



Nano Fe₃O₄: A Novel and Magnetically Recyclable Catalyst for the Synthesis of 1,2,4,5-Tetrasubstituted Imidazoles in Solvent-Free Conditions

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A convenient and efficient one-pot four-component synthesis of 1,2,4,5-tetrasubstituted imidazoles using nano Fe₃O₄ as magnetically recyclable catalyst is reported. The results show that the methodology has several advantages such as low loading of catalyst, excellent yield, short reaction time, operational simplicity and solvent-free conditions.

Key Words: Nano Fe₃O₄, Tetrasubstituted imidazoles, Solvent-free conditions, Reusable catalyst.

INTRODUCTION

Imidazoles are very important compounds with wide spectrum of biological activities such as antiinflammatory¹, anti-allergic², antibacterial³, antitumor⁴ and plant growth regulators⁵, activities. Furthermore, they act as glucagon receptors⁶. Recent advances in green chemistry and organo-metallic catalysis has extended the application of imidazoles as ionic liquids⁷ and *N*-heterocyclic carbenes⁸.

The design and development of multi component reactions for the generation of heterocycles receive growing interest^{9a,b}. One example of multi component reactions is four-component, one-pot synthesis of tetrasubstituted imidazoles.

In view of different biological and chemical applications of imidazoles, the development of suitable synthetic methodologies for their generation has been a topic of great interest in recent times. The general method involves four component condensation of 1,2-diketones, aromatic aldehydes, primary amines and ammonium acetate in the presence of various catalysts, such as zinc oxide¹⁰, carbon-based solid acid¹¹, Bronsted acidic ionic liquid¹², silica gel/NaHSO₄¹³, K₅CoW₁₂O₄.3H₂O¹⁴, BF₃-SiO₂¹⁵, molecular iodine¹⁶, HClO₄-SiO₂¹⁷ and L-proline¹⁸. In addition, they can also be accessed by the condensation of a 1,2-diketone with an aryl nitrile and primary amine under microwave irradiation¹⁹, cycloaddition reaction of mesoionic 1,3-oxazolium-5-olates with *N*-(arylmethylene)-benzenesulfonamide²⁰ and *N*-(2-oxo)amides with ammonium trifluoroacetate²¹. However, in spite of their potential utility, some of the reported methods suffer from certain drawbacks such as expensive reagents, harsh conditions, use of toxic catalysts and organic solvents that are

harmful to environment and moderate yields. Therefore, to avoid these limitations there is still a need for the development of a new protocol for the synthesis of 1,2,4,5-tetrasubstituted imidazoles in terms of operational simplicity, reusability of the catalyst, high-yielding and economic viability.

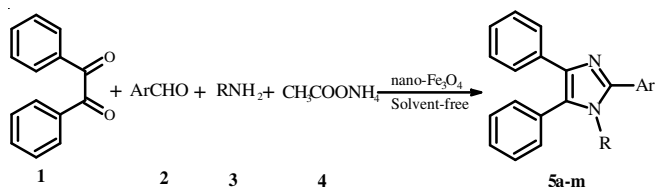
Recently, metal nanoparticles have attracted a great attention as heterogeneous catalysts because of their interesting structure and high catalytic activities^{22a,b}. In particular, magnetite nanoparticles have emerged as one of the most useful heterogeneous catalysts due to their numerous applications in biotechnology and medicine^{23a,b}. Of these, Fe₃O₄ nanoparticles are the most promising catalysts because of their ease of handling, ease of recovery with external magnetic field, high catalytic activities and reactivates in various organic transformations^{24a,b}. However, there are no reports on the use of Fe₃O₄ nanoparticles for one-pot four-component synthesis of 1,2,4,5-tetrasubstituted imidazoles.

In continuation of our previous works on the applications of reusable catalysts in the synthesis of heterocyclic compounds^{25a-c}, in this article, we report nano-Fe₃O₄ as a highly efficient, (iron oxide (Fe₃O₄), 98 %, 20-30 nm; nanostructured and amorphous materials, Inc. USA), clean and economically valuable catalyst for the one-pot, four-component synthesis of 1,2,4,5-tetrasubstituted imidazoles **5a-m** from reaction of benzil **1**, aromatic aldehydes **2**, primary amines **3** and ammonium acetate **4** under solvent-free conditions (**Scheme-I**).

EXPERIMENTAL

All chemicals were available commercially and used without additional purification. Melting points were recorded on

an electrothermal type 9100 melting point apparatus. The IR spectra were obtained using 4300 Shimadzu spectrophotometer as KBr disks. The ^1H NMR, 400 MHz spectra were recorded with a Bruker DRX 400 spectrometers.



Scheme-I: Synthesis of 1,2,4,5-tetrasubstituted imidazoles using Fe_3O_4 as catalyst

Synthesis of 1,2,4,5-tetrasubstituted imidazoles: A mixture of benzil (1 mmol), aromatic aldehydes (1 mmol), primary amine (1 mmol), ammonium acetate (1 mmol) and nano- Fe_3O_4 (0.15 mmol) was heated on the oil bath at $140\text{ }^\circ\text{C}$ for 30-60 min. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature, boiling ethanol 95 % was added and the mixture was heated under reflux for 1 min. The Fe_3O_4 nanoparticles were absorbed on to the magnetic stirring bar. After cooling to room temperature, the crude product was collected and recrystallized from ethanol to give compounds **5a-m** in high to excellent yields. All products were known and characterized by comparison of their physical and spectroscopic data with those of reported techniques.

Recycling and reusing of the catalyst: The recyclability of the catalyst in the reaction of benzil, benzaldehyde, aniline, ammonium acetate in the presence of nano Fe_3O_4 was checked. The separated catalyst can be reused after washing twice with ethanol 95 %, drying at $100\text{ }^\circ\text{C}$ under vacuum and reused in another reaction. It showed the same activity as fresh catalyst without any loss of its activity.

2-(4-chlorophenyl)-1-(4-nitrophenyl)-4,5-diphenyl-1H-imidazole (5g): m.p. $167\text{-}169\text{ }^\circ\text{C}$; IR (KBr, ν_{max} , cm^{-1}): 3100, 1530, 1475, 1350; ^1H NMR (DMSO- d_6 400 MHz) δ : 6.76-7.71 (m, 18H, ArH); ^{13}C NMR (DMSO- d_6 100 MHz) δ : 146.35, 137.59, 137.50, 134.81, 134.06, 131.29, 131.07, 130.87, 130.66, 130.04, 129.47, 129.16, 129.06, 128.60, 127.74, 126.84, 126.58, 126.10.

1-Benzyl-2-(4-nitrophenyl)-4,5-diphenyl-1H-imidazole (5h): m.p. $166\text{-}168\text{ }^\circ\text{C}$; IR (KBr, cm^{-1}): 3100, 1520, 1470, 1350; ^1H NMR (DMSO- d_6 400 MHz) δ : 5.27 (s, 2H, CH_2), 6.79-8.30 (m, 19H, ArH); ^{13}C NMR (DMSO- d_6 100 MHz) δ : 147.50, 145.25, 138.30, 137.27, 137.20, 134.51, 132.36, 131.28, 130.51, 129.73, 129.69, 129.57, 129.13, 129.07, 129.01, 128.67, 127.86, 127.11, 126.67, 126.15, 126.09, 124.32.

2-(4-Methoxyphenyl)-1,4,5-triphenyl-1H-imidazole (5k): m.p. $157\text{-}160\text{ }^\circ\text{C}$; IR (KBr, ν_{max} , cm^{-1}): 3120, 1475; ^1H NMR (DMSO- d_6 400 MHz) δ : 3.73 (s, 3H, CH_3), 6.84-7.51 (m, 19H, ArH); ^{13}C NMR (DMSO- d_6 100 MHz) δ : 159.68, 146.48, 137.26, 137.02, 134.98, 131.61, 131.31, 131.00, 130.12, 129.63, 129.26, 129.17, 128.92, 128.81, 128.62, 126.84, 126.81, 123.28, 114.08, 55.59.

RESULTS AND DISCUSSION

Due to the increasing demand in modern organic processes for reusability of catalysts, we decided to investigate the

efficiency of this nanoparticles (Fe_3O_4) as heterogeneous catalyst in the synthesis of 1,2,4,5-tetrasubstituted imidazoles under solvent-free condition. Initially, the one-pot four-component coupling of benzil, benzaldehyde, aniline and ammonium acetate as a simple model substrates was investigated to establish the feasibility of the strategy and optimize the reaction conditions.

A mixture of benzil (1 mmol), benzaldehyde (1 mmol), aniline (1 mmol) and ammonium acetate (1 mmol) was heated on the oil bath at different temperatures in the presence of various amounts of nano Fe_3O_4 as heterogeneous catalyst under solvent-free conditions (Table-1). As can be seen from this Table, the yield of compound **5a** is affected by the catalyst amount and reaction temperature. No product was obtained in the absence of the catalyst (Entry 1) or in the presence of the catalyst at room temperature (Entry 2) indicating that the catalyst and temperature are necessary for the reaction. Increasing the amount of the catalyst and reaction temperature up to 15 mol % and $140\text{ }^\circ\text{C}$, respectively, increased the yield of the product **5a**. Further increase in both catalyst amount and temperature did not increase the yield noticeably (entries 1-18).

TABLE-1
EFFECT OF NANO Fe_3O_4 AMOUNT AND TEMPERATURE ON THE MODEL REACTION

| Entry | Amount of catalyst (mol. %) | T ($^\circ\text{C}$) | Time (min) | Yield ^b (%) |
|-------|-----------------------------|------------------------|------------|------------------------|
| 1 | None | 110 | 60 | None |
| 2 | 15 | r.t. | 60 | None |
| 3 | 10 | 110 | 40 | 62 |
| 4 | 10 | 130 | 20 | 76 |
| 5 | 10 | 140 | 20 | 89 |
| 6 | 10 | 150 | 20 | 82 |
| 7 | 15 | 110 | 26 | 68 |
| 8 | 15 | 130 | 20 | 82 |
| 9 | 15 | 140 | 20 | 94 |
| 10 | 15 | 150 | 20 | 88 |
| 11 | 20 | 110 | 20 | 54 |
| 12 | 20 | 130 | 20 | 72 |
| 13 | 20 | 140 | 20 | 79 |
| 14 | 20 | 150 | 20 | 77 |
| 15 | 25 | 110 | 40 | 42 |
| 16 | 25 | 130 | 20 | 52 |
| 17 | 25 | 140 | 15 | 71 |
| 18 | 25 | 150 | 15 | 76 |

^a1 mmol benzil, 1 mmol benzaldehyde, 1 mmol aniline and 1 mmol ammonium acetate under neat conditions. ^b Isolated yields

Also, the model reaction was carried out in various solvents such as EtOH, H_2O , CHCl_3 and CH_2Cl_2 using 15 mol % of the catalyst. The use of H_2O gave the product **5a** in low yield (48 %). MeOH, CH_2Cl_2 and CHCl_3 gave moderate yields 60, 60 and 63 % respectively. In addition the use of EtOH gave the product **5a** in good yield (84 %).

We next made a study on the catalytic activity of powdered Fe_3O_4 loading in model reaction. In comparison with Fe_3O_4 nanoparticles, the reaction times were longer and the yield were considerably lower.

Under the above optimized conditions, the scope of this MCR process was next examined using various aromatic aldehydes

TABLE-2
 NANO Fe₃O₄ CATALYZED SYNTHESIS OF 1, 2, 4, 5-TETRASUBSTITUTED^a

| Entry | Ar | R | Product ^b | Time (min) | Yield ^c (%) | m.p. (°C) | |
|-------|--|---|----------------------|------------|------------------------|-----------|-----------------------|
| | | | | | | Found | Reported |
| 1 | C ₆ H ₅ | C ₆ H ₅ | 5a | 20 | 94 | 215-218 | 213-215 ¹² |
| 2 | C ₆ H ₅ | CH ₂ C ₆ H ₅ | 5b | 30 | 92 | 162-164 | 161-163 ¹² |
| 3 | 4-NO ₂ C ₆ H ₄ | 4-MeC ₆ H ₄ | 5c | 45 | 80 | 221-222 | 220 ¹⁰ |
| 4 | 4-ClC ₆ H ₄ | C ₆ H ₅ | 5d | 45 | 85 | 149-150 | 146-148 ¹² |
| 5 | 4-MeC ₆ H ₄ | CH ₂ C ₆ H ₅ | 5e | 45 | 75 | 165-166 | 167 ¹⁰ |
| 6 | 4-CH ₃ C ₆ H ₄ | C ₆ H ₅ | 5f | 30 | 91 | 180-183 | 183-184 ¹² |
| 7 | 4-ClC ₆ H ₄ | 4-NO ₂ C ₆ H ₄ | 5g | 60 | 79 | 167-169 | - |
| 8 | 4-NO ₂ C ₆ H ₄ | CH ₂ C ₆ H ₅ | 5h | 45 | 81 | 166-168 | - |
| 9 | 4-CH ₃ C ₆ H ₄ | CH ₂ C ₆ H ₅ | 5i | 45 | 87 | 160-162 | 163-165 ¹² |
| 10 | 4-ClC ₆ H ₄ | CH ₂ C ₆ H ₅ | 5j | 30 | 82 | 163-165 | 163-164 ¹⁰ |
| 11 | 4-CH ₃ OC ₆ H ₄ | C ₆ H ₅ | 5k | 60 | 92 | 157-160 | - |
| 12 | 4-CH ₃ OC ₆ H ₄ | CH ₂ C ₆ H ₅ | 5l | 60 | 93 | 158-160 | 155-157 ¹² |
| 13 | C ₆ H ₅ | CH ₃ | 5m | 45 | 80 | 142-144 | 144-145 ¹⁸ |

^a1 mmol benzil, 1 mmol aromatic aldehyde, 1 mmol primary amine, 1 mmol ammonium acetate and 0.15 mmol nano Fe₃O₄ at 140 °C under solvent-free conditions. ^bThe products were characterized by comparison of their spectroscopic and physical data with authentic sample synthesized by reported procedures. ^cIsolated yields

and primary amines (Table-2). In all cases, the obtained yields were excellent without formation of any side products such as 2,4,5-trisubstituted imidazoles. Aromatic aldehydes containing electron-donating or electron-withdrawing groups and various primary amines reacted efficiently and gave the expected products with excellent yields in relatively short reaction times. While aliphatic aldehydes such as pentanal and butanal produced only trace amounts of imidazoles that could not be isolated, aliphatic amines, such as methyl amine, produced high yield of the corresponding imidazole (Table-2, entry 13).

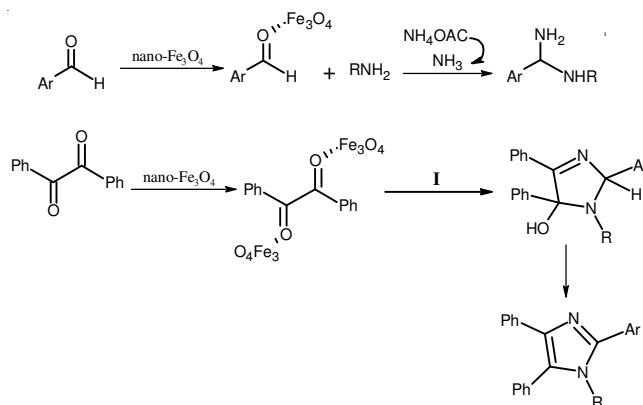
The principle advantage of the use of heterogeneous solid acid catalysts in organic transformations is their reusability. Hence, we decided to study the catalytic activity of recycled nano Fe₃O₄ in the synthesis of compound **5a**. After the completion of the reaction, the catalyst was recovered according to the procedure mentioned in experimental part and reused for a similar reaction. The catalyst could be reused at least five times with only slight reduction in the catalytic activity (Table-3).

 TABLE-3
 RECOVERY AND REUSE OF NANO Fe₃O₄
 FOR THE SYNTHESIS OF **5a**

| Cycle | Yield ^a (%) |
|-------|------------------------|
| 1 | 93 |
| 2 | 93 |
| 3 | 91 |
| 4 | 90 |
| 5 | 90 |
| 6 | 88 |
| 7 | 86 |
| 8 | 86 |
| 9 | 84 |
| 10 | 83 |

^aisolated yield

N-nucleophilic attack of the primary amine and ammonia, obtained from NH₄OAc, at activated carbonyl group in aryl aldehyde by nano Fe₃O₄ yields the intermediate (I) which subsequently reacts with activated benzil to form intermediate (II). Dehydration of this intermediate produces the final products (Scheme-II).



Scheme-II: Plausible mechanism for the synthesis of 1,2,4,5-tetrasubstituted imidazoles using Fe₃O₄ as catalyst

Conclusion

In conclusion, nano Fe₃O₄ has shown to be an excellent catalyst for one pot four-component synthesis of 1,2,4,5-tetrasubstituted imidazoles under solvent-free conditions. Easy isolation and recycling of the catalyst, simple work up procedure, short reaction time and excellent yields are some advantages of this method. Henceforth, this methodology works well and is environmentally benign and may prove beneficial to both academia and industry for the socio-econom change.

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