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Zinc-catalyzed multicomponent reactions: Facile synthesis of fully substituted pyridines

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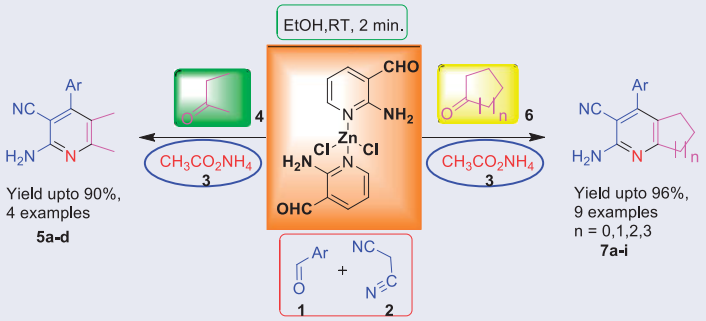
ABSTRACT

A first example of environmentally benign zinc complex catalyzed one-pot four-component reaction between malononitrile, ketone, ammonium acetate and aromatic aldehyde for the facile synthesis of fully substituted pyridines just within 2 min in environmentally friendly solvent ethanol has been optimized.

GRAPHICAL ABSTRACT



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KEYWORDS
Atom economy; fully substituted pyridines; green chemistry; multicomponent reaction; zinc catalyst

Introduction

Zinc is one of the highly abundant, cheaper and low toxic metals of the periodic table. It can be easily separated/extracted in high purity from the corresponding minerals than many other metals. The biological relevance of zinc makes it an essential trace element to regulate the enzymatic function of both animal and plant kingdom. Besides, at present the current research in 'green chemistry' is focusing on the use of cheaper and low toxic metals as catalysts or stoichiometric reagents to develop environmentally sustainable protocols in organic synthesis and pharmaceutical synthesis.[1] In line of these precedents, the use of zinc based catalysts (homogeneous/heterogeneous) and reagents would be a good choice to meet the requirements of green chemistry.[1b,2]

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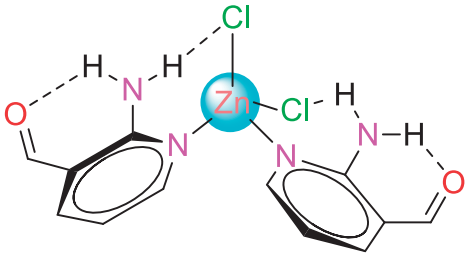


Figure 1. Structure of $Zn(ANA)_2Cl_2$ complex.

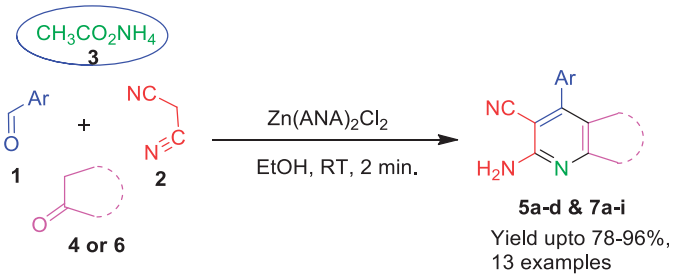
Since the discovery of first organometallic diethyl zinc, a variety of catalytic and stoichiometric reagent applications of zinc compounds have been found in organic synthesis. For instance, the use of zinc in Negishi coupling, Reformatskii and Fukuyama reactions has been recognized as breakthrough reactions of organic synthesis.[3,4] However, as compared to other metals, the use of zinc compounds in organic synthesis is still under developing stage due to its position in the periodic table, where zinc is placed between transition and main group elements. The filled d-orbital electronic configuration provides zinc a different chemistry than those of other d-block elements and more related chemistry to main group elements, which is quite simple and predictable. However, recent trends in green chemistry have been strongly recommending the development of cheaper and low toxic zinc based organic transformations of C–C, C-heteroatom bond forming reactions for sustainable environment.[1c,5]

The concept of multicomponent reaction (MCR) is one type of modern perspective emerged in green chemistry, wherein three or more than three components reacts in one-pot through sequential reactions and provides selectively the desired product by reducing the waste. MCRs are indeed cost-effective, time-saving and environmentally benign as compared to step-by-step reactions of traditional organic synthesis in achieving the desired final/target product. Majority of MCRs require a multifunctional catalyst to control the selectivity in the sequential reactions. At present, catalyzed MCRs are in common practice to synthesize a variety heterocycles and heteroatomic organic compounds.[6]

We are interested in developing a facile MCR protocol to synthesize highly substituted pyridines in view of their intriguing applications in medicinal and materials chemistry.[7] The use of a variety of homogeneous and heterogeneous catalysts has been reported previously to synthesize various densely substituted pyridines *via* traditional organic synthesis or MCR synthesis.[8,10a,10b]

Results and discussion

Herein we report usefulness of homogeneous $Zn(ANA)_2Cl_2$ complex (ANA = 2-Aminonicotinaldehyde; Fig. 1) as catalyst for the one-pot four-component condensation of malononitrile, ketone and ammonium acetate as partners to aromatic aldehydes to form a variety of fully substituted pyridines in environmentally friendly solvent ethanol (EtOH; Scheme 1) at room temperature (RT) conditions. It is a considerable topic that the green aspect is connected not only with the use of water as reaction medium but also with the possibility to use other green solvents such as ethanol to improve the yields and selectivity.



Scheme 1. Synthesis of fully substituted pyridines.

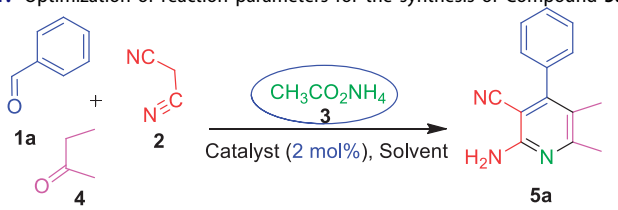
The $Zn(ANA)_2Cl_2$ complex was prepared on mixing freshly prepared solutions of ANA dissolved in 20 ml ethanol and Zinc chloride tetrahydrate ($ZnCl_2.4H_2O$) dissolved in 10 ml ethanol, at reflux temperature for about 3 h. At the end of the reaction excess ethanol was removed by vacuum and filtered after cooling to obtain pure $Zn(ANA)_2Cl_2$ complex. The $Zn(ANA)_2Cl_2$ complex has been reported by us recently[9] and now we extend the studies to explore its catalytic ability in MCR. It is worth noting that previously there were only few reports found in literature about the catalytic MCR synthesis of fully substituted pyridines. However, there was no information about the use of zinc catalysts in the MCR synthesis of fully substituted pyridines.

Initially we choose to probe a four-component sequential one-pot reaction (MCR) between benzaldehyde (Compound **1a)** malononitrile (Compound **2**), ammonium acetate (Compound **3**) and 2-butanone (Compound **4**; acyclic ketone) in ethanol in the presence of different zinc salts and a $Zn(ANA)_2Cl_2$ complex for the synthesis of substituted pyridine (Compound **5a**). The details of the reaction and the results are given in Table 1.

The intended MCR was not observed in the absence of catalyst at RT conditions in ethanol (Table 1, Entry1). Later, we have investigated the above MCR in the presence of different zinc salts including zinc acetate ($Zn(OAc)_2$), zinc trifluoromethanesulfonate ($Zn(OTf)_2$), zinc chloride ($ZnCl_2$), zinc nitrate ($Zn(NO_3)_2$), zinc bromide ($ZnBr_2$), zinc tetrafluoroborate hydrate ($Zn(BF_4)_2$), zinc iodide (ZnI_2;Table 1, Entries 2–8) and copper salts cupric chloride ($CuCl_2$) and copper(II) bromide ($CuBr_2$) as catalysts (Table 1, Entries 9, 10) at RT conditions. However, we have noticed that the simple zinc salts and copper salts did not facilitate the intended MCR at RT. In this situation, when $Zn(ANA)_2Cl_2$ (Fig. 1) was employed as a catalyst, there was a dramatic acceleration in the proposed MCR at RT only and yielded the expected/desired substituted pyridine (Compound **5a**) selectively just in 2 min in good yield (92%, Table 1, Entry 11). It is also important to note that the above $Zn(ANA)_2Cl_2$ catalyzed reaction was observed to be sluggish and non-selective in non-protic solvents, tetrahydrofuran (THF), acetonitrile (CH_3CN), dichloromethane (DCM), dioxane, benzene (Table 1, Entries 12–16). This information outlines that the choice of solvent is also one of the key factors in this catalyzed MCR.

Literature information reveals that there were few similar MCR strategies (malononitrile, ketone, ammonium acetate and aromatic aldehyde) were developed with or without using catalysts.[10,11] However, except the one with the use of Ag(I)-NHC catalysts[10a], those remained methodologies reported the requirement of refluxing or microwave conditions and longer reaction times.[11] Our results indicates the efficiency of zinc catalyst ($Zn(ANA)_2Cl_2$) in catalyzing the MCR at just RT conditions to produce Compound **5a**

Table 1. Optimization of reaction parameters for the synthesis of Compound **5a**.



Entry	Catalyst	Solvent	Yield (%)[a]
1	No catalyst	EtOH	–
2	$Zn(OAc)_2$	EtOH	24
3	$Zn(OTf)_2$	EtOH	36
4	$ZnCl_2$	EtOH	35
5	$Zn(NO_3)_2$	EtOH	30
6	$ZnBr_2$	EtOH	32
7	$Zn(BF_4)_2$	EtOH	35
8	ZnI_2	EtOH	35
9	$CuCl_2$	EtOH	28
10	$CuBr_2$	EtOH	26
11	$Zn(ANA)_2Cl_2$	EtOH	92
12	$Zn(ANA)_2Cl_2$	THF	22
13	$Zn(ANA)_2Cl_2$	CH_3CN	18
14	$Zn(ANA)_2Cl_2$	DCM	20
15	$Zn(ANA)_2Cl_2$	Dioxane	Trace
16	$Zn(ANA)_2Cl_2$	Benzene	Trace

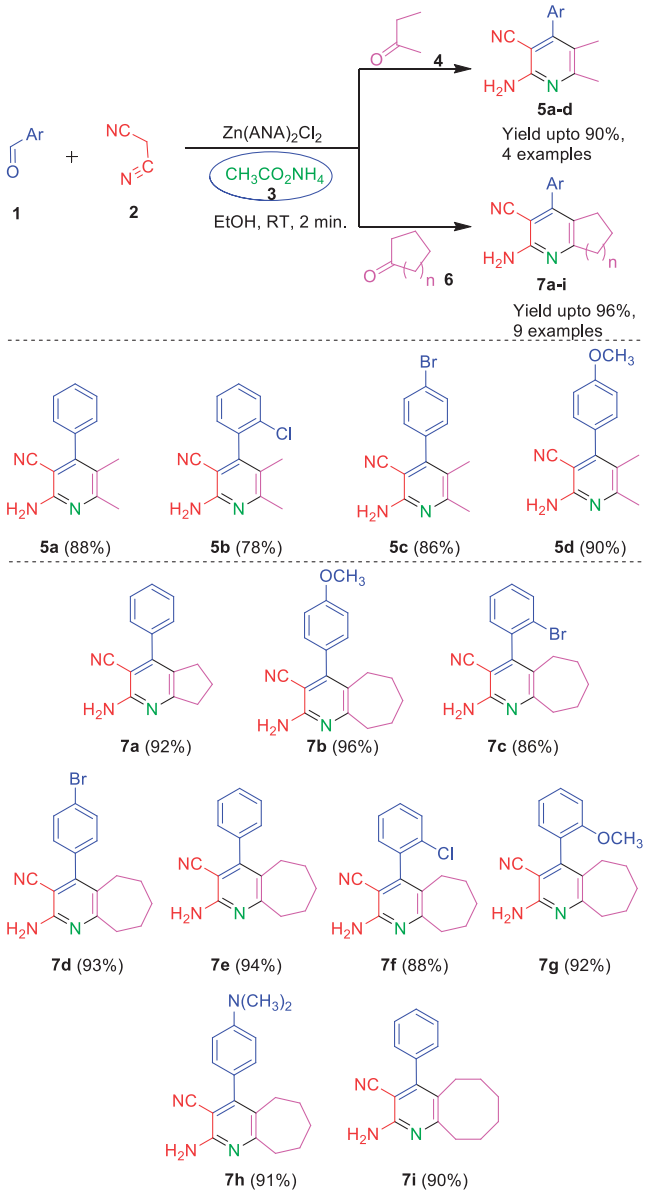
[a]GC yields.

to meet the requirements of green catalysis. The solid product of Compound **5a** obtained in our work was further identified and quantified on the basis of its analytical and spectral data (Refer the "Experimental" section).

Using the above optimized conditions ($Zn(ANA)_2Cl_2$, 2 mol%, 2 min, RT, ethanol) for four-component MCR, we extended substrate scope to synthesize some diverse fully substituted pyridines. We have used various structurally different aldehydes (Compounds **1b**–**g**), acyclic ketones (Compound **4**) and cyclic ketones (Compound **6a**–**c**)) in the MCR to study the electronic effects. The results are summarized in Scheme 2. The results indicate that the $Zn(ANA)_2Cl_2$ is highly also efficient in facilitating the MCRs of Scheme 2 and providing the good yields in shorter reaction times. The substrates of MCR bearing electron donating or electron-withdrawing groups on the aromatic ring proceeded smoothly and formed the corresponding fully substituted pyridines in good yields.

Structures of the substituted pyridines (Compounds **5(a–d)** and **7(a–i)**, Scheme 2) were established on the basis of elemental analysis and spectral data (^1H and ^{13}C NMR). The details of the product characterization are presented in the "Experimental" section.

Finally, based on the results obtained in our work and previous reports concerning the MCR synthesis of fully substituted pyridines including control experiments, a plausible mechanism has been deduced in Scheme 3. The reaction may proceed *via* forming enamine (Compound **A**) the condensed product of ketone and ammonium acetate, then activated by $Zn(ANA)_2Cl_2$, which then reacts with alkylidenemalononitrile (Compound **B**; Compound **C**; Michael adduct). The Michael adduct then undergoes cycloaddition and isomerization to give 1,4-dihydropyridine (Compound **D**). The subsequent oxidative aromatization of 1,4-dihydropyridine (Compound **D**) under air atmosphere will produce



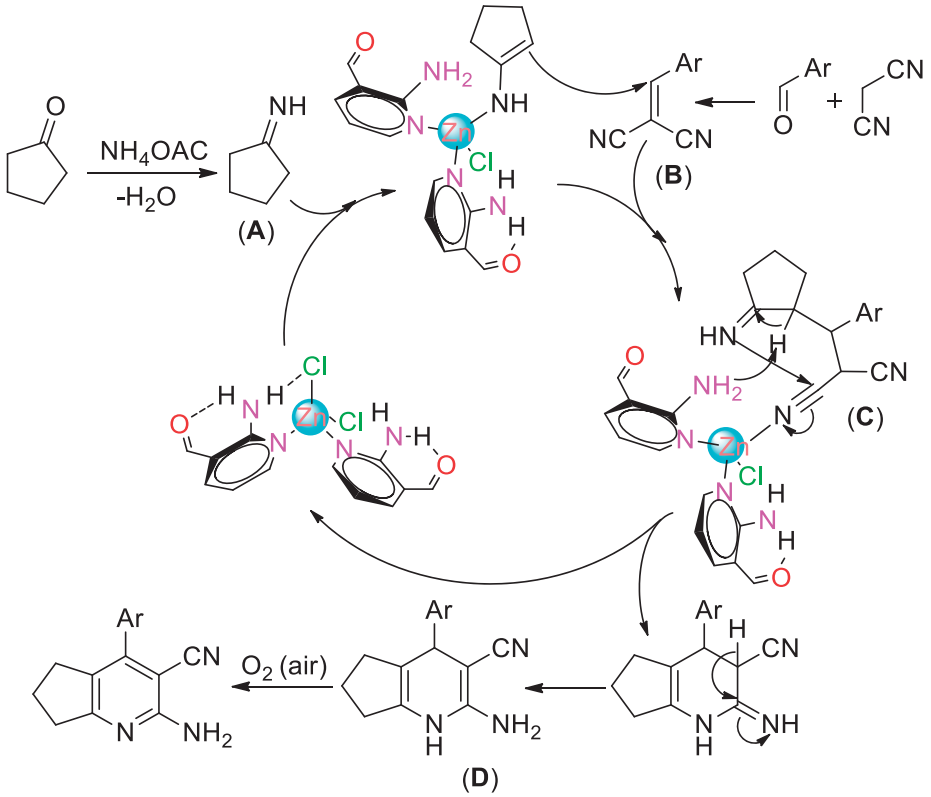
Scheme 2. Synthesized fully substituted pyridine derivatives.

the desired fully substituted pyridines (Compounds **5(a–d) and 7(a–i)**) as shown in Scheme 3.

Experimental

General

All commercially available reagents were used without further purification. Reaction solvents were dried by standard methods before use. Purity of the compounds was checked by thin layer chromatography (TLC) using Merck 60F254 silica gel plates. Elemental



Scheme 3. A plausible mechanism for the formation fully substituted pyridines.

analyses were obtained with an Elemental Analyser Perkin-Elmer 240C apparatus. ^{1}H- and ^{13}C NMR spectra were recorded with a Mercuryplus 400 spectrometer (operating at 400 MHz for ^{1}H and 100.58 MHz for ^{13}C); chemical shifts were referenced to trimethyl silane. Electron impact (EI) mass spectra (at an ionising voltage of 70 eV) were obtained using a Shimadzu QP5050A quadrupole-based mass spectrometer.

Catalyst preparation

General procedure for the synthesis of $[Zn(ANA)_2Cl_2]$ complex

The freshly purified ligand (0.488 g, 4 mmol) was dissolved in EtOH (20 ml) and added ethanolic solution of $ZnCl_2.4H_2O$ (0.273 g, 2 mmol) were stirred at reflux temperature after mixing the solution for about 3 h. At the end of the reaction the excess ethanol was removed in vacuum and filtered after cooling without further purification to obtain 75% yield. Yellow solid: mp 288–290 °C; IR (KBr, cm^{-1}): 3412 (N–H), 1678 (C=O), 1564(C=N (py)). ^{1}H NMR (400 MHz, DMSO): $\delta = 6.73$–6.76 (m, 2H), 7.56 (s, 4H), 8.00 (d, $J = 8.0$ Hz, 2H), 8.24 (d, $J = 8.0$ Hz, 2H), 9.85 (s, 2H) ppm. ^{13}C NMR (100 MHz, DMSO): $\delta = 112.69$, 113.49, 145.08, 155.31, 158.68and 194.10 ppm. Anal. calculated (calcd; %) for $Zn(C_6H_6N_2O)_2Cl_2$: Calcd: C, 37.85; H, 3.17and N, 14.72. Found: C, 37.80; H, 3.15and N 14.69.

General procedure for the synthesis of pyridines (Compounds 5(a–d) and 7(a-i))

Aromatic aldehydes (Compound **1**; 1 mmol) and malononitrile (1 mmol) was dissolved in EtOH (10 ml) and added the ethanolic solution of cyclic ketone/ethyl methyl ketone (Compounds **2(a–c)** or **2d;** 1.2 mmol), ammonium acetate (1.2 mmol) and catalyst $Zn(ANA)_2Cl_2$ (2 mol%) were stirred over a period of 2 min at room temperature. Complete consumption of starting material as judged by TLC and Gas chromatography (GC) analysis. The reaction mass was filtered and washed with ethanol to obtained off-white solid crude product which was subjected to recrystallization in hot ethyl acetate to afford pure products (Compounds **5(a–d)** and **7(a-i)**).

2-Amino-5,6-dimethyl-4-phenyl-nicotinonitrile (5a): The product was obtained as off-white solid: Yield (88%); mp 240–241 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.95$ (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 5.05 (s, 2H, NH_2), and 7.23–7.50 (m, 5H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 15.30$, 23.72, 89.72, 116.80, 119.69, 128.33, 128.64, 128.77, 136.79, 153.86, 157.23 and 161.57 ppm. Anal. calcd (%) for $C_{14}H_{13}N_3$: Calcd: C, 75.31; H, 5.87and N, 18.82. Found: C, 75.37; H, 5.89and N 18.78.

*2-Amino-4-phenyl-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carbonitrile (Compound **7a**):* The product was obtained as off-white solid: Yield (92%); mp 220–221 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.90$–1.98 (m, 2H), 2.60 (t, $J = 7.3$ Hz, 2H), 2.80 (t, $J = 7.6$ Hz, 2H), 6.66 (s, 2H, NH_2), and 7.42–7.51 (m, 5H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 22.22$, 28.78, 34.50, 85.52, 117.39, 123.02, 128.24, 128.49, 128.92, 135.92, 149.16, 160.99, and 169.64 ppm. Anal. calcd (%) for $C_{15}H_{13}N_3$: Calcd: C, 76.57; H, 5.57and N, 17.86. Found: C, 76.59; H, 5.58and N, 17.89.

Conclusion

In conclusion, we have demonstrated the usefulness of a cheaper, low toxic and environmentally benign zinc metal complex, $Zn(ANA)_2Cl_2$ as catalyst in the MCR between aldehyde, ammonium acetate, ketone and malononitrile to produce a variety of fully substituted pyridines in good yields. The use of ethanol is not only favored the fast accomplishment of MCR at RT conditions, but also promoted the non-toxic solvents for green chemical synthesis. Further studies are warranted to address the nature of the active catalysts under these conditions. The presence of reactive $-CN$ and $-NH_2$ groups at five and six positions, respectively, renders these compounds for further transformations towards more complex heterocycles.

Acknowledgements

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