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Ultrasound-promoted synthesis of 2-amino-6-(arylthio)-4-arylpyridine-3,5-dicarbonitriles using $ZrOCl_2{\cdot}8H_2O/NaNH_2$ as the catalyst in the ionic liquid $[bmim]BF_4$ at room temperature

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ABSTRACT

We herein present an efficient and environmentally benign protocol for the synthesis of 2-amino-6-(arylthio)-4-arylpyridine-3,5-dicarbonitrile derivatives via the three-component condensation of a variety of aldehydes, arylthiols, and malononitrile catalyzed by $ZrOCl_2{\cdot}8H_2O/NaNH_2$ (20 mol %) in the ionic liquid $[bmim]BF_4$ under ultrasound irradiation at room temperature.

Compounds possessing a 2-amino-3,5-dicarbonitrile-6-thiopyridine ring system exhibit diverse pharmacological activities and are useful as anti-prion,[1] anti-hepatitis B,[2] antibacterial,[3] and anticancer agents,[4] and as potassium channel openers for the treatment of urinary incontinence.[5] In addition, several of these compounds were discovered to be highly selective ligands for adenosine receptors,[6] which are recognized as potential targets for the development of new drugs for the treatment of Parkinson's disease, hypoxia/ischemia, asthma, kidney disease, epilepsy, and cancer.[7] A three-component condensation of an aldehyde, malononitrile, and a thiol represents an important existing procedure for the synthesis of 2-amino-3,5-dicarbonitrile-6-thiopyridines. Generally, this condensation has been carried out under basic conditions using bases such as, Et_3N, DABCO,[8] piperidine, morpholine, thiomorpholine, pyrrolidine, DIPEA, pyridine, 2,4,6-collidine, DMAP, aniline, *N*-methylaniline, *N*,*N*-dimethylaniline, and *N*,*N*-diethylaniline.[9] Moreover, the basic ionic liquid 1-methyl-3-butylimidazolium hydroxide ([bmim]OH),[10] DBU[11] and TBAH[12] were also found to be efficient basic catalysts for the synthesis of such polysubstituted pyridines. However, most of these methods suffer from the formation of side products, which results in lower yields of the desired products. This three-component condensation has been carried out using a Lewis acid catalyst ($ZnCl_2$)[13] and boric acid,[14] which show improved results when compared to the base-catalyzed reactions.[15] Ultrasonic-assisted organic synthesis as a green approach is a powerful technique employed for organic reactions leading to higher yields, shorter reaction times, and milder conditions, and is considered a processing aid in terms of energy conservation and waste minimization compared with traditional methods.[15a,16,17] We report herein, a simple, mild and. expeditious synthesis of 2-amino-6-(arylthio)-4-arylpyridine-3,5-dicarbonitrile derivatives in high yields by the reaction of aryl aldehydes **1a–j**, thiols **2a–d,** and malononitrile (**3**) catalyzed by $ZrOCl_2{\cdot}8H_2O/NaNH_2$ in the ionic liquid $[bmim]BF_4$ under ultrasound irradiation at room temperature.

In order to avoid the disadvantages of volatility and toxicity that many organic solvents demonstrate, we employed an ionic liquid in this three-component reaction as an environmentally benign medium. The reaction of arylaldehydes **1a–j**, thiols **2a–d,** and malononitrile (**3**) in $[bmim]BF_4$ catalyzed by $ZrOCl_2{\cdot}8H_2O/NaNH_2$ under mild conditions and ultrasonic irradiation at 25 °C, afforded high yields of 2-amino-6-(arylthio)-4-arylpyridine-3,5-dicarbonitriles **4aa–ja, 4ab, 4gb, 4hb, 4ec, 4ic, 4ad,** and **4bd** (Scheme 1).

In the search for optimum conditions, the reaction of benzaldehyde (**1a**), 2,3,4,5,6-pentafluorobenzenethiol (**2a**), and malononitrile (**3**) in the presence of $ZrOCl_2{\cdot}8H_2O/NaNH_2$ as the catalyst in $[bmim]BF_4$ was examined as a model system (Scheme 2).

A summary of the optimization studies is provided in Table 1. In the absence of zirconium oxychloride, sodium amide, $[bmim]BF_4$ and sonication, or elements of these, no reaction took place (Table 1, entries 1–3 and 5–6). Next we screened various combinations of

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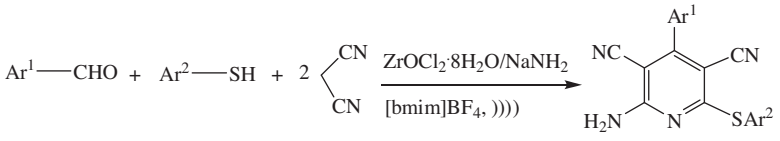
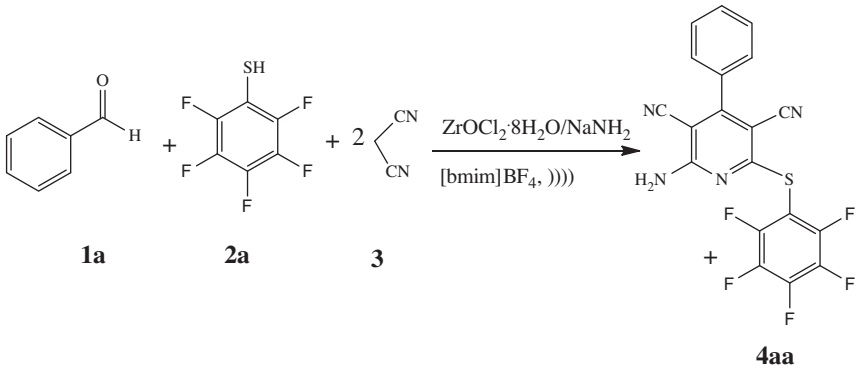


1a-j **2a-d** **3** **4aa-4ja**
4ab, 4gb, 4hb
4ec, 4ic
4ad, 4bd

Ar^1:C_6H_5, *o*-$NO_2C_6H_4$, *p*-$CH_3C_6H_4$, *p*-$Me_2NC_6H_4$, *p*-BrC_6H_4, 2,4-$(NO_2)_2C_6H_3$, *p*-FC_6H_4, *p*-$CF_3C_6H_4$, 2-naphthyl, 2-furyl
Ar^2: C_6F_5, C_6H_5, *p*-BrC_6H_4, 2-naphthyl

Scheme 1. Synthesis of 2-amino-6-(arylthio)-4-arylpyridine-3,5-dicarbonitrile derivatives **4**.



1a **2a** **3** **4aa**

Scheme 2. Standard model reaction.

Table 1
Optimization of the catalytic system[a]

Entry	Reaction system	Time (min)	Yield[b] (%)
1	—	120	—
2	$ZrOCl_2{\cdot}8H_2O$	120	—
3	$NaNH_2$	120	—
4	$ZrOCl_2{\cdot}8H_2O/NaNH_2$	120	15
5	$[bmim]BF_4$	120	—
6	))))	120	—
7	$[bmim]BF_4$,))))	120	Trace
8	$ZrOCl_2{\cdot}8H_2O/[bmim]BF_4$	120	30
9	$ZrOCl_2{\cdot}8H_2O/[bmim]BF_4$,))))	120	40
10	$ZrOCl_2{\cdot}8H_2O/NaNH_2$, $[bmim]BF_4$	120	35
11	**$ZrOCl_2{\cdot}8H_2O/NaNH_2$, $[bmim]BF_4$,))))**	**5**	**95**

Note: Bold values denotes are optimized conditions.
[a] Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), **3** (2 mmol), catalyst (20 mol %), rt.
[b] Isolated yield.

Table 2
Effect of the catalyst concentration[a]

Entry	$ZrOCl_2{\cdot}8H_2O/NaNH_2$ (mol %)	Yield[b] (%)
1	5	45
2	10	69
3	15	81
4	**20**	**92**
5	25	91

Note: Bold values denotes are optimized conditions.
[a] Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), **3** (2 mmol), $[bmim]BF_4$ (2 mL), ultrasound irradiation, rt.
[b] Isolated yield.

Table 3
Recycling studies on $[bmim]BF_4$

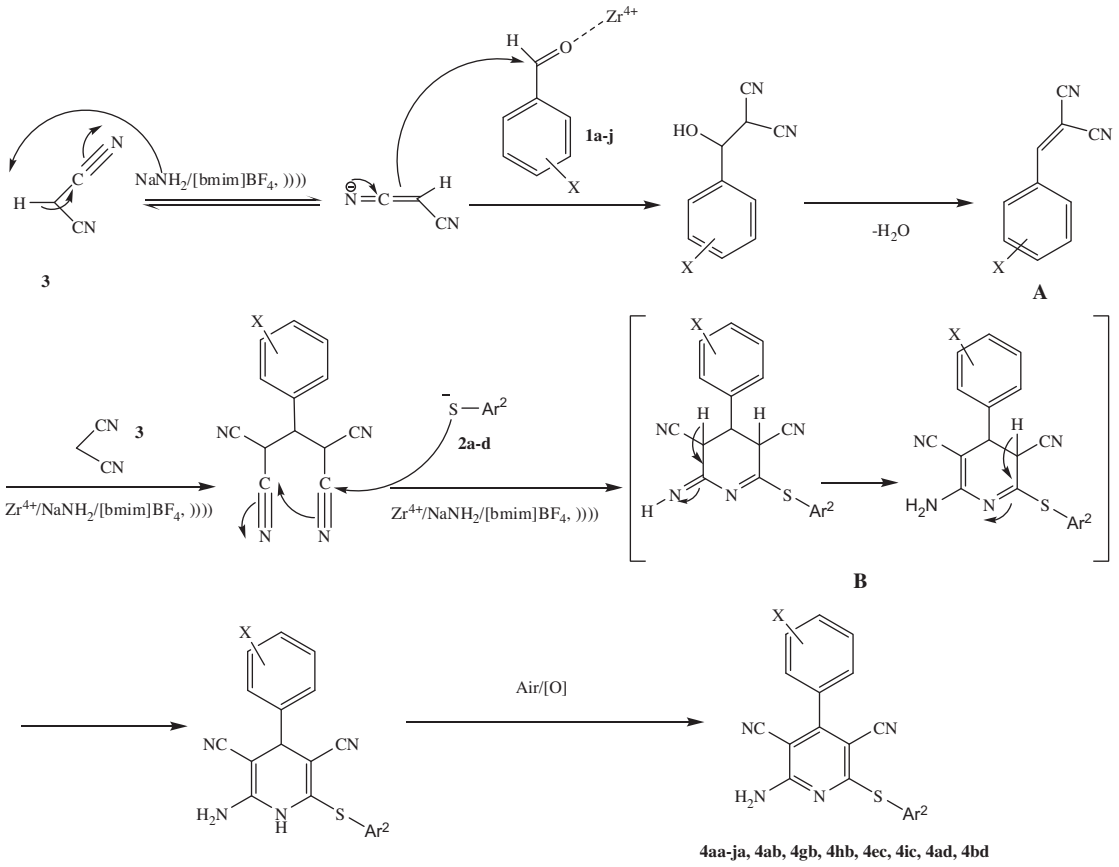
Run[a]	Time (min)	Yield[b] (%)
1	10	92
2	10	92
3	10	91
4	12	90
5	15	88

[a] Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), **3** (2 mmol), $ZrOCl_2{\cdot}8H_2O/NaNH_2$ (20 mol %), $[bmim]BF_4$ (2 mL), ultrasound irradiation, rt.
[b] Isolated yield.

Table 4
Synthesis of 2-amino-6-(arylthio)-4-arylpyridine-3,5-dicarbonitrile derivatives **4**

Entry	Ar^1	Ar^2	Time (min)	Product	Yield[a] (%)
1	C_6H_5	C_6F_5	10	**4aa**	92
2	*o*-$NO_2C_6H_4$	C_6F_5	5	**4ba**	97
3	*p*-$CH_3C_6H_4$	C_6F_5	15	**4ca**	90
4	*p*-$Me_2NC_6H_4$	C_6F_5	20	**4da**	90
5	*p*-BrC_6H_4	C_6F_5	15	**4ea**	91
6	2,4-$(NO_2)_2C_6H_3$	C_6F_5	2	**4fa**	95
7	*p*-FC_6H_4	C_6F_5	5	**4ga**	95
8	*p*-$CF_3C_6H_4$	C_6F_5	2	**4ha**	98
9	2-Naphthyl	C_6F_5	10	**4ia**	95
10	2-Furyl	C_6F_5	20	**4ja**	93
11	C_6H_5	C_6H_5	15	**4ab**	91
12	*p*-FC_6H_4	C_6H_5	5	**4gb**	93
13	*p*-$CF_3C_6H_4$	C_6H_5	10	**4hb**	94
14	*p*-BrC_6H_4	*p*-BrC_6H_4	10	**4ec**	92
15	2-Naphthyl	*p*-BrC_6H_4	5	**4ic**	93
16	C_6H_5	2-Naphthyl	15	**4ad**	94
17	*o*-$NO_2C_6H_4$	2-Naphthyl	12	**4bd**	97

[a] Isolated yield.



Scheme 3. Proposed mechanism for the synthesis of 2-amino-6-(arylthio)-4-arylpyridine-3,5-dicarbonitrile derivatives **4**.

the above components. The product **4aa** was obtained in moderate 15%, trace, 30%, 40%, and 35% yields within 120 min (Table 1, entries 4 and 7–10). However, the use of zirconium oxychloride/sodium amide in [bmim]BF_4 under sonication proved to be the most efficient system which gave a 95% yield of product within 5 min (Table 1, entry 11).

To determine the appropriate concentration of the zirconium oxychloride catalyst, we investigated the model reaction at different concentrations. The product was obtained in yields ranging from 45% to 92% (Table 2). The results showed that 20 mol % of zirconium oxychloride/sodium amide was sufficient to carry out the reaction smoothly.

We next studied the catalytic activity of recycled [bmim]BF_4 in the synthesis of **4aa**. The reactions were complete within 2–20 min and the products were easily isolated by extraction with ethyl acetate. The remaining ionic liquid containing the catalyst was recovered and reused in subsequent reactions with only a gradual decrease in the activity being observed. For instance, 2-amino-6-(perfluorophenylthio)-4-phenylpyridine-3,5-dicarbonitrile derivative **4aa** was obtained in 92%, 92%, 91%, 90%, and 88% yields over five cycles (Table 3).

In order to demonstrate the efficiency and scope of the present method, we performed the reactions of a variety of arylaldehydes **1a–j**, 2,3,4,5,6-pentafluorobenzenethiol, and nonfluorinated arylthiols **2a–d** with malononitrile (**3**) at room temperature in [bmim]BF_4. As shown in Table 4, aromatic substrates containing electron-withdrawing groups (halide, nitro, trifluoromethyl) or electron-donating groups (alkyl, *N*,*N*-dimethylamino), reacted well with **3** to give the corresponding products **4** in high yields under the optimized reaction conditions (Table 4, entries 1–17).

In accordance with the mechanism outlined by Evdokimov et al.,[18] the reaction is thought to proceed through $ZrOCl_2{\cdot}8H_2O$/$NaNH_2$[19] catalyzed Michael addition of the second molecule of malononitrile to the Knoevenagel adduct **A**, followed by thiolate addition to a C≡N group of the adduct and cyclization to give the dihydropyridine. Aromatization and oxidation (air) under the reaction conditions led to pyridine derivative **4** (Scheme 3).

In conclusion, we have reported an environmentally benign method for the synthesis of 2-amino-6-(arylthio)-4-arylpyridine-3,5-dicarbonitrile derivatives via the three-component reaction of arylaldehydes, malononitrile, and thiols using $ZrOCl_2{\cdot}8H_2O$/$NaNH_2$ as the catalyst in the ionic liquid [bmim]BF_4 under ultrasound irradiation. The advantages of this procedure are mild reaction conditions, high yields, and operational simplicity.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.10.031.

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19. *Typical experimental procedure*: A mixture of benzaldehyde (**1a**) (1 mmol), 2,3,4,5,6-pentafluorobenzenethiol (**2a**) (1 mmol), malononitrile (**3**) (2 mmol), $ZrOCl_2{\cdot}8H_2O/NaNH_2$ (20 mol %) and [bmim]BF_4 (2 mL) was sonicated at 25 °C for 10 min. After completion of the reaction as indicated by TLC, the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried, concentrated in vacuo and purified by column chromatography on silica gel (Merck, 100–200 mesh, EtOAc-hexane, 6%) to afford pure 2-amino-6-(perfluorophenylthio)-4-phenylpyridine-3,5-dicarbonitrile (**4aa**).

Characterization data of representative compounds:

2-Amino-6-(perfluorophenylthio)-4-phenylpyridine-3,5-dicarbonitrile (**4aa**). 0.384 g (92%); pale yellow solid; mp 214–215 °C. IR (KBr) (ν_{max}/cm^{-1}): 3520, 3075, 2196, 1635, 1510, 1455, 810. ^1H NMR ($CDCl_3$, 500 MHz): δ 6.17 (s, 2H, $-NH_2$), 7.30 (tt, 1H, J = 1.8, 7.3 Hz, Ar-H), 7.35 (tt, 2H, J = 1.8, 7.3, Ar-H), 7.43–7.46 (m, 2H, Ar-H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 111.01, 112.33, 114.18, 115.02, 127.20, 128.25, 129.31, 129.14, 129.49, 131.20 (dd, $^1J_{CF}$ = 254.5 Hz, $^2J_{CF}$ = 15.3 Hz, C-2, C-6), 133.23 (dd, $^1J_{CF}$ = 253.8 Hz, $^2J_{CF}$ = 15.2 Hz, C-3, C-5), 135.17 (dd, $^1J_{CF}$ = 254.0 Hz, $^2J_{CF}$ = 15.0 Hz, C-4), 158.46, 159.76, 169.81. ^{19}F NMR ($CDCl_3$, 470 MHz): −67.61, −85.83, −97.09. MS (EI), m/z (%) 418 (M^+, 70), 418 (100), 386 (45), 251 (65). HRMS (EI) Found: M^+, 418.0341. $C_{19}H_7F_5N_4S$ requires M^+, 418.0310. Anal. Calcd for $C_{19}H_7F_5N_4S$: C, 54.55; H, 1.69; N, 13.39; S, 7.66. Found: C, 54.21; H, 1.86; N, 13.65; S, 7.54.

2-Amino-6-(perfluorophenylthio)-4-p-tolylpyridine-3,5-dicarbonitrile (**4ca**). 0.381 g (90%); white solid; mp 201–202 °C. IR (KBr) (ν_{max}/cm^{-1}): 3432, 3100, 2921, 2201, 1651, 1532, 1443, 723. ^1H NMR ($CDCl_3$, 500 MHz): δ 3.75 (s, 3H, CH_3), 6.34 (s, 2H, $-NH_2$), 7.58 (d, 2H, J = 2.1 Hz, Ar-H), 7.89 (d, 2H, J = 2.1, Ar-H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 87.64, 112.17, 112.86, 114.87, 123.87, 125.36, 126.55, 127.31, 128.77, 130.84, 132.27 (dd, $^1J_{CF}$ = 250.4 Hz, $^2J_{CF}$ = 16.1 Hz, C-2, C-6), 134.33 (dd, $^1J_{CF}$ = 251.4 Hz, $^2J_{CF}$ = 15.0 Hz, C-3, C-5), 136.58 (dd, $^1J_{CF}$ = 250.6 Hz, $^2J_{CF}$ = 15.0 Hz, C-4), 155.78, 157.29, 163.83. ^{19}F NMR ($CDCl_3$, 470 MHz): −66.99, −83.98, −99.21. MS (EI), m/z (%) 432 (M^+, 70), 360 (100), 265 (55), 416 (20). HRMS (EI) Found: M^+, 432.3701. $C_{20}H_9F_5N_4S$ requires M^+, 432.2109. Anal. Calcd for $C_{19}H_7F_5N_4S$: C, 55.56; H, 2.10; N, 12.96; S, 7.42. Found: C, 55.65; H, 2.32; N, 12.87; S, 7.51.