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One pot synthesis of penta substituted pyridine 2-amino-6-((2-aminophenyl) sulfanyl)-4-aryl pyridine-3,5-dicarbonitriles derivatives using sodium bicarbonate as the catalyst in binary mixture of ethanol-water as a solvent.

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Abstract: An efficient one pot synthesis of 2-amino-6-((2-aminophenyl)sulfanyl)-4-arylpyridine-3,5-dicarbonitriles derivatives was investigated via the three-component condensation of a variety of aromatic aldehydes, 2-amino thiophenol and malanonitrile catalyzed by sodium bicarbonate in binary mixture of ethanol-water as a solvent. The main highlights of the present synthetic strategy is short reaction time, consistently excellent yield, use of readily available catalytic system, low catalyst loading and simple workup procedure.

Keywords: Pyridine derivatives, 2-amino thiophenol, one pot synthesis, catalyst

1. Introduction

Substituted pyridine derivatives are constituent of a wide range of naturally occurring and synthetic bioactive compounds. They have considerable chemical and pharmacological important because of a broad range of biological activities displayed by these class of compounds [1]. Among these, pyridine ring with thio contain groups at 6th position especially 2-amino-3,5-dicarbonitrile-6-thio pyridine derivatives furnishes a class of medicinally significant compounds. They are important heterocyclic compounds having important biological activities such as anti hepatitis [2], antibacterial [3], anticancer agent [4], antipirone [5], non- nucleoside agents of human adenosine A_1 [6], an inhibitor of *HIV*-1 integrase [7], anti-inflammatory agents, analgesics and muscle relaxants [8-11]. These compounds can inhibit the accumulation of PrP^{sc} in the regulation of androgenic receptor [12].

The various methodologies have been described for the synthesis of 3,5- dicarbonitrile-6-thio pyridine derivatives. However existing methods suffer with some drawbacks such as low yield, prolonged reaction time, harsh

reaction conditions, inevitable side products, product isolation and purification. There are several methods for synthesis of penta substituted pyridines have been reported using triethyl amine [8], DABCO [13], piperidine and tetrabutylammonium hydroxide [10], $ZnCl_2$ [14], silica nano particles [15], KF-Al_2O_3 [16], TBAF [17], [bmim]BF_4, [18], $ZrOCl_2.8H_2O/NaNH_2$ [19], DMSO containing dimsyl sodium [20], ammonium hydroxide [21], phosphotungstic acid in aqueous medium [22], K_2CO_3 [23] as well as zinc(II) and Cd(II) metal-organic frameworks [24] as a catalyst. These all reports have shown up to 70% to 90% yield of synthesized compounds. They are not as mush cost effective. Generally all reported method containing use of very costly catalyst while some are tedious when remove in work up procedure and so it is necessary to develop a method, which can be use very descent manner and which increase the yield and not required further purification. Many researchers have also been reported use of ionic liquid such as SO_3H functional acidic ionic liquids [25-26], 1-(2-amino ethyl)pyridinium hydroxide [AEPy] [OH] [27], [bmim]Br [28] and 2-hydroxy ethylammonium acetate (2-HEAA) [29] but the synthesis and recovery of the catalyst is very tedious and cost consumable. In fact, searching for new, readily available and easily removable catalyst during workup for these compounds is still being actively pursued.

In our present work, we have chosen sodium bicarbonate as a catalyst. Our main purpose is to make the reaction cost effective with use of readily available catalyst which can be removed easily during work up. We synthesized some 2-amino-6-((2-aminophenyl)sulfanyl)-4-arylpyridine-3,5-dicarbonitriles derivatives in the presence of $NaHCO_3$ as a catalyst in binary mixture of ethanol-water as a solvent.

2. Materials and methods:

2.1 Chemistry

All chemicals were purchased and used without any further purification. Reactions were monitored by thin layer chromatography (TLC) on silica gel-G plates of 0.5 mm thickness, visualizing with ultraviolet light. Melting points were recorded in open capillary tubes and are uncorrected. IR spectra were recorded on Shimadzu FT-IR-8400 instrument using DRS (diffusive reflectance system) method and are expressed in cm^{-1} (KBr). Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using direct inlet probe technique. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 MHz and Bruker DRX 100 MHz spectrometer in DMSO-d_6 respectively. Chemical shift values (δ) are expressed in (parts per million) ppm relative to TMS. Elemental analysis of the all the synthesized compounds were carried out on Euro EA 3000 elemental analyzer and the results are in agreements with the structures assigned.

2.2 General procedure for synthesis of 2-Amino-6-((2-aminophenyl)thio)-4-(substitutedphenyl) pyridine-3,5-dicarbonitriles (5a-5t):

In a typical experiment, substituted aromatic aldehyde (10 mmol) and malononitrile (20 mmol) in 10 mL 1:1 (v/v) EtOH–H_2O taken and $NaHCO_3$ (10 mol %) were added. The reaction was stirred at room temperature for 1 minute in a round-bottomed flask and then the 2-amino thiophenol (10 ammol) was added. The mixture was stirred continuously for 7 minute under reflux condition at 110°C temperature. On completion of the reaction monitored by TLC, the solid was separated by filtration and washed with water followed by ethanol to obtained analytical grade pure product. All products were characterized by IR, ^1H NMR, ^{13}C NMR and M.P. by comparison with literature data (Table 5).

2.3 Spectral data for representative compound:

2-Amino-6-((2-aminophenyl)thio)-4-(4-fluorophenyl)pyridine-3,5-dicarbonitrile (5e)

^{1}H NMR (DMSO-d_6,400 MHz) δppm: 7.72 (m, 2H,-NH_2), 7.62 (m, 2H, ArH), 7.20 (t, J = 3.4 Hz, 3H, ArH), 6.81 (s, 1H, ArH), 6.58 (s, 1H, ArH), 6.51 (s, 1H, ArH), 5.44 (m, 2H, -NH_2); ^{13}C NMR(DMSO-d_6,100 MHz) δppm: 166.76,164.33, 161.87, 159.56, 157.41, 151.22, 137.18, 131.72, 131.06, 130.97, 130.38, 116.31, 115.98, 115.76, 115.15, 107.32, 93.58, 86.43, 56.00; IR(KBr) v: 3414, 3327, 3223, 2218, 1639, 1543, 1419, 1309, 1236, 1159, 1026, 840, 752, 5 34 cm^{-1}; ES-MS m/z: 361.04 (M^+); Anal. Calcd. for $C_{19}H_{12}FN_5S$; C, 63.15; H, 3.35; N, 19.38; Found: C, 63.20; H, 3.37; N, 19.40%.

2-Amino-6-((2-aminophenyl)thio)-4-(3-methoxyphenyl)pyridine-3,5-dicarbonitrile (5c)

^{1}H NMR (DMSO-d_6,400 MHz) δppm: 7.75 (m, 2H,-NH_2), 7.47 (s, 1H, ArH), 7.27(m,2H), 7.19 (d, J = 1.4 Hz, 1H, ArH), 7.10 (d, J = 20.1 Hz, 2H, ArH), 6.70 (s, 1H, ArH), 6.50 (s, 1H, ArH), 5.44 (m, 2H, -NH_2), 3.82 (s, 3H, -OCH_3); ^{13}C NMR(DMSO-d_6,100 MHz) δppm: 166.73, 159.59, 159.03, 158.10, 151.22, 137.21, 135.26, 131.71, 130.04, 120.45, 116.33, 115.73, 115.59, 115.25, 114.01, 107.39, 93.49, 86.31, 55.30; IR (KBr) v: 3437, 3325, 3213, 2970, 2841, 2210, 1631, 1543, 1508, 1450, 1244, 1184, 1030, 945, 842, 775, 682, 534, 480 cm^{-1}; ES-MS m/z: 372 $(M-H)^+$; Anal. Calcd. for $C_{20}H_{15}N_5OS$; C, 64.33; H, 4.05; N, 18.75; Found: C, 64.35; H, 4.00; N, 18.73%.

2-Amino-6-((2-aminophenyl)thio)-4-(4-bromophenyl)pyridine-3,5-dicarbonitrile (5q)

^{1}H NMR (DMSO-d_6,400 MHz) δppm: 7.80 (m, 2H,-NH_2), 7.77 (m, 2H, ArH), 7.52 (m, 2H, ArH), 7.22 (s, 1H, ArH), 6.81 (s, 1H, ArH), 6.60 (s, 1H, ArH), 6.56 (s, 1H, ArH) 5.44 (m, 2H, -NH_2); ^{13}C NMR(DMSO-d_6,100 MHz) δppm: 166.79, 159.52, 157.25, 151.21, 137.17, 133.24, 131.83, 130.57, 124.05, 116.32, 115.52, 115.06, 107.30, 93.34, 86.19; IR (KBr) v: 3338, 3217, 2214, 1631, 1539, 1485, 1309, 1259, 1147, 1076, 1020, 831, 754, 675, 551, 486 cm^{-1}; ES-MS m/z: 420 (M^+), 422 $(M+2)^+$; Anal. Calcd. for $C_{19}H_{12}BrN_5S$; C, 54.04; H, 2.86; N, 16.58; Found: C, 54.10; H, 2.87; N, 16.50 %.

3. Results and discussion

Initially, one-pot three component condensation reaction of *p*-flouro benzaldehyde, malanonitrile and 2-amino thiophenol was carried out as a model reaction in 1:1 (*v/v*) EtOH-H_2O binary mixture at room temperature for different length of time to investigate catalytic performance. One more thing, if reaction is carried out in multistep then yield of product decreases so we have carried out the reaction in one-pot without isolation of the arylidine intermediate which is generated by the reaction between aromatic aldehyde and malanonitrile.

It was shown that no desired product could be detected when a mixture of benzaldehyde, malanonitrile and thoiphenol was stirred at room temperature for 240 min in the absence of catalyst, which indicated that catalysts were necessary for this one-pot three-component reaction. Among these catalysts, $NaHCO_3$ was the best for this reaction at those conditions. To determine the appropriate concentration of the sodium bicarbonate catalyst, we investigated the model reaction at different concentration (Table 1).

Table 1 Screening of $NaHCO_3$ catalyst molar ratio at 27 ^{0}C

Entry	Molar ratio (mol%)	Time (min.)	Yield (%)
1	-	240	-
2	2	35	30
3	4	35	62
4	6	35	70
5	8	35	75
6	**10**	**35**	**82**
7	12	35	82
8	15	35	82
9	20	35	82
10	25	35	82

Optimal loading of $NaHCO_3$ was revealed to be 10 mol% (Table-1, entry 6) as it gave highest yield (82%). With increase of catalyst ratio up to 25%, there was no increase in yield. Therefore, the condition described in Table 1, entry 6 was found to be optimal for the highest conversion into product.

To determine the effect of solvents, we examined reaction in different solvents as depicted in Table 2. It can be noted that the polar protic solvents such as ethanol, methanol and water gave better yields than polar aprotic solvents such as dichloromethane and acetonitrile. Considering the reaction rate and yield, a mixture of EtOH and H_2O (1:1) was confirmed to be the optimum medium (Table 2, entry 7).

Table 2 $NaHCO_3$ catalyzed model reaction in different solvents

Entry	Solvent	Time (min.)	Isolated yield (%)
1	H_2O	35	66
2	MeOH	35	70
3	EtOH	35	82
4	DMF	35	58
5	CH_3CN	35	75
6	CH_2Cl_2	35	25
7	**EtOH-H_2O**	**35**	**82**

We further investigated the effect of temperature on the rate of reaction. For this purpose the reaction was carried out at different temperatures (Table 3, entry 1-10). It was observed that the reaction rate enhanced significantly with increased temperature up to 110^{o}C. At that temperature percentage of isolated yield was maximum(entry 10).

Table 3 Effect of temperature

Entry	Temperature (^{o}C)	Time (min.)	Isolated Yield (%)
1	30	35	58
2	35	30	60
3	40	27	63
4	50	25	68
5	55	22	72
6	65	18	78
7	75	15	82
8	85	13	85
9	100	12	88
10	**110**	**10**	**90**

The results obtained with benzaldehyde, malononitrile, and 2-amino thiophenol under the optimized conditions were compared with literature results reported for use of other catalysts in this reaction. Table 4 shows that the sodium bicarbonate was a relatively a good catalyst for synthesis of 2-amino-6-((2-aminophenyl)thio)-4-(substitutedphenyl) pyridine-3,5-dicarbonitriles.

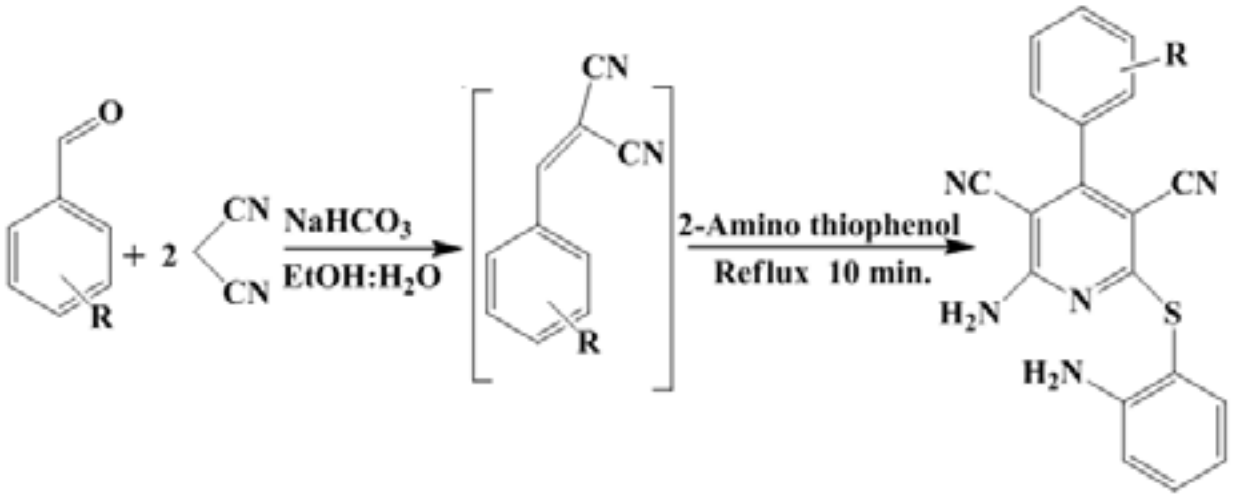
Table 4 Comparison of our results with those from previously reported methods

Entry	Catalyst	Reaction conditions	Time (min.)	Yield (%)
1	$ZnCl_2$	EtOH/reflux or EtOH/MW	120 or 2	65
2	DBU	10 % H_2O in EtOH/ 35 ^{0}C	15	80
3	[bmim]BF_4	50 ^{0}C	30	82
4	[AEPy][OH]	1:1 (v/v) EtOH–H_2O/r.t.	30	85
5	$KF.Al_2O_3$	EtOH/r.t.	30	87
6	Piperidine	EtOH/reflux	180	88
7	[bmim]OH	EtOH/r.t.	61	92
8	$ZrOCl_2.8H_2O$/ $NaNH_2$ (20 mol %)	[bmim] BF_4,Ultrasound irradiation, r.t.	5	95
9	**$NaHCO_3$ (10 mol%)**	**1:1 (v/v) EtOH–H_2O,110^{o}C**	**10**	**90**

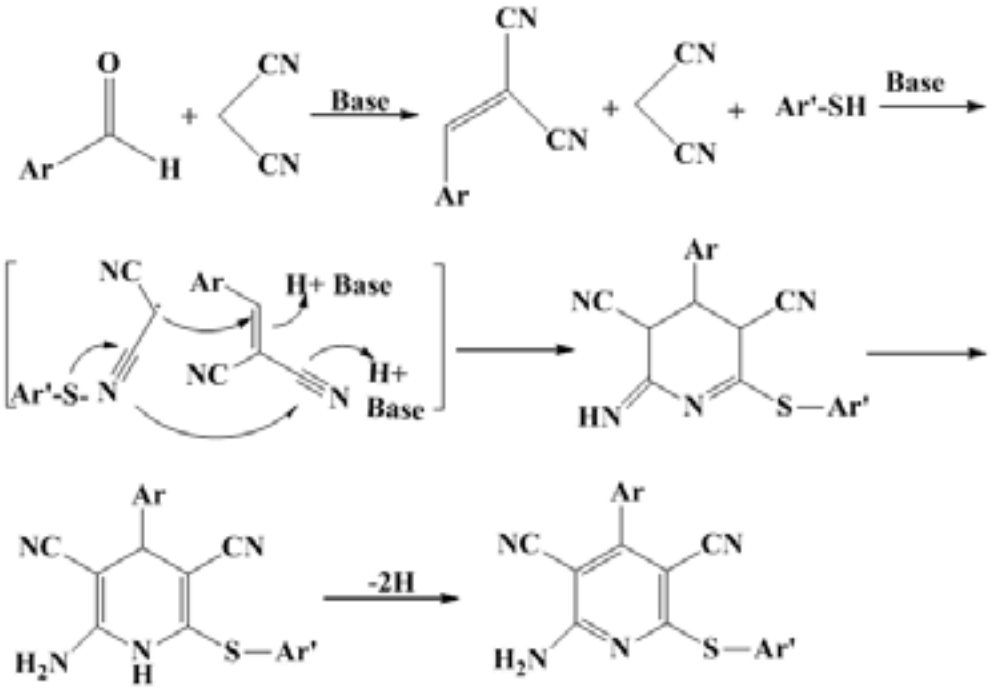
Table 5 Synthesis of 2-amino-3,5-dicarbonitrile-6-thio pyridines

Entry	Substitution R	Time (Min.)	Yield (%)	M.P. (^{o}C)
5a	H	10	90	189-191
5b	4-CH_3	12	91	179-181
5c	3-OCH3	11	92	178-180
5d	4-Cl	11	88	188-190
5e	4-F	10	92	226-228
5f	3,4-$(OCH_3)_2$	15	89	221-223
5g	3-Cl	12	90	231-233
5h	2-Cl	11	92	173-175
5i	4-COOH	13	88	212-214
5j	4-OH	15	91	199-201
5k	2,5-$(OCH_3)_2$	14	92	156-158
5l	1-Nepthyl	11	93	123-124
5m	4-N$(CH3)_2$	12	88	157-159
5n	3-indolyl	10	87	153-155
5o	2-OH	11	90	127-129
5p	Hydrocinnamyl	12	88	110-112
5q	4-Br	11	90	113-115
5r	Cinnamamyl	12	92	199-201
5s	2,4-Cl_2	10	90	182-183
5t	9-anthracyl	10	87	171-173

Reaction conditions: Aldehyde (10 mmol), 2-amino thiophenol (10 mmol), malanonitrile (20 mmol), $NaHCO_3$ (10 mol %) and 1:1 (v/v) EtOH–H_2O (10 ml), reflux.



Scheme 1 Standard model reaction



Scheme 2 A plausible mechanism of reaction

4. Conclusions

In summary, we have demonstrated a most concise, highly efficient and facile protocol for the synthesis of 2-amino-3,5-dicarbonitrile-6-thio derivatives. This approach features products in good to excellent yield within short reaction time. In addition, present method offers marked improvements with regard to easy work up and less possibility of unwanted side reactions. This method is less laborious than our previously reported method.

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