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2-Hydroxyethylammonium acetate: A reusable task-specific ionic liquid promoting one-pot, three-component synthesis of 2-amino-3, 5-dicarbonitrile-6-thio-pyridines

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ABSTRACT

2-Hydroxyethylammonium acetate (2-HEAA) as a task-specific ionic liquid, efficiently promotes one-pot three-component reaction of aryl/heteroaryl/alkyl aldehydes with aryl/alkyl thiols and malononitrile at room temperature. This protocol offers several advantages such as using a reusable and cost-effective ionic liquid, being amenable to scale-up and produces the corresponding 2-amino-3,5-dicarbonitrile-6-thio-pyridines in a short reaction time (5 min) and in good to high yields.

1. Introduction

The synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridine derivatives has attracted much attention of organic chemists for their various biological activities. Compounds containing a 2-amino-3,5-dicarbonitrile-6-thio-pyridine ring system are useful as anti-prion [1], anti-hepatitis B virus [2], anti-bacterial [3], and anticancer [4] agents and as potassium channel openers for treatment of urinary incontinence [5]. These compounds were reported to inhibit PrP^{Sc} accumulation in scrapie-infected mouse neuroblastoma cells (ScN2a) [1a], MAPK-activated PK-2 [4b], IKK-2 for treating HBV infection [2], and modulate androgen receptor function [6]. In addition, it was found that several of these compounds are selective ligands towards adenosine receptors [7]. They were recently recognized as potential targets in the development of new drugs for the treatment of diseases such as Parkinson, hypoxia/ischemia, asthma, epilepsy [8] and Creutzfeldt-Jacob [1a,b] and also kidney problems [8]. One of the most significant existing methods for the synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines involves the three-component condensation of aldehyde, malononitrile, and thiol [9]. The condensation has been carried out under basic conditions using various bases including Et_3N, DABCO [10], DBU [11], TBAH, piperidine [12], nanocrystaline MgO (NAP-MgO) [13], nano silica [14], KF/alumina [15], basic alumina [16], TBAF [17], sodium silicate [18], K_2CO_3 [19] and microporous molecular sieves [20]. Some acids such as $ZrOCl_2.8H_2O$ [21], $ZnCl_2$ [22], *o*-iodoxybenzoic acid (IBX) [23] and H_3BO_3 [24] were also addressed for the promotion of this reaction. Moreover, ionic liquids such as [bmIm]OH [25] and [bmIm]Br [26] were found to catalyze the synthesis of polysubstituted pyridines. However, some of these protocols suffer from drawbacks such as formation of inevitable side products, prolonged reaction times, low yields, harsh reaction conditions, tedious workup and use of expensive and environmentally toxic catalysts as well

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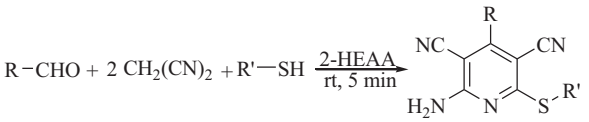
as solvents. Thus, organic chemists have struggled to overwhelm these shortcomings and develop efficient methods for these nucleus using milder non-hazardous and inexpensive reagents.

In recent years, room temperature ionic liquids have received considerable attention as an alternative green reaction medium for numerous organic reactions due to their favorable properties, such as good solvating capability, wide liquid range, negligible vapor pressure, tunable polarity, high thermal stability and ease of recyclability [27]. Ionic liquids have also played a significant role in controlling the reactions as catalysts [28]. The major concern in using ionic liquids as reaction media in industrial process is the cost of the ionic liquid, which would be directly dependent on the price of the cations and anions that are used for their production [29]. The currently popular ionic liquids incorporate expensive cations such as alkyl methyl imidazolium or dialkyl imidazolium and expensive anions such as tetrafluroborate or hexaflurophosphate. Thus, introducing of cost-effective ionic liquids as reaction media is indispensable. Moreover, despite the great attention for methylimidazolium (mIm) based-ionic liquids, taken from EC_{50} data, the other existed ionic liquids are better candidates [30].

As part of our continued interest on the development of new eco-friendly methods for the synthesis of organic compounds [31], we have recently synthesized β-phosphonomalonates, 4-substituted 2-amino-4H-chromenes and bis(pyrazolyl)methanes in the presence of task-specific ionic liquids [32]. In this connection, herein, we wish to report 2-hydroxyethylammonium acetate (2-HEAA) [33] as a task-specific ionic liquid for the synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines at room temperature (Scheme 1).



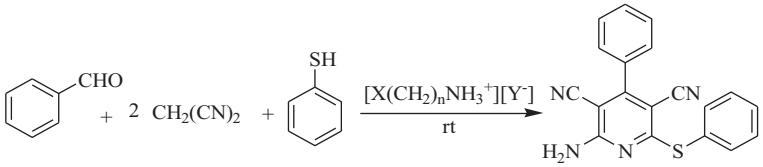
Scheme 1. Synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines.

2. Results and discussion

Initially, we have optimized different reaction parameters for the synthesis of 2-amino-4-phenyl-6-(phenylsulfanyl)-3,5-pyridinedicarbonitrile (**1**) using one-pot three-component reaction of benzaldehyde, malononitrile and thiophenol (Table 1).

As it is summarized in Table 1, 0.5 mL of 2-HEAA efficiently promoted the reaction leading to the desired product **1** in excellent yield (Entry 3). A similar reaction in the presence of $[EtNH_3^+][AcO^-]$ proceeded with a longer reaction time (2.5 h) compared with 2-HEAA (5 min) and produced the desired product in low yield (Entry 4). The obtained results showed the specific role of OH group of 2-HEAA in imparting the catalytic property and indicated that 2-HEAA could act not only as a solvent but also as a functionalized or task-specific ionic liquid in this method. The same reaction was not successful in the absence of 2-HEAA even after 24 h (Entry 5). It was also found that the reaction outcome does not dependent on the anion in $[HO(CH_2)_2NH_3^+][Y^-]$ or the length of the alkyl chain in $[HO(CH_2)_nNH_3^+][AcO^-]$ (Entries 6–11). Increasing interest of organic chemists for the use of water as a solvent of choice and its unique properties encouraged us to examine the present reaction in water (Entry 12). Reaction in aqueous media was observed to proceed in a short reaction time (5 min) but produced the desired product in moderate yield (69%) due to the formation of a by-product.

Table 1
Synthesis of 2-amino-4-phenyl-6-(phenylsulfanyl)-3,5-pyridinedicarbonitrile (**1**) in the presence of different $[X(CH_2)_nNH_3^+][Y^-]$.

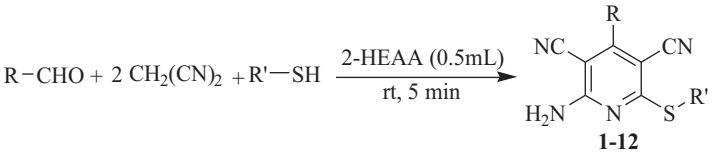


1

Entry	$[X(CH_2)_nNH_3^+][Y^-]$	Amount of IL (mL)	Time (min)	Yield[a] (%)
1	$n = 2$, X = OH, Y = AcO	0.125	5	88
2	$n = 2$, X = OH, Y = AcO	0.25	5	88
3	$n = 2$, X = OH, Y = AcO	0.5	5	96
4	$n = 2$, X = H, Y = AcO	0.5	2.5 h	48[b]
5	–	–	24 h	0
6	$n = 2$, X = OH, Y = CF_3CO_2	0.5	5	95
7	$n = 2$, X = OH, Y = HCO_2	0.5	5	96
8	$n = 2$, X = OH, Y = CH_3SO_3	0.5	5	95
9	$n = 2$, X = OH, Y = NO_3	0.5	5	96
10	$n = 3$, X = OH, Y = AcO	0.5	5	96
11	$n = 5$, X = OH, Y = AcO	0.5	5	98
12[c]	$n = 2$, X = OH, Y = AcO	0.5	5	69[b]

[a] Isolated yield. Conditions: benzaldehyde (1 mmol), malononitrile (2 mmol), thiophenol (1 mmol).
[b] The desired product (**1**) plus a mixture of by-products were formed.
[c] H_2O was used as solvent.

Table 2
Synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridine derivatives in the presence of 2-HEAA at room temperature.



1-12

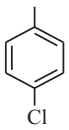
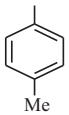
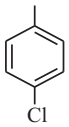
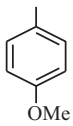
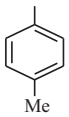
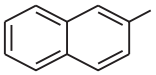
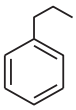
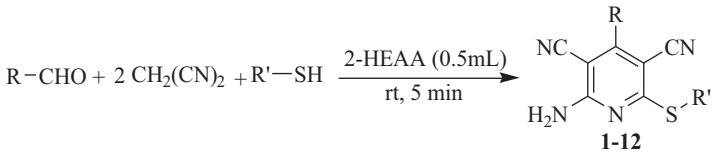
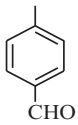
Entry	R	R′	Product	Yield[a] (%)	MP (°C) Found	MP (°C) Reported [ref]
1			**1**	96	219–220	215–216 [9]
2			**2**	85	222–223	222–224 [25]
3			**3**	86	212–213	208–211 [25]
4			**4**	86	228–229	228–230 [25]
5			**5**	78	228–229	228–229 [15]
6			**6**	76	238–239	238 [11]
7			**7**	84	238–240	236 [11]
8			**8**	81	305–306	305–306 [10]
9			**9**	72	218–220	–
10	Me		**10**	90	224–225	225–226 [9]
11		*n*-Bu	**11**	70	178–179	182–183 [34]

Table 2 (*Continued*)



1-12

Entry	R	R′	Product	Yield[a] (%)	MP (°C) Found	MP (°C) Reported [ref]
12			**12**	85[b]	310–311	–

[a] Isolated yield. Conditions: aldehyde/malononitrile/thiophenol: 1/2/1.
[b] Conditions: aldehyde/malononitrile/thiophenol: 1/4/2.

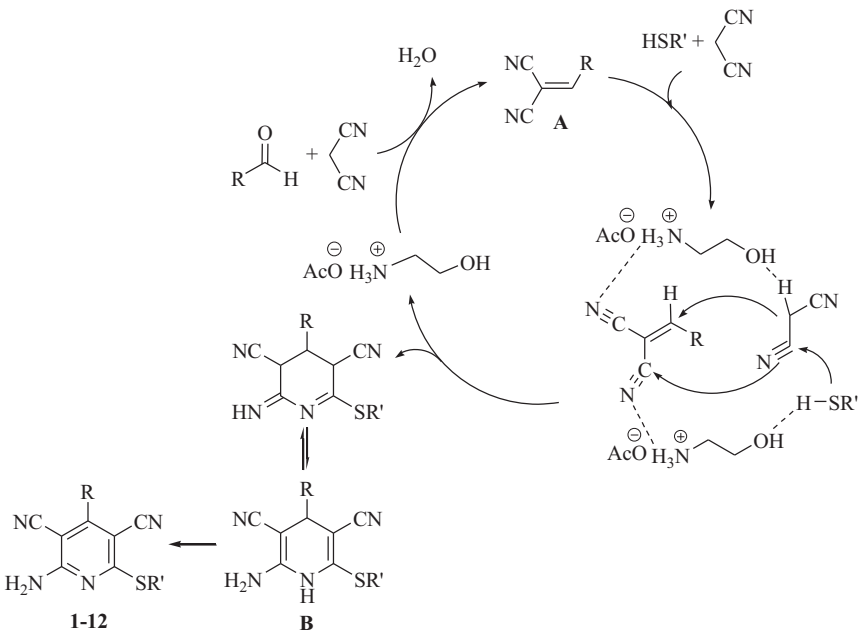
After performing the reaction of benzaldehyde, malononitrile and thiophenol in the presence of 2-HEAA (0.5 mL as the optimal amount), water was added to the reaction mixture, and the product was filtered off and purified by recrystallization in EtOH. The ionic liquid was recovered after evaporation of the filtrate and drying in vacuo at 100 °C for 24 h. Elemental analysis showed high purity of the recovered ionic liquid. A similar reaction in the presence of recovered ionic liquid proceeded well to produce the desired product **1** after 5 min in 95% yield.

This protocol was also easily amenable to scale-up. For example, the reaction of benzaldehyde, malononitrile and thiophenol in a semi scale-up procedure (10 times) in the presence of 2-HEAA was carried out successfully and the desired product was isolated in 92% yield.

To investigate the scope and general applicability of this procedure, the synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines was studied using different aldehydes and thiols under optimized reaction conditions (Table 2).

As the results of Table 2 indicates, 2-amino-3,5-dicarbonitrile-6-thio-pyridines **1–6** were produced from a series of various substituted benzaldehyde and thiophenol in good to high yields (Entries 1–6). 1-Naphthaldehyde as a polynuclear aldehyde and pyridine-3-carbaldehyde as a heteroaromatic aldehyde underwent the condensation reaction to afford the corresponding pyridines in good yields (Entries 7 and 8). Interestingly, 2-HEAA efficiently promoted the synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines using aliphatic aldehydes and thiols (Entries 9–11). It is worth to note that both carbonyl groups in terephthalaldehyde reacted with malononitrile and thiophenol and produced the desired product **12** in 85% yield (Entry 12).

In accordance with the mechanism delineated by Evdokinov et al. and Guo et al. [9], the first step of the process involves the Knoevenagel condensation of an aldehyde with malononitrile to form the corresponding Knoevenagel product **A**. The reaction proceeds through



Scheme 2. Suggested mechanism for the synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines in the presence of 2-HEAA.

Table 3
Synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines in the presence of reported reagents or catalysts.

Entry	Catalyst or reagent	Aldehyde/Thiol	Time	Yield (%)[a] [ref]
1	Et_3N or DABCO	Aryl/Aryl	2 h [9], 40–90 min [10]	20–48 [9], 55–96 [10]
		Alkyl/Aryl	2 h [9], 40–90 min [10]	20–29 [9], 39–55 [10]
		Aryl/Alkyl	2 h [9], 40–90 min [10]	21–47 [9], 42–92 [10]
2	KF/alumina	Aryl/Aryl	5–70 min	56–93 [15]
3	$ZnCl_2$	Aryl/Aryl	2 min–2.5 h	50–77 [22]
		Alkyl/Aryl	3 min–2.5 h	46 [22]
4	Sodium silicate[b]	Aryl/Aryl	1 h	78–82 [18]
5	NAP-MgO	Aryl/Aryl	2–9 h	48–69 [13]
		Aryl/Alkyl	4–8 h	41–56 [13]
6	Piperidine or TBAH	Aryl/Aryl	1–24 h	40–67 [12]
		Alkyl/Aryl	1–24 h	5–6 [12]
7	Microporous molecular sieves	Aryl/Aryl	30–120 min	78–91 [21]
8	H_3BO_3	Aryl/Aryl	8–50 min	80–94 [24]
9	DBU	Aryl/Aryl	10–40 min	75–91 [11]
10	[bmlm]OH	Aryl/Aryl	0.5–1.5 h	62–92 [25]
11	[bmlm]Br	Aryl/Aryl	4–12 min	75-86 [26]
12	Nano silica	Aryl/Aryl	2.5–3 h	70–85 [14]
		Alkyl/Aryl	6 h	60 [14]
		Aryl/Alkyl	6 h	60–65 [14]
13	$ZrOCl_2.8H_2O/NaNH_2/[bmim]BF_4$	Aryl/Aryl	2–20 min	90–98 [21]
14	Basic alumina	Aryl/Aryl	50–100 min	79–90 [16]
15	TBAF	Aryl/Aryl	45–120 min	87–96 [17]
		Alkyl/Aryl	420–630 min	62–64 [17]
16	$K_2CO_3/KMnO_4$	Aryl/Aryl	40–180 min	70–89 [19]
		Alkyl/Aryl	90 min	80 [19]
		Aryl/Alkyl	75–90 min	60–61 [19]
17	IBX	Aryl/Aryl	1.5–2.5 h	69–83 [23]
18	2-HEAA	Aryl/Aryl	5 min	76–96[c]
		Alkyl/Aryl	5 min	72–90[c]
		Aryl/Alkyl	5 min	70[c]

[a] Isolated yield.
[b] GC yield.
[c] This work.

thiolate addition to nitrile of the Knoevenagel product **A** followed by Michael addition of the second molecule of malononitrile to the adduct and produces dihydropyridine (**B**). Aromatization of **B** under the reaction conditions gives pyridine **1–12** (Scheme 2). In this three-component reaction, it is supposed that dual activation of substrates by 2-HEAA has taken place. The Lewis base moiety of the catalyst (OH) activates the malononitrile and thiol, and its Lewis acid moiety (NH_3^+) activates the aldehyde and nitrile of the Knoevenagel product **A**. To show the role of the hydroxyl group in the Knoevenagel condensation, the reaction of benzaldehyde and malononitrile in the presence of 2-HEAA and ethylammonium acetate was studied. The reactions proceed with the same yield and rate. These results showed that in the first step of the mechanism (Knoevenagel condensation), hydroxyl group of 2-HEAA does not play any role.

In order to show the merit of the present method for the synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines, we have compared our results obtained using 2-HEAA with some of those reported in the literature for the synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines (Table 3). These results indicate well the superior activity of 2-HEAA than those of other promoters especially for the synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines from aliphatic aldehydes or thiols. Most of the reported methods also suffer from lack of generality for the synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines from arylaldehydes/arylthiols, alkylaldehydes/arylthiols and arylaldehydes/alkylthiols.

3. Conclusion

In summary, a facile, economical and green protocol for one-pot three-component condensation of aldehydes, malononitrile and thiols in the presence of 2-HEAA as a task-specific ionic liquid has been described. Surprisingly, this ionic liquid efficiently promoted the condensation of both aromatic and aliphatic aldehydes and thiols with

malononitrile leading to 2-amino-3,5-dicarbonitrile-6-thio-pyridines in good to high yields in a short reaction time (5 min). All the reactions proceed under nearly neutral conditions reducing the possibility of unwanted side reactions. In addition, the present protocol offers several advantages such as using a reusable and cost-effective ionic liquid, an environmentally benign reaction media avoiding hazardous organic solvents and toxic catalysts, and being amenable to scale-up.

4. Experimental

4.1. Materials and techniques

Chemicals were purchased from Merck and Fluka Chemical Companies. NMR spectra were recorded in ppm in DMSO on a Bruker Avance DPX-400 instrument using TMS as internal standard. Elemental analysis for C, H, N and S were obtained using a *Elementar, Vario EL III*. IR spectra were run on a Perkin–Elmer 780 instrument. Melting points were determined by Buchi 510 apparatus and are uncorrected. The purification of the products and the progress of the reactions were accomplished by TLC on silica-gel polygram SILG/UV_{254} plates.

4.2. Typical procedure for the synthesis of 2-HEAA

2-HEAA was prepared according to the previously reported procedure [33]. A solution of acetic acid (50 mmol, 3.00 g) in EtOH (1.5 mL) was added dropwise to a stirring solution of 2-aminoethanol (50 mmol, 3.05 g) in EtOH (1.5 mL) at room temperature within 1 h. The resultant solution was stirred at room temperature for another 20 h. EtOH was removed in *vacuo* and the oil in residue was dried in *vacuo* at 50 °C for 48 h to give 2-HEAA as a yellow viscous liquid (pH = 7.96 at 25 °C, b.p. 191 °C, density = 1.11 g cm^{-3} at 25 °C, electrochemical stability = between −0.6 and 0.7 V, conductivity = 263.3 μs cm^{-1}).

4.3. General procedure for the synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines in the presence of 2-HEAA

A mixture of aldehyde (1 mmol), malononitrile (2 mmol), thiol (1 mmol) and 2-HEAA (0.5 mL) was stirred at room temperature for 5 min. H_2O (20 mL) was added to the reaction mixture and the resulting solid was filtered and washed with H_2O (2 × 10 mL). Pure product was obtained from the resulting solid by recrystallization in EtOH. Ionic liquid was recovered after evaporation of the filtrate and drying in vacuo at 100 °C for 24 h.

4.4. Spectral data for known 2-amino-3,5-dicarbonitrile-6-thio-pyridines

4.4.1. 2-Amino-4-phenyl-6-phenylsulfanyl-pyridine-3,5-dicarbonitrile (1)

314.8 mg, yield 96%; mp 219–220 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 7.84 (2H, br, NH_2), 7.63–7.59 (7H, m, Ar), 7.53–7.51 (3H, m, Ar); IR (KBr) (ν_{max}/cm^{-1}): 3471 (NH), 3349 (NH), 2196 (CN).

4.4.2. 2-Amino-4-(4-chloro-phenyl)-6-phenylsulfanyl-pyridine-3,5-dicarbonitrile (2)

308.5 mg, 85%; mp 222–223 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 7.88 (2H, br, NH_2), 7.68 (2H, d, J = 8.4 Hz, Ar), 7.61 (4H, d, J = 8.4 Hz, Ar), 7.53–7.50 (3H, m, Ar); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C (ppm) 166.7, 159.9, 158.0, 135.8, 135.3, 133.2, 130.9, 130.3, 130.0, 129.4, 127.5, 115.7, 115.3, 93.7, 87.6; IR (KBr) (ν_{max}/cm^{-1}): 3470 (NH), 3331 (NH), 2200 (CN).

4.4.3. 2-Amino-4-(4-methyl-phenyl)-6-phenylsulfanyl-pyridine-3,5-dicarbonitrile (3)

294.1 mg, 86%; mp 212–213 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 7.81 (2H, br, NH_2), 7.62–7.60 (2H, m, Ar), 7.52–7.50 (3H, m, Ar), 7.45 (2H, d, J = 7.6 Hz, Ar), 7.39 (2H, d, J = 8.0 Hz, Ar), 2.42 (3H, s, CH_3); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C (ppm) 166.6, 160.1, 159.2, 140.8, 135.3, 131.4, 130.2, 129.9, 129.8, 128.9, 127.6, 115.9, 115.6, 93.8, 87.4, 21.4; IR (KBr) (ν_{max}/cm^{-1}): 3460 (NH), 3318 (NH), 2200 (CN).

4.4.4. 2-Amino-6-(4-chloro-phenylsulfanyl)-4-phenyl-pyridine-3,5-dicarbonitrile (4)

312.1 mg, 86%; mp 228–229 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 7.89 (2H, br, NH_2), 7.63 (3H, d, J = 8.4 Hz, Ar), 7.60–7.56 (6H, m, Ar); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C (ppm) 166.3, 160.0, 159.1, 137.2, 135.3, 134.3, 130.9, 129.9, 129.2, 128.9, 126.5, 115.7, 115.5, 93.7, 87.6; IR (KBr) (ν_{max}/cm^{-1}): 3438 (NH), 3315 (NH), 2203 (CN).

4.4.5. 2-Amino-6-(4-methoxy-phenylsulfanyl)-4-phenyl-pyridine-3,5-dicarbonitrile (5)

279.2 mg, 78%; mp 228–229 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 7.79 (2H, br, NH_2), 7.59–7.55 (5H, m, Ar), 7.52 (2H, d, J = 8.4 Hz, Ar), 7.07 (2H, d, J = 8.4 H, Ar), 3.83 (3H, s, OCH_3); IR (KBr) (ν_{max}/cm^{-1}): 3427 (NH), 3322 (NH), 2100 (CN).

4.4.6. 2-Amino-6-(4-methyl-phenylsulfanyl)-4-phenyl-pyridine-3,5-dicarbonitrile (6)

259.9 mg, 76%; mp 238–239 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 7.84 (2H, br, NH_2), 7.63–7.57 (6H, m, Ar), 7.52–7.50 (3H, m, Ar), 2.51 (3H, s, CH_3); IR (KBr) (ν_{max}/cm^{-1}): 3467 (NH), 3348 (NH), 2195 (CN).

4.4.7. 2-Amino-4-(2-naphthyl)-6-phenylsulfanyl-pyridine-3,5-dicarbonitrile (7)

317.5 mg, 84%; mp 238–240 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 8.18 (1H, s, Ar), 8.13 (1H, d, J = 8.8 Hz, Ar), 8.09–8.05 (2H, m, Ar), 7.89 (2H, br, NH_2), 7.71–7.64 (5H, m, Ar), 7.54–7.52 (3H, m, Ar); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C (ppm) 166.7, 160.1, 159.2, 135.4, 133.8, 132.7, 131.9, 130.2, 130.0, 129.0, 128.9, 128.3, 128.2, 127.6, 125.9, 115.9, 115.6, 94.1, 87.7; IR (KBr) (ν_{max}/cm^{-1}): 3431 (NH), 3301 (NH), 2170 (CN).

4.4.8. 2-Amino-4-(3-pyridinyl)-6-phenylsulfanyl-pyridine-3,5-dicarbonitrile (8)

266.5 mg, 81%; mp 305–306 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 8.80–8.78 (2H, m, Ar), 8.07 (1H, d,

J = 7.6 Hz, Ar), 7.94 (2H, br, NH_2), 7.67–7.61 (3H, m, Ar), 7.53–7.52 (3H, m, Ar); IR (KBr) (ν_{max}/cm^{-1}): 3360 (NH), 3290 (NH), 2200 (CN).

*4.4.9. 2-Amino-4-methyl-6-phenylsulfanyl-pyridine-3,5-dicarbonitrile (**10**)*

239.4 mg, 90%; mp 224–225 °C; ^1H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 7.71 (2H, br, NH_2), 7.58–7.56 (2H, m, Ar), 7.50–7.47 (3H, m, Ar), 2.46 (3H, s, CH_3); IR (KBr) (ν_{max}/cm^{-1}): 3396 (NH), 3310 (NH), 2202 (CN).

*4.4.10. 2-Amino-4-phenyl-6-(n-butylsulfanyl)-pyridine-3,5-dicarbonitrile (**11**)*

215.6 mg, 70%; mp 178–179 °C; ^1H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 8.04 (2H, br, NH_2), 7.58–7.53 (5H, m, Ar), 3.25 (2H, t, J = 7.2 Hz, CH_2), 1.69–1.62 (2H, m, CH_2), 1.48-1.39 (2H, m, CH_2), 0.93 (3H, t, J = 7.2 Hz, CH_3); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C (ppm) 167.7, 160.1, 158.7, 134.5, 130.8, 129.2, 128.9, 115.9, 115.8, 94.0, 86.0, 31.2, 29.7, 21.8, 14.0; IR (KBr) (ν_{max}/cm^{-1}): 3452 (NH), 3313 (NH), 2200 (CN).

4.5. Spectral data for unknown 2-amino-3,5-dicarbonitrile-6-thio-pyridines

*4.5.1. 2-Amino-4-phenethyl-6-phenylsulfanyl-pyridine-3,5-dicarbonitrile (**9**)*

256.3 mg, 72%; mp 218–220 °C; [Found: C, 70.37; H, 4.51; N, 15.61; S, 8.86. $C_{21}H_{16}N_4S$ requires C, 70.76; H, 4.52; N, 15.72; S, 9.00%]; ^1H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 7.77 (2H, br, NH_2), 7.59–7.57 (2H, m, Ar), 7.50–7.47 (3H, m, Ar), 7.35 (2H, t, J = 7.2 Hz, Ar), 7.28–7.22 (3H, m, Ar), 3.03–2.99 (2H, m, CH_2), 2.92-2.89 (2H, m, CH_2); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C (ppm) 166.3, 160.4, 160.1, 139.9, 135.2, 130.1, 129.9, 129.1, 128.7, 127.6, 127.1, 115.4, 115.0, 93.9, 87.6, 36.1, 35.1; IR (KBr) (ν_{max}/cm^{-1}): 3442 (NH), 3344 (NH), 2215 (CN).

*4.5.2. 1,4-bis(2-amino-6-phenylsufanyl-4-pyridyl-3,5-dicarbonitrile)benzene (**12**)*

492.1 mg, 85%; mp 310–311 °C; [Found: C, 66.27; H, 3.18; N, 19.29; S, 11.43. $C_{32}H_{18}N_8S_2$ requires C, 66.42; H, 3.14; N, 19.36; S, 11.08%]; ^1H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 7.90 (4H, br, NH_2), 7.80 (4H, s, Ar), 7.64–7.62 (4H, m, Ar), 7.54–7.51 (6H, m, Ar); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C (ppm) 166.8, 160.2, 158.2, 139.5, 136.1, 135.3, 129.9, 129.4, 127.5, 115.7, 115.4, 93.7, 87.5; IR (KBr) (ν_{max}/cm^{-1}): 3407 (NH), 3325 (NH), 2216 (CN).

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References

[1] (a) V. Perrier, A.C. Wallace, K. Kaneko, J. Safar, S.B. Prusiner, F.E. Cohen, Proc. Natl Acad. Sci. U S A 97 (2000) 6073;
(b) T.R.K. Reddy, R. Mutter, W. Heal, K. Guo, V.J. Gillet, S. Pratt, B. Chen, J. Med. Chem. 46 (2006) 607;
(c) B.C.H. May, J.A. Zorn, J. Witkop, J. Sherrill, A.C. Wallace, G. Legname, S.B. Prusiner, F.E. Cohen, J. Med. Chem. 50 (2007) 65.
[2] H. Chen, W. Zhang, R. Tam, A.K. Raney, PCT Int. Appl. WO 2005058315 A1 20050630, 2005.
[3] S.B. Levy, M.N. Alekshun, B.L. Podlogar, K. Ohemeng, A.K. Verma, T. Warchol, B. Bhatia, T. Bowser, M. Grier, US Patent Appl., 2005124678 A1 20050609, 2005.
[4] (a) M.T. Cocco, C. Congiu, V. Lilliu, V. Onnis, Eur. J. Med. Chem. 40 (2005) 1365;
(b) D.R. Anderson, N.W. Stehle, S.A. Kolodziej, E.J. Reinhard, PCT Int. Appl. WO 2004055015 A1 20040701, 2004.
[5] H. Harada, S. Watanuki, T. Takuwa, K. Kawaguchi, T. Okazaki, Y. Hirano, C. Saitoh, PCT Int. Appl. WO 2002006237 A1 20020124, 2002.
[6] A.A. Nirschl, L.G. Hamann, US Pat. Appl. Publ. US 2,005,182,105 A1 20,050,818, 2005.
[7] (a) M.W. Beukers, L.C.W. Chang, J.K.F.D. Künzel, T. Mulder- Krieger, R.F. Spanjersberg, J. Brussee, A.P.I. Jzerman, J. Med. Chem. 47 (2004) 3707;
(b) L.C.W. Chang, J.K.F.D. Künzel, T. Mulder-Krieger, R.F. Spanjersberg, S.F. Roerink, G. Hout, M.W. Beukers, J. Brussee, A.P.I. Jzerman, J. Med. Chem. 48 (2005) 2045;
(c) U. Rosentreter, T. Kraemer, M. Shimada, W. Huebsch, N. Diedrichs, T. Krahn, K. Henninger, J.P. Stasch, DE 10238113 A1 20030618, 2003;
(d) U. Rosentreter, T. Kraemer, A. Vaupel, W. Huebsch, N. Diedrichs, T. Krahn, K. Dembowsky, J.P. Stasch, M. Shimada, WO 2002079195 A1 20021010, 2002;
(e) U. Rosentreter, T. Kraemer, A. Vaupel, W. Huebsch, N. Diedrichs, T. Krahn, K. Dembowsky, J.P. Stasch, WO 2002070520 A1 20020912, 2002;
(f) U. Rosentreter, T. Kraemer, A. Vaupel, W. Huebsch, N. Diedrichs, T. Krahn, K. Dembowsky, J.P. Stasch, WO 2002070485 A1 20020912, 2002;
(g) U. Rosentreter, R. Henning, M. Bauser, T. Kraemer, A. Vaupel, W. Huebsch, K. Dembowsky, O. Salcher-Schraufstaetter, J.P. Stasch, T. Krahn, E. Perzborn, WO 2001025210 A2 2001041 2, 2001.
[8] B.B. Fredholm, A.P.I. Jzerman, K.A. Jacobson, K.N. Klotz, J. Linden, Pharmacol. Rev. 53 (2001) 527.
[9] (a) N.M. Evdokimov, I.V. Magedov, A.S. Kireev, A. Kornienko, Org. Lett. 8 (2006) 899;
(b) K. Guo, M.J. Thompson, T.R.K. Reddy, R. Mutter, B. Chen. Tetrahedron 63 (2007) 5300.
[10] N.M. Evdokimov, A.S. Kireev, A.A. Yakovenko, M.Y. Antipin, I.V. Magedov, A. Kornienko, J. Org. Chem. 72 (2007) 3443.
[11] R. Mamgain, R. Singh, D.S. Rawat, J. Heterocycl. Chem. 46 (2009) 69.
[12] K. Guo, M.J. Thompson, B. Chen, J. Org. Chem. 74 (2009) 6999.
[13] M.L. Kantam, K. Mahendar, S. Bhargava, J. Chem. Sci. 122 (2010) 63.
[14] S. Banerjee, G. Sereda, Tetrahedron Lett. 50 (2009) 6959.
[15] K.N. Singh, S.K. Singh, ARKIVOC xiii (2009) 153.
[16] P.V. Shinde, B.B. Shingate, M.S. Shingare, Bull. Korean Chem. Soc. 32 (2011) 459.
[17] P.V. Shinde, B.B. Shingate, M.S. Shingare, Chin. J. Chem. 29 (2011) 1049.
[18] M.M. Heravi, M. Khorshidi, Y.S. Beheshtia, B. Baghernejad, Bull. Korean Chem. Soc. 31 (2010) 1343.
[19] S. Mishra, R. Ghosh, Synth. Commun. 42 (2012) 2229.
[20] P.V. Shinde, V.B. Labade, B.B. Shingate, M.S. Shingare, J. Mol. Catal. A: Chem. 336 (2011) 100.
[21] M.R. Poor Heravi, F. Fakhr, Tetrahedron Lett. 52 (2011) 6779.
[22] M. Sridhar, B.C. Ramanaiah, C. Narsaiah, B. Mahesh, M. Kumaraswamy, K.K.R. Mallu, V.M. Ankathi, P.S. Rao, Tetrahedron Lett. 50 (2009) 3897.
[23] S. Takale, J. Patil, V. Padalkar, R. Pisal, A. Chaskar, J. Braz. Chem. Soc. 23 (2012) 966.
[24] P.V. Shinde, S.S. Sonar, B.B. Shingate, M.S. Shingare, Tetrahedron Lett. 51 (2010) 1309.
[25] B.C. Ranu, R. Jana, S. Sowmiah, J. Org. Chem. 72 (2007) 3152.
[26] A. Davoodnia, P. Attar, H. Eshghi, A. Morsali, N. Tavakoli-Hoseini, A. Tavakoli-Nishaburi, Asian. J. Chem. 23 (2011) 1273.
[27] (a) T. Welton, Chem. Rev. 99 (1999) 2071;
(b) P. Wasserscheid, W. Keim, Angew. Chem. Int. Ed. 39 (2000) 3772;
(c) T. Welton, Coord. Chem. Rev. 248 (2004) 2459;
(d) X. Mi, S. Luo, J.P. Cheng, J. Org. Chem. 7 (2005) 2338.
[28] (a) R.V. Hangarge, D.V. Jarikoteb, M.S. Shingare, Green Chem. 4 (2002) 266;
(b) V. Singh, S. Kaur, V. Sapehiyi, Catal. Commun. 6 (2005) 57.
[29] P. Wasserscheid, T. Welton (Eds.), Ionic Liquid in Synthesis, Wiley-VCH, Weinheim, 2004.
[30] R.F.M. Frade, C.A.M. Afonso, Hum. Exp. Toxicol. 29 (2010) 1038.
[31] (a) S. Sobhani, Z. Pakdin Parizi, Tetrahedron 67 (2011) 3540;
(b) S. Sobhani, Z. Pakdin Parizi, N. Razavi, Appl. Catal. A: Chem. 169 (2011) 409;
(c) S. Sobhani, A. Vafaee, J. Iran. Chem. Soc. 7 (2010) 227;
(d) S. Sobhani, A. Vafaee, Synthesis (2009) 1909;

(e) S. Sobhani, Z. Tashrifi, Heteroat. Chem. (2009) 109;
(f) S. Sobhani, Z. Tashrifi, Synth. Commun. 39 (2009) 120;
(j) S. Sobhani, E. Safaei, M. Asadi, F. Jalili, J. Organomet. Chem. 693 (2008) 3313;
(h) S. Sobhani, E. Safaei, M. Asadi, F. Jalili, Z. Tashrifi, J. Porphyrins Phthalocyanines 12 (2008) 849.

[32] (a) S. Sobhani, M. Honarmand, J. Iran. Chem. Soc. 9 (2012) 661;
(b) S. Sobhani, R. Nasseri, M. Honarmand, Can. J. Chem. (2012), http://dx.doi.org/10.1139/v2012-059.
[33] S.J. Zhang, X.L. Yuan, Y.H. Chen, Y.Q. Zhang, Chin Patent 10069408.5, 2005.
[34] Z.Q. Wang, Z.M. Ge, T.M. Cheng, R.T. Li, Synlett. (2009) 2020.