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Synthesis, characterisation of bisacridines using nano ferrite as an efficient catalyst

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ABSTRACT

The present report highlights the usage of nano ferrite as an efficient catalyst for the one pot synthesis of Bisacridines from dimedone, Terephthalaldehyde and substituted anilines under solvent free conditions. The main advantages of this protocol include excellent yields, mild reaction conditions, short reaction times and reusability of catalyst.

INTRODUCTION

Acridines represent an important class of nitrogen heterocycles having several significant properties such as pigment, dye properties, photochemical/physical properties and electrochemical properties, antimalarial, anti cancer and anti fungal activity [1, 2]. Natural, 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 Bis-acridines is a continuing focal point of current research because these moieties are Active Pharmaceutical Ingredients (APIs) and also valuable reactive intermediates for both synthetic and medicinal chemists [5]. Literature survey reveals that only one methodology has been reported for the synthesis of Bisacridines [6]. However the reported methodologies have some disadvantages such as long reaction time, high catalytic loading, usage of solvents and deactivation of catalyst on repeated use. Hence there is a need to develop an environmentally benign protocol for the synthesis of bis-acridinediones. Recently, because of the unique properties of nano particles, synthetic chemists have paid much attention on nano-catalysts. Recent reports showed that magnetic nano particles are widely used as catalysts and can be easily separated from the reaction mixture [7]. The high surface to volume ratio of metal nano particles is mainly responsible for their high catalytic performance. Ferrite nano material is one such reusable catalyst which shows profound catalytic activity in organic synthesis. Nano ferrite is a non-hygroscopic, inexpensive, non-toxic material which has been utilized as a heterogeneous catalyst for various organic reactions. Therefore, synthesis of catalysts with lower dimensions has become the most interesting topic of research. Moreover, due to quantum size effects, nano-sized particles may exhibit unique properties for a wide range of applications. Keeping the above facts in view and as a part of our ongoing research, herein we report for the first time the use of nano ferrite as heterogeneous support for the synthesis of Bis-acridines. This method offers advantages such as short reaction time, recyclability of the catalyst and easy to work-up procedure.

EXPERIMENTAL SECTION

2.1 Synthesis of nano ferrite particles:

$Fe(NO_3)_3 \cdot 9H_2O$, poly ethylene glycol (PEG 2000) and potassium chloride (KCl) were of analytical grade. Double distilled water was used in preparation. Initially, 0.006 mol Fe $(NO_3)_3 \cdot 9H_2O$ was dissolved in 100 ml aqueous solution of PEG 2000 with a NO_3-/PEG2000 molar ratio of 1. Then, the desired amount of KCl was added to the above solution and the resulting transparent solution was thoroughly stirred by a magnetic mixer at 70 ^oC until a

homogeneous sol-like solution was formed. Afterwards, the above solution was dried at 100 ^{o} C for 24 h. The obtained gel was placed in a silica crucible and heated in air until the gel was ignited. The burned powders were boiled in deionized water to remove the salt. Final product was obtained after washing with deionized water and ethanol, drying at 80 ^{o}C for 2 h.

2.2 General synthetic procedure for the synthesis of Bisacridines (4, 6a-h):

A mixture of Dimedone **(1)** (4 eq), Terephthalaldehyde **(2)** (1 eq), Ammonium acetate **(3)** or substituted anilines **(5a-h)** (2 eq) and freshly prepared nano catalyst *viz*. ferrite (15 mol%) were stirred at 120 ^{o}C in oil bath under neat condition for 30 minutes. After completion of the reaction (indicated by TLC), solid was obtained by allowing the contents to room temperature. The solid was extracted with ethyl acetate and the catalyst was recovered by magnetization. The crude product was further purified by silica gel (100-200 mesh) column chromatography and recrystallized from ethanol. All the synthesized products were characterized by NMR, IR and mass spectroscopic data.

2.2.1 3,4,6,7-tetrahydro-9-(4-(1,2,3,4,5,6,7,8,9,10-decahydro-3,3,6,6-tetramethyl-1,8-dioxoacridin -9-yl)phenyl)-3,3,6,6-tetramethylacridine-1,8(2H,5H,9H,10H)-dione (4): m.p-266-268 ^{o}C, ^{1}HNMR (400MHz, DMSO d_6) δ 0.65 (s, 12H), 0.87 (s, 12H), 1.74-1.78 (d, 4H), 1.96-2.00 (d, 4H), 2.13-2.18 (m, 8H), 5.00 (s, 2H), 7.14. (s, 4H), 7.45 (s, 4H), 7.67-7.69 (d, 4H); ^{13}CNMR (100MHz, DMSO d_6) δ 28.88, 29.18, 31.93, 40.84, 113.07, 126.86, 130.03, 137.28,195.05; 149.99,154.55,165.19, 171.36, 172.64, 193.73, 194.26; HRMS: Calcd. for 620 [M^+]; found 643 [M+Na]$^+$; FT IR (KBr cm^{-1}):1265, 1568, 1632, 2942

2.2.2 3,4,6,7-tetrahydro-9-(4-3,4,6,7-tetrahydro-9-(4(1,2,3,4,5,6,7,8,9,10-decahydro-3,3,6,6-tetra methyl-1,8-dioxo-10-phenylacridin-9-yl)phenyl)-3,3,6,6-tetramethyl-10-phenyl acridine-1,8 (2H,5H,9H,10H)-dione (6a): m.p-215-218 ^{o}C, ^{1}HNMR (400MHz, DMSO d_6) δ 0.65 (s, 12H), 0.87 (s, 12H), 1.74-1.78 (d, 4H), 1.96-200 (d, 4H), 2.13-2.18 (m, 8H), 5.00 (s, 2H), 7.04-7.07 (d, 2H), 7.42-7.45 (m, 2H), 7.56 (s, 2H), 7.94-7.95 (d, 2H); ESI-MS: Calcd. for 772 [M^+], found 773 [M+H]$^+$; FT IR (KBr cm^{-1}):1231, 1542, 1645, 2951.

2.2.3 10-(4-fluorophenyl)-9-(4-(10-(4-fluorophenyl)-1,2,3,4,5,6,7,8,9,10-decahydro-3,3, 6,6-tetramethyl-1,8-dioxoacridin-9-yl)phenyl)-3,4,6,7-tetrahydro-3,3,6,6-tetramethyl acridine-1,8 (2H,5H,9H,10H)-dione (6b): m.p-287-288 ^{o}C, ^{1}HNMR (400MHz, DMSO d_6) δ 0.79 (s, 12H), 0.85 (s, 12H), 1.62-2.13 (m, 16H), 5.21 (s, 2H), 7.15-8.05 (m, 12H); ESI-MS: Calcd. for 808 [M^+], found 809 [M+H]$^+$; FT IR (KBr cm^{-1}):1255, 1532, 1654, 2965

2.2.4 10-(4-chlorophenyl)-9-(4-(10-(4-chlorophenyl)-1,2,3,4,5,6,7,8,9,10-decahydro-3,3, 6,6-tetramethyl-1,8-dioxoacridin-9-yl)phenyl)-3,4,6,7-tetrahydro-3,3,6,6-tetramethyl acridine-1,8 (2H,5H,9H,10H)-dione (6c): m.p-212-214 ^{o}C, ^{1}HNMR (400MHz, DMSO d_6) δ 0.65 (s, 12H), 0.87 (s, 12H), 1.74-1.78 (d, 4H), 1.96-200 (d, 4H), 2.13-2.18 (m, 8H), 5.00 (s, 2H), 7.14-7.07 (s, 4H), 7.36-7.38 (d, 4H), 7.80-7.82 (d, 4H), 7.94-7.95 (d, 2H); HRMS: Calcd. for 840 [M^+], found 841 [M+H]$^+$, FT IR (KBr cm^{-1}):1258, 1568, 1654, 2977.

2.2.5 10-(4-bromophenyl)-9-(4-(10-(4-bromophenyl)-1,2,3,4,5,6,7,8,9,10-decahydro-3,3,6, 6-tetramethyl-1,8-dioxoacridin-9-yl)phenyl)-3,4,6,7-tetrahydro-3,3,6,6-tetramethylacridine-1,8 (2H,5H,9H,10H)-dione (6d): m.p-298-299 ^{o}C, ^{1}HNMR (400MHz, DMSO d_6) δ 0.73 (s, 12H), 0.81 (s, 12H), 1.72-2.18 (m, 16H), 5.02 (s, 2H), 7.22-8.17 (m, 12H), ESI-MS: Calcd. for 928 [M^+], 930 [M+2]$^+$ found 929 [M+H]$^+$,931 [M+H+2]$^+$; FT IR (KBr cm^{-1}):1295, 1577, 1682, 2965.

2.2.6 3,4,6,7-tetrahydro-9-(4-(1,2,3,4,5,6,7,8,9,10-decahydro-3,3,6,6-tetramethyl-10-(4-nitro phenyl)-1,8-dioxoacridin-9-yl)phenyl)-3,3,6,6-tetramethyl-10-(4-nitrophenyl)acridine-1,8(2H,5H,9H,10H)-dione (6e): m.p-269-270 ^{o}C, ^{1}HNMR (400MHz, DMSO d_6) δ 0.84 (s, 12H), 0.97 (s, 12H), 1.77-2.19 (m, 16H), 5.08 (s, 2H), 7.09-7.82 (m, 12H), ESI-MS: Calcd. for 862 [M^+], found 885 [M+Na]$^+$; FT IR (KBr cm^{-1}): 1244, 1597, 1692, 2900.

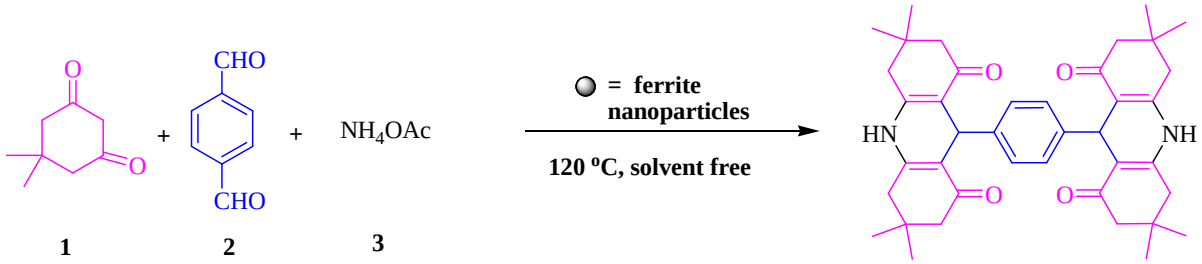
2.2.7 3,4,6,7-tetrahydro-9-(4-(1,2,3,4,5,6,7,8,9,10-decahydro-3,3,6,6-tetramethyl-1,8-di oxo-10-o-tolylacridin-9-yl)phenyl)-3,3,6,6-tetramethyl-10-o-tolylacridine-1,8(2H,5H,9H, 10H)-dione (6f): m.p-236-239 ^{o}C, ^{1}HNMR (400MHz, DMSO d_6) δ 0.76 (s, 12H), 0.83 (s, 12H), 1.63-2.07 (m, 16H), 2.31 (s, 6H),4.1 (m, 4H), 5.01 (s, 2H), 7.05-7.94 (m, 12H), ESI-MS: Calcd. for 803 [M^+], found 804 [M+H]$^+$; FT IR (KBr cm^{-1}):1279, 1586, 1674, 2927

2.2.8 3,4,6,7-tetrahydro-9-(4-(1,2,3,4,5,6,7,8,9,10-decahydro-3,3,6,6-tetramethyl-1,8-di oxo-10-m-tolylacridin-9-yl)phenyl)-3,3,6,6-tetramethyl-10-m-tolylacridine-1,8(2H,5H,9H, 10H)-dione (6g): m.p-276-279 ^{o}C, ^{1}HNMR (400MHz, DMSO d_6) δ 0.86 (s, 12H), 1.00 (s, 12H), 1.91-2.504 (m, 8H), 4.1(s, 4H), 4.81 (s, 2H), 7.01-7.25 (m, 12H), ; ESI-MS: Calcd. for 803 [M^+] found 804 [M+H]; FT IR (KBr cm^{-1}):1268, 1589, 1645, 2988

2.2.9 3,4,6,7-tetrahydro-9-(4-(1,2,3,4,5,6,7,8,9,10-decahydro-3,3,6,6-tetramethyl-1,8-di oxo-10-p-tolylacridin-9-yl)phenyl)-3,3,6,6-tetramethyl-10-p-tolylacridine-1,8(2H,5H,9H, 10H)-dione (6h): m.p-281-283 ^{o}C, ^{1}HNMR (400MHz, DMSO d_6) δ 0.79 (s, 12H), 0.88 (s, 12H), 1.53-2.02 (m, 16H), 2.29 (s, 6H),4.4 (m, 4H), 5.51 (s, 2H), 7.48-7.89 (m, 12H), ESI-MS: Calcd. for 803 [M^{+}], found 804 [M+H]$^{+}$; FT IR (KBr cm^{-1}):1278, 1512, 1669, 2995

RESULTS AND DISCUSSION

In an effort to explore a novel catalyst for the synthesis of bis-acridines, we have screened the model reaction of 5,5-dimethylcyclohexane-1,3-dione (dimedone) **(1)** (4 eq), Terephthalaldehyde **(2)** (1 eq), Ammonium acetate **(3)**, (3 eq) and freshly prepared nano catalyst *viz*. ferrite were stirred at 120 ^{o}C in oil bath under neat condition for 30 minutes **(Scheme-1).**

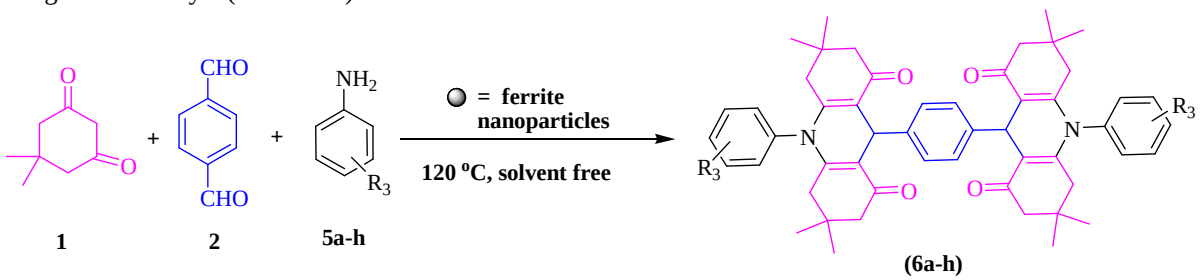


1 **2** **3** **4**

Scheme-1: Synthesis of 3,4,6,7-tetrahydro-9-(4-(1,2,3,4,5,6,7,8,9,10-decahydro-3,3,6,6-tetramethyl-1,8-dioxoacridin-9-yl)phenyl)-3,3,6,6-tetramethylacridine-1,8(2H,5H,9H,10H)-dione (4) using nano ferrite

In an initial endeavour, a blank reaction was performed using (dimedone) **(1)**, Terephthalaldehyde **(2)**, and ammonium acetate **(3)** (mole ratio 4:1:2) at 120 ^{o}C in the absence of catalyst to establish the reaction and the results showed that desired product was not formed even after 12 hours of heating. In order to evaluate the most appropriate catalytic percentage, a model reaction in **Scheme-1** was carried out using 0 -20 mol% of nano ferrite under solvent-free conditions. It was observed that at 15 mol% of nano ferrite showed high yield in short reaction time at 120 ^{o}C. It is proposed to examine the reaction with different organic solvents viz.; acetonitrile, THF, EtOH, 1,4-dioxane, MeOH, Water and also under solvent free conditions. From the results it was observed that the reaction in neat conditions gives the desired product in good yield.

With the optimised result in hand, we have made an attempt for the synthesis of Bisacridines **(6a-h)** by the reaction of dimedone **(1),** Terephthalaldehyde **(2)** and substituted anilines **(5a-h)** utilizing 15 mol% nano ferrite as solid heterogeneous catalyst (**Scheme-2**).



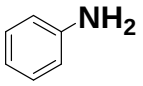
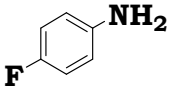
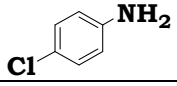
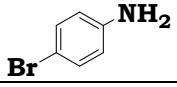
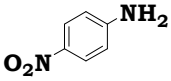
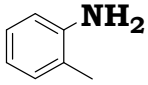
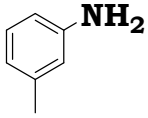
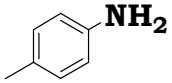
1 **2** **5a-h** **(6a-h)**

R_3 = H, 4-F, 4-Cl, 4-Br, 4-NO_2, 2-CH_3, 3-CH_3, 4-CH_3

Scheme-2: Synthesis of nano ferrite catalysed bisacridines (6a-h)

As expected, satisfactory results were obtained, and the results are summarized in **Table 3**.

Table-1. The reaction time, percentage of yields of nano ferrite catalysed bisacridines (4, 6a-h)

Entry	Amines	Product	Time (min)	Yield (%)[a]
1	NH_4OAc	**4**	5	88
2		**6a**	7	85
3		**6b**	6	85
4		**6c**	7	86
5		**6d**	6	86
6		**6e**	8	85
7		**6f**	6	87
8		**6g**	7	88
9		**6h**	6	86

[a] *isolated yields.*

Reusability of nano catalyst:

The catalyst was recovered by magnetization after completion of the reaction, washed with diethyl ether and the recovered catalyst was reused for four cycles. During washing with the solvent, it was observed that there was no leaching of catalyst and was confirmed by performing the reaction with the filtrate. From our investigations, we observe that nano catalyst shows excellent to good reactivity with promising yields. **(Table 2).**

Table-2. Reusability of nano catalyst

Entry	Catalyst recovery (%)	Yield [a]
1	-	88
2	97	85
3	86	79
4	80	76

[a] *isolated products.*

CONCLUSION

In conclusion we synthesized nano ferrite and applied it as a catalyst in the synthesis of Bisacridines. The main advantages of this catalyst include excellent yields, short reaction times and reusability of catalyst.

Acknowledgement

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