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ONE-POT SYNTHESIS OF 1,8-DIOXO-DECAHYDROACRIDINE DERIVATIVES BY USING NANO-Fe_2O_3 AS A HIGHLY EFFICIENT AND REUSABLE HETEROGENEOUS CATALYST UNDER SOLVENT-FREE CONDITIONS

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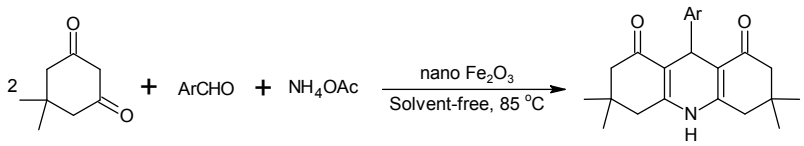
A simple and convenient one-step method for synthesis of 1,8-dioxo-decahydroacridines via a multi-component reaction of dimedone, aromatic aldehydes and ammonium acetate catalyzed by nano-Fe_2O_3 as a catalyst was investigated. The structural features of the synthesized compounds were characterized by melting point, IR and ^{1}H-NMR analysis. The reported catalyst is one-pot, cheap, reusable and safe to handle. The advantages of this protocol are: eco-friendly procedure, mild reaction conditions, excellent yields, operational simplicity and ecofriendly preparation of catalyst.



INTRODUCTION

Multi-component reactions have emerged as powerful tools for assembling three or more reactants and preparation higher molecular weight compounds. In recent years multi-component reaction are valuable device for develops for the synthesis of heterocyclic compounds receives growing interest. The multi-component condensation reactions were an important tool in the organic synthesis as they possess ability of building up the pharmaceuticals. Pharmacies are trying to develop green chemistry reactions.[1-5]

1,4-dihydropyridines are an important class of nitrogen-containing heterocyclic compounds which have attracted significant synthetic interest due to their reactivity and biological activity. These compounds had shown interesting biological properties including antimalarial,[6] anticancer,[7] anticarcinogenic,[8] antitumor,[9] cytotoxic,[10] antimicrobial,[11] antimultidrug-resistant,[12]fungicidal,[13] and widely prescribed as calcium b-blockers.[14]

Thus, in recent years several methods were established to improve the use of Proline,[15] Amberlyst-15,[16] ammonium chloride, $Zn(OAc)_2$ H_2O,[17] microwave irradiation,[18–20] SiO_2-Pr-SO_3H,[21] ZnO nanoparticles,[22] nano-Fe_3O_4,[23] Nano titanium dioxide,[24] Ultrasound,[25]Nanoparticles tungstophosphoric acid supported on polyamic acid,[26] sulfonic acid functionalized LUS-1,[27] [BPY]HSO_4,[28] and different ways have been reported.

Previously, in continuation of our investigations, we have synthesized a number of heterocyclic compounds.[29-33] In this research, herein, we report an innovative, convenient, mild and efficient procedure for the synthesis of 1,8-dioxo-decahydroacridine derivatives. 1,8-dioxo-decahydroacridine derivatives were synthesized by one-pot three component condensations of aromatic aldehydes, dimedone and ammonium acetate in the presence of nano-Fe_2O_3 as a catalyst under solvent-free conditions (Scheme 1).

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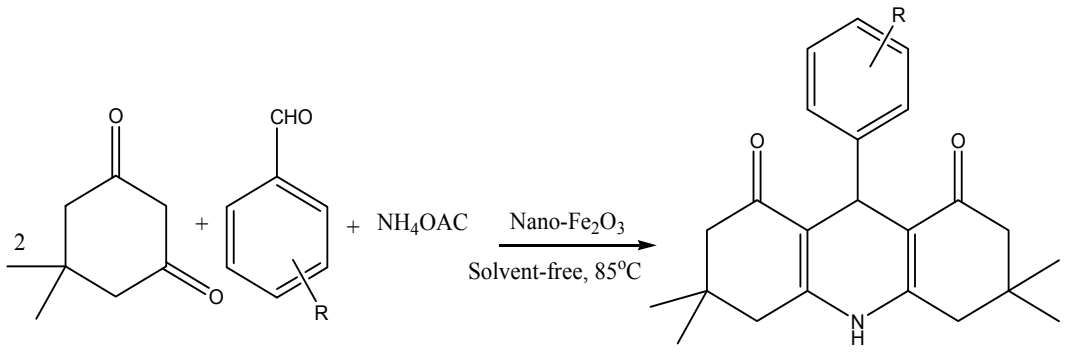
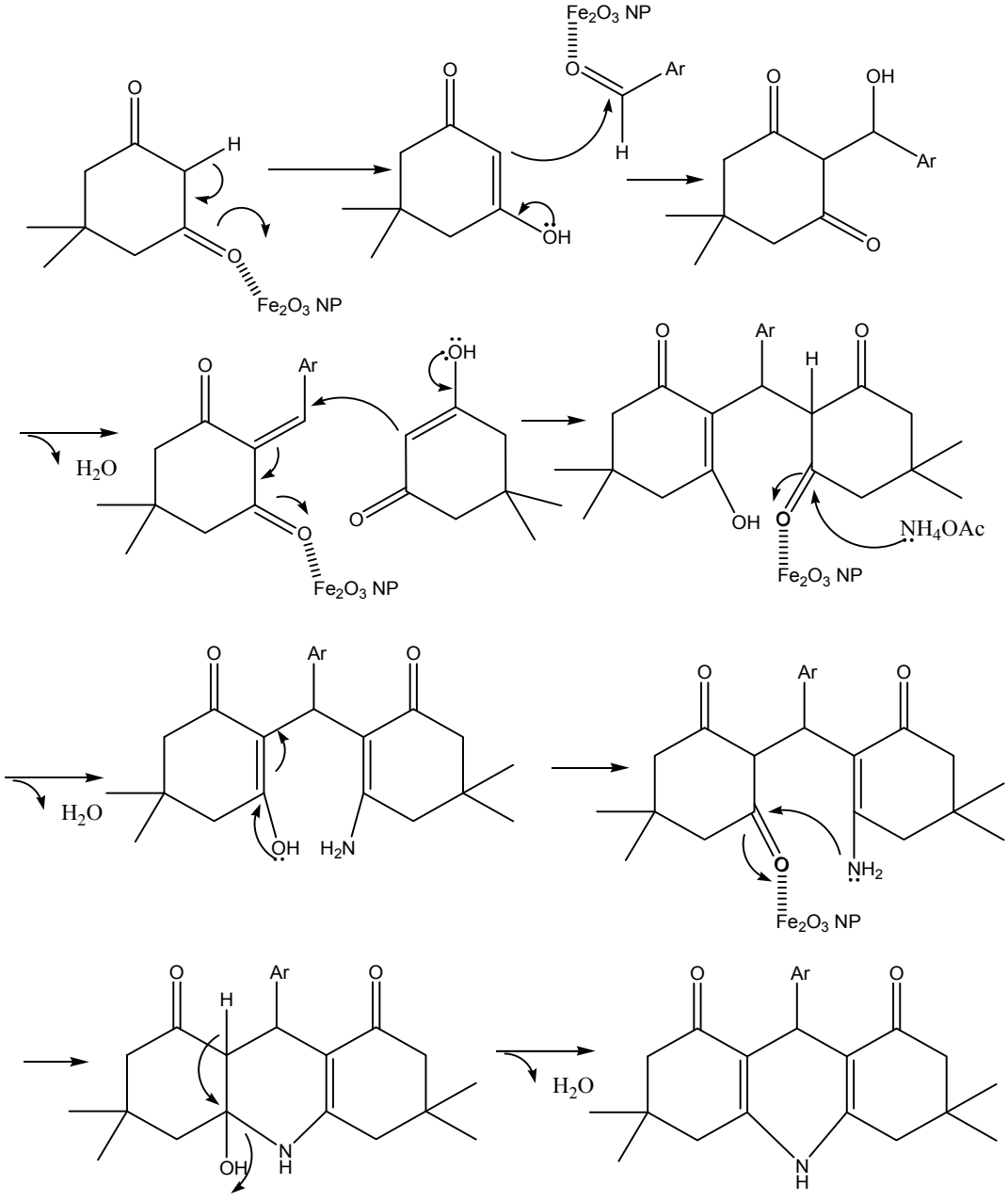


R: H, CH_3, OCH_3, NO_2, Cl, F

Scheme 1 – Synthesis of 1,8-dioxo-decahydroacridine derivatives using nano-Fe_2O_3 as a catalyst.



Scheme 2 – Mechanism of formation of 1,8-dioxo-decahydroacridines.

RESULTS AND DISCUSSION

Nowadays, Nano-Fe_2O_3 is used as a catalyst in the synthesis of organic compounds. Features of this catalyst that are of interest include: easy separation, environmentally friendly, clean, and economical.[33-36] The proposed mechanism of formation of 1,8-dioxo-decahydroacridines using Nano-Fe_2O_3 as a catalyst is shown in Scheme 2.

At first, for the optimization of the reaction conditions, the condensation of benzaldehyde, dimedone and ammonium acetate was investigated. Then, we decided to examine the effect of the various solvents with amount of catalyst on the reaction. As shown in Table 1, the best results in terms of yield and time were obtained using 10 mol% of nano-Fe_2O_3 in refluxing ethanol (entry 11).

After pursuing the best solvent with catalyst, we evaluated the scope of nano-Fe_2O_3 catalyzed 1,8-dioxo-decahydroacridines synthesis reaction using a variety of aldehydes. Aromatic aldehydes bearing both electron-donating and electron withdrawing groups were employed for the synthesis of 1,8-dioxo-decahydroacridines derivatives and the expected products were obtained in high yields. The results of the synthesis of substituted 1,8-dioxo-decahydroacridine derivatives are summarized in Table 2.

Comparison of reaction conditions and product yield between previously reported methods and the present method are shown in Table 3.

The catalyst was easily recovered by simple filtration after dilution of the reaction mixture with ethyl acetate and was reused after being vacuum dried. Nano-Fe_2O_3 was reused for four runs without significant loss of activity. The results are shown in Table 4.

Table 1

Solvent effect with amount catalyst in the synthesis of 1,8-dioxo-decahydroacridine[a]

Entry	Catalyst (mol%)	Solvent	Condition	Time (min)	Yield (%)[b]
1	---	Ethanol	R.T.	100	45
2	---	Water	R.T.	100	36
3	---	Dichloromethane	R.T.	100	NP
4	---	Acetonitrile	R.T.	100	33
5	---	Ethanol-water	Reflux	100	50
6	---	Ethanol	Reflux	100	52
7	---	Water	Reflux	100	45
8	---	Dichloromethane	Reflux	100	NP
9	---	Acetonitrile	Reflux	100	38
10	5	Solvent-free	Reflux	50	85
11	10	Solvent-free	Reflux	30	93
12	15	Solvent-free	Reflux	35	93
13	5	Ethanol	Reflux	60	78
14	10	Ethanol	Reflux	60	80
15	15	Ethanol	Reflux	60	83
16	10	Ethanol-water	Reflux	60	71
17	10	Water	Reflux	60	68
18	10	Dichloromethane	Reflux	60	22
19	10	Acetonitrile	Reflux	60	63

Reaction condition: [a] benzaldehyde (1 mmol), dimedone (1 mmol), ammonium acetate (1 mmol); [b] Isolated yield.

Table 2

Nano-Fe_2O_3catalyzed synthesis of 1,8-dioxo-decahydroacridine derivatives[a]

Entry	ArCHO	Yield (%)[b]	M.P. ^oC (Found)	M.P. ^oC (Reported in Lit.)
F1	C_6H_4CHO	93	193-194	192-195 [37]
F2	4-Me C_6H_4CHO	94	270-271	269-271[38]
F3	4-MeO C_6H_4CHO	95	269-272	270-272[38]
F4	3-NO_2 C_6H_4CHO	91	289-291	288-291 [38]
F5	4-Cl C_6H_4CHO	90	302-303	300-302[38]
F6	2-F C_6H_4CHO	91	257-258	257-258 [38]

Reaction condition: [a] aldehyde (1 mmol), dimedone (1 mmol), ammonium acetate (1 mmol), nano-Fe_2O_3 (10 mol%); [b] Isolated yield.

Table 3

Comparison of reaction conditions and yield of product with reported methods versus the present method

Catalyst	Condition	Time (min)	Yield (%)	Ref.
Nano TiO_2	Reflux, Ethanol	60	85-91	[24]
Cu-doped ZnO	Solvent-free, 130°C	90	85-95	[39]
Nano ZnO	Solvent-free, 90°C	90	73-97	[22]
Nano Fe_3O_4	Solvent-free, 120°C	20	85-90	[23]
$[Al(DS)_3].3H_2O$	Water, 130°C	25	75-93	[40]
DBH or DCH	Solvent-free, 130°C	30	84-96	[41]
SiO_2-$ZnCl_2$	Solvent-free, 100°C	30	70-90	[42]
SBA-Pr-SO_3H	Solvent-free, 140°C	5	83-96	[43]
Saccharose	Solvent-free, 85°C	60	81-92	[44]
Nano Fe_2O_3	Solvent-free, 85°C	30	90-95	In this Rresearch

Table 4

Reusability of nano-Fe_2O_3 catalyst in the synthesis of 9-phenyl-3,4,6,7-tetrahydro-3,3,6,6-tetramethylacridine-1,8 (2H, 5H, 9H, 10H)-dione

Run No.	Time (min)	**Yield (%)[a]**
1	40	93
2	50	91
3	65	89
4	80	88

[a] Isolated yield

EXPERIMENTAL

1. Materials and methods

The materials were purchased from Sigma-Aldrich and Merck chemical companies and were used without any additional purification. Melting points were measured using an Electrothermal 9100 apparatus. Silica gel SILG/UV 254 plates were used for TLC. IR spectra were measured using a Shimadzu IR-470 Spectrophotometer. The ^{1}H-NMR spectra were scanned in $CDCl_3$ using a Brucker NMR spectrometer operating at 300.13 MHz. The products were characterized by comparison of their ^{1}H-NMR, IR spectra and physical data with those reported in the literature.

2. General procedure for the synthesis of 9-phenyl-3,4,6,7-tetrahydro-3,3,6,6-tetramethylacridine-1,8)2H, 5H, 9H, 10H(-dione (F1)

A mixture of benzaldehyde (1.0 mmol), dimedone (2.0 mmol), ammonium acetate (1.2 mmol) and nano-Fe_2O_3 as a catalyst (10 mol%) was heated in an oil bath at 85 °C for 30 min. The progress of the reaction was monitored by TLC (chloroform/methanol 8:2). After completion of the reaction, the reaction mixture was cooled to room temperature and hot ethanol (15 mL) was added. The catalyst was precipitated, which was collected by filtration. The resulting solid (crude product) was filtered and then recrystallized with ethanol–water to obtain compounds **F1** in high to excellent yields. The physical data (mp, IR and ^{1}H-NMR) of these known compounds were identical with those reported in the literature.

Spectral data for the synthesis of 1,8-dioxo-decahydroacridine derivatives (F1-8)

9-phenyl-3, 4, 6, 7-tetrahydro-3, 3, 6, 6-tetramethylacridine-1, 8)2H, 5H, 9H, 10H(-dione (**F1**):

Pale yellow Crystals. Yield: 0.32g (93%), m.p 193-194 °C. FT-IR (V_{max}/cm^{-1}) (KBr disc): 3424 (N-H Str.); 3026 (CH arom. Str.); 2963, 2931 (CH aliph. Str.); 1593 (C=O Str.); 1491, 1449 (C=C Str.); 1374 (C-N). ^{1}H-NMR (300.13 MHz $CDCl_3$) δ (ppm) = 1.12 (6*H*, s, $2CH_3$); 1.25 (6*H*, s, $2CH_3$); 2.27-2.52 (8*H*, m, $4CH_2$); 5.57 (1*H*, s, CH_2); 7.10-7.31 (5*H*, m, 5CH); 11.98 (1*H*, S, NH).

9-(4-Methylphenyl)-3, 4, 6, 7-tetrahydro-3, 3, 6, 6-tetramethylacridine-1, 8(2H, 5H, 9H, 10H)-dione (**F2**):

Pale yellow Crystals. Yield: 0.34g (94%), m.p 270-271 °C. FT-IR (V_{max}/cm^{-1}) (KBr disc): 3450 (NH Str); 3040 (arom. CH Str.); 2960, 2929 (CH aliph Str.); 1598 (C=O Str.); 1510, 1451 (C=C Str.); 1371 (C-N). ^{1}H-NMR (300.13 MHz $CDCl_3$) δ (ppm) = 1.11 (6*H*, s, $2CH_3$); 1.24 (6*H*, s, $2CH_3$); 2.26-2.51 (8*H*, m, $4CH_2$); 2.31 (3*H*, s, CH_3); 5.53 (*H*, s, CH); 7.00 (2*H*, d, ^3J=8.1 Hz, 2CH); 7.09 (2*H*, d, ^3J=8.1 Hz, 2CH); 11.98 (*H*, s, NH).

9-(4-methoxyphenyl)-3, 4, 6, 7-tetrahydro-3, 3, 6, 6-tetramethylacridine-1, 8)2H, 5H, 9H, 10H(-dione (**F3**):

Pale yellow Crystals. Yield: 0.36g (95%), m.p 269-272 °C. FT-IR (V_{max}/cm^{-1}) (KBr disc): 3410 (N-H Str); 3089 (CH arom. Str.); 2962, 2872 (CH aliph. Str.); 1602 (C=O Str.); 1528, 1462 (C=C Str.); 1380 (C-N). ^{1}H-NMR (300.13 MHz $CDCl_3$) δ (ppm) = 1.07 (6*H*, s, $2CH_3$); 1.24 (6*H*, s, $2CH_3$);

2.27-2.51 (8*H*, m, $4CH_2$); 3.75 (3*H*, s, CH_3); 5.51 (*H*, s, CH); 6.82 (2*H*, d, ^3J=8.7 Hz, 2CH); 7.02 (2*H*, d, ^3J=8.7 Hz, 2CH); 11.99 (*H*, s, NH).

*9-(3-Nitrophenyl)-3, 4, 6, 7-tetrahydro-3, 3, 6, 6-tetramethylacridine-1, 8)2H, 5H, 9H, 10H(-dione (***F4**):

Pale yellow Crystals. Yield: 0.36g (91%), m.p 289-291 °C. FT-IR (V_{max}/cm^{-1}) (KBr disc): 3425 (NH Str.); 3016 (CH arom. Str.); 2960, 2931 (CH aliph. Str.); 1597 (C=O Str.); 1509, 1415 (C=C Str.); 1370 (C-N Str.); 1458, 1309 (N-O Str.). ^{1}H-NMR (300.13 MHz $CDCl_3$) δ (ppm) = 1.14 (6*H*, s, $2CH_3$); 1.29 (6*H*, s, $2CH_3$); 2.32-2.55 (8*H*, m, $4CH_3$); 5.56 (1*H*, s, CH); 7.43 (2*H*, m, 2CH); 8.04 (2*H*, m, 2CH); 11.91 (1*H*, s, NH).

9-(4-cholorophenyl)-3, 4, 6, 7-tetrahydro-3, 3, 6, 6-tetramethylacridine-1, 8)2H, 5H, 9H, 10H(-dione (**F5**):

Pale yellow Crystals. Yield: 0.34g (90%), m.p 302-303 °C. FT-IR (V_{max}/cm^{-1}) (KBr disc): 3446 (NH Str.); 3015 (CH arom. Str.); 2961, 2880 (CH aliph. Str.); 1590 (C=O Str.); 1490, 1456 (C=C); 1376 (C-N Str.). ^{1}H-NMR (300.13 MHz $CDCl_3$) δ (ppm) = 1.11 (6*H*, s, $2CH_3$); 1.23 (6*H*, s, $2CH_3$); 2.20-2.51 (8*H*, m, $4CH_3$); 5.44 (*H*, s, CH); 7.02 (2*H*, d, ^3J=7.8 Hz, 2CH); 7.24 (2*H*, d, ^3J=7.8 Hz, 2CH); 11.92 (*H*, s, NH).

9-(2-foluro)-3,4,6,7-tetrahydro-3,3,6,6-tetramethylacridine-1, 8)2H, 5H, 9H, 10H(-dione (**F6**):

Pale yellow Crystals. Yield: 0.33g (91%), m.p 257-258 °C. FT-IR (V_{max}/cm^{-1}) (KBr disc): 3379 (NH Str.); 3018 (CH arom. Str.); 2959, 2930 (CH aliph. Str.); 1723 (C=O Str.); 1612, 1468 (C=C); 1289 (C-N Str.). ^{1}H-NMR (300.13 MHz $CDCl_3$) δ (ppm) = 1.12 (6*H*, s, $2CH_3$); 1.25 (6*H*, s, $2CH_3$); 2.27-2.52 (8*H*, m, $4CH_3$); 5.57 (*H*, s, CH); 7.11 (*H*, d, ^3J=8.1 Hz, CH); 7.20 (*H*, d, ^3J=6.6 Hz,); 7.28 (2*H*, dd, ^3J=7.8 Hz, ^3J=7.2 Hz, 2CH); 11.97 (*H*, s, NH).

CONCLUSION

We have demonstrated nano-Fe_2O_3 as an efficient catalyst for the synthesis of substituted 1,8-dioxo-decahydroacridines derivatives. The advantages of this method using nano-Fe_2O_3 include high yields, short reaction time, one-pot, experimental simplicity, environmentally friendly, easy separation and reusable of this catalyst.

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