



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 A¹, molecule B is recognized as an effective inhibitor of HIV-1 integrase², type C molecule acts as antitumor agent against numerous human cancer cells³.

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 pyridines⁵, the Diels-Alder cycloadditions of oximinosulfonates⁶, Vilsmeier-Haack reaction of α hydroxyl ketene dithioacetals⁷, reaction

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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 40-50°C for 15 min then thiophenol (1 mmol) was added. The reaction mixture was heated at 70°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: CHCl₃ (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 Na₂SO₄ and concentrated under vacuum to afford the crude compound, which after washing with cyclohexane: CHCl₃ (7:3) gave pure product.

Spectral data

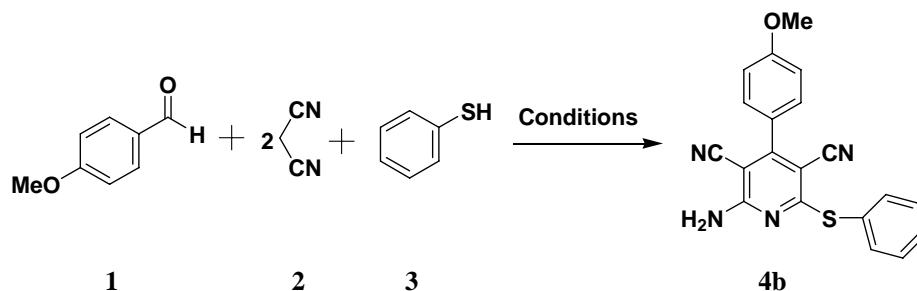
2-Amino-4-(4-methoxyphenyl)-6-(phenylsulfanyl)-3,5-pyridinedicarbonitrile (4b)
m.p: 240-242°C; ¹H NMR (DMSO-d₆): δ (ppm) 3.87 (s, 3H), 7.10 (d, J = 8.85 Hz, 2H), 7.48 (m, 3H), 7.50 (d, 2H), 7.59 (m, 2H), 8.19 (bs, 2H); ¹³C NMR (DMSO d₆): δ (ppm) 166.3, 160.8, 159.76, 157.96, 135.3, 130.0, 129.3, 129.17, 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°C; ¹H NMR (DMSO-d₆) δ (ppm): 6.88-6.96 (m, 3H), 7.32-7.76 (m, 8H), 9.90 (s, 1H); ¹³C 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°C (Table 1, Entry 3-8). Among tested various solvents, EtOH, water, toluene 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°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 °C, no improvement in the yield was observed (Table 1, Entry 10).

Table 1: Optimization of reaction conditions (4b)



Entry	Solvent	Catalyst (mol %)	Temperature (°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 (°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})

Entry	R	Product	Time	Yield	M.P. (°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. (°C)	
					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 benzylidenemalonitrile intermediate via Knoevenagel condensation between aldehyde and malonitrile followed by Michael addition of second molecule of malonitrile to benzylidenemalonitrile 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°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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