Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2012, 4(11):4953-4956

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Ammonia solution catalyzed one-pot synthesis of highly functionalized pyridine derivatives

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ABSTRACT

A simple and efficient one-pot synthesis of highly functionalized pyridine derivatives using ammonia solution as a catalyst via three component condensations of aldehydes, malonitrile and thiols at ambient temperature just by stirring in methanol is described. It is an efficient and promising synthetic protocol to build the highly functionalized pyridine derivatives.

Keywords: Multi-component reaction; highly functionalized pyridines derivatives; ammonia.

INTRODUCTION

MCRs constitute an especially attractive synthetic strategy since they provide easy and rapid access to large libraries of organic compounds with diverse substitution patterns[1]. As MCRs are one-pot reactions, they are easier to carry out than multi step syntheses. The developing of new MCRs and improving known multi-component reactions are an area of considerable current interest. One such reaction is the synthesis of pyridine. Coupled with high-throughput library screening, this strategy was an important development in the drug discovery in the context of rapid identification and optimization of biologically active lead compounds. Among them, 2-amino-3,5-dicarbonitrile-6-sulfanylpyridines exhibit various pharmacological activities and are useful as anti hepatitis B virus[2] , antiprion,[3] antibacterial[4] , anti cancer agents[5] and as potassium channel openers for treatment of urinary incontinence[6]. Moreover, some of these compounds were found to be highly selective ligands for adenosine receptors[7], implicated Parkinson's disease, hypoxia/ischemia, asthma, kidney disease, and epilepsy [8].

A three-component condensation of aldehyde, malononitrile, and thiol is one of the most prominent existing procedures used for the synthesis of 2-amino-3, 5-dicarbonitrile-6-thio-pyridines. Generally, this condensation has been carried out under basic conditions using various bases such as, Et_3N, DABCO, piperidine[9], morpholine, thiomorpholine, pyrrolidine, N,N-DIPEA, pyridine, 2,4,6-collidine, DMAP, aniline, N-methylaniline, N,N-dimethylaniline, and N,N-diethylaniline and DBU [10]. Moreover, basic ionic liquid 1- methyl-3-butylimidazolium Lewis hydroxide, that is [bmim] OH [11] and using a variety of Lewis acids such $ZnCl_2$, $AlCl_3$, $FeCl_3$, I_2, Cu $(OTf)_3$, $InCl_3$, and $BF_3.Et_2O$[12] .

However, most of these methods suffer by the formation of inevitable side products, which results in lower yield of desired product with long reaction time. Keeping the medicinal values of pyridine-3, 5-dicarbonitriles in mind, we considered it necessary to develop an efficient high yielding synthetic protocol for the synthesis of this class of compounds.

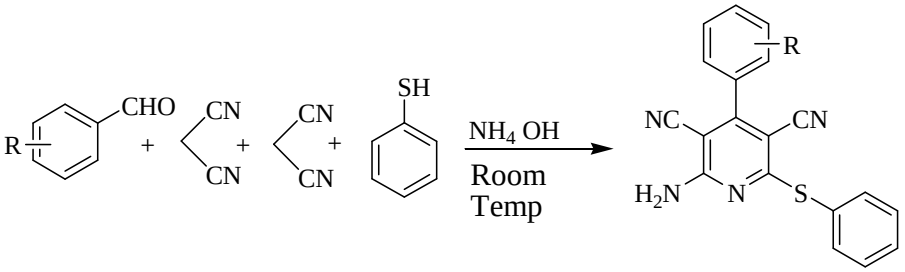
EXPERIMENTAL SECTION

All reagents were purchased from Merck and Loba and used without further purification.

Melting points were measured in open capillary and are uncorrected. The products were characterized by IR spectra and ^{1}H NMR. IR spectra were recorded on Perkin–Elmer FT-IR-1710 instrument. ^{1}H NMR was recorded on BrukerMSL-300 MHz and BrukerMSL-200 MHz instrument using TMS as an internal standard. Elemental analyses were determined by Carlo Erba elemental analyzer (CHNS-O, EA 1108).

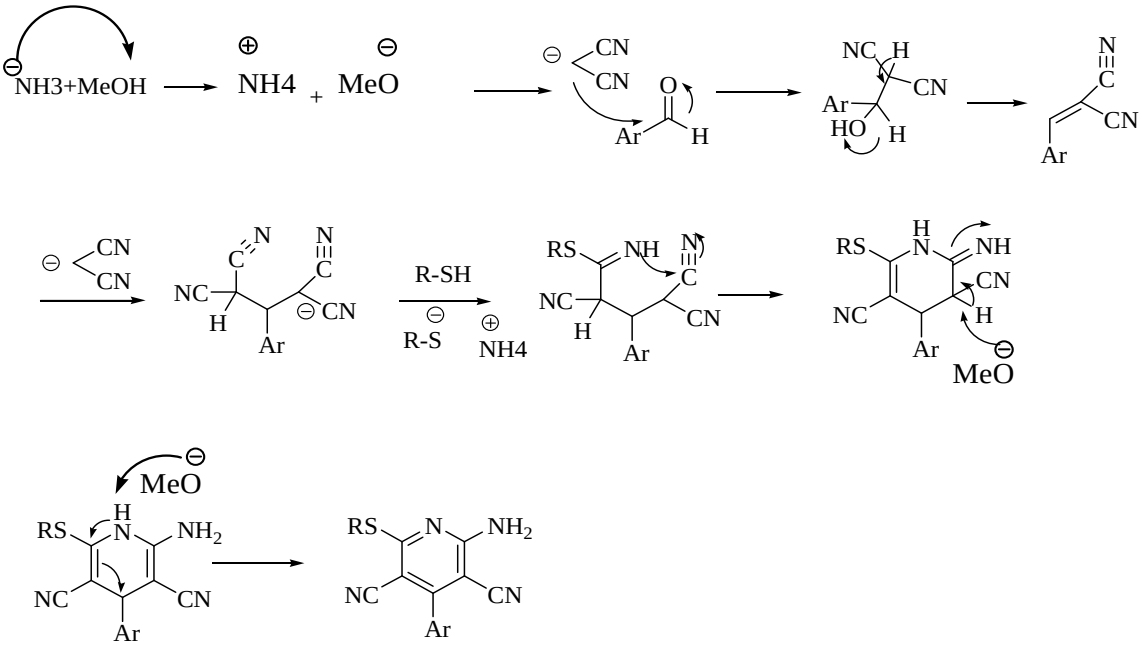
Reaction:-

Scheme 1: Synthesis of highly functionalized pyridine derivatives using thiophenol.



1. R=H , 2. R= 4-OCH_3 , 3. R= 4-OH, 4. R= 2-OCH_3, 5.R= 3,4-$(OCH_3)_2$, 6. R= 2-NO_2

Mechanism of the reaction:



General Stirring procedure for synthesis of poly substituted pyridines:

Aldehyde (1mmol), malononitrile (2.1mmol), thiophenol (1mmol) and anhydrous methanol (10 ml) Ammonia (12 mol %) were mixed and placed in R.B. flask. After the completion of the reaction, monitored by TLC, the reaction

mixture was cooled and precipitate formed was filtered and recrystallized from acetonitrile/methanol to yield the pure product.

RESULTS AND DISCUSSION

In view of the potential medicinal importance of the products and considering the limitations of the existing methods, we have investigated a ammonia (12 mol %) catalyzed, one-pot, simple and efficient procedure for the rapid construction of substituted pyridines via a three-component reaction of aldehydes (1mmol), malononitrile (2.1mmol) and thiophenol (1mmol) in methanol under thermal method by stirring (Scheme 1).

In the absence of catalyst the reaction was slow and product formed in traces. In the next step, we have screened different acidic, basic and phase transfer catalyst In comparison with these, Ammonia proved to be almost efficient catalyst in methanol that gave higher yield within 6 hrs (Table 1). Ammonia plays a complex role in accelerating the coupling reaction and thus promotes the formation of products. To investigate the reaction in detail, it was carried out in various solvents, the results are depicted in (Table 1), also investigated the affect of concentrations of catalyst (Table 2). To evaluate the efficiency of this methodology, various substituted aromatic aldehydes with either electron-donating or electron-withdrawing groups were used and it is found that the reaction underwent smoothly and gave the products in excellent yields (Table 3).

3.1. Spectral data and elemental analysis for new compounds:

*3.1. 2-amino-4-(2-methoxyphenyl)-6-(phenylthio)pyridine-3, 5-dicarbonitrile (entry **4**):*

IR(KBr): 3406, 3328, 3230, 2961, 2214, 2363, 2214, 2164, 1551, 1467, 1489, 1318, 1247, 1150, 1029. ^{1}HNMR(200MHz, DMSO-d6)δ: 7.83(brs, NH_2, 2H), 7.61-7.16(m, Ar-9H), 3.86(s, OCH_3); $C_{20}H_{14}N_4OS$; Anal. Calc. for C, 67.02; H, 3.94; N, 15.63; S, 8.95; Found C, 67.07; H, 3.98; N, 15.67; S, 8.99

*3.1.2 3-amino-4-(2-nitrophenyl)-6-(phenylthio) pyridine-3, 5-dicarbonitrile (entry **6**):*

IR(KBr): 3404, 3323, 3153, 3132, 3078, 2754, 2218, 1685, 1660, 1610, 1579, 1477, 1435, 1325, 1257, 1151, 1085;^{1}HNMR(200MHz, DMSO-d6)δ: 8.42(brs, NH_2, 2H), 802-7.65(m, Ar-9H); $C_{19}H_{11}N_5O_2S$; Anal. Calc. for C, 61.12; H, 2.97; N, 18.76; S, 8.59; Found C, 61.14; H, 2.94; N, 8.81; S, 8.63.

Table 1: Synthesis of 2-amino-4-(phenyl)-6-(phenylthio) pyridine-3,5dicaronitrile in the presence of different solvents using Ammonium hydroxide (12 mol %) as a catalyst.

Yields refer to the pure isolated products

Entry	Solvent	Time(hrs)	Yield(%)
1	….	6	….
1	Ethanol	6	52
1	Ethanol 50%	6	40
1	Water	6	….
1	Methanol	6	85

Table 2: Effect of concentrations of catalyst in methanol

Entry	Ammonium hydroxide in (mol%)	Time (in hours)	Yield (%)
1	4	6	05.00
1	8	6	11.55
1	12	6	85.00
1	16	6	28.22
1	20	6	15.00

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

Entry	Time in (Hrs)	Practical Yield (%)	M.P.^{0}C(Obs/Lit)
1	6	85	216-217(215-217)[14]
2	6	90	241-243(238-240)[13]
3	6	86	312-314(315-316)[13]
4	6	80	280-282
5	6	87	227-229-(226-228)[15]
6	6	60	290-292

All known products have been reported previously in the literature and were characterized by comparison of IR and NMR spectra with authentic samples. All new compounds characterized by melting point, IR, NMR (1H and 13C) and elemental analyses.

CONCLUSION

An efficient and environmentally benign strategy for the synthesis of highly functionalized Pyridine derivatives is developed. The method offers several advantages including high yield of products, short reaction time, easily availability of catalyst, ease of work-up and low-cost.

Acknowledgment
Authors are thankful to University Grants Commission, New Delhi, for financial assistance under minor research project.

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