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POT, ATOM AND STEP ECONOMIC (PASE) SYNTHESIS OF 2-AMINO-3, 5-DICARBONITRILE-6-THIO-PYRIDINES IN AQUEOUS PEG-400 PROMOTED BY SODIUM BENZOATE

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ABSTRACT

An efficient pot, atom and step economic (PASE), sodium benzoate promoted synthesis of 2-amino pyridine-3, 5 dicarbonitriles by the reaction of aldehydes, malonitrile and thiophenol in PEG-400 in water is reported. This new protocol has the advantages of convenient procedure, eco-friendliness, shorter reaction times and higher yields.

Key words: 2-Amino pyridine-3, 5-Dicarbonitriles, Sodium benzoate, PEG-400: Water.

INTRODUCTION

The pyridine-3, 5-dicarbonitrile is a "privileged medicinal scaffolds" has established a varied range of biological activities. The molecules A-C having the pyridine framework exhibit several significant medicinal utilities. One of them is antiprion agent A[1], molecule B is recognized as an effective inhibitor of HIV-1 integrase[2], type C molecule acts as antitumor agent against numerous human cancer cells[3].

Furthermore, some of the molecular structures having pyridine-3,5-dicarbonitrile motif were found to be capable of providing selective ligands for adenosine receptors, kidney disease, Parkinson's disease, epilepsy, hypoxia and asthma.[4] The huge applications in medicinal field attracted medicinal chemists to design and developed new synthetic strategies for the pyridine scaffolds. The reported synthetic routes includes conversion of ketene dithioacetals to substituted pyridines[5], the Diels-Alder cycloadditions of oximinosulfonates[6], Vilsmeier-Haack reaction of α hydroxyl ketene dithioacetals[7], reaction

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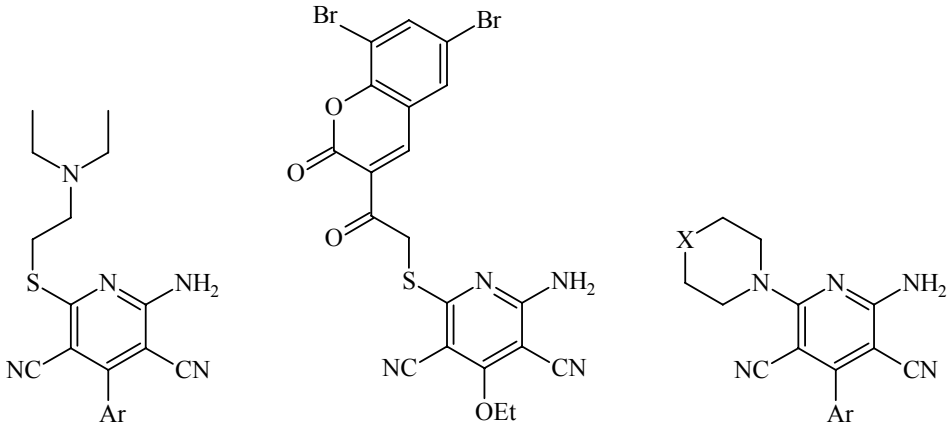
of 3-siloxy-1-aza-1,3-butadiens and 2H-1,4-oxazinones with acetylenes[8], cyclo-isomerization of 3-azadienynes[9] and azaelectro-cyclization of azatrienes[10]. However, most of these routes involve multistep synthesis, use of expensive and toxic catalysts, low yields and tedious procedures. Recently synthesis of pyridine-3, 5-dicarbonitriles has been achieved through multicomponent reaction (MCR) of thiols, malonitrile and various aldehydes. This multicomponent condensation has been carried out by using different reagents and catalyst such as Et_3N[11], DBU[12], KF/Alumina[13], $ZnCl_2$[14], TBAH and [bmim]OH[15], boric acid[16], microporous molecular sieves[17], silica nanoparticles[18], CaO nanoparticles[19], sodium chloride[20] and diethyl amine[21]. In spite of potential efficacy of these protocols, some of them bear limitations such as long reaction times, forcing conditions for catalyst preparation, low yields and the use of toxic solvents. To overcome these demerits, we developed a new procedure for more efficient and cleaner synthesis of pyridine-3, 5-dicarbonitrile derivatives.



A **B** **C (X = O, S)**

Recently, the use of PEG-400 in organic transformations has drawn great attention as it is being used in food and cosmetic products, easy to handle, inexpensive, thermally stable, non- toxic and non volatile reaction media[22-25]. Thus, great attention has been focused on its application in organic reactions[26-30]. Polyethylene glycol (PEG) and its aqueous solutions represent interesting solvent system for solvent substitution.

Sodium benzoate is a common, commercially available, safe food preservative and antimicrobial agent[31-36]. It is non-toxic, less expensive and insensitive to moisture and air. Not much work has been reported, which explored the activity of sodium benzoate as a catalyst in organic reactions. In continuation of our work related to the development of new synthetic protocols for some diverse heterocyclic scaffolds[37-40], we report here for the first time an efficient multicomponent synthesis of 2-amino pyridine-3, 5-dicarbonitriles

catalyzed by sodium benzoate as an efficient catalyst and mediated by PEG-400 in water as a green solvent system.

EXPERIMENTAL

All chemicals and solvents were purchased from commercial suppliers and used without further purification. The reactions and purity of the products were monitored by thin layer chromatography (TLC) using silica gel coated aluminum sheets (Merck made). The spots were detected either under ultraviolet (UV) light or by placing TLC plates in an iodine chamber. Melting points are determined on open capillary tubes and are uncorrected. MS were determined on Shimadzu LC MS spectrometer. NMR spectra were recorded on a Bruker advance II 400 NMR Spectrometer.

General procedure for the synthesis of 2-amino pyridine-3, 5 dicarbonitriles

To a solution of a selected aldehyde (1mmol) and malononitrile (2 mmol) in 4 mL of PEG-400: Water (1:1), was added sodium benzoate (0.1 mmol). The resulting mixture was heated to 40-50ºC for 15 min then thiophenol (1 mmol) was added. The reaction mixture was heated at 70^{o}C for an appropriate time (Table 2, entry 1-8) as monitored by TLC. In workup procedure, for some products, the reaction mixture was cooled to room temperature and poured in to ice cold water. The obtained solid product was filtered and washed with cyclohexane: $CHCl_3$ (7:3) and dried to afford the pure product. To some products after completion, the reaction mixture was cooled to room temperature and partitioned between ethyl acetate and water. The aqueous and organic layers were then separated and the aqueous layer was extracted by ethyl acetate twice. The combined ethyl acetate extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford the crude compound, which after washing with cyclohexane: $CHCl_3$ (7:3) gave pure product.

Spectral data

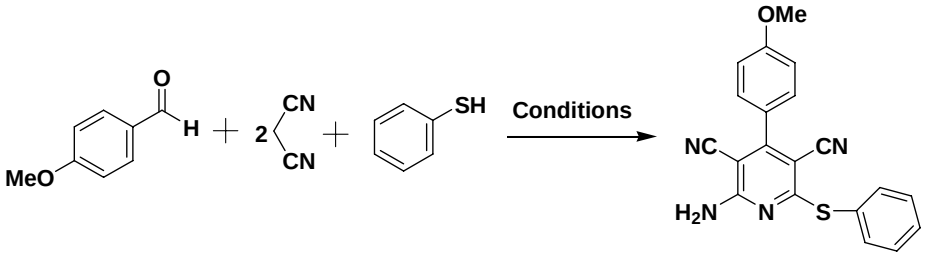
2-Amino-4-(4-methoxyphenyl)-6-(phenylsulfanyl)-3,5-pyridinedicarbonitrile (4b) m.p: 240-242^{o}C: ^{1}H NMR (DMSO-d_6): δ (ppm) 3.87 (s, 3H), 7.10 (d, J = 8.85 Hz, 2H), 7.48 (m, 3H), 7.50 (d, 2H), 7.59 (m, 2H), 8.19 (bs, 2H); ^{13}C NMR (DMSO d6): δ (ppm) 166.3, 160.8, 159.76, 157.96, 135.3, 130.0, 129.3, 129.17, 127.3, 125.65, 115.3, 115.1, 113.9, 93.3, 86.8, 55.1; Mass: (M+1) 359.2.

2-Amino-4-(3-hydroxy phenyl)-6-(phenyl sulfanyl)-3,5-pyridinedicarbonitrile (4e) mp 260-262^{o}C; ^{1}H NMR (DMSO-d6) δ (ppm): 6.88-6.96 (m, 3H), 7.32–7.76 (m, 8H), 9.90 (s,1H); ^{13}C NMR (DMSO-d6) δ (ppm): 166.6, 160.1, 159.1, 157.8, 135.5, 135.2, 130.4, 130.1, 129.9, 127.7, 119.4, 117 .8, 115.7, 115.5, 115.4, 93.9, 87.5; Mass: (M+1) 345.1.

RESULTS AND DISCUSSION

In order to determine the real efficiency of sodium benzoate for the synthesis of pyridine-3, 5-dicarbonitrile, a test reaction was carried out without catalyst using malonitrile, 4-methoxybenzaldehyde and thiophenol in ethanol (**4b**). It was observed that no product was obtained in the absence of catalyst after several hours at room temperature or at reflux conditions (Table 1, entry 1). 10 mole % of sodium benzoate gave 60% of yield in ethanol at reflux conditions (Table 1, entry 3), whereas at room temperature low yield was obtained (Table, entry 2). Once we found sodium benzoate as a good catalyst for the reaction, we focused on the solvent and temperature screening in order to increase the yields. We optimized different solvents such as ethanol, acetonitrile, water, THF, toluene and PEG-400 at room temperature to 100^{o}C (Table 1, Entry 3-8). Among tested various solvents, EtOH, water, toulene and PEG-400 found to give better yields (Table 1, Entries 3, 4, 6, and 8). To our surprise, when mixture of PEG-400/Water (1:1) was used at 70^{o}C, the reaction gave maximum yield (Table 1, Entry 9). Here also, the reaction is highly effected by the temperature as the yield was only 30% after stirring at room temperature for several hours in PEG-400/Water(1:1) medium (Table 1, Entry 11), whereas when the temperature was increased to 90 ^{0}C , no improvement in the yield was observed (Table 1, Entry 10).

Table 1: Optimization of reaction conditions (*4b*)



1 **2** **3** **4b**

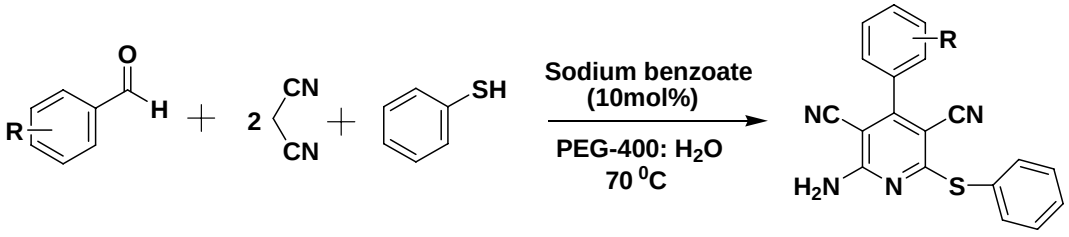
Entry	Solvent	Catalyst (mol %)	Temperature (^{o}C)	Time (min)	Yield (%)
1	EtOH	---	R.T/70	120	No product
2	EtOH	10	R.T	120	20
3	EtOH	10	70	120	60
4	Water	10	100	130	40
5	Acetonitrile	10	80	150	30

Cont…

Entry	Solvent	Catalyst (mol %)	Temperature (^{o}C)	Time (min)	Yield (%)
6	Toulene	10	100	120	50
7	THF	10	70	160	20
8	PEG-400	10	70	120	60
9	PEG:Water (1:1)	10	70	90	88
10	PEG:Water (1:1)	10	90	90	87
11	PEG:Water (1:1)	10	R.T	120	30
12	PEG:Water (1:1)	20	70	90	88
13	PEG:Water (1:1)	5	70	120	70

Once found best solvent and temperature condition, we examined the influence of varying amounts of sodium benzoate for this multicomponent reaction. In order to estimate the appropriate catalyst concentration, reactions were carried out using 5 to 20 mol% of the sodium benzoate. It was observed that 10 mol % of the catalyst gave maximum yield in minimum duration (Table 1. Entry 9). 20 mol% of catalyst loading neither shortens the conversion duration nor increases the yield (Table 1.Entry 12). However, a lower amount of the catalyst (5 mol %) resulted in lower yields (Table 1, entry 13). So, optimal quantity of 10 mol % of the catalyst was sufficient to promote the reaction (Table 1. Entry 9).

Table 2: Synthesis of 2-amino pyridine-3, 5-dicarbonitriles (4^{a-h})



1 **2** **3** **4 a-h**

Entry	R	Product	Time	Yield	M.P. (^{o}C)	
					Observed	Reported
1	H	4a	100	85	215-217	216-218[14]
2	4-MeO	4b	90	88	240-242	242-244[21]
3	4-Cl	4c	90	87	220-222	223-224[20]

Cont…

Entry	R	Product	Time	Yield	M.P. (^oC)	
					Observed	Reported
4	3-NO_2	4d	110	82	214-216	216-218[21]
5	3-OH	4e	90	86	262-264	265-267[19]
6	4-Me	4f	90	88	207-209	208-211[14]
7	4-OH	4g	100	85	322-322	318-320[21]
8	4-Br	4h	90	86	257-259	256-258[21]

To explore the extent and general applicability of this protocol, different substituted aldehydes were then tested and the results are mentioned in Table 2. All the reactions regardless the positions of substituent's and their electronic nature or steric hindrance, afforded the corresponding products in excellent yields (Table 2, entries 1-8).

Sodium benzoate acting as a base, thereby promoting the reaction through *in situ*-generated benzylidenemalononitrile intermediate via Knoevenagel condensation between aldehyde and malonitrile followed by Michael addition of second molecule of malonitrile to benzylidenemalononitrile adduct. This then reacts with thiophenol produces dihydropyridine, which undergoes air oxidation to afford the final product. The catalytic activity of sodium benzoate has been increased in aqueous polyethylene glycol medium at 70^{o}C as compared to other conditions (Table 1, entries 1-14) and accelerates the synthesis of 2-amino pyridine-3,5-dicarbonitriles more effectively.

CONCLUSION

We have described an efficient one-pot reaction of aldehyde, malonitrile and thiophenol for the synthesis of 2-amino pyridine-3, 5 dicarbonitriles catalyzed by sodium benzoate as a cheap, non-toxic and readily available organocatalyst. PEG-400: water also offers a convenient, inexpensive, non-toxic and very efficient reaction medium. Moreover, this method offers several other merits such as environmental friendliness, convenient procedure higher yields and shorter reaction time.

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