyl	H	85	96	23—232
11	**4k**	2-Thienyl	H	120	92	210—212
12	**4l**	2-Furyl	H	120	93	178—180
13	**4m**	Me	H	420	64	228—230
14	**4n**	Et	H	630	62	146—147
15	**4o**	Ph	NH_2	45	91	226—228
16	**4p**	4-ClC_6H_4	NH_2	70	91	234—236
17	**4q**	4-$MeOC_6H_4$	NH_2	55	88	229—231
18	**4r**	4-HOC_6H_4	NH_2	60	90	172—173
19	**4s**	4-$NO_2C_6H_4$	NH_2	50	96	207—208
20	**4t**	4-MeC_6H_4	NH_2	60	89	208—210
21	**4u**	4-HO-3-$MeOC_6H_3$	NH_2	55	92	232—233

[a] Reaction conditions: **1** (1 mmol), **2** (2 mmol), **3** (1 mmol), TBAF (10 mol%), in water (5 mL) at 80 ℃; [b] isolated yields; [c] melting points match with literature reports.[14c,14d,15]

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Conclusions

In summary, a facile, economic, and green protocol for one-pot multicomponent cyclocondensation of aldehydes, malononitrile, and thiols has been described. All the reactions proceed under essentially neutral conditions reducing the possibility of unwanted side reactions. In addition, present method offers marked improvements with regard to operational simplicity, reaction time, high isolated yields of products, and greenness of procedure, avoiding hazardous organic solvents and toxic catalysts. This process is less laborious than our previously reported procedure[15b] and provides a better, clean and practical alternative to the existing protocols.

Experimental section

General

All chemicals were purchased and used without any further purification. Melting points were recorded on a Veego apparatus and are uncorrected. Infrared spectra were recorded on a Bruker spectrophotometer in a KBr disc, and the absorption bands are expressed in cm^{-1}. ^1H NMR spectra were recorded on a Varian AS 400 MHz spectrometer in DMSO-d_6, chemical shifts (δ) are relative to TMS. Mass spectra were recorded on a macro mass spectrometer (Waters) by electro-spray (ES) method.

General experimental procedure

A mixture of aldehyde **1** (1 mmol), malononitrile **2** (2 mmol), thiophenol **3** (1 mmol) and TBAF ((1.0 mol/L in THF) (10 mol%)) in water (5 mL) was stirred at 80 ℃. Reaction progress was monitored by TLC [*V*(ethyl acetate)∶*V*(*n*-hexane)=1∶7]. After completion of the reaction, obtained solid product was collected by simple filtration and washed with water. The crude product **4** was recrystallized from aqueous ethanol to obtain pure product without any need of further purification.

Spectroscopic data for representative compounds

2-Amino-4-(4-chlorophenyl)-6-phenylsulfanylpyridine-3,5-dicarbo-nitrile (4a) ^1H NMR (DMSO-d_6, 400 MHz) δ: 7.83 (brs, 2H, NH_2), 7.64 (d, J=8.0 Hz, 2H, ArH), 7.59 (d, J=8.0 Hz, 2H, ArH), 7.57 (d, J=8.0 Hz, 2H, ArH), 7.49—7.46 (m, 3H, ArH); IR (KBr) *v*: 3489, 3342, 3221, 2216, 1628, 1544, 1487, 1259, 1091, 839, 791 cm^{-1}; ES-MS *m/z*: 363.04 (M^+), 365.03 (M^++2).

2-Amino-4-(benzo[*d*][1,3]dioxol-5-yl)-6-phenylsulfanylpyridine-3,5-dicarbonitrile (4j) ^1H NMR (DMSO-d_6, 400 MHz) δ: 7.72 (brs, 2H, NH_2), 7.57—7.55 (m, 2H, ArH), 7.48—7.46 (m, 3H, ArH), 7.14 (d, J=1.2 Hz, 1H, Ar-H), 7.07 (d, J=8.0 Hz, 1H, ArH), 7.03—7.00 (m, 1H, ArH), 6.12 (s, 2H, OCH_2O); IR (KBr) *v*: 3458, 3338, 3229, 2907, 2217, 1636, 1558, 1492, 1251, 1037, 825 cm^{-1}; ES-MS *m/z*: 373.14 (M^+).

2-Amino-4-(thiophene-2-yl)-6-phenylsulfanylpyridine-3,5-dicarbo-nitrile (4k) ^1H NMR (DMSO-d_6, 400 MHz) δ: 7.94 (d, J=4.8 Hz, 1H, ArH), 7.61 (brs, 2H, NH_2), 7.45—7.42 (m, 2H, ArH), 7.35—7.32 (m, 3H, ArH), 7.24 (d, J=4.0 Hz, 1H, ArH), 6.68 (t, J=4.0 Hz, 1H, ArH); IR (KBr) *v*: 3438, 3360, 3210, 2984, 2210, 1617, 1512, 1257, 1064, 722 cm^{-1}; ES-MS *m/z*: 335.07 (M^+).

2-Amino-4-(furan-2-yl)-6-phenylsulfanylpyridine-3,5-dicarbo-nitrile(4l) ^1H NMR (DMSO-d_6, 400 MHz) δ: 7.93 (d, J=5.2 Hz, 1H, ArH), 7.79 (brs, 2H, NH_2), 7.58—7.54 (m, 3H, ArH), 7.48—7.46 (m, 3H, ArH), 7.26 (t, J=4.0 Hz, 1H, ArH); IR (KBr) *v*: 3380, 3328, 3210, 2992, 2215, 1650, 1518, 1264, 1029, 766 cm^{-1}; ES-MS *m/z*: 319.09 (M^+).

2-Amino-4-ethyl-6-phenylsulfanylpyridine-3,5-dicarbonitrile (4n) ^1H NMR (DMSO-d_6, 400 MHz) δ: 7.69 (brs, 2H, NH_2), 7.56—7.54 (m, 2H, ArH), 7.47—7.44 (m, 3H, ArH), 2.71 (q, J=7.6 Hz, 2H, CH_2CH_3), 1.20 (t, J=7.6 Hz, 3H, CH_2CH_3); IR (KBr) *v*: 3425, 3148, 2218, 1639, 1547, 1476, 1263, 1177, 1024, 748 cm^{-1}; ES-MS *m/z*: 281.08 (M^+).

2-Amino-4-(4-hydroxy-3-methoxyphenyl)-6-(2-amino-phenylsulfanyl)pyridine-3,5-dicarbonitrile (4u) ^1H NMR (DMSO-d_6, 400 MHz) δ: 9.65 (brs, 1H, OH), 7.57 (brs, 2H, NH_2-(pyridine ring)), 7.25—7.23 (dd, J=1.6 Hz, 8.0 Hz, 1H, ArH), 7.20—7.15 (t, J=8.0 Hz, 1H, ArH), 7.12 (d, J=1.6 Hz, 1H, ArH), 6.98—6.91 (m, 2H, ArH), 6.77 (d, J=8.0 Hz, 1H, ArH), 6.57 (t, J=8.0 Hz, 1H, ArH), 5.37 (brs, 2H, NH_2-thiophenol ring), 3.80 (s, 3H, OCH_3); IR (KBr) *v*: 3473, 3348, 3290, 2958, 2212, 1625, 1533, 1281, 1020, 756 cm^{-1}; ES-MS *m/z*: 390.02 (M^+).

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