Current Chemistry Letters 10 (2021) 169–174

Contents lists available at GrowingScience

Current Chemistry Letters

homepage: www.GrowingScience.com

# One-pot multicomponent synthesis of highly substituted pyridines using hydrotalcite as a solid base and reusable catalyst

**Sandip R. Kale[a*] and Santosh Kumar Surve[a]**

[a]*Department of Chemistry, Yogeshwari Mahavidyalaya, Ambajogai, Beed-431517, India*

**C H R O N I C L E**

*Article history*:
Received October 1, 2020
Received in revised form
November 29, 2020
Accepted January 3, 2021
Available online
January 3, 2021

*Keywords*:
*Multicomponent reaction*
*Heterogeneous catalyst*
*Hydrotalcite*
*Pyridine*
*One-pot reaction*

**A B S T R A C T**

One-pot synthesis of highly substituted pyridines has been demonstrated via multicomponent reaction of aldehydes, malononitrile and thiophenol using Mg-Al hydrotalcite as a solid base and reusable catalyst. The catalytic activity is intimately connected to the basicity of the catalyst. The best activities were observed with the Mg/Al: 5 catalyst. The catalyst could be reused for further run without a significant loss in activity. The protocol was also applicable for various aromatic aldehydes which affords desired product in good to excellent yield.



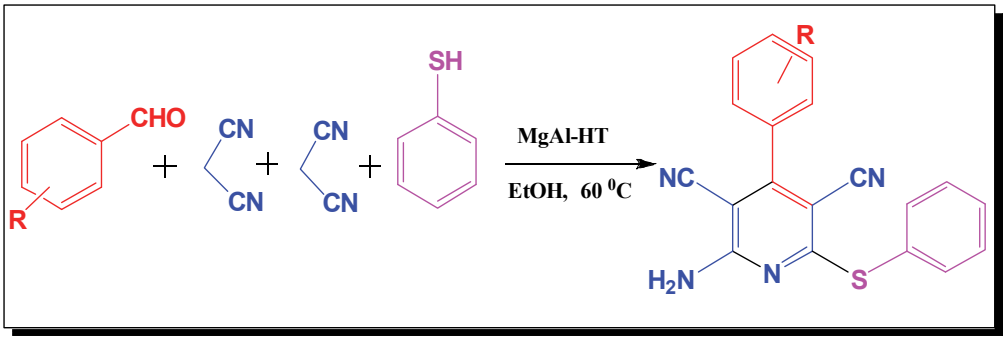
## 1. Introduction

The synthesis of highly substituted pyridine moieties through multicomponent reaction[1-4] of aldehydes, malononitrile and thiol is of considerable interest as the pyridine ring is the key intermediate in pharmaceutical chemistry. The substituted pyridine ring exhibits various biological activities[5-8]. Various synthetic methods[9-14] have been developed for the synthesis of pentasubstituted pyridine ring using different protocols such as hetero-Diels-Alder reaction of 3-siloxy-1-aza-1,3-butadiene, Mannich reaction of aldehydes and iminium salts, ruthenium-catalyzed cycloisomerization of 3-azadienynes, Vilsmeier-Haack reaction of α-hydroxyketenedithioacetals. A convenient route for the synthesis of highly substituted pyridine ring was developed by Evdokimov et al.[15-16] Multicomponent reactions using heterogeneous catalysts have been developed interesting tool in synthetic organic chemistry[17-18] because of their operational simplicity, reusability and ease of separation of product as well as catalyst.

In continuation of our efforts to develop an efficient catalytic protocol for various multicomponent reactions[19-23], we herein report the synthesis of a highly substituted pyridine using malononitrile, aldehydes and thiophenol in the presence of Mg/Al-hydrotalcite as a solid base catalyst (Scheme 1). To the best of our knowledge the synthesis of substituted pyridine using hydrotalcite catalyst has not been explored previously.

* Corresponding author.
E-mail address: 1sandipkale@gmail.com (S. R. Kale)


doi: 10.5267/j.ccl.2021.1.001

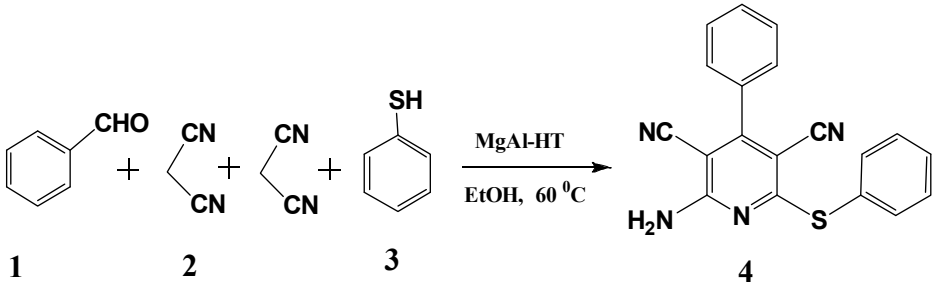



R=H, 2-Cl, 3-Cl, 4-$NO_2$, 3-$NO_2$, 4-OMe, 3,4-$(OMe)_2$, 2,4-$(OMe)_2$, 4-OH

**Scheme 1**

## 2. Results and Discussions

As a first step, we have optimized different reaction parameters such as time, temperature and catalyst loading, Mg/Al ratio of the catalyst for the synthesis of pentasubstituted pyridine derivatives using multicomponent reaction of benzaldehyde, malononitrile and thiophenol as a model reaction (Scheme 2). We observed that the reaction does not take place to any measurable extent in the absence of catalyst.




**Scheme 2**

It is found that the Mg/Al Hydrotalcite with Mg/Al ratio 5.0 is an effective catalyst for the synthesis of compound **4**. The higher activity of Mg/Al: 5.0 may be attributed to highest surface area and basicity (0.131 mmol/g) of the catalyst. Increase in temperature and time beyond 60 $^0$C or 4 h had no profound effect on the yield of reaction.

**Table 1.** Study of reaction parameters for the synthesis of substituted pyridine (R=H)[a]

| **Effect of different catalyst** | | | | |
|---|---|---|---|---|
| Entry | Catalyst | Time (h) | Temp. ($^0$C) | Yield (%)[b] |
| 1 | - | 24 | 60 | 0 |
| 2 | Mg/Al: 2 | 4 | 60 | 51 |
| 3 | Mg/Al: 3 | 4 | 60 | 65 |
| 4 | Mg/Al: 4 | 4 | 60 | 69 |
| 5 | Mg/Al: 5 | 4 | 60 | 81 |
| **Effect of time:** | | | | |
| Entry | Catalyst | Time (h) | Temp. ($^0$C) | Yield (%)[b] |
| 6 | - | 24 | 60 | 0 |
| 7 | Mg/Al: 5 | 2 | 60 | 35 |
| 8 | Mg/Al: 5 | 3 | 60 | 69 |
| 9 | Mg/Al: 5 | 4 | 60 | 81 |
| 10 | Mg/Al: 5 | 5 | 60 | 82 |
| **Effect of temperature:** | | | | |
| Entry | Catalyst | Time (h) | Temp. ($^0$C) | Yield (%)[b] |
| 11 | Mg/Al: 5 | 4 | rt | 47 |
| 12 | Mg/Al: 5 | 4 | 60 | 81 |
| 13 | Mg/Al: 5 | 4 | 80 | 81 |

[a] Reaction condition: benzaldehyde (1 mmol), malononitrile (2 mmol), thiophenol (1 mmol), catalyst (0.05 g), 4 ml EtOH.
[b] Isolated Yield.

**Table 2.** Surface area and basicity of the catalysts

| Entry | Catalyst | Surface area ($m^2/g$) | Basicity (mmol/g) |
|---|---|---|---|
| 1 | Mg/Al: 2 | 145 | 0.087 |
| 2 | Mg/Al: 3 | 186 | 0.095 |
| 3 | Mg/Al: 4 | 236 | 0.117 |
| 4 | Mg/Al: 5 | 269 | 0.131 |

Basic site of the catalyst abstract acidic proton of the malononitrile to give carbanion. Carbanion is then attack on carbonyl carbon of the aldehyde group and undergoes condensation reaction. We get SPh group at 2nd position by the attack of thiophenol sulfur lone pair on cyanide carbon. Second molecule of the malononitrile undergoes Michael addition and then cyclization process gives heterocyclic ring. In order to investigate the scope of above protocol, various aromatic aldehydes were employed in the three-component reaction (Table 3). It was observed that the aldehyde containing electron donating groups underwent the reaction easily to form the corresponding pyridine derivatives in moderate yield, whereas aldehyde containing electron withdrawing group such as $–NO_2$, Cl (-I effect) gives good yield of product. Electron withdrawing groups increases electrophilicity of the carbonyl carbon, which is more susceptible for nucleophilic attack. To understand the role of the base catalyst for the three- component reaction, it is important to know the structure and active sites of the catalyst.

**Table 3.** Synthesis of substituted pyridine **4**

| **Entry** | **R** | **Time (h)** | **Yield (%)[b]** |
|---|---|---|---|
| 1 | H | 4 | 81 |
| 2 | 4-Cl | 4 | 69 |
| 3 | 3-Cl | 4 | 72 |
| 4 | 4-$NO_2$ | 4 | 82 |
| 5 | 3- $NO_2$ | 4 | 81 |
| 6 | 4-OMe | 4 | 65 |
| 7 | 3,4-$(OMe)_2$ | 4 | 64 |
| 8 | 2,4-$(OMe)_2$ | 4 | 61 |
| 9 | 4-OH | 4 | 71 |

[a] Reaction condition: aldehyde (1 mmol), malononitrile (2 mmol), thiophenol (1 mmol), catalyst (0.05 g), 4 ml EtOH.
[b] Isolated Yield,

To understand the role of the base catalyst for the three-component reaction, it is important to know the structure and active sites of the catalyst. The hydrotalcite or layer double hydroxide is anionic clay. On calcinations hydrotalcite forms Lewis acidic sites $Mg^{2+}$ and Lewis basic sites $O^{2-}$. The Lewis basic sites of the catalyst are expected to be responsible for the activity of the catalyst. It was observed that as compared to other hydrotalcite catalysts (Table 2, Entry 1-4), Mg/Al: 5.0 have higher basicity (0.131mmol/g) and higher surface area (269 $m^2/g$). Hence this catalyst is used for further study (Table 1). The basicity of the catalyst was measured by phenol adsorption method. The amount of phenol adsorb by the catalysts was determined using following formula,

$$q_e = \frac{(Co-Ce) \times V}{W}$$

where, $q_e$ – quantity of phenol adsorb,
Co- initial conc. of phenol,
Ce- conc. of phenol at equilibrium,
W- wt. of the catalyst (gm)

We carried out standard leaching experiment. It was found that the reaction proceeded heterogeneously and no homogeneous catalyst was involved while performing the reaction.

## 3. Conclusion

In this work an efficient methodology for rapid synthesis of substituted pyridines with excellent yield via multicomponent reaction using Mg/Al hydrotalcite as a heterogeneous base catalyst is developed. The protocol was also applicable for various aldehydes which afford desired products in good yield under the given condition. All the compounds are reported[24]. The catalyst could be reused in the same reaction medium. Further studies aimed at broadening the panel of application of this highly stable, active, inexpensive, heterogeneous and easily prepared hydrotalcite catalyst are in progress. The catalyst could be reused at least four cycles using same reaction parameters.

## 4. Experimental Section

### *4.1 General*

The chemicals required were purchased from S. D. Fine and Sigma Aldrich and were used as received. NMR spectra were recorded on a Varian Mercury Plus NMR spectrometer (1H NMR at 300 MHz and $^{13}$C NMR at 75 MHz) in pure deuterated solvents. IR spectra were recorded using a Perkin Elmer FT-IR spectrum 100 spectrophotometer. Melting points were determined in capillary using digital melting point apparatus. Elemental analysis was done on Harieus rapid analyser. The reactions were monitored by TLC. Column chromatography of some compounds was carried out using silica gel having 60-120 mesh size. Wide angle XRD patterns of the catalyst were obtained on a Rigaku, Japan, miniflex X-ray Diffractometer with monochromatic Cu-Kα beam (λ =0.154 nm). The diffractometer was operated at 30KV and 15mA using a scanning step of 2 in two theta and a dwell time of 1 second was used.

### *4.2 Preparation of the hydrotalcite catalysts*

Mg/Al hydrotalcite catalyst was prepared by co-precipitation method. An aqueous solution (100 ml) of magnesium nitrate (25.6 g) and aluminum nitrate (7.5 g) with Mg/Al molar ratio of 5 was added dropwise into 500 ml beaker. Simultaneously 100 ml of NaOH (14 g) and $Na_2CO_3$ (10 g) of was added into the same beaker with vigorous stirring. After the addition the suspension was stirred for 2 h. Then the mixture was heated to 60 $^0$C for 4 h. The resultant slurry was then digested for about 18 h. Similarly, other catalysts Mg/Al: 2.1, Mg/Al: 3.1, Mg/Al: 4.1 were prepared through the same procedure.

### *4.3 General procedure for the formation of substituted pyridine*

Aldehyde (1 mmol), malononitrile (2 mmol) and thiophenol (1 mmol) were taken into 25 ml round bottom flask. The catalyst and 4 ml of ethanol was added into it. The resulting mixture was refluxed at given condition. The progress of the reaction was monitored by thin layer chromatography (pet ether / ethyl acetate = 3.2). After reaction completed, the reaction mixture was allowed to cool at room temperature. The crude product was extracted with ethyl acetate. The organic layer was washed with water and the solvent was evaporated under vacuum. After reaction the catalyst was separated by simple filtration and the reaction was subjected to analysis.

**2-Amino-4-(4-chloro-phenyl)-6-phenylsulfanyl-pyridine-3,5-dicarbonitrile**

Colourless solid, mp (222-224 $^0$C); IR (KBr): 3485, 3344, 3220, 2925, 2214, 1633, 1544, 1494, 1257, 1093 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-d6): δ 7.48-7.55(m, 3H), 7.57-7.64 (m, 6H), 7.79 (broad, 2H)

**2-Amino-4-(4-nitro-phenyl)-6-phenylsulfanyl-pyridine-3,5-dicarbonitrile:** Colourless solid, mp 287-289 $^0$C; IR (KBr): 3406, 3328, 3234, 2227, 2214, 1645, 1552, 1350, 756 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-d6): δ 7.46-7.48 (m, 3H), 7.56-7.59 (m, 2H), 7.85 (d, J = 8.6 Hz, 2H), 7.90 (broad, 2H), 8.39

(d, J = 8.6 Hz, 2H); $^{13}$C NMR (75 MHz): δ 87.2, 93.3, 114.9, 115.3, 124.2 (2C), 127.2, 129.8 (2C), 130.1, 130.5 (2C), 135.1 (2C), 140.5, 148.9, 157.0, 159.8, 166.5.

**2-Amino-4-(4-hydroxy-phenyl)-6-phenylsulfanyl-pyridine-3,5-dicarbonitrile:**
Colourless solid, mp 315-316 $^0$C; IR (KBr): 3496, 3367, 3236, 2222, 2216, 1631, 1609, 1552, 758 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-d6): δ 6.93 (d, J = 8.5 Hz, 2H), 7.39 (d, J = 8.5 Hz, 2H), 7.50 (m, 3H), 7.60 (m, 2H), 7.69 (broad, 2H), 10.04 (bs, 1H).

*4.6 Recycling of the catalyst*

For practical application of heterogeneous system, the stability of the catalyst and its reusability are the most important factor. For that reaction of benzaldehyde, malononitrile and thiophenol was chosen to test the catalyst reusability. The reaction was performed at the optimized reaction condition.

**Reusability of the catalyst**

| Run | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| Yield (%) | 81 | 80 | 78 | 78 |

[a] Reaction condition: benzaldehyde (1 mmol), malononitrile (2 mmol), thiophenol (1 mmol), catalyst (0.05 g), 4 ml EtOH.
[b] Isolated Yield

## Acknowledgement

S. R. Kale thankful to the Authority of Yogeshwari Mahavidyalaya, Ambajogai for providing us the platform to do research and IIT Mumbai for characterization of compounds

## References

1. Ugi, I., Dombling, A. and Werner, B. (**2000**) New chemistry of multicomponent reactions and their libraries, including their heterocyclic chemistry. *J. Heterocyclic Chem.*, 37, 647.
2. Bienayme, H., Hulme, C., Oddon, G. and Schmitt, P. (**2000**) Maximizing synthetic efficiency: multi-component transformations lead the way *Chem. Eur. J. 6*, 3221–3329.
3. Dömling, A. (**2006**) Recent Developments in Isocyanide Based Multicomponent Reactions in Applied Chemistry. *Chem. Rev*., 106, 17-89.
4. Ramón, D. J. and Yus, M. (**2005**) Asymmetric multicomponent reactions (AMCRs): the new frontier *Angew. Chem*., *Int. Ed*., *44*, 1602–1634.
5. Perrier, V., Wallace, A. C., Kaneko, K., Safar, J., Prusiner, S. B. and Cohen, F. E. (**2000**) Mimicking dominant negative inhibition of prion replication through structure-based drug design *Proc. Natl. Acad. Sci. U.S.A.*, *97*, 6073–6078.
6. Reddy, T. R. K., Mutter, R., Heal, W., Guo, K., Gillet, V. J., Pratt, S. and Chen, B. (**2006**) Library Design, Synthesis, and Screening: Pyridine Dicarbonitriles as Potential Prion Disease Therapeutics *J. Med. Chem*., *46*, 607–615.
7. May, B. C. H., Zorn, J. A., Witkop, J., Sherrill, J., Wallace, A. C., Legname, G., Prusiner, S. B. and Cohen, F. E. (**2007**) Structure−Activity Relationship Study of Prion Inhibition by 2-Aminopyridine-3,5-dicarbonitrile-Based Compounds: Parallel Synthesis, Bioactivity, and in Vitro Pharmacokinetics *J. Med. Chem*., *50*, 65–73.
8. Cocco, M. T., Congiu, C., Lilliu, V. and Onnis, V. (**2005**) Synthesis and antiproliferative activity of 2,6-dibenzylamino-3,5-dicyanopyridines on human cancer cell lines *Eur. J. Med. Chem*., *40*, 1365-1372.
9. Fletcher, M. D., Hurst, T. E., Miles, T. J. and Moody, C. J. (**2006**) Synthesis of highly-functionalized pyridines via hetero-Diels–Alder methodology: reaction of 3-siloxy-1-aza-1,3-butadienes with electron deficient acetylenes. *Tetrahedron*, *62*, 5454-5463.
10. Van Aken, K. J., Lux, G. M., Deroover, G. G., Meerpoel, L. and Hoornaert, G. J. (**1994**) The Synthesis of 3-Functionalized 5-chloro-6-methyl-2*H*-1,4-oxazin-2-ones and of pyridines from cycloaddition-elimination

reactions with substituted acetylenic compounds. *Tetrahedron*, *50*, 5211-5224.
11. Winter, A. and Risch, N. (**2003**) Cross Mannich Reaction of Aldehydes; Efficient Synthesis of Substituted Pyridines. *Synthesis*, 2667.
12. Thomas, A. D. and Asokan, C. V. (**2002**) Vilsmeier–Haack reactions of α-hydroxyketenedithioacetals: a facile synthesis of substituted pyridines. *Tetrahedron Lett., 43,* 2273.
13. Vijn, R. J., Arts, H. J., Green, R. and Castelijns, A. M. (**1994**) Synthesis of alkyl-and aryl-substituted pyridines from (α, β-unsaturated) imines or oximes and carbonyl compounds. *Synthesis,* 573.
14. Bhuiyan, M. M. H., Matin, M. M., Kabir, E. and Alam, M. (**2013**) Multicomponent reactions: Synthesis and characterization of pyrimido[4,5-D]pyrimidine derivatives. Chittagong Univ. J. Sci., 36, 28-36.
15. Evdokimov, N. M., Kireev, A. S., Yakovenko, A. A., Antipin, M. Y., Magedov, I. V. and Kornienko, A. (**2007**) One-step Synthesis of Heterocyclic Privileged Medicinal Scaffolds by a Multicomponent Reaction of Malononitrile with Aldehydes and Thiols. *J. Org. Chem*., *72*, 3443–3453.
16. Evdokimov, N. M., Magedov, I. V., Kireev, A. S. and Konienko, A. (**2006**) One-Step, Three-Component Synthesis of Pyridines and 1,4-Dihydropyridines with Manifold Medicinal Utility. *Org. Lett*., *8,* 899–902.
17. H. Hiddesh (**1995**) Heterogeneous Basic catalyst Chem. Rev. *95*, 537-550
18. Y. Lunxiang and J. Liebscer (**2007**) Carbon-carbon coupling reactions catalyzed by heterogeneous palladium catalysts. *Chem. Rev*. 107, 133-173.
19. Kale S. R., Kahandal S. S., Disale S. and Jayaram R. V. (**2012**) Conventional and microwave-assisted multicomponent reaction of alkyne, halide and sodium azide catalyzed by copper apatite as heterogeneous base and catalyst in water. *Current Chemistry Letter*, 47-58.
20. Kale S. R., Kahandal S. S., Gawande M. and Jayaram R.V. (**2013**) Magnetically recyclable-$Fe_2O_3$/HAP nanoparticles for cycloaddition reaction of alkyne, halide and azide in aqueous medium. *RSC Advances*, 13 (3) 8184-8192.
21. Parghi K., Kale S. R., Kahandal S. S., Gawande M. and Jayaram R.V. (**2013**) Sequential synthesis of b-amino alcohols using a $CeO_2$–$ZrO_2$ bifunctional catalyst system. *Catalysis Science and Technology*, 13, 1308-1313.
22. Kale S. R., Kahandal S. S., Burange A., Gawande M. and Jayaram R. V. (**2013**) A benign synthesis of 2-amino-4H-chromene in aqueous medium using hydrotalcite (HT) as a heterogeneous base catalyst. *Catalysis Science and Technology*, 13, 2050-2056.
23. Kahandal S. S., Kale S. R., Gawande M. and Jayaram R. V. (**2014**) A mild route for one-pot synthesis of 5,6-unsubstituted 1,4-dihydropyridines catalyzed by Sulphated mixed metal oxides. *Catalysis Science and Technology*, 4, 672-680.
24. Dong H., Zhong Y., Shen X., Yang J and Fang D. (**2012**) Synthesis of 2-amino-4-phenyl-6-(phenylsulfanyl)-3,5-dicyanopyridines by tandem reaction. *Res Chem Intermed*, 40 (2) 587-594.