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# By Using Ammonia Solution as a Catalyst a Multicomponent Reaction can be directed to Land up to Polyfunctional Pyridine or Pyran Derivatives.

**GM Nazeruddin*, YI Shaikh, and AA Shaikh.**

Department of Chemistry (P.G. & Research Centre), Poona College of Arts, Science & Commerce, Pune, India.

**ABSTRACT**

A simple and efficient synthesis of highly functionalized pyridine or pyran derivatives using ammonia solution as a catalyst via three component condensations of aromatic aldehydes, malonitrile and thiols or aceto acetic ester at ambient temperature just by stirring in methanol is described.

**Keywords:** Multi-component reaction; highly functionalized pyridine/pyran derivatives; ammonia.

*Corresponding author*

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## 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].

Similarly,4*H*-pyrans are an important class of heterocycles because the core fragment is constituted by a great variety of natural products and biologically active compounds. On the other hand polyfunctionalized 4*H*-pyran derivatives have attracted great attention recently in synthetic organic chemistry due to their wide range of biological activity and pharmacological property, such as anti-coagulant, anti-cancer, spasmolytic, diuretic, and anti-ancaphylactin[13]. The pharmacological activities exhibited by these compounds are mainly due to the presence of different heterocyclic ring systems. These compounds can be used for the treatment of neuro-degenerative diseases, including Alzheimer's disease, as well as for the treatment of schizophrenia and myoclonus. Furthermore, a number of 2-amino-4*H*-pyran derivatives are useful as photoactive materials[14]. 4H-pyrans are also useful intermediates for the synthesis of various compounds, such as pyranopyridine derivatives[15], polyazanaphthalenes, pyrano[2,3-*d*]pyrazoles[16], pyrano pyrimidines and pyridin-2-ones[17] with various other biological activities. Thus, in view of their wide utility, researchers have synthesized the 4*H*-pyran unit using different methods including radioactive and non-radioactive techniques such as microwave irradiation[18]. Generally, 2-amino-4-aryl-3-cyano-4*H*-pyrans were synthesized by the cyclization of arylidenemalononitriles and active methylene compounds in the presence of organic bases such as piperidine[19], pyridine[20], triethylamine[21,22]. In addition, the one-pot synthesis of 4*H*-pyrans has been reported using tetrabutylammonium bromide[23], (S)-proline, rare earth perfluorooctanoates, and hexadecyltrimethylammonium bromide[24]. Moreover, the cyclization arylidenemalononitriles and ethyl acetoacetate in the presence of triethylbenzylammonium

chloride, as phase-transfer catalysts, in an aqueous medium has been reported[25]. Recently, one-pot synthesis of these compounds has been reported using Mg/La mixed oxide[23], MgO[26,27] and tetramethylguanidine[28] as basic catalyst. But most of the reported reagents are associated with certain disadvantages such as tedious work-up, expensive nature of the reagent, toxic nature etc.

Keeping the medicinal values of pyridine-3, 5-dicarbonitriles and 4H-pyrans in mind, we considered it necessary to develop an efficient high yielding synthetic protocol of this class of compounds. A simple and efficient synthesis of highly functionalized pyridine or pyran derivatives using ammonia solution as a catalyst via three component condensations of aromatic aldehydes, malonitrile and thiols or aceto acetic ester at ambient temperature just by stirring in methanol is described.

## EXPERIMENTAL

### Materials and methods

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

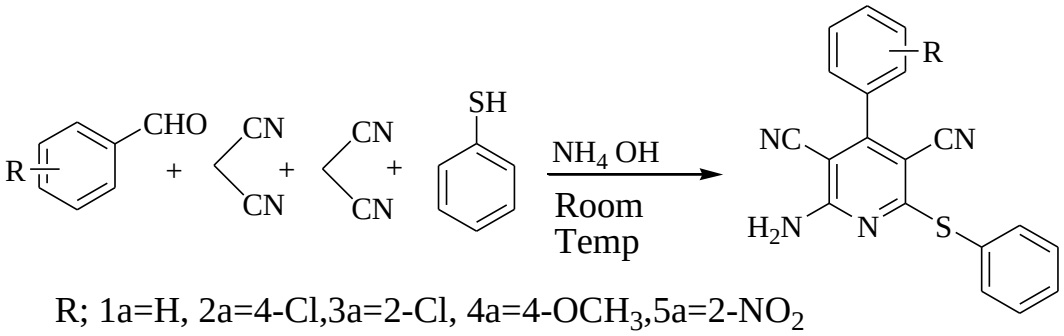
### Apparatus

Melting points were measured in open capillary and are uncorrected. The products were characterized by IR spectra, $^1$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. Magnetic stirrer was used REMI 2L; REMI 1MLH.

### General Stirring procedure for synthesis of poly substituted pyridines

Aldehyde (1 mmol), malononitrile (2.1 mmol), thiophenol (1 mmol) and anhydrous methanol (10 ml) Ammonia (12 mol %) were mixed and placed in R.B. flask. After the completion of reaction, monitored by TLC, the reaction mixture was cooled and precipitate formed was filtered and recrystallized from acetonitrile/methanol to yield the pure product.

### Reaction:




R; 1a=H, 2a=4-Cl,3a=2-Cl, 4a=4-$OCH_3$,5a=2-$NO_2$

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

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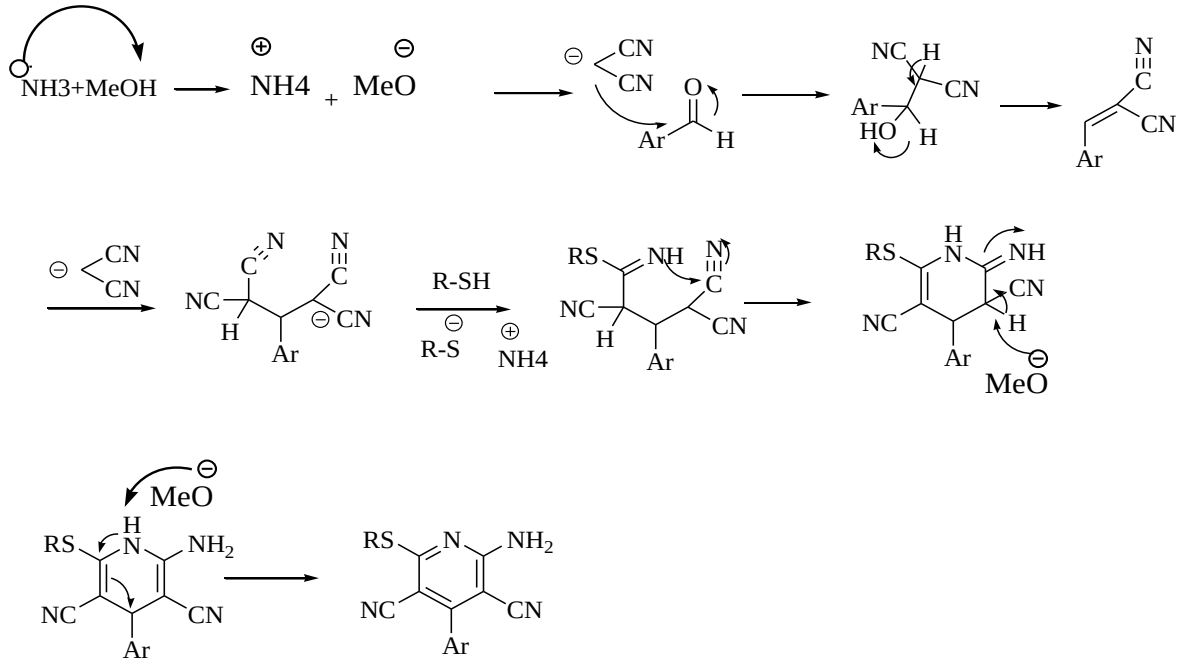
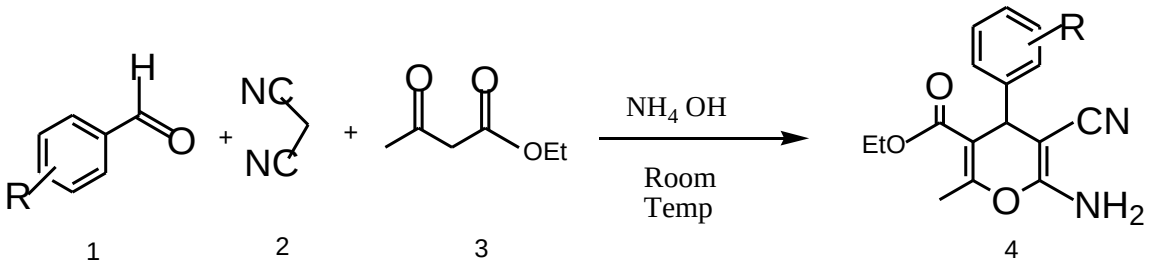
**Mechanism**: Proposed mechanism for synthesis of highly functionalized pyridine derivatives




**General Stirring procedure for synthesis of pyrans**

Aldehyde (1 mmol), malononitrile (1 mmol),ethyl acetoacetate(1mm), thiophenol (1 mmol) and anhydrous methanol (10 ml) Ammonia (12 mol %) were mixed and placed in R.B. flask. After the completion of reaction monitored by TLC, the reaction mixture was cooled and precipitate formed was filtered and recrystallized from acetonitrile/methanol to yield the pure product.




R; 1b=H, 2b=4-Cl,3b=2-Cl, 4b=4-$OCH_3$,5b=2-$NO_2$

**Scheme 2: Synthesis of 4H-pyran derivatives**

**Mechanism**: Proposed mechanisms for the synthesis of pyrans.

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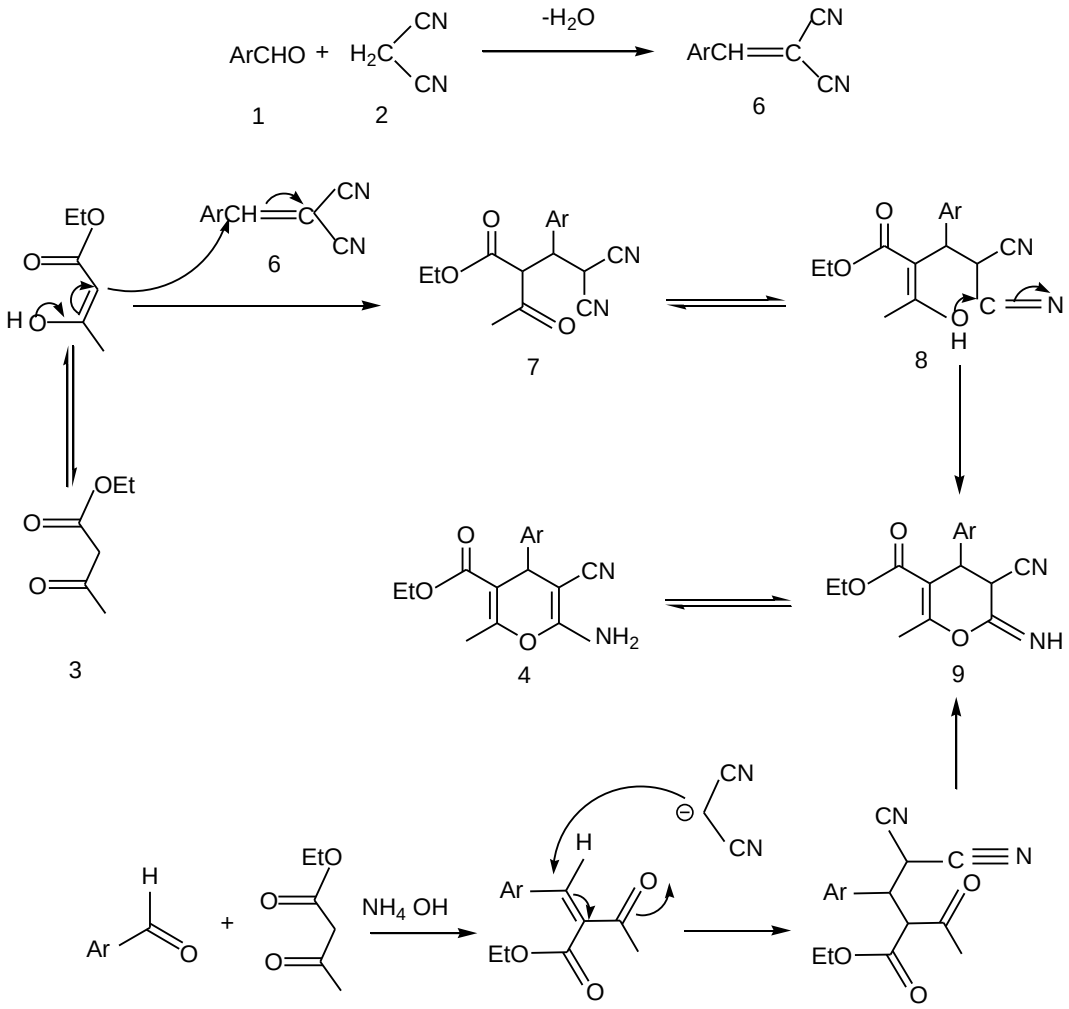

**RESULTS AND DISCUSSION**

In view of the potential medicinal importance of the products and considering the limitations of the existing methods, we have investigated ammonia (12 mol %) catalyzed, one-pot, simple and efficient procedure for the rapid construction of substituted pyridines and 4H-pyrans**.** Result are depicted in Table 1 and 2

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 3). 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 3), also investigated the affect of concentrations of catalyst (Table 4). To evaluate the efficiency of this methodology, various substituted aromatic and hetero-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.

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**Table1: Synthesis of 2-amino-3, 5-dicarbonitrile-6-thio-pyridines in the presence of methanol as a solvent, using Ammonium hydroxide (12 mol %) as a catalyst. Yields refer to the pure isolated products**

| Entry | Substrate | Time(hrs) | Yield(%) | M.P.$^0$C(Obs./Lit.) |
|---|---|---|---|---|
| 1a | Benzaldehyde | 6 | 85 | 216-217/216-217[29] |
| 2a | 4-chloro- benzaldehyde | 6 | 88 | 169-171/170-172[29] |
| 3a | 2-chloro-bezaldehyde | 6 | 86 | 158-160/158-160[24] |
| 4a | 4-methoxy-benzaldehyde | 6 | 90 | 241-243/241-243[29] |
| 5a | 2-nitro-benzaldehyde | 6 | 75 | 290-292/290-292[29] |

**Table 2: Synthesis of 4H-pyran derivatives in the presence of methanol solvent using Ammonium hydroxide (12 mol %) as a catalyst. Yields refer to the pure isolated products**

| Entry | Substrate | Time(hrs) | Yield(%) | M.P.$^0$C(Obs./Lit.) |
|---|---|---|---|---|
| 1b | Benzaldehyde | 6 | 85 | 178-179/178-179[30] |
| 2b | 4-chloro- benzaldehyde | 6 | 90 | 171-172/171-172[30] |
| 3b | 2-chloro-bezaldehyde | 6 | 88 | 179-181/171-181[30] |
| 4b | 4-methoxy-benzaldehyde | 6 | 90 | 132-133/132-133[30] |
| 5b | 2-nitro-benzaldehyde | 6 | 70 | 164-165/164-165[30] |

**Table 3: Synthesis of 2-amino-3, 5-dicarbonitrile-6-thio-pyridines 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(%) |
|---|---|---|---|
| 1a | …. | 6 | …. |
| 1a | Ethanol | 6 | 52 |
| 1a | Ethanol 50% | 6 | 40 |
| 1a | Water | 6 | …. |
| 1a | Methanol | 6 | 85 |

**Table 4: Effect of concentrations of catalyst in methanol**

| Entry | Ammonium hydroxide in ml | Time (in hours) | Yield (%) |
|---|---|---|---|
| 1a | 1 | 6 | _ |
| 1a | 3 | 6 | 11 |
| 1a | 4 | 6 | 85.00 |
| 1a | 5 | 6 | 28. |
| 1a | 6 | 6 | 11 |

All known products have been reported previously in the literature and were characterized by comparison of IR and NMR spectra with authentic samples.

## CONCLUSION

An efficient and environmentally benign strategy for the synthesis of highly functionalized Pyridine derivatives and 4H-pyran 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.

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