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# Magnetically Separable Recyclable Nano-ferrite Catalyst for the Synthesis of Acridinediones and Their Derivatives under Solvent-free Conditions

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Catalytic activity of nano-ferrite is explored in the synthesis of acridinedione and their derivatives under benign conditions; a greener protocol is reported in terms of excellent yield and recyclability under solvent-free reactions without using any additive/cocatalyst. Nano-ferrite catalyst is synthesized using sol–gel process at low temperatures. X-ray diffraction (XRD) and transmission electron microscopy (TEM) results exhibit cubic phase of maghemite ($\gamma$-$Fe_2O_3$) with average particle size of 18 nm. Furthermore, the catalyst can be easily separated using an external magnet and reused up to nine cycles without any significant loss of activity.

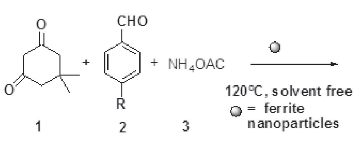
Acridines represent an important class of nitrogen heterocycles with several significant properties such as pigment, dye properties, photochemical/physical properties, electrochemical properties, potent anti-malarial, anticancer, and anti-fungal activities, etc.[1,2] Natural and synthetic acridines and their derivatives are effective DNA and RNA-binding compounds owing to their intercalation abilities as well as being a lipophilic carrier molecule.[3,4] Synthesis of acridinediones is a continuing focal point of current research because these moieties are active pharmaceutical ingredients (APIs) and valuable reactive intermediates for both synthetic and medicinal chemists.[5]

Literature survey reveals that various methods[6–9] have been reported for preparation of acridinediones and substituted acridinediones. The reported method for the synthesis of 9-aryl-3,3,6,6-tetramethylhexahydroacridine-1,8-diones involves the reaction of two molecules of dimedone (5,5-dimethyl-1,3-cyclohexadione) with various aromatic aldehydes and ammonium acetate by using different Lewis acid catalysts.[10–13] However many of these catalysts undergo disadvantages such as long reaction time, high catalyst loading, use of solvents, and deactivation of catalyst on repeated use. Hence there is a need to develop an environmentally benign protocol for the synthesis of acridinediones.

Though there are many advantages of homogeneous metal catalysts there are some difficulties in recovering the catalyst from the reaction mixture, which severely inhibit their use in industry and this drawback can be overcome with heterogeneous nano-ferrite-based catalysts.[14–17] Recent reports showed that magnetic nanoparticles are efficient catalysts and they can be easily separated from the reaction mixture.[18] The high surface to volume ratio of metal oxide nanoparticles is mainly responsible for their high catalytic performance. Ferrite nanomaterial is one such reusable catalyst which shows profound catalytic activity in organic synthesis. Nano-ferrite is a non-hygroscopic, inexpensive, and non-toxic material, which has been utilized as a heterogeneous catalyst for various organic reactions. Recently, because of the unique properties of nanoparticles, synthetic chemists have concentrated on nanocatalysts.[14–18] Therefore, synthesis and characterization of catalysts with lower dimensions have become a most interesting topic of research. Moreover, due to quantum size effects, nanometer-sized particles may exhibit unique properties for a wide range of applications. Keeping the above facts in mind and as part of our ongoing research, herein we report the use of nano-ferrite as heterogeneous catalyst for the first time in the synthesis of 9-aryl-substituted-3,3,6,6-tetramethylhexahydroacridine-1,8-diones. This method offers advantageous such as short reaction time, recyclability of the catalyst, and easy work-up procedure.

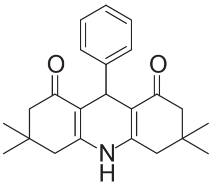
In this study, we report a simple, efficient, and one-pot reaction of dimedone, aldehydes, and ammonium acetate using nano ferrite at 120 °C for the preparation of acridinediones and their derivatives (Scheme 1). The experimental section for the synthesis of catalyst and acridinediones and their derivatives has been provided in supplementary section.

XRD patterns (Supporting Information (SI), Figure 1) confirm the formation of cubic phase maghemite, $\gamma$-$Fe_2O_3$ (matched with PDF No. 01-089-5892) and the major XRD peak was obtained at $2\theta = 35.9°$ while the other observed peaks were at $2\theta = 30.5, 43.6, 54.0, 57.5,$ and $63.2°$ which suggests strongly that $\gamma$-phase $Fe_2O_3$ is the major phase in this material.[19] The average grain size of $\gamma$-$Fe_2O_3$ nanoparticles is calculated using the Scherrer formula and was found to be about 18 nm indicating nanocrystalline nature. The morphology and size of the $\gamma$-$Fe_2O_3$ nano particles before reaction and after nine runs were analyzed by transmission electron microscopy (TEM) as shown in SI, Figures 3a and 3b respectively. The particle size was about 15–20 nm and their shape was found spheroidal when assessed with TEM. The presence of some larger particles is attributed to aggregating or overlapping of smaller particles after nine runs. It was observed that there is no significant change in morphology and size of the $\gamma$-$Fe_2O_3$ nanoparticles after nine runs.



**Scheme 1.** Synthesis of 9-aryl-3,3,6,6-tetramethylhexahydroacridine-1,8-diones employing reusable nano-ferrite as catalyst.

**Table 1.** Optimization of the catalyst loading[a]

| Product | Catalyst /mol % | Yield[b] /% | Time /min |
|---|---|---|---|
|  | 0 | 0 | 12 (h) |
| | 5 | 96 | 8 |
| | 10 | 96 | 6 |
| | 15 | 95 | 5 |
| | 20 | 94 | 7 |

[a]Catalyst 0–20 mol %, 5,5-dimethyl-1,3-cyclohexanedione (2 equiv), benzaldehyde (1 equiv), ammonium acetate (1 equiv), reaction temperature 120 °C. [b]Yields compared to isolated products.

**Table 2.** The reaction of arylaldehyde, dimedone, and ammonium acetate: Effect of solvent[a]

| Entry | Solvent | Amount of catalyst /mol % | Time /h | Yield[b] /% |
|---|---|---|---|---|
| 1 | Acetonitrile | 10 | 2.5 | 60 |
| 2 | THF | 10 | 3.0 | 45 |
| 3 | Ethanol | 10 | 3.0 | 72 |
| 4 | 1,4-Dioxane | 10 | 4.0 | 58 |
| 5 | Methanol | 10 | 3.0 | 58 |
| 6 | Water | 10 | 4.0 | 40 |
| 7 | Neat | 10 | 6 (min) | 96, **88**[c] |

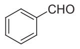
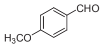
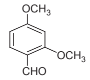
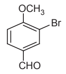
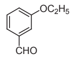
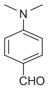
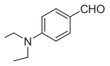
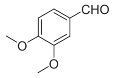
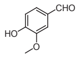
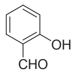
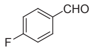
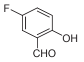
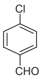
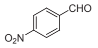
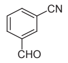
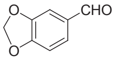
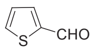
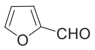
[a]Catalyst 10 mol %, 5,5-dimethyl-1,3-cyclohexanedione (2 equiv), benzaldehyde (1 equiv), ammonium acetate (1 equiv), reaction temperature 120 °C, solvent 15 mL. [b]Yields compared to isolated products. [c]Yield after 9 cycles.

Fourier transform infrared (FT-IR) studies were performed to ascertain the metal–oxygen bonding. The FT-IR spectra of as-synthesized γ-$Fe_2O_3$ nanoparticles before reaction (SI, Figure 3a) and after nine runs (SI, Figure 3b) are shown in SI, Figure 2. The γ-$Fe_2O_3$ shows the absorption in regions of 3742, 2347, 1124, 550, and 396 $cm^{-1}$. The peaks at 540 and 435 $cm^{-1}$ correspond to the metal–oxygen vibrational modes. The metal–oxygen frequencies observed for γ-$Fe_2O_3$ nanoparticles were in accordance with values. There was no significant difference and no additional peaks were observed of the as prepared catalyst and after nine runs.

Initially, a blank reaction was performed using benzaldehyde, dimedone, and ammonium acetate (mole rate 1:2:1) at 120 °C in the absence of nano-ferrite to establish the efficacy of the catalyst and the results showed that desired product was not formed even after 12 h of heating. Then focus was diverted to optimize the amount of catalyst and solvent effect. In order to evaluate the most appropriate catalyst percentage, a model reaction using benzaldehyde, ammoniam acetate, and dimedone (mole ratio 1:1:2) was carried out using 0–20 mol % of nano-ferrite under solvent-free conditions (Table 1).

It was found that 10 mol % of nano-ferrite shows high yield in short reaction time at 120 °C (Table 1). During our ongoing studies, effect of solvent was studied for the above model reaction with 10 mol % of catalyst (Table 2). Ultimately solvent-free reactions were preferable in terms of excellent yield in short reaction times.

**Table 3.** Synthesis of products **4a–4p** by the reaction of aromatic aldehydes with dimedone and ammonium acetate[a]

| Entry | Aldehyde | Product | Time /min | Yield /%[b] | Mp/°C |
|---|---|---|---|---|---|
| 1 |  | **4a** | 6 | 96 | 276–278 |
| 2 | HCHO | **4b** | 7 | 89 | 256–259 |
| 3 |  | **4c** | 7 | 93 | 271–273 |
| 4 |  | **4d** | 6 | 91 | 244–246 |
| 5 |  | **4e** | 7 | 88 | 253–255 |
| 6 |  | **4f** | 8 | 84 | 234–238 |
| 7 |  | **4g** | 6 | 93 | 166–168 |
| 8 |  | **4h** | 8 | 96 | 260–264 |
| 9 |  | **4i** | 8 | 95 | 258–260 |
| 10 |  | **4j** | 8 | 97 | 271–273 |
| 11 |  | **4k** | 9 | 96 | 271–273 |
| 12 |  | **4l** | 7 | 97 | 274–276 |
| 13 |  | **4m** | 6 | 95 | 227–230 |
| 14 |  | **4n** | 7 | 97 | 247–249 |
| 15 |  | **4o** | 7 | 93 | 260–262 |
| 16 |  | **4p** | 9 | 89 | 236–238 |
| 17 |  | **4r** | 8 | 98 | 310–312 |
| 18 |  | **4s** | 7 | 94 | 330–333 |
| 19 |  | **4t** | 10 | 72 | 249–251 |

[a]Catalyst 10 mol %, 5,5-dimethyl-1,3-cyclohexanedione (2 equiv), aromatic aldehydes (1 equiv), ammonium acetate (1 equiv), reaction temperature 120 °C. [b]Yields compared to isolated products.

Catalyst recovery and reusability have potential advantages in heterogeneous catalysis for organic reactions and/or transformations in order to employ as industrial applications. The catalyst was recovered by magnetization after completion of the reaction, washed with diethyl ether, and the recovered catalyst was reused for nine cycles. From our investigations, we observe that nanocatalyst shows excellent to good reactivity with promising yields even for the next nine cycles in the same reaction (SI, Table 1).

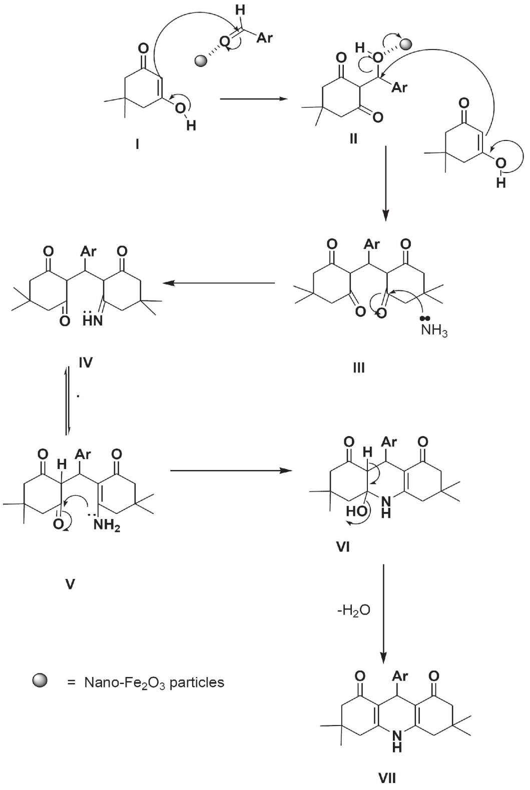


**Figure 1.** Plausible mechanism for the $Fe_2O_3$ NPs catalyzed synthesis of acridines.

The recovered nanocatalyst shows a slight decrease in its catalytic activity. The slight loss of catalytic efficiency was most likely due to the loss of catalyst during the handling i.e., recovering, washing, and reusing. TEM and FT-IR analysis (SI, Figures 2 and 3) exhibits similar properties confirming good stability and recyclability of catalyst for the synthesis of acridinediones and their derivatives.

Under the optimized conditions, aromatic aldehyde **3a**–**4j** containing electron-donating as well as electron-withdrawing groups with different substitution patterns was effectively cyclized to give 9-aryl-3,3,6,6-tetramethylhexahydroacridine-1,8-diones (Table 3). From Table 3, it was observed that various aldehydes with electron-donating and electron-withdrawing groups gave the corresponding products in good to excellent yields.

A plausible mechanism (Figure 1) for the formation of acridines involves the activation of aldehyde followed by the attack of enol form of the 5,5-dimethyl-1,3-cyclohexanedione (**II**) to give intermediate **III**, which reacts with ammonia to form imine intermediate (**IV**), which tautomerises to corresponding emine intermediate (**V**). Subsequently, compound **V** cyclizes to **VI** by the nucleophlic attack of amino group at carbonyl carbon, which affords the desired product **VII** by the elimination of a water molecule.[10] In the present work γ-$Fe_2O_3$ nanoparticle catalyst plays a crucial role in the success rate of reaction and their rate of reaction depends on the total surface area and the number of active sites on the catalyst. This results in good catalytic activity due to smaller particle size and high surface area of γ-$Fe_2O_3$ catalyst.

In conclusion, a convenient and highly efficient method for the synthesis of 9-aryl-3,3,6,6-tetramethylhexahydroacridine-1,8-diones by condensation reaction of aldehydes with 1,3-cyclohexanediones by the use of nano-γ-$Fe_2O_3$ as an inexpensive and easily recoverable catalyst has been described. The attractive features of this synthetic protocol are easy work up procedure, operational simplicity, and reusability of the catalyst. Furthermore, products were isolated in good to excellent yields.

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Supporting Information is available electronically on J-STAGE.

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