Sodium chloride: A proficient additive for the synthesis of pyridine derivatives in aqueous medium

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Sodium chloride: A proficient additive for the synthesis of pyridine derivatives in aqueous medium.

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Abstract:

A facile and convenient synthesis of substituted pyridine derivatives catalyzed by NaCl in the presence aqueous media under reflux and ultrasound irradiation has been developed via a one-pot multicomponent reaction, in which four new bonds were formed. Particularly valuable features of this protocol including mild conditions, simple execution, broad substrate scope, and good yields of products make it an efficient and promising synthetic strategy to build pyridine skeleton.

Keywords: Pyridines, sodium chloride, aqueous medium, salting effect, hydrophobic effect.

Introduction:

Nitrogen-containing heterocyclic compounds are widespread in nature, and their applications in biologically active pharmaceuticals, agrochemicals, and functional materials are getting more and more important[1], densely substituted pyridine derivatives are one of the most important classes of compounds owing to their widespread occurance as key structural subunits in numerous natural products that exhibit many interesting biological activities[2]. In addition, these heterocyclic compounds have found variety of applications in medicinal and pharmaceutical sciences. Particular pyridine scaffold is core structure of a wide range of naturally occurring bioactive molecules, pharmaceuticals, and functional materials[3-5]. Polysubstituted pyridine have also found to be antiprion[6], antihepatitis B virus[7], antibacterial[8], anticancer agents[9] and as potassium channel openers for treatment of urinary incontinence[10]. Moreover, some of the compounds were discovered to be highly selective ligands for adenosine receptors[11], which are recently recognized as potential targets for the development of new drugs for the treatment of Parkinson's disease, hypoxia/ischemia, asthma, kidney disease, epilepsy [12].

Multicomponent reactions (MCRs) have drawn interesting efforts owing to their exceptional synthetic efficiency, intrinsic atom economy, high selectivity, and procedural simplicity[13]. MCRs are useful for the expedient creation of chemical libraries of structurally related, medicinally significant

drug-like compounds[14]. Therefore, the design of new MCRs attracted great attention especially in the areas of drug discovery and organic synthesis.

In most of the existing studies on 2-amino-3, 5-dicarbonitrile-6-thio pyridine derivatives, these compounds have been synthesized following three-component condensation reaction of aldehydes, malononitrile and thiophenol either in the presence of Lewis/Bronsted acids or bases[15]. Amongst the various catalysts utilized for this purpose include DBU, DABCO, Et_3N, piperidine, KF/alumina, $K_2CO_3/KMnO_4$, $ZnCl_2$, Si & Mg nanoparticles, ionic liquids, Zn(II) or a Cd(II) metal–organic framework etc. More importantly, most of these methods require the use of hazardous organic solvents and some of them need harsh reaction conditions and many of them are either not eco-friendly or cause environmental pollution. Consequently, there is still need to develop a more efficient, simple, milder and high yield protocol for the synthesis of highly substituted pyridines.

During the last three decades ultrasound mediated reactions have emerged as efficient and attractive methodologies in organic synthesis[16]. Compared with traditional methods, these reactions are more convenient and advantageous. Thus, various organic reactions can be carried out under ultrasound irradiation within shorter reaction time and mild conditions affording high yields of desired products[17].

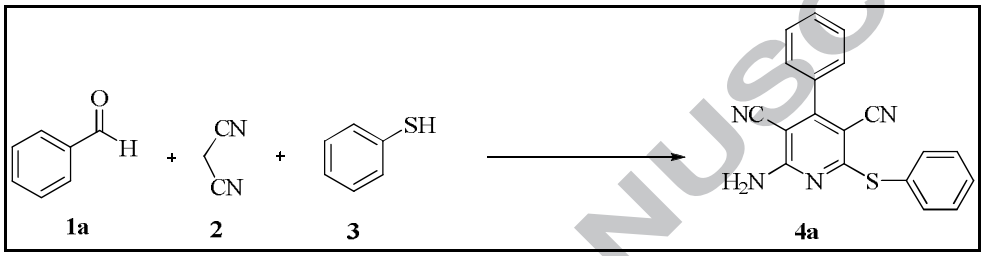
Recently there has been increasing concern with regard to the tight legislation on the maintainence of 'greenness' in the synthetic pathways and processes. Due to gr`owing environmental concern, designing of straightforward and practical chemical syntheses of drugs and fine chemicals that satisfy economic criteria is a major challenge[18]. The use of water is the preferred non-conventional reaction medium in the design of green chemical syntheses[19] and significant efforts has been made in performing organic synthesis in aqueous medium[20]. The NaCl has emerged as a useful catalyst for the construction of various carbon–carbon and carbon–heteroatom bonds. Several advantages such as its excellent solubility in water, eco-friendly nature, easy handling, cost-effectiveness, high reactivity, and easy work-up procedures made NaCl as an effective catalyst in organic synthesis[21].

Therefore, in an endeavor towards the development of greener synthetic protocols for the synthesis of highly functionalized pyridine derivatives herein, we describe the one-pot three component condensation of aryl aldehyde, malanonitrile and thiophenol using sodium chloride as an additive in aqueous media under ultrasonic irradiation as well as at conventional technique, which afford 2- amino-3, 5-dicarbonitrile-6-thio-pyridines in higher yields within shorter reaction times by avoiding toxic catalysts and hazardous solvents.

Results and Discussion

In continuation of our research work on the synthesis of heterocyclic compounds[22], we have designed a unique synthetic route to privileged heterocyclic scaffolds of medicinal significance that combine synthetic efficency of multicomponent protocols with the environmental benefit of using water as a reaction medium.

Initially, in order to optimize the reaction conditions, we have choosen the reaction of benzaldeyde (**1a**), malononitrile (**2**) and thiophenol (**3**) as a standard model reaction (**Scheme 1**).) In addition, ultrasound irradiation technique is successfully implemented to carry out the reactions.



Scheme 1. Standard model reaction

The effect of various catalysts on the model reaction was conducted (**Table 1**). The results indicated that the catalyst had a significant effect on the product yield. According to literature, it has become apparent that formation of pyridine does not take place in the absence of catalyst/additive [15]. Neat reaction only leads to Knoevenagel condensation product of aldehyde and malononitrile. This clarified the need of catalyst/additive for the formation of pyridine. In an order to evaluate the effect of additives, various additives were used for performing the model reaction. Intentionally, chlorides of the first group elements, i.e., Hydrochloric acid (HCl), Lithium Chloride (LiCl), Sodium Chloride (NaCl), Potassium Chloride (KCl) and similar analogue of these salts *viz.* Ammonium Chloride (NH_4Cl) and some sodium halide NaBr and NaI were utilized for our purpose.

Our attempts started with the use of bronsted acid i.e., HCl (**Table 1**, **entry 2**) as an additive. But, formation for the product was not observed during the reaction. However some Non acidic neutral salts (metal chlorides) such as LiCl, KCl and acidic salt like NH_4Cl (**Table 1**, **entry 3-5**) were used as additive, however yields of the product in each case were found to be low to moderate. With this results, some sodium halides such as NaBr and NaI and NaCl have been used for our further study and it was observed that when we utilize some sodium halides reaction seems to proceed smoothly (**Table 1**, **entry 6, 7**). Surprisingly, when non-acidic salt, i.e. NaCl was used as an additive, the reaction was completed in a shorter time with excellent yield of desired product.

Further, to know the precise role of a solvent, model reaction was performed under solvent free condition at 100 °C. To our surprise, reaction in neat condition was observed to result with 55% yield (**Table 1**, **entry 13**). Whereas, no product formation was observed in the absence of catalyst **(Table 1, entry 14).** As the selection of an appropriate reaction medium is of crucial importance for the success of the reaction the model reaction was screened by various solvents in the presence of NaCl under conventional heating conditions and ultrasound irradiation. The results show that the effectiveness of solvents on the product yield. The use of toluene, acetonitrile gave poor yields (**Table 1**, **entries, 11, 12**). Solvents like EtOH, MeOH and DMF gave moderate yields (**Table 1**, **entries, 8-10**). The best conversion was observed when the reaction was performed in water (**Table 1**, **entry 1**) based on these results, water was then selected as the medium for the further investigations. In order to establish the appropriate quantity of water, the model reaction was investigated using 4, 6, 8, 10, and 12 mL of water yielding desired product in 40%, 55%, 65%, 90% and 90% respectively **(Table 1, entries, 15-19)**. In these experiments, it was observed that 10 mL of water is sufficient to carry out the reaction efficiently.

Table 1. Screening of the catalysts, solvents and amount of solvents[a]

Entry	Catalyst	Solvent	Yield[b] (%)
1	NaCl	Water	90
2	HCl	Water	NR
3	LiCl	Water	52
4	KCl	Water	69
5	NH_4Cl	Water	62
6	NaBr	Water	74
7	NaI	Water	70
8	NaCl	Ethanol	65
9	NaCl	Methanol	59
10	NaCl	DMF	62
11	NaCl	Acetonitrile	40
12	NaCl	Toluene	36
13	NaCl	Neat*	55
14	No Catalyst	Water	NR
15	NaCl	Water (4 mL)	64
16	NaCl	Water (6 mL)	69
17	NaCl	Water (8 mL)	78
18	NaCl	Water (10 mL)	90
19	NaCl	Water (12 mL)	90

[a]*Reaction conditions*: **1a** (1 mmol), **2** (2 mmol), **3** (1 mmol), Catalyst (15 mol%), in solvent (10 mL) at reflux temp. for 2 h; *At neat condition reaction temp. was 100 °C; NR= No reaction;[b]Isolated yields.

In order to know the reaction condition, we have used the combination of NaCl and water to model reaction at room temperature. It was noted that, the reaction leads to only Knoevenagel condensation of an aldehyde and malononitrile, and trace amount of product formed, **(Table 2, entry 1)**. Therefore, in an attempt to reduce reaction time and increase product yields, model reaction tested at higher temperature. To evaluate the appropriate temperature we carried out the model reaction at 60°C, 80°C and reflux condition, (**Table 2, Entries, 2, 3, 4)** however increasing the temperature enhances the reaction rate substantially with respective 45%, 62% and 90% yield.

To evaluate the appropriate concentration of the catalyst for the model reaction, we investigate the model reaction at different concentration of NaCl such as 5, 10, 15 and 20 mol%. The product was formed in 60, 72, 90 and 90% yield, respectively, (**Table 2, Entries, 4-7)**. This shows that 15% of NaCl is sufficient to carry out the reaction efficiently. With these satisfactory results in hand, it was decided to use NaCl for further studies. To generalize the optimized reaction condition, some substituted aldehydes were allowed to undergo this three-component reaction.

Table 2. Effect of the concentration of catalyst and temperature[a]

Entry	Temperature(°C)	Catalyst (%)	Yield[b] (%)
1	R.T.	15	Trace
2	60	15	45
3	80	15	62
4	Reflux	15	90
5	Reflux	5	60
6	Reflux	10	72
7	Reflux	20	90

[a]*Reaction conditions*: **1** (1 mmol), **2** (2 mmol), **3a** (1 mmol), and NaCl (15 mol%) in water (10 mL) for 2 h; [b]Isolated yields.

Selectivity of NaCl for catalysing this reaction is attributed to the salting effect. It is well known that most of the organic molecules show dislike nature towards the water and hence in the presence of water molecules organic substrates come much closer during the reaction due to the hydrophobic effect. Ultimately hydrophobic effect enhances the concentration of organic substrate in the reaction medium, thereby causing the more and more collisions of reacting species, which generates the activation energy in the favour of product formation. This hydrophobic effect can be increased by addition of NaCl in medium, specifically when reaction medium is aqueous due to the salting out effect. When NaCl is added in water it dissociate into Na^+ and Cl^- ions. These ions afterword get solveted by water molecules resulting in the less availability of water molecules for interaction with organic molecules. Therefore, solute-solute interaction becomes stronger than solute-

solvent interaction, which is supported by volume contraction. Above discussed salting out effect of NaCl is well understood in literature[23]. This salting out effect is more pronounced for NaCl than for KCl[24] which shows the advantage of NaCl as a catalyst. The reaction was proposed via the Knoevenagel condensation of an aldehyde and malanonitrile, followed by the Michael addition of second molecule of malanonitrile on the Knoevenagel product. This then reacts with thiophenol and under goes air oxidation to afford final product (**Figure 1**).

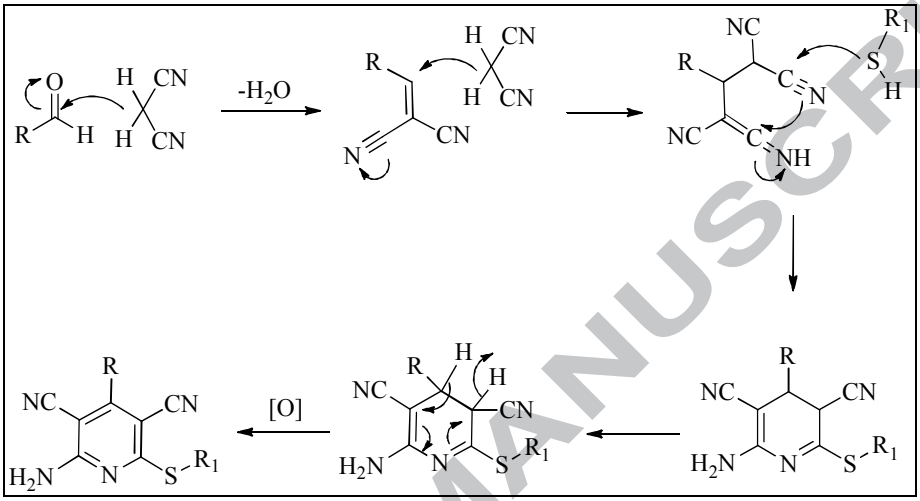
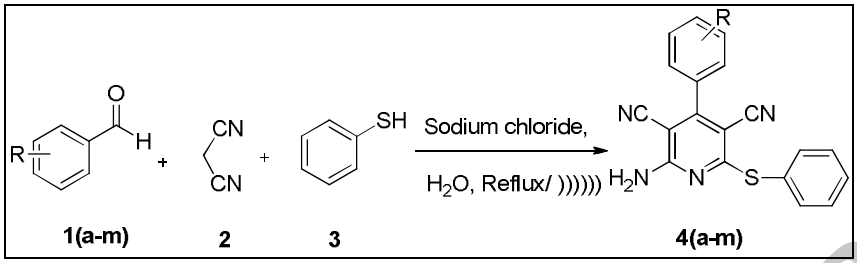


Figure 1: Possible mechanism for the synthesis of Highly Functionalized Pyridines.

Table 3. Synthesis of highly functionalized pyridines.[a]



Product	R	With US[a]		Without US[b]		M. P. (°C)[d]
		Time (Min)	Yield[c] (%)	Time (hrs)	Yield[c] (%)	
4a	4-Cl	20	91	2	90	223-224 [15]
4b	H	20	88	2	87	212-214 [15]
4c	4-OMe	22	85	2	85	242-245 [15]
4d	4-NO_2	20	92	2	90	286-288 [15]
4e	Piperonyl	20	84	2	82	230-234 [15]
4f	4-OH-3-OMe	20	82	2	80	217-220 [15]
4g	3,4-$(OMe)_2$	25	85	2	84	226-229 [15]
4h	2-Thienyl	20	84	2	82	212-215 [15]
4i	2-Furyl	25	80	2	80	178-180 [15]
4j	4-OH	25	87	2	85	310-314 [15]
4k	4-Me	20	85	2	83	206-210 [15]
4l	Acetaldehyde	35	25	3	20	228-230 [15]
4m	Propionaldehyde	30	22	3	18	145-147 [15]

[a]*Reaction conditions*: **1a** (1 mmol), **2** (2 mmol), **3** (1 mmol), Catalyst (15 mol%), in water (10 mL) under ultra sonic waves. [b]Reaction conditions: **1a** (1 mmol), **2** (2 mmol), **3** (1 mmol), Catalyst (15 mol%), in solvent (10 mL) at reflux condition. [c]Isolated yield. [d]Compounds were characterized by 1H NMR, MS spectral data and were compared with the reference compounds.[15]

In further set of experiment, model reaction has been performed using non-classical activation energy source, that is, ultrasound irradiation. In this experiment, model reaction was found to proceed effectively within very short reaction time delivering the desired product in excellent yield. Inspire by this, it was decided to synthesize number of derivatives following developed reaction condition by classical as well as non-classical method.

For assessing the generality of optimized reaction condition, wide range of substituted aldehydes were allowed to undergo this three component condensation reaction. Aromatic aldehydes with several functionalities were found to be compatible under the optimized reaction conditions. Heteroaromatic aldehydes such as piperonal, thiophene-2-carbaldehyde and furfuraldehyde also proved to be amenable under these reaction conditions. Unfortunately, aliphatic aldehydes such as acetaldehyde and propionaldehyde afforded the desired product in lower yields. All the synthesized compounds were charecterized by spectral data and compared (MS, NMR) with authentic sample. This comparison revealed that the compounds synthesized by this newly developed method were exactly similar in all aspects to the reference compounds[15]. The developed method is simple, efficient and good contribution in field of pyridines.

Conclusion:

In conclusion, we have developed one pot multicomponent protocol for the synthesis of highly functionalized pyridines using aldehydes, malononitrile and thiophenol in the presence of sodium chloride as a readily available reaction accelerator. Utilization of NaCl in aqueous solvent system is proved as a green reaction medium for carrying out organic transformations. Developed synthetic method has several advantages such as wide scope of substrate, easily available catalyst, operational simplicity, easy work up procedure and higher product yields.

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General experimental procedure for the synthesis of highly functionalized pyridines (4a-m):

Conventional method: To a mixture of aldehyde 1 (1 mmol) and malononitrile 2 (2 mmol) in 10 mL water, catalytic amount of sodium chloride (NaCl) (15 mol %) was added. After 10-15 minutes of stirring, solid was precipitated out indicating the rapid knoevenagel condensation. To this reaction mass, thiophenol 3 (1 mmol) was added and reaction mass was refluxed for time specified in Table 3, until the complete conversion of the starting materials was achieved. Progress of the reactions was monitored with the help of TLC. After completion of the reaction, thick reaction mass thus obtained was poured on crushed ice, stirred well and collected by simple filtration, which was further washed with water (10 mL) followed by aqueous ethanol (10 mL) to afford crude product 4. This crude product (4a) was purified by recrystallization technique from 10% aqueous ethanol as a solvent.

Ultrasound method: To a mixture of aldehyde 1 (1 mmol) and malononitrile 2 (2 mmol) in 10 mL water, catalytic amount of sodium chloride (NaCl) (15 mol %) was added and it was subjected to ultrasound irradiation for 3 min. After 3 minutes, thiophenol 3 (1 mmol) was added and reaction mass was irradiated for time specified in Table 3, until the complete conversion of the starting materials was achieved. Reaction progress was monitored by TLC (ethyl acetate/n-hexane: 1:9). After completion of the reaction, thick reaction mass thus obtained was poured on crushed ice, stirred well and collected by simple filtration, which was

further washed with water (10 mL) followed by aqueous ethanol (10 mL) to afford crude product 4. This crude product (4a) was purified by recrystallization technique from 10% aqueous ethanol as a solvent.

Spectral Data of Representative compound:

2-Amino-4-(4-chlorophenyl)-6-phenylsulfanylpyridine-3,5-dicarbo-nitrile (4a): ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.46-7.49 (m, 3H, Ar-H), 7.57 (d, 2H, J = 8 Hz, Ar-H), 7.59 (d, 2H, J = 8 Hz, Ar-H), 7.64 (d, 2H, J = 8 Hz.) 7.82 (brs, 2H, -NH_2); ^{13}C NMR (50 MHz, $CDCl_3$): δ 87.19, 93.32, 114.78, 115.19, 117.12, 125.38, 127.61, 128.92, 130.18, 130.43, 132.74, 135.29, 157.82, 159.61, 166.09; ES-MS: 361.2 (M^-), 363.2 (M^-+2).

Graphical Abstract

Sodium chloride: A proficient additive for the synthesis of pyridine derivatives in aqueous medium.

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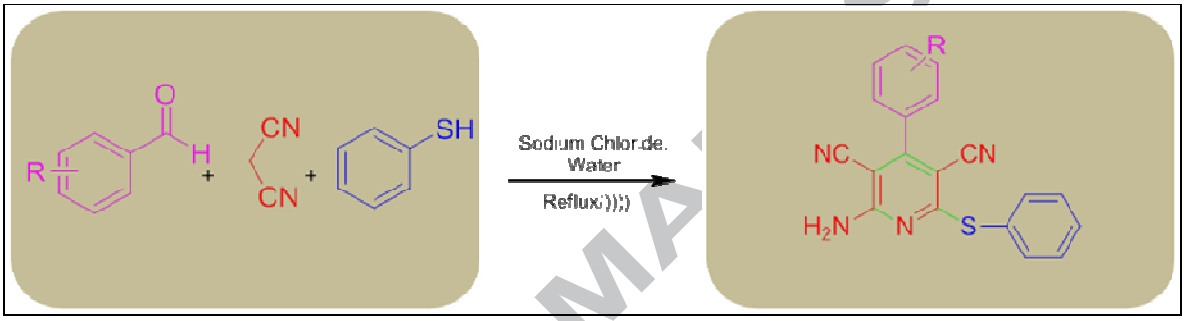

In the present work, a facile and convenient synthesis of substituted pyridines has been developed via a one-pot multicomponent reaction of easily available aromatic aldehydes, malononitrile and thiophenol under aqueous media and in the presence of NaCl as mild conditions. A series of functionalized pyridines were thus obtained by this multicomponent reaction, in which four new bonds were formed. Particularly valuable features of this protocol including mild conditions, simple execution, broad substrate scope, and good yields of products make it an efficient and promising synthetic strategy to build pyridine skeleton