



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 catalysed 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.

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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 occurrence as key structural subunits in numerous natural products that exhibit many interesting biological activities.² In addition, these heterocyclic compounds have found a variety of applications in medicinal and pharmaceutical sciences. Particular pyridine scaffold is the core structure of a wide range of naturally occurring bioactive molecules, pharmaceuticals and functional materials.^{3–5} Polysubstituted pyridines have also found to be antiprion,⁶ antihepatitis B virus,⁷ antibacterial,⁸ anticancer agents² and as potassium channel openers for treatment of urinary incontinence.⁹ Moreover, some of the compounds were discovered to be highly selective ligands for adenosine receptors,¹⁰ which are recently recognized as potential targets for the development of new drugs for the treatment of Parkinson's disease, hypoxia/ischaemia, asthma, kidney disease and epilepsy.¹¹

Multicomponent reactions (MCRs) have drawn interesting efforts owing to their exceptional synthetic efficiency, intrinsic atom economy, high selectivity and procedural simplicity.¹² MCRs are useful for the expedient creation of chemical libraries of

structurally related, medically significant drug-like compounds.¹³ 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.¹⁴ Various catalysts utilized for this purpose include DBU, DABCO, Et₃N, piperidine, KF/alumina, K₂CO₃/KMnO₄, ZnCl₂, 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 a 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.¹⁵ 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.¹⁶

Recently there has been increasing concern with regard to the tight legislation on the maintenance of 'greenness' in the synthetic pathways and processes. Due to growing environmental concern, designing of straightforward and practical chemical syntheses of drugs and fine chemicals that satisfy economic criteria is a major

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challenge.¹⁷ The use of water is the preferred nonconventional reaction medium in the design of green chemical syntheses¹⁸ and significant efforts have been made in performing organic synthesis in aqueous medium.¹⁹ 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.²⁰

Therefore, in an endeavour 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, malononitrile 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,²¹ we have designed a unique synthetic route to privileged heterocyclic scaffolds of medicinal significance that combine synthetic efficiency of multicomponent protocols with the environmental benefit of using water as a reaction medium.

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

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 the literature, it has become apparent that formation of pyridine does not take place in the absence of catalyst/additive.¹⁴ 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, that is, hydrochloric acid (HCl), lithium chloride (LiCl), sodium chloride (NaCl), potassium chloride (KCl) and similar analogues of these salts viz. ammonium chloride (NH₄Cl) and some sodium halide NaBr and NaI were utilized for our purpose.

Our attempts started with the use of Bronsted acid that is, HCl (Table 1, entry 2) as an additive. But, formation for the product was not observed during the reaction. However some nonacidic neutral salts (metal chlorides) such as LiCl, KCl and acidic salt like NH₄Cl (Table 1, entries 3–5) were used as additive, however yields of the product in each case were found to be low to moderate. With these 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 the reaction seems to proceed smoothly (Table 1, entries 6 and 7). Surprisingly, when nonacidic salt, that is, NaCl was used as an additive, the reaction

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 ₄ Cl	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 ^c	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

NR = No reaction.

^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.

^b Isolated yields.

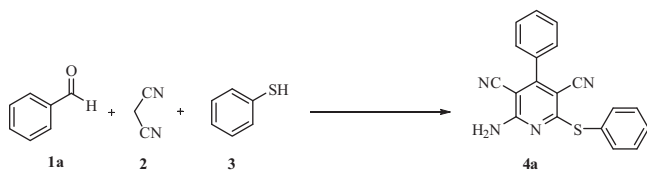
^c At neat condition reaction temp was 100 °C.

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 in 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 the effectiveness of solvents on the product yield. The use of toluene, acetonitrile gave poor yields (Table 1, entries 11 and 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.

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 was 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 2–4) however increasing the temperature enhances the reaction rate substantially with respective 45%, 62% and 90% yields.

To evaluate the appropriate concentration of the catalyst for the model reaction, we investigate the model reaction at different concentrations of NaCl such as 5, 10, 15 and 20 mol %. The product was formed in 60, 72, 90 and 90% yields, 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



Scheme 1. Standard model reaction.

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