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Tetrabutylammonium bromide-Cesium carbonate: new reagent system for the synthesis of substituted pyridines at room temperature

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Abstract

The highly substituted pyridine derivatives are found to exhibit diverse pharmacological activities. They are also emerged as potential medicinal leads in developing therapeutic agents for the treatment of various diseases. In this work, a series of 2-amino-3,5-dicarbonitrile-6-thio-pyridine derivatives have been synthesized at room temperature via one-pot, multi-component reaction of various aromatic aldehydes, malononitrile and thiophenols using catalytic amount of tetrabutylammonium bromide (TBAB) and cesium carbonate in methanol. In the mentioned method, the use of thermal condition is avoided. In addition, the advantages such as operational simplicity, economic viability, ecologically benign nature make this protocol a very efficient alternative to the literature methods.

Keywords: aldehydes; malononitrile; thiophenol; substituted pyridines; tetrabutylammonium bromide; cesium carbonate.

Introduction

Pyridine nucleus is a medicinally useful scaffold which occurs in wide variety of both naturally and synthetic bioactive compounds [1]. The highly substituted pyridine derivatives, like 2-amino-4-aryl-3,5-dicyano-6-

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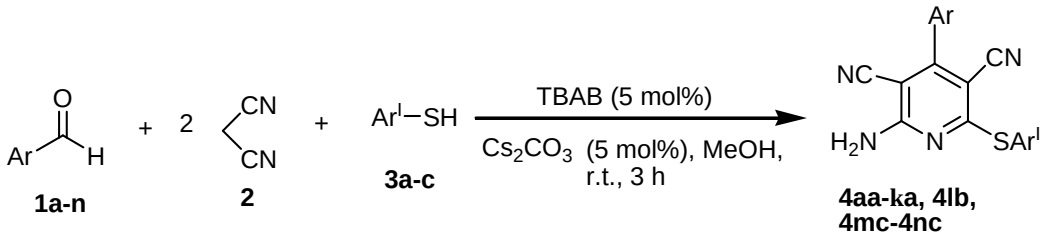
sulfonyl pyridines exhibit diverse pharmacological activities and are useful as antibacterial [2], anti-prion [3], anti-hepatitis B virus [4], anti-cancer[5] agents, and as potassium channel openers for the treatment of urinary incontinence [6]. In addition, many of these compounds which are found to be highly selective ligands for adenosine receptors [7], are also 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 [8]. They are also emerged as potential medicinal leads in developing therapeutic agents for the treatment of Creutzfeldt-Jacob disease [9].

Owing to the broad utility of substituted pyridine derivatives, various methods have been employed for their preparation. These includes ruthenium-catalyzed cycloisomerization of 3-azadienynes [10], hetero-Diels-Alder reaction of 3-siloxy-1-aza-1,3-butadines and 2*H*-1,4-oxazinones with acetylenes [11], Mannich reaction of aldehydes and iminium salts [12], Vilsmeier-Haack reaction of α-hydroxy ketene dithioacetals [13], catalytic oxidation of 1,4-dihydropyridines by $RuCl_3/O_2$[14], [4+2] cycloaddition of oximinosulfonates [15], conversion of conjugated oximes under Vilsmeier conditions [16], the reaction of N-methylene tert-butylamine with enamines [17], and conversion of ketene dithioacetals to substituted pyridines [18].

Recently, several elegant multi-component strategies for the synthesis of substituted pyridines by the cyclocondensation of aldehydes, malononitrile and thiols utilizing different types of catalysts have been reported. These includes Et_3N/DABCO [19], [bmim]OH [20], DBU [21], TBAH [22], $ZnCl_2$[23], boric acid [24], KF/alumina [25], nanocrystalline magnesium oxide [26], silica nanoparticles [27], $ZrOCl_2.8H_2O/NaNH_2$ in ionic liquid [bmim]BF_4[28], and iodoxybenzoic acid [29]. The reported methods show varying degrees of successes as well as limitations such as harsh reaction conditions, expensive catalyst/reagent usage, toxic organic solvents, low product yields, long reaction times, and co-occurrence of several side products. Therefore, there still remains a high demand for the development of more general, efficient, economically viable, and eco-compatible protocol to assemble such scaffolds.

Tetrabutylammonium bromide (TBAB) is a low cost, mild, water-tolerant catalyst and has found to be effective in various organic transformations such as Biginelli-type reaction [30], synthesis of biscoumarine and

3,4-dihydropyrano[*c*]chromene derivatives [31], and highly substituted imidazole derivatives [32]. In addition, TBAB which is one of the most common phase-transfer (PT) catalysts; is employed in numerous C–C, C–N, C–O, C–S, and C–P bond forming reactions performed under liquid–liquid and liquid–solid phase-transfer catalysis (PTC) conditions, as well as in halogenation and oxidation reactions [33]. Among these, many C–C, and C–N bond forming reactions have been carried out by using catalytic amount of TBAB and inorganic bases [34-39]. This has prompted us to explore TBAB as a catalyst for the synthesis of substituted pyridines. Herein, we report a mild and practical method for the synthesis of highly substituted pyridines (**4a-n**) from the reaction of aldehyde (**1a-n**), malononitrile (**2**) and thiophenols (**3a-c**) in the presence of tetrabutylammonium bromide (5 mol%) in combination with cesium carbonate (5 mol%) in methanol at room temperature (Scheme 1).



1a-n **2** **3a-c** **4aa-ka, 4lb, 4mc-4nc**

Scheme 1

Experimental

Materials and instruments

All chemicals were purchased from Aldrich Chemical Co., USA, and were used without further purification. Melting points were determined on a Veego apparatus and are uncorrected. The FT-IR spectra of compounds were recorded on a Perkin–Elmer System 1600 FTIR instrument using KBr pellets. ^{1}H NMR spectra were recorded on a Bruker 400 MHz instrument in DMSO-d_6 with chemical shifts reported in ppm relative to the internal standard tetramethylsilane. Mass spectra were recorded on a Shimadzu LCMS-QP 1000 EX spectrophotometer.

Typical experimental procedure

A mixture of benzaldehyde **1a** (1 mmol), malononitrile **2** (2 mmol), thiophenol **3a** (1 mmol), tetrabutylammonium bromide (5 mol%) and cesium carbonate (5 mol%) in methanol (10 mL) was vigorously stirred at room temperature for 3 h. Upon completion of the reaction (TLC), the obtained crystalline product was filtered, washed with water (25 mL), and dried in vacuo. The obtained crude product was recrystallized from

aqueous methanol in order to have pure product. This procedure was applied in obtaining all the products.

Spectral data of synthesized compounds

2-Amino-4-phenyl-6-(phenylsulfanyl)-3,5-pyridinedicarbonitrile (4a)

Mp: 217-218 ^{o}C (Lit. [23] mp: 216-218 ^{o}C); ^{1}H NMR (DMSO-d_6) δ = 7.55 (m, 3H), 7.67 (m, 7H), 7.89 (bs, 2H); IR (KBr): 3420, 3365, 3060, 2215, 2210, 1620, 1545, 1515, 1460, 1265, 765 cm^{-1}; Anal. Calcd for $C_{19}H_{12}N_4S$ (328.39): C, 69.49; H, 3.69; N, 17.06; Found: C, 69.35; H 3.59; N, 16.95; Es-MS: 329.24 (M+1).

2-Amino-4-(4-methylphenyl)-6-(phenylsulfanyl)-3,5 pyridinedicarbonitrile (4b)

Mp: 210-211^{o}C (Lit. [23] mp: 208-211 ^{o}C); ^{1}H NMR (DMSO-d_6) δ = 2.45 (s, 3H), 7.36-7.48 (m, 6H), 7.50-7.55 (m, 3H), 7.90 (bs, 2H);IR (KBr):3475, 3350, 3215,2920, 2215, 1610, 1535, 1510, 1305, 1255, 1120, 1020, 875, 760 cm^{-1}; Anal. Calcd for $C_{20}H_{14}N_4S$ (342.42): C, 70.15; H, 4.12; N, 16.36. Found: C, 70.05; H, 4.23; N, 16.21; Es-MS: 343.30 (M+1).

2-Amino-4-(4-fluorophenyl)-6-(phenylsulfanyl)-3,5 pyridinedicarbonitrile (4c)

Mp: 222-223^{o}C (Lit. [23] mp: 221-223 ^{o}C); ^{1}H NMR (DMSO-d_6) δ = 7.41-4.48 (m, 3H), 7.50-7.70 (m, 6H), 8.05 (bs, 2H); IR (KBr): 3450, 3345, 3210, 2210, 1630, 1605, 1545, 1525, 1515, 1465, 1260, 1160, 1025, 850, 785 cm^{-1}; Anal. Calcd for $C_{19}H_{11}FN_4S$ (346.38): C, 65.88; H, 3.20; N, 16.17; Found: C, 65.70; H, 3.25; N, 16.20; Es-MS: 347.14 (M+1).

2-Amino-4-(4-chlorophenyl)-6-(phenylsulfanyl)-3,5 pyridinedicarbonitrile (4d)

Mp: 221-222 ^{o}C (Lit. [24] mp: 222-223 ^{o}C); ^{1}H NMR (DMSO-d_6) δ = 7.50 - 7.70 (m, 9H), 7.87 (bs, 2H); IR (KBr): 3455, 3340, 3215, 2210, 1635, 1602, 1541, 1520, 1512, 1460, 1260, 1160, 1025, 780 cm^{-1}; Anal. Calcd for $C_{19}H_{11}ClN_4S$ (362.84): C, 62.89; H, 3.06; N, 15.14; Found: C, 62.50; H, 2.95; N, 15.33; Es-MS: 363.05 (M+1).

2-Amino-4-(4-nitrophenyl)-6-(phenylsulfanyl)-3,5 pyridinedicarbonitrile (4e)

Mp: 288-289^{o}C (Lit. [23] mp: 287-289 ^{o}C); ^{1}H NMR (DMSO-d_6) δ = 7.48-7.53 (m, 3H), 7.62-7.66 (m, 2H), 7.82-786 (d, 2H), 8.05 (bs, 2H), 8.34 (d, 2H); IR (KBr): 3440, 3320, 3215, 3075, 2930, 2835, 2215, 1635, 1550, 1530, 1465, 1260, 1175, 1005, 820, 795 cm^{-1}; Anal. Calcd for $C_{19}H_{11}N_5O_2S$ (373.39): C, 61.12; H, 2.97; N, 18.76. Found: C, 60.94; H, 2.95; N, 18.90.

2-Amino-4-(4-hydroxy-3-methoxyphenyl)-6-(phenylsulfanyl)-3,5–pyridinedicarbonitrile (4f)

Mp: 218-219^{o}C (Lit. [24] mp: 216-218 ^{o}C); ^{1}H NMR (DMSO-d_6) δ = 3.80 (s, 3H), 6.95-7.03(m, 5H), 7.14 (s, 1H), 7.50 (d, 2H), 7.65 (bs, 2H), 9.05 (s, 1H); IR (KBr): 3476, 3375, 3236, 2212, 2190, 1642, 1552, 1465, 1442, 1256, 1216, 1194, 1022, 780 cm^{-1}; Anal. Calcd for $C_{20}H_{14}N_4O_2S$ (374.42): C, 64.16; H, 3.77; N, 14.96; Found: C, 64.24; H, 3.65; N, 14.90.

2-Amino-4-(3,4-dimethoxyphenyl)-6-(phenylsulfanyl)-3,5 pyridinedicarbonitrile (4g)

Mp: 225-227 ^{o}C (Lit. [23] mp: 226-228 ^{o}C); ^{1}H NMR (DMSO-d_6) δ = 3.84 (s, 3H), 3.90 (s, 3H), 7.15-7.23 (m, 2H), 7.28 (d, 1H), 7.55-7.65 (m, 5H), 7.65 (bs, 2H); IR (KBr): 3430, 3335, 3220, 2975, 2930, 2837, 2215, 1685, 1650, 1650, 1640, 1600, 1550, 1530, 1520, 1463, 1450, 1424, 1335, 1310, 1260, 1230,1145,1024,758, 710 cm^{-1}; Anal. Calcd for $C_{21}H_{16}N_4O_2S$ (388.45): C, 64.93; H, 4.16; N, 14.43; Found: C, 64.75; H, 4.05; N, 14.57.

2-Amino-4-(4-methoxyphenyl)-6-(phenylsulfanyl)-3,5 pyridinedicarbonitrile (4h)

Mp: 242-243 ^{o}C (Lit. [24] mp: 242-243 ^{o}C); ^{1}H NMR (DMSO-d_6) δ = 3.86 (s, 3H), 7.12-7.15 (m, 3H), 7.48-7.56 (m, 6H), 7.66 (bs, 2H); IR (KBr): 3440, 3335, 3224, 2840, 2216, 1642,1576, 1550, 1534, 1188, 1018, 816, 756 cm^{-1}; Anal. Calcd for $C_{20}H_{14}N_4OS$ (358.42): C, 67.02; H, 3.94; N, 15.63; Found: C, 66.75; H, 3.90; N, 15.70.

2-Amino-4-(4-hydroxyphenyl)-6-(phenylsulfanyl)-3,5 pyridinedicarbonitrile (4i)

Mp: 315-316^{o}C (Lit. [24] mp: 314-316^{o}C); ^{1}H NMR (DMSO-d_6) δ = 6.93-7.12 (m, 3H), 7.39-7.49 (m, 6H), 7.70 (bs, 2H), 10.04 (bs, 1H);IR (KBr): 3650, 3460, 3365, 3236, 2221, 2216, 1632, 1610, 1595, 1552, 1510, 1470, 1425, 1354, 1250, 1171, 1012, 846, 782 cm^{-1}; Anal. Calcd for $C_{19}H_{12}N_4OS$ (344.39): C, 66.26; H, 3.52; N, 16.27; Found: C, 66.05; H, 3.60; N, 16.20.

2-Amino-4-(2-thienyl)-6-(phenylsulfanyl)-3,5-pyridinedicarbonitrile (4j)

Mp: 207-209 ^{o}C (Lit. [24] mp: 208-210 ^{o}C); ^{1}H NMR (DMSO-d_6) δ = 7.20 (t, 1H), 7.45–7.55 (m, 6H), 7.75 (bs, 2H), 7.90 (d, 1H); IR (KBr): 3440, 3365, 3215, 2970, 2215, 1620, 1520, 1255, 1065, 725 cm^{-1}; Anal. Calcd for $C_{17}H_{10}N_4S_2$ (334.42): C, 61.05; H, 3.02; N, 16.76; Found: C, 60.88; H, 2.95; N, 16.82; Es-MS: 335.25 (M+1).

2-Amino-4-(2-furfuryl)-6-(phenylsulfanyl-3,5-pyridinedicarbonitrile (4k)

Mp: 175-177 ^{o}C (Lit. [24] mp: 176-178 ^{o}C);

^{1}H NMR (DMSO-d_6) δ = 6.75 (t, 1H), 7.30 (d, 1H), 7.37–7.45 (m, 5H), 7.68 (bs, 2H), 7.98 (d, 1H); IR (KBr): 3410, 3325, 3220, 2982, 2212, 1655, 1520, 1265, 1030, 775 cm^{-1}.

2-Amino-4-(4-phenyl)-6-(4-methylphenylsulfanyl)-3,5-pyridinedicarbonitrile (4l)

Mp: 217-219 ^{o}C (Lit. [25] mp: 218-220 ^{o}C); ^{1}H NMR (DMSO-d_6) δ = 2.42 (s, 3H), 7.25-7.33 (m, 3H), 7.53-7.58 (m, 6H), 7.89 (bs, 2H);IR (KBr): 3430, 3320, 3204, 3057, 2918, 2217, 1630, 1545, 1458, 1310, 1170, 1025, 754 cm^{-1}; Anal. Calcd for $C_{20}H_{14}N_4S$(342.42): C, 70.15; H, 4.12; N, 16.36. Found: C, 70.25; H, 4.12; N, 16.42.

2-Amino-4-(4-phenyl)-6-(4-methoxyphenylsulfanyl)-3,5-pyridinedicarbonitrile (4m)

Mp: 226-227 ^{o}C (Lit. [25] mp: 228-229 ^{o}C); ^{1}H NMR (DMSO-d_6) δ = 3.90 (s, 3H), 7.12-7.17 (m, 3H), 7.45-7.59 (m, 6H), 7.82 (bs, 2H); IR (KBr): 3442, 3315, 3220, 3055, 2676, 2212, 1630, 1545, 1420, 1255, 1180, 1025, 790 cm^{-1}; Anal. Calcd for $C_{20}H_{14}N_4OS$(358.42): C, 67.02; H, 3.94; N, 15.63. Found: C, 66.95; H, 3.85; N, 15.65.

2-Amino-4-(4-methoxyphenyl)-6-(4-methoxyphenylsulfanyl)-3,5-pyridinedicarbonitrile (4n)

Mp: 218-219 ^{o}C (Lit. [25] mp: 218-220 ^{o}C); ^{1}H NMR (DMSO-d_6) δ = 3.91 (s, 3H), 3.97 (s, 3H), 7.12-7.18 (m, 4H), 7.54-7.59 (m, 4H), 7.77 (bs, 2H); IR (KBr): 3410, 3311, 3220, 2930, 2845, 2217, 1645, 1540, 1505, 1465, 1250, 1175, 1022, 830 cm^{-1}. Anal. Calcd for $C_{21}H_{16}N_4O_2S$(388.44): C, 64.93; H, 4.15; N, 14.42. Found: C, 64.80; H, 4.20; N, 14.39.

Results and discussion

Initially, we have screened the reaction of benzaldehyde (**1a**), malononitrile (**2**) and thiophenol (**3a**) under different reaction conditions. The reaction of benzaldehyde (**1a**, 1 mmol), malononitrile (**2**, 2 mmol), and thiophenol (**3a**, 1 mmol) in methanol at room temperature with 10 mol% of TBAB leads to a sticky product after a prolonged reaction time. On the other hand, the addition of cesium carbonate (10 mol%) with TBAB (10 mol%) dramatically enhanced the reactivity to give solid product **4aa** in 70% yield (Table 1, Entry 2). This result clearly demonstrates the need of cesium carbonate as co-catalyst for conversion of sticky product into solid product **4aa**. Using cesium carbonate alone (10 mol%) also resulted in the formation of sticky product after a prolonged reaction time (Table 1, Entry 3). Further optimization revealed that lower catalyst loading (TBAB: 5 mol%; Cs_2CO_3: 5 mol%) at room tempera-

ture in methanol was enough to complete the reaction within 3 h, and gave product **4aa** in 92% yield (Table 1, Entry 4). A reduced yield was observed when the amount of TBAB and Cs_2CO_3 was decreased respectively (Table 1, Entries 5-7). Subsequent screening of co-catalysts revealed that Cs_2CO_3 was the best additive of choice (Table 1, Entries 8-9).

Table 1: Synthesis of substituted pyridine **4aa** under various reaction conditions

Entry	TBAB (mol%)	Base (mol%)	Conditions	Yield[a] (%)
1	10	None	MeOH, rt, 7h	Sticky product
2	10	Cs_2CO_3 (10)	MeOH, rt, 7h	70
3	None	Cs_2CO_3 (10)	MeOH, rt, 7h	Sticky product
4	5	Cs_2CO_3 (5)	MeOH, rt, 3h	92
5	3	Cs_2CO_3 (3)	MeOH, rt, 6h	84
6	2	Cs_2CO_3 (2)	MeOH, rt, 7h	80
7	1	Cs_2CO_3 (1)	MeOH, rt, 9h	75
8	5	Na_2CO_3 (5)	MeOH, rt, 4h	78
9	5	K_2CO_3 (5)	MeOH, rt, 4h	75

[a]Isolated yields.

Next, in order to establish the effect of reaction medium on the yield of product **4aa**, we investigated various solvents such as ethanol, water, chloroform, PEG-400, acetonitrile and methanol for the reaction of benzaldehyde (**1a**), malononitrile (**2**) and thiophenol (**3a**) at room temperature. The results are summarized in Table 2. Methanol brought the reaction to completion efficiently to furnish the product **4aa** in excellent 92% yield (Table 2, Entry 6). Whereas, reaction in ethanol, water, chloroform, PEG-400 and acetonitrile resulted in low yields (60-80%) and require long reaction time (Table 2, Entries 1-5). The results summarized in Table 2 indicate that use of polar solvents is better as compared to non polar solvents.

Table 2: Effect of various solvent on the synthesis of substituted pyridine **4aa**

Entry	Reaction medium	Time (h)	Yield[a] (%)
1	EtOH	3.5	80
2	H_2O	7	60
3	$CHCl_3$	5	55
4	PEG-400	5.5	65
5	CH_3CN	6.5	50
6	MeOH	3	92

[a]Isolated yields.

Having established the best reaction conditions, variety of electronically divergent aldehydes with thiophenol, 4-methyl and 4-methoxy thiophenol were examined. Aromatic aldehydes with various functionalities such as Me, OMe, NO_2, F, Cl, OH were found to be compatible with the optimized reaction conditions. Heterocyclic aldehydes such as furan-2-carbaldehyde and thiophene-2-carbaldehyde were found to be well tolerated under optimized reaction conditions. For all examples excellent yields were obtained. Under the conditions described here, formation of products **4aa-4ka**, **4lb** and **4mc-4nc** is less sensitive to the nature of substituents on benzaldehyde. When the benzaldehyde bears electron donating or withdrawing substituents, products are obtained in 3 h with high yields. All the results are presented in Table 3.

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

Entry	Compound	Ar	Ar'	Yield[a] (%)
1	**4aa**	Ph	Ph	92
2	**4ba**	4-Me-Ph	Ph	90
3	**4ca**	4-F-Ph	Ph	89
4	**4da**	4-Cl-Ph	Ph	90
5	**4ea**	4-NO_2-Ph	Ph	90
6	**4fa**	3-OMe, 4-OH-Ph	Ph	88
7	**4ga**	3,4-OMe-Ph	Ph	87
8	**4ha**	4-OMe	Ph	91
9	**4ia**	4-OH-Ph	Ph	85
10	**4ja**	2-Thienyl	Ph	91
11	**4ka**	2-Furfuryl	Ph	90
12	**4lb**	Ph	4-Me-Ph	87
13	**4mc**	Ph	4-OMe-Ph	90
14	**4nc**	4-OMe-Ph	4-OMe-Ph	86

[a]Isolated yields

A comparison of the current method with those reported in the literature for the synthesis of 2-amino-4-phenyl-3,5-dicarbonitrile-6-thio-pyridine **4aa** as the example has been provided. It is evident from Table 4 that the current method proves faster with higher yield. The reported methods not only required longer reaction times but also suffered from use of drastic conditions and poorer yields.

Table 4: Comparison of catalytic activity of TBAB-Cs_2CO_3 with some literature methods in the synthesis of **4aa**.

Entry	Catalyst	Solvent	Condition	Time (min)/[h]	Yield (%)	Ref.
1	Et_3N	EtOH	reflux	[2.5]	35	19
2	$ZnCl_2$	EtOH	reflux	[2]	65	23
3	Boric acid	H_2O	80^0C	(40)	90	24
4	KF/alumina	neat	MW	(5)	86	25
5	Silica nanoparticles	EtOH	reflux	[3]	70	27
6	$ZrOCl_2.8H_2O$	[bmin]BF_4	ultrasonic sonication	(15)	91	28
7	O-iodoxybenzoic acid	H_2O	70^0C	[1.5]	80	29
8	Nanocrystalline MgO	EtOH	50^0C	[2]	64	26
9	TBAB-Cs_2CO_3	MeOH	r.t.	[3]	92	-

Conclusion

In conclusion, we have devised a simple and efficient one-pot approach to construct the structurally diverse 2-amino-3,5-dicarbonitrile-6-thio-pyridines via three-component coupling of aldehydes, malononitrile, and thiophenols at room temperature promoted by tetrabutylammonium bromide clubbed with cesium carbonate. Compared with the previous methods, the present procedure avoids the use of heating condition. Moreover, the advantages of operational simplicity, and economic viability, make this protocol an efficient alternative to the literature methods. To the best of our knowledge, this is the first example on using room temperature conditions to perform the synthesis of substituted pyridines.

Acknowledgements

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