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SYNERGETIC CATALYTIC BLEACHING EARTH CLAY AND PEG-400 FOR RAPID SYNTHESIS OF HIGHLY EFFICIENT SYNTHESIS OF SUBSTITUTED PYRIDINES

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ABSTRACT : One pot, three component synthesis of 2-amino-4-aryl-3, 5-dicyano-6-sulfonyl pyridines from the reaction of aromatic aldehydes, malononitrile and thiophenol in presence of effective synergetic catalytic system basic Bleaching Earth Clay and PEG-400 as catalyst at room temperature is described.

KEYWORDS: Synergetic catalytic bleaching earth clay, PEG-400, substituted pyridines, three component synthesis, room temperature.

INTRODUCTION

Pyridine nucleus is medicinally useful scaffold which occurs in wild variety of both naturally and synthetic bioactive compounds[i]. The highly substituted pyridine derivatives like 2-amino-4-aryl-3, 5-dicyano-6-sulfonyl pyridines exhibit diverse pharmacological activities and are useful as anti-bacterial[ii], anti-prior[iii], anti-hepatitis B virus[iv], anti-cancer agents[v] and as potassium channel openers for the treatment of urinary incontinence[vi]. In addition, many of these compounds are found to be highly selective ligands for adenosine receptors[vii], which were 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[viii]. They are also immerged in potential medicinal used in developing therapeutic agents for the treatment of Creutzfeldt-Jacob disease[ix].

Owing their vast medicinal usefulness, various methods have been explored for the preparation of substituted pyridine. These includes ruthenium-catalyzed cyclo-isomerization of 3-azadienynes[x], hetero-Diels-Alder reaction of 3-siloxy-1-aza-1,3-butadines and 2H-1,4-oxazinones with acetylenes[xi], Mannich reaction of aldehydes and iminium salts[xii], Vilsmeier-Hack reaction of α-hydroxy ketene dithioacetals[xiii], 6-π aza-electrocyclization of azatrienes. Catalytic oxidation of 1,4-dihydropyridines by $RuCl_3/O_2$[xiv], [4+2] cycloaddition of

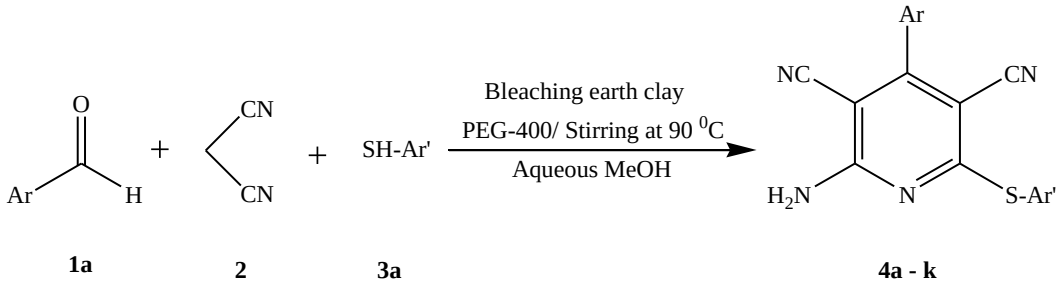
oximinosulfonates[xv], conversion of conjugated oximes under Vilsmeier condition[xvi], N-methylene butylamine with enamines[xvii], conversion of ketene dithioacetals to substituted pyridines[xviii].

A few multicomponent condensation of aldehyde, malononitrile and thiols are also reported using bases Et_3N/DABCO[xix], [bmIm]OH[xx], DBU[xxi], TBAH[xxii], and acids such as $ZnCl_2$[xxiii], boric acid[xxiv], KF/aluima[25xxv] and nano crystalline magnesium oxide. However most of the methods have drawbacks which involve reacting at high temperature, using of expensive catalyst or commercial unavailability, formation of side products which leads to low yield of desired product. Therefore, we divided to choice a new reagent or reagent systems to overcome above limitations.

Among the heterogeneous catalysts, naturally occurring clay has unique physical and chemical properties such as selectivity, acidic/basic nature and thermal stability. Bleaching earth clay is a highly efficient heterogeneous base catalyst that has been used for several base catalyzed organic reactions[xxvi-xxviii].

RESULTS AND DISCUSSION

Herein, we report a mild and practical method for the synthesis of highly substituted pyridines from the reaction of aldehyde (1), malononitrile (2) and thiophenol in presence of polyethylene glycol-400 (PEG-400) as a green reaction solvent by using Bleaching Earth Clay in aqueous methanol (**Scheme 1**).



1a **2** **3a** **4a - k**

Scheme-1

A set of experiments were performed to find the best condition for the synthesis of 2-amino-4-(phenyl)-6-phenylsulfanylpyridine-3,5-dicarbonitrile (4a), using benzaldehyde (1a), malononitrile (2) and thiophenol (3a) as a model reaction.

In our preliminary studies, we have investigated the multicomponent reaction of benzaldehyde (1a), with malononitrile (2) and thiophenol (3) using different supports and solvents. The results are presented in **Table 1, and 2**. By the results described in **Table 1**, one can observed that the use of silica is a very convenient solid support for the reaction, performed without any solvent. However, as the reaction under dry media condition was not efficient, with 80% yield in silica after 5h, we turned our attention to the use of solvent. We observed moderate yields using MeCN, CH_2Cl_2, $CHCl_3$ and AcOEt (**Table 2, entry 1-4**), whereas optimal result were achieved using EtOH and MeOH (**Table 2, entries 5-6**).

Our next attention was devoted to minimum amounts of iodine to have good reaction rate. We observed that amount of iodine can be reduced substantially, to 10 mol% (**Table 2, entry 9**). Under the standard conditions, the absence of iodine decreases the yield of product substantially with the requirement of long reaction time (**Table 2, entry10**).

Table 1: Synthesis of substituted pyridines at different supports

Entry	Support[a]	Time [h]	Yield (%)
1.	--	5	10
2.	PEG	5	60
3.	PEG-600	5	58
4.	PEG-600	5	62
5.	SiO_2	5	86

[a] Benzaldehyde (1 mmol), malononitrile (2 mmol), thiophenol (1 mmol)

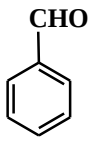
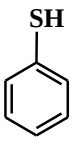
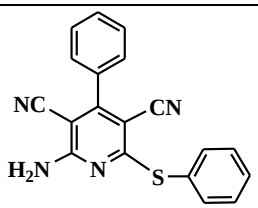
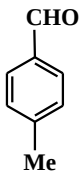
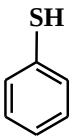
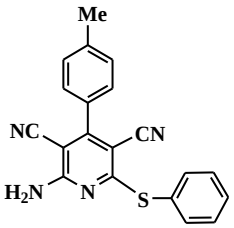
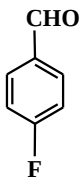
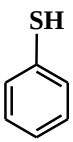
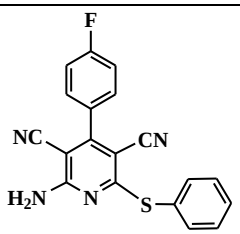
Table 2: Synthesis of substituted pyridines under different solvents.

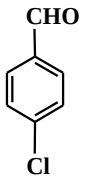
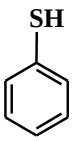
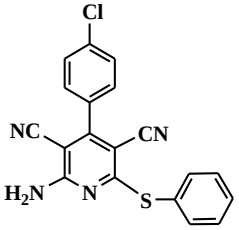
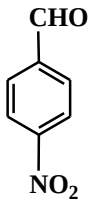
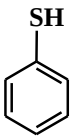
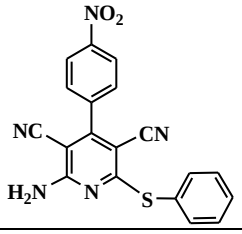
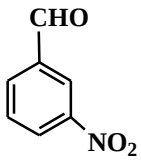
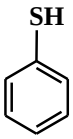
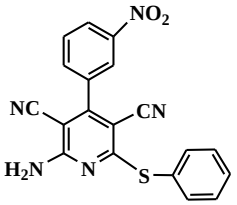
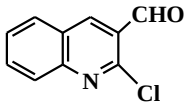
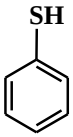
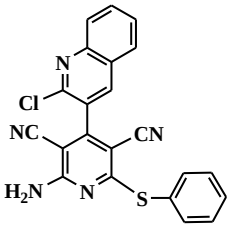
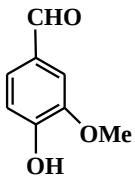
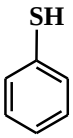
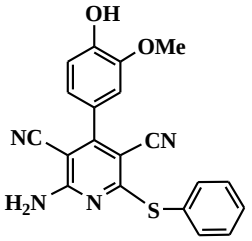
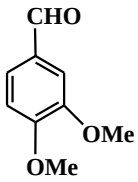
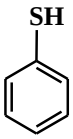
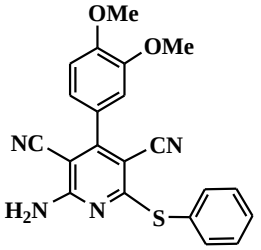
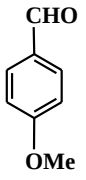
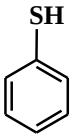
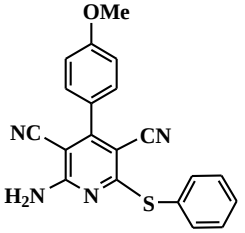
Entry	Solvent	Time [min/h]	I_2 (mmol)	Yield (%)
1.	MeCN	[5]	0.5	68
2.	CH_2Cl_2	[5]	0.5	65
3.	$CHCl_3$	[5]	0.5	70
4.	AcOEt	[5]	0.5	68
5.	EtOH	[1]	0.5	87
6.	MeOH	25	0.5	92
7.	MeOH	25	0.4	92
8.	MeOH	25	0.2	92
9.	MeOH	25	0.1	92
10.	MeOH	[5]	--	40
11.	MeOH	[5]	0.1	80[b]

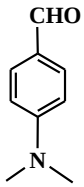
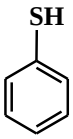
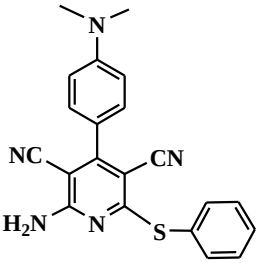
[a] Solvent (1 ml/mmol), Benzaldehyde (1 mmol), malononitrile (2 mmol), thiophenol (1 mmol)
[b] Yields refer to isolated yield

All the result are presented in **Table 3**. Formation of the derived products was confirmed with the help of IR, ^{1}HNMR, ^{13}C NMR and mass spectroscopic data.

Table 3: Synthesis of highly Substituted pyridines

Entry	Aldehyde	Thiophenol	Product	Time (min.)	Yield (%)	M.P. (^{0}C)
1			 **4a**	25	80	217-218
2			 **4b**	25	80	217-218
3			 **4c**	25	85	225-226

4			 **4d**	20	85	221-222
5			 **4e**	30	80	289-290
6			 **4f**	25	85	235-236
7			 **4g**	30	70	198-199
8			 **4h**	40	78	272-274
9			 **4i**	25	75	225-227
10			 **4j**	30	75	229-230

11			 **4k**	40	70	203-205

CHARACTERIZATION DATA

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

^{1}H NMR (DMSO-d_6) δ 7.51 (m, 3H), 7.58 (m, 7H), 7.80 (bs, 2H); ^{13}C NMR (DMSO-d_6) δ 166.7, 160.2, 159.2, 135.4, 134.5, 130.9, 130.2, 130.0, 129.3, 129.1, 129.0, 127.7, 115.8, 115.5, 93.9, 87.7; IR (KBr) 3360, 3058, 2212, 2208, 1620, 1544, 1516, 1460, 1264, 760, 746, 704, 688 cm^{-1}. Anal. Calcd for $C_{19}H_{12}N_4S$ (328.399): C, 69.49; H, 3.69; N, 17.06; S: 9.76. Found: C, 69.38; H 3.61; N, 16.92; S, 9.90.

2-Amino-6-(benzylsulfanyl)-4-(4-flourophenyl)-3,5-pyridinedicarbonitrile (4c):

^{1}H NMR (DMSO-d_6) δ 4.52 (s, 2H), 7.29 (m, 3H), 7.38 (d, *J* = 8.85 Hz, 2H), 7.50 (dd, *J* = 1.53, 8.24 Hz, 2H), 7.58 (dd, *J* = 5.49, 8.85 Hz, 2H), 8.00 (bs, 2H); ^{13}C NMR (DMSO-d_6) δ 166.7, 165.3, 162.0, 160.0, 158.0, 138.1, 131.6, 131.5, 130.9, 129.9, 128.9, 127.8, 116.5, 116.2, 115.8, 93.9, 86.6, 33.7; IR (KBr) 3444, 3340, 3212, 2212, 1624, 1606, 1546, 1520, 1510, 1460, 1262, 1236, 1166, 1028, 848, 824, 780, 696, 672, 560, 524 cm^{-1}. Anal. Calcd for $C_{20}H_{13}FN_4S$ (360.409): C, 66.65; H, 3.64; N, 15.55; S: 8.90. Found: C, 66.46; H, 3.70; N, 15.67; S, 8.84.

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

^{1}H NMR (DMSO-d_6) δ 7.49 - 7.69 (m, 9H), 7.87 (bs, 2H); ^{13}C NMR (DMSO-d_6) δ 166.7, 160.1, 158.1, 135.9, 135.4, 133.3, 131.0, 130.3, 130.0, 129.5, 127.6, 115.7, 115.5, 93.9, 87.7. HRMS *m/z* (ESI) calcd for $C_{19}H_{12}N_4SCl$ $(M+H)^+$ 363.0471, found 363.0481.

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

^{1}H NMR (DMSO-d_6) δ 7.47 (m, 3H), 7.57 (m, 2H), 7.76 (bs, 2H), 7.83 (d, *J* = 8.85 Hz, 2H), 8.37 (d, *J* = 8.85 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 166.8, 160.0, 157.3, 149.1, 140.8, 135.4, 130.8, 130.3, 130.0, 127.5, 124.4, 115.5, 115.2, 93.5, 87.5; IR (KBr) 3422, 3328, 3226, 3086, 2214, 2210, 1634, 1602, 1549, 1532, 1514, 1460, 1420, 1348, 1348, 1318, 1262, 1238, 1178, 1109, 1024, 1000, 898, 868, 850, 802, 798, 758, 710, 553 cm^{-1}. Anal. Calcd for $C_{19}H_{11}N_5O_2S$ (373.398): C, 61.11; H, 2.98; N, 18.76; S, 8.59. Found: C, 60.88; H, 2.73; N, 18.95; S, 8.67.

2-Amino-4-(3-hydroxy-4-methoxyphenyl)-6-(phenylsulfanyl)-3,5–pyridinedi carbonitrile (4i):

^{1}H NMR (DMSO-d_6) δ 3.85 (s, 3H), 6.94 (dd, *J*= 2.19, 8.77 Hz, 1H), 6.96 (d, *J*= 2.19 Hz, 1H), 7.10 (d, *J* = 8.77 Hz, 1H), 7.50 (m, 3H), 7.60 (m, 2H), 7.70 (bs, 2H); ^{13}C NMR (DMSO-d_6) δ 166.6, 160.3, 158.9, 150.0, 146.9, 135.3, 130.2, 129.9, 127.9, 127.8, 126.6, 120.6, 116.0, 115.8, 112.5, 93.9, 87.5, 56.1; IR (KBr) 3512, 3476, 3428, 3376, 3340, 3236, 2208, 1642, 1552, 1524, 1520, 1512, 1466, 1442, 1256, 1216, 1194, 1022, 532 cm^{-1}. HRMS *m/z* (ESI) calcd for $C_{20}H_{15}N_4O_2S$ $(M+H)^+$ 375.0916, found 375.0908.

2-Amino-4-(3,4-dimethoxyphenyl)-6-(phenylsulfanyl)-3,5-pyridinedicarbo nitrile (4j):

^{1}H NMR (DMSO-d_6) δ 3.81 (s, 3H), 3.85 (s, 3H), 7.11 (dd, *J* = 1.52, 8.24 Hz, 1H), 7.14 (d, *J* = 8.24 Hz, 1H), 7.19 (d, *J* = 1.52 Hz, 1H), 7.50-7.60 (m, 5H), 7.60 (bs, 2H); ^{13}C NMR (DMSO-*d6*) δ 166.6, 160.3, 158.9, 151.0, 148.9, 135.3, 130.2, 130.0, 127.8, 126.3, 122.1, 116.2, 115.9, 112.9, 112.1, 94.0, 87.6, 56.3, 56.1; IR (KBr) 3420, 3332, 3226, 3008, 2972, 2936, 2836, 2216, 1684, 1652, 1648, 1640, 1600, 1548, 1528, 1520, 1510, 1462, 1450, 1424,

1334, 1308, 1260, 1230,1144,1024,758, 708, 692, 586 cm^{-1}. Anal. Calcd for $C_{21}H_{16}N_4O_2S$ (388.453): C, 64.93; H, 4.16; N, 14.43; S, 8.25. Found: C, 64.71; H, 3.99; N, 14.59; S, 8.38.

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

^1H NMR (DMSO-d_6) δ 3.85 (s, 3H), 7.12 (d, J = 8.85 Hz, 2H), 7.48 (m, 3H), 7.51 (d, J = 8.85 Hz, 2H), 7.60 (m, 2H), 7.65 (bs, 2H); ^{13}C NMR (DMSO-d_6) δ 166.7, 161.4, 160.3, 158.9, 135.3, 130.8, 130.2, 130.0, 127.8, 126.4, 116.1, 115.8, 114.7, 93.9, 87.5, 55.9; IR (KBr) 3436, 3336, 3224, 2228, 2216, 1642, 1606, 1576, 1550, 1534, 1504, 1462, 1450, 1420, 1290, 1260, 1188, 1018, 816, 756, 528 cm^{-1}. HRMS *m/z* (ESI) calcd for $C_{20}H_{15}N_4OS$ $(M+H)^+$ 359.0967, found 359.0978.

CONCLUSION

Careful analysis revealed that the optimum conditions for three component of aldehyde, malononitrile and thiophenol were found to be the use of MeOH at room temperature. Having established the best yields of substituted pyridines, variety of electronically divergent aldehyde with report to thiophenol and 2-amino thiophenol were examined. Aromatic aldehyde with various functionalities such as Me, OMe, NO_2, F, Cl, OH, NMe_2, were found to be compatible with the optimized reaction condition. Heterocyclic aldehyde 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 with the requirement of water as a co-solvent and adjustment of pH.

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CONFLICTS OF INTREST

The authors declare no conflict of interest.

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