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RESEARCH ARTICLE

A Facile, Efficient and Convenient Synthesis of 1,8-Dioxodecahydroacridines with PMA-SiO_2 Reusable Catalyst

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Abstract: Multi component reactions (MCRs) are emerged as the most an effective and efficient tool in modern synthetic organic chemistry in the recent years. Syntheses of complex and diverse organic molecules from simple and readily available starting materials in a single step can be achieved by MCRs. We achieved PMA-SiO_2 catalysed synthesis of 1,8-dioxodecahydroacridines through multi component reactions (MCRs) of 5, 5-dimethylcyclohexane-1, 3-dione, aldehydes and anilines in PEG-400. Moreover, varieties of dioxodecahydroacridine derivatives were also synthesized in good yields by using PMA-SiO_2 catalyst. The reaction proceeded efficiently in all these cases affording a diversity of 5-substituted 1, 8-dioxodecahydroacridine derivatives **6(a-i)**, in reasonably good yields. A range of electron donating and electron with drawing groups present on the aromatic ring of aldehydes was well tolerated for the titled catalyst, PMA-SiO_2 and obtained good yields. PMA-SiO_2 in PEG-400 catalyst offers several advantages like shorter reaction times, non-toxic, mild reaction conditions, cleaner reactions, high yield of the products, lower catalytic loading *etc*. Moreover, this catalyst could be recovered and recycled easily for several cycles without losing its activity. This study can provide a road map to design new green synthetic methodologies for single step cyclo-condensation reaction through MCRs with better yields.

Keywords: Acridines, multi component reactions, PEG-400, PMA-SiO_2, catalyst, DHP.

1. INTRODUCTION

Multi component reactions (MCRs) are emerged [1-8] as the most an effective and efficient tool in modern synthetic organic chemistry in the recent years. Syntheses of complex and diverse organic molecules from simple and readily available starting materials in a single step can be achieved by MCRs. Moreover, this is a fast and efficient method to achieve target organic molecules without isolation of any intermediates. Some advantages of this approach include its superior atom-economy, simplicity, low costs, and bond forming efficiency [1-7]. We have been targeting to synthesis of very expensive and problematic organic molecules by MCRs using heterogeneous catalysis. It is well known that, 1, 8-Dioxodecahydroacridines derivatives, constitute a 1, 4-dihydropyridine (DHP) ring [8] system have been shown to possess a broad range of pharmacological applications like angina pectoris [9, 10, 12], hypertension [11], and calcium channel blockers [13, 14] and also compounds containing acridine derivatives skeleton have also been developed as drugs, for example Mepacrine **1** (Antimalerial drug) and Nitracrine **2** (Antitumer drug) and these two drugs are shown in Fig. (**1**). Furthermore, 1,4-dihydropyridine derivatives have found applications in dye industry [15-17].

Synthesis of various acridine derivatives has been achieved by many well-designed methods. Nevertheless, one of the best methods involves the cyclocondensation of dimedone, aldehydes, and different anilines or ammonium acetates *via* one-pot multicomponent reaction. This reaction can

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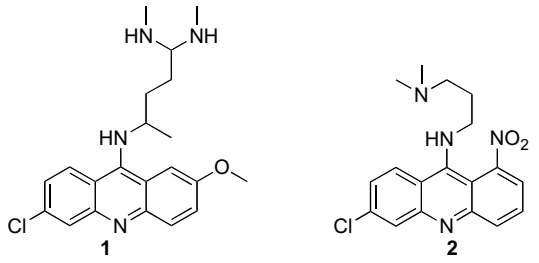


Fig. (1). Structures of Acridine based known drugs.

be carried out in the presence of different catalysts such as proline [8], asp-dodecylbenezene sulfonicacid (DBSA) [18], amberlyst-15 [19], MCM-41-SO_3H [20], [Hmim]TFA [21], and Bronsted acidic imidazolium salts containing perfluoro alkyl tails [22, 23]. Though, many of these methods are effective for the preparation of target acridine derivatives. However, some of these suffer with low yields, prolonged reaction time, harsh reaction conditions and excess catalyst *etc.* Consequently, development of an efficient, atom-economy and eco-friendly method for synthesis of 1,8-dioxodecahydroacridines, from readily available starting materials under mild conditions, is highly desirable. In this context, PMA-SiO_2 is a promising green heterogeneous catalyst for the synthesis of acridine derivatives, with low-cost and recyclable conditions. Furthermore, it can be easily handled and removed by simple filtration from the reaction mixture [24, 25].

To the best of our knowledge, PMA-SiO_2 catalysed based synthesis of 1, 8-dioxodecahydro acridines and their derivatives through MCRs were not explored earlier. Herein, we report a new green, PMA-SiO_2 heterogeneous catalysed methodology for the synthesis of 1,8-dioxodecahydro acridines by using 5, 5-dimethylcyclohexane-1, 3-dione **3**, aldehydes **4** and anilines **5** in the presence of PEG-400 as a solvent and it is shown in Scheme (**1**).

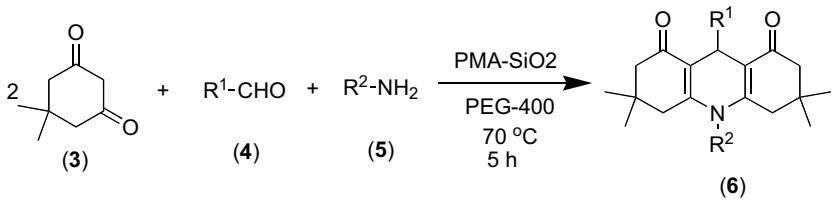
2. RESULTS AND DISCUSSION

The optimized reaction conditions for the synthesis of desired 1,8-dioxodeca hydroacridine (**6a**) using various organic components like 5,5-dimethylcyclohexane-1,3-dione (**3**), aldehydes (**4**) and aniline (**5**) as MCRs are shown in Table **1**. Initially, the reactions were carried out at 70°C in the presence of different catalysts like, PMA-SiO_2, Amberlyte-IR 120 and Amberlyst-15 in PEG-400 as a solvent for 5 h. The targeted 1, 8-dioxodecahydroacridine (**6a**), was isolated in **98** % yield, when PMA-SiO_2 (20 mol%) used as a heterogeneous catalyst (Entry 1, Table **1**). When the same reaction was carried out using Amberlyte-IR 120 (20 mol%) as catalyst in similar solvent PEG-400 for 5 h, the 1,8-dioxodecahydroacridine (**6a**) was isolated in 45 % yield (entry 2, Table **1**). Similarly Amberlyst-15, as catalyst 1,8-dioxodecahydroacridines (**6a**) yielded 70 % (entry 3, Table **1**). Parallel reactions were carried out using all the three catalysts, PMA-SiO_2 (20 mol%) (Entry 4, Table **1**), Ambrelyte-IR 120 (20 mol %) and Amberlyst-15 (20 mol%) at lower temperature like 40°C for the synthesis of **6a**, the yields were also low. Next step, we examined the use of other solvents like acetonitrile (Entry 5, Table **1**) and methanol (Entry 6, Table **1**) in place of PEG-400 in similar reaction conditions at 70°C yielded 30 % and 55 %, respectively. From the above attempted reactions, we can conclude that, PMA-SiO_2 (20 mol %), is the better catalyst for the synthesis of **6a**, with 98 % yield at 70°C in PEG-400 as solvent. To test the recyclability of the PMA-SiO_2 catalyst, the recovered sample by simple filtration followed by activation at 70°C was used for further cycles. The activated catalyst was reused in the similar reaction conditions for the synthesis of **6a**, the isolated yields were, 96, 92 and 90 %, respectively for 1st, 2nd and 3rd recovery samples (Entries 3, Table **1**). This study indicated that, PMA-SiO_2, is the best catalyst for the synthesis of **6a**, at 70°C in PEG-400 solvent without significant loss of its yield even when we used recycled sample of the catalyst.

In order to expand the scope and overview of this PMA-SiO_2 catalyst was also examined for similar kind of reactions intended for the synthesis of 1, 8-dioxodecahydroacridine derivatives. A range of anilines (**4**) and aldehydes (**5**) were used for the synthesis of 1, 8-dioxodecahydro acridine derivatives under the optimized reaction conditions and results are summarized in Table **2**. The reaction proceeded efficiently in all these cases affording a diversity of 5-substituted 1, 8-dioxodecahydroacridine derivatives (**6b-l**), in reasonably good yields. A range of electron donating and electron with drawing groups present on the aromatic ring of aldehydes was well tolerated for the titled catalyst, PMA-SiO_2 and obtained good yields.

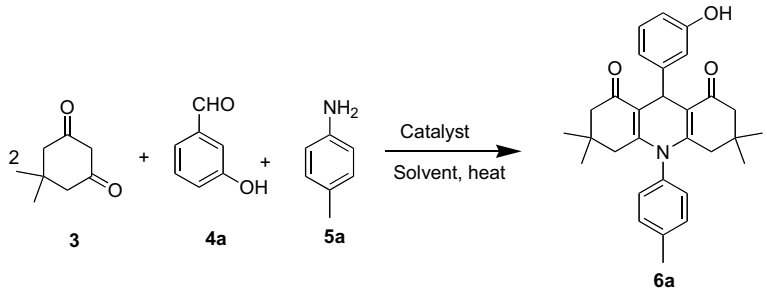
3. EXPERIMENTAL SECTION

Melting points are recorded with a micro melting point apparatus and the data used as uncorrected. Column chromatography was performed over silica gel (mesh 230-400) and hexane/ethyl acetate combination was used as the eluent. The ^{1}H NMR spectra were recorded at Bruker Avance 400 MHz and ^{13}C NMR spectra were recorded at 100 MHz. Proton chemical shifts (δ) are relative to tetra methyl silane (TMS, δ = 0.00) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), t (triplet)



Scheme (1). PMA-SiO_2catalyzed synthesis of 1,8-dioxodecahydroacridines in PEG-400.

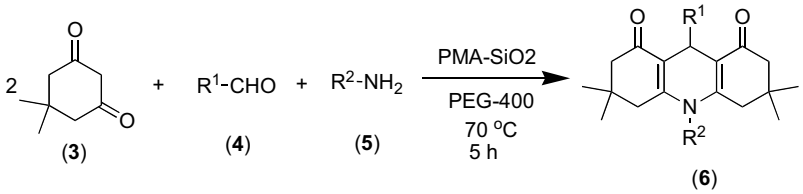
Table 1. Effect of reaction conditions on the MCR of 3, 4a and 5a.

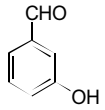
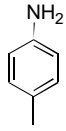
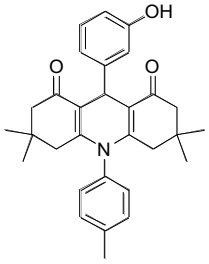
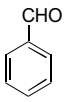
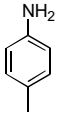
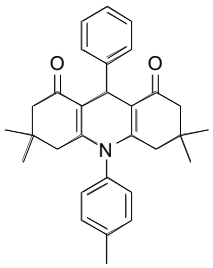


Entry	Catalyst	Solvent	Temp.°C	Yield (%)
1	Amberlyte-IR120 (20 mol%)	PEG-400	70	45
2	Amberlyst-15 (20 mol%)	PEG-400	70	70
3	PMA-SiO_2 (20 mol%)	PEG-400	70	98 (96, 92, 90)[a]
4	PMA-SiO_2 (20 mol%)	PEG-400	40	70
5	PMA-SiO_2 (20mol%)	CH_3CN	70	30
6	PMA-SiO_2 (20 mol%)	MeOH	70	55

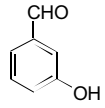
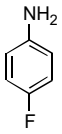
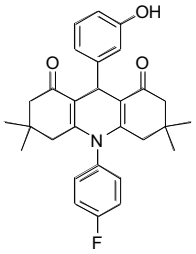
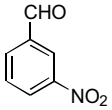
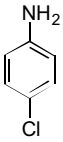
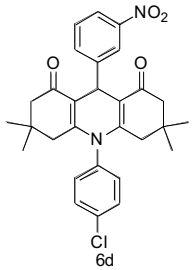
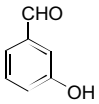
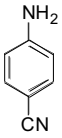
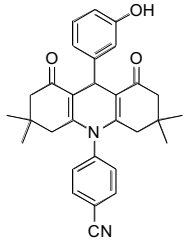
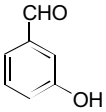
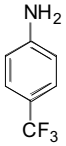
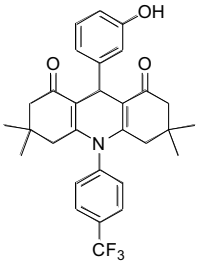
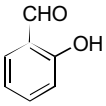
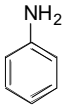
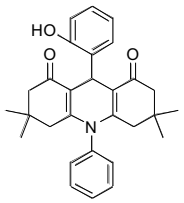
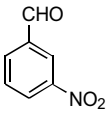
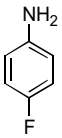
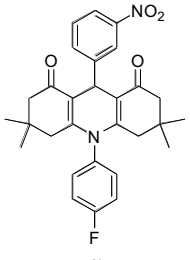
[a]The catalyst was reused for an additional three runs and the figures within parentheses indicate the corresponding yield for each run.

Table 2. PMA-SiO_2catalyzed synthesis of 1,8-dioxodecahydroacridines in PEG-400 (Scheme1)[a].



Entry	Aldehyde (4)	Aniline (5)	Product (6)[b]	Yield[c] (%)
1			 6a	98
2			 6b	96

(Table 2) Contd….

Entry	Aldehyde (4)	Aniline (5)	Product (6)[b]	Yield[c] (%)
3			 6c	94
4			 6d	96
5			 6e	95
6			 6f	97
7			 6g	95
8			 6h	97

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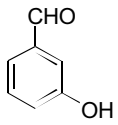
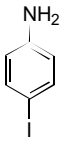
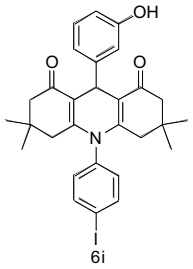
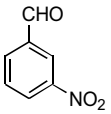
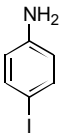
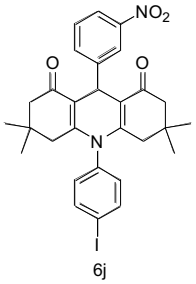
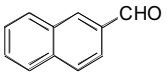
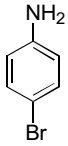
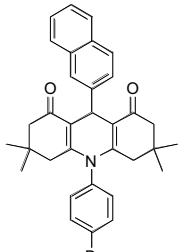
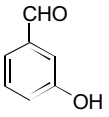
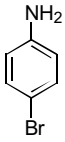
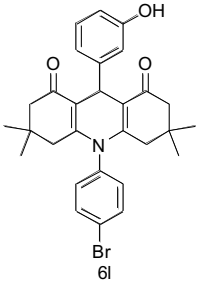
9			 6i	85
10			 6j	98
11			 6k	89
12			 6l	92

[a]Reaction and conditions: all the reactions were carried out using 5,5-dimethyl-1,3-cyclohexanedione (**3**) (2 mmol), aldehyde (**4**) (1 mmol), amine (**5**) (1 mmol) and PMA-SiO_2(20 mol%) in PEG-400 (3 mL) at 70°C for 5 h [b] Isolated yield. [c]After purification by column chromatography.

and m (multiplet) as well as b (broad). Coupling constants (*J*) are given in hertz. IR spectra were recorded using Perkin-Elmer model 1700 instrument in KBr pellet phase. MS spectra were obtained on a VG micromass70-70 H instrument spectrometer. CHN analysis was carried out using Vario Micro Cube Elemental instrument.

3.1. General Procedure for the Preparation of Compound (6)

A reaction mixture of 5,5-dimethyl-1, 3-cyclohexanedione (**3**) (1 mmol), amine (**4**) (0.5 mmol), aldehyde (0.5 mmol) (**5**) and PMA-SiO_2 (20 mol%) in PEG-400 (3 mL) was stirred at 70°C for 5hrs. After the completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature and filtered. The filtrate and elute were collected separately and then solvent was evaporated from elute under vacuum. The crude product obtained was purified with column chromatography by using *n*-hexane/ethyl acetate on silica gel to give the pure products (see Table 2). The catalyst obtained after filtration was washed with ethyl acetate (3 x 10 mL) and was dried in an oven at 70°C for 1h, which was reused for further trails. The detailed synthesis procedure for first 1, 8-dioxodecahydroacridine, **6a** described as a model synthesis below.

3.1.1. 9-(3-Hydroxyphenyl)-3,3,6,6-tetramethyl-10-p-tolyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (6a):

White solid; M.P: 255-256°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 0.86 (s, 6H), 0.96 (s, 6H), 1.87 (d, *J* = 16.4 Hz, 2H), 2.06 (d, *J* = 17.8 Hz, 2H), 2.11-2.23 (m, 4H), 2.50 (s, 3H), 5.27 (s, 1H), 6.65 (dd, *J* = 7.9, 1.8 Hz, 1H), 6.86 (d, *J* = 7.8 Hz, 1H), 7.14 (d, *J* = 6.5 Hz, 4H), 7.36 (d, *J*= 7.8

Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 26.5, 26.7, 26.9, 29.6 (2C), 29.5, 32.3 (4C), 41.6, 41.8, 49.9 (2C), 114.5 (2C), 118.8, 128.5 (2C), 136.2 (2C), 139.5, 147.4 (2C), 150.9, 150.8, 155.9 (2C), 196.5 (2C); IR(KBr) *vmax* (cm^{-1}): 3875, 1567, 1287, 678; MS (ESI) m/z : 456.230 [M+ H]. Elemental Anal. Calcd: C, 79.09; H, 7.30; N, 3.07; found: C, 79.01; H, 7.40; N, 3.02.

3.1.2. 10-(4-Fluorophenyl)-9-(3-hydroxyphenyl)-3,3,6,6tetramethyl-3,4,6,7,9,10-hexahydro acridine-1,8(2H,5H)-dione (6b)

White solid; M.P: 290-292°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 0.76 (s, 6H), 0.93 (s, 6H), 1.74 (d, *J* = 17.2 Hz, 2H), 1.98 (d, *J* = 5.0 Hz, 1H), 2.01 (s, 1H), 2.16 (m, 4H), 5.17 (s, 1H), 6.58 (d, *J* = 7.9 Hz, 1H), 6.85(d, *J* = 7.6 Hz, 1H), 7.0 (d, *J* = 8.6 Hz, 2H), 7.16 (s, 2H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.59 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, CDCl3) δ ppm: 26.0, 26.4, 29.5, 29.8, 32.3 (4C), 43.4 (2C), 50.2, 54.7, 109.9 (2C), 112.3, 114.4, 119.2, 120.4, 125.8 (2C), 128.8, 130.2, 134.4, 148.0, 153.4 (2C), 157.3, 196.1 (2C); IR(KBr) *vmax* (cm^{-1}): 3458, 2945, 1617, 1228; MS (ESI) m/z : 460.31 [M + H]. Elemental Anal. Calcd: C, 75.79; H, 6.58; N, 3.05; found: C, 75.68; H, 6.52; N, 2.98.

3.1.3. 10-(4-chlorophenyl)-3,3,6,6-tetramethyl-9-(3-nitrophenyl)-3,4,6,7,9,10-hexahydro acridine-1,8 (2H,5H)-dione (6c)

Light yellow solid; M.P: 267-269°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 0.70 (s, 6H), 0.76 (s, 6H), 1.62 (d, *J* = 17.3 Hz, 2H), 1.89 (d, *J* =14.8 Hz, 2H), 1.94-2.08 (m, 4H), 5.06 (s, 1H), 6.40-6.47 (m, 1H), 6.75 (d, *J* = 7.7 Hz, 2H), 6.89 (t, *J* = 7.7 Hz, 1H), 7.32 (d, *J* =7.9 Hz, 2H), 7.69 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 26.7, 26.8, 26.9, 29.5, 29.6, 32.5 (4C), 41.8, 50.0 (2C), 114.7 (2C), 118.9, 123.4 (2C), 130.0 (2C), 137.6, 143.0, 147.1 (2C), 149.6 (2C), 156.2 (2C), 196.4, 196.9; IR (KBr) *vmax* (cm^{-1}): 2738, 1558, 1251, 721; MS (ESI) m/z : 505.000 [M + H]. Elemental Anal. Calcd: C, 68.97; H, 5.79; N, 5.55; found: C, 70.01; H, 5.85 N, 5.51.

3.1.4. 4-(9-(3-hydroxyphenyl)-3,3,6,6-tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacri din-10(9H)-yl)benzonitrile (6d)

Light green solid; M.P: 288-289°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 0.74 (s, 6H), 0.87 (s, 6H), 1.71 (s, 2H), 2.05-2.46 (m, 6H), 4.99 (s, 1H), 6.49-6.54 (m, 1H), 6.70-6.79 (m, 2H), 6.93-7.03 (m, 1H), 7.33 (s, 2H), 7.76 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 26.0, 26.3, 28.4, 28.5, 31.9 (4C), 49.3 (2C), 52.8, 112.7, 113.9 (2C), 116.9, 118.2, 128.3 (2C), 130.4 (2C), 133.1, 142.1, 146.3 (2C), 148.3 (2C), 156.3 (2C), 194.9 (2C); IR(KBr) *vmax* (cm^{-1}): 3392, 2940, , 1561, 1239, 760; MS (ESI) m/z : 467.130 [M + H]. Elemental Anal. Calcd: C, 77.23; H, 6.48; N, 6.00; found: C, 77.15; H, 6.40; N, 5.93.

3.1.5. 9-(3-hydroxyphenyl)-3,3,6,6-tetramethyl-10-(4-(trifluoromethyl)phenyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione(6e)

Light green solid; M.P: 288-289°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 0.67 (s, 6H), 0.83 (s, 6H), 1.65 (s, 2H), 1.85-2.16 (m, 6H), 5.04 (s, 1H), 6.41 (m, 1H), 6.70-6.79 (m, 2H), 6.83-6.93 (m, 1H), 7.35 (s, 2H), 7.76 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 26.6, 26.8, 29.4, 29.5, 32.3 (4C), 41.6 (2C), 50.0, 113.3, 114.6 (2C), 122.0, 128.8 (2C), 130.3 (2C), 130.5, 142.1, 147.0 (2C), 148.8 (2C), 156.9 (2C), 195.5 (2); IR (KBr) *vmax* (cm^{-1}): 3389, 2944, 1563, 1241, 757; MS (ESI) m/z : 510.120 [M + H]. Elemental Anal. Calcd: C, 70.71; H, 5.93; N, 2.73; found: C, 70.66; H, 6.03; N, 2.83.

3.1.6. 10-(4-fluorophenyl)-3,3,6,6-tetramethyl-9-(3-nitrophenyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (6f)

White solid; M.P: 254-256°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 0.74 (s, 6H), 0.87 (s, 6H), 1.78 (s, 2H), 2.05-2.21 (m, 6H), 5.21 (s, 1H), 6.55-6.61 (m, 1H), 6.80-6.89 (m, 1H), 6.95-7.05 (m, 2H), 7.23 (s, 2H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 26.0, 26.1, 29.7, 29.9, 32.4 (4C), 43.4 (2C), 50.1, 54.8, 109.9, 112.3 (2C), 114.4, 119.3, 120.4 (2C), 125.9 (2C), 128.9, 130.4, 134.1, 147.9 (2C), 153.1 (2C), 157.4 (2C), 196.0 (2); IR (KBr) *vmax* (cm^{-1}): 2840, 1556, 1249, 741; MS (ESI) m/z : 489.170 [M + H]. Elemental Anal. Calcd: C, 71.29; H, 5.98; N, 5.73; found: C, 71.18; H, 6.04; N, 5.81.

CONCLUSION

In summary, PMA-SiO_2 catalyst has been found as a highly efficient green catalyst for the synthesis of pharmacological active 1, 8-dioxodecahydroacridine derivatives. We explored variety of MCRs like aldehydes and aniline derivatives in PEG-400 to produce 1, 8-dioxodeca hydroacridine derivatives with excellent yields. PMA-SiO_2 in PEG-400 catalyst offers several advantages like shorter reaction times, non-toxic, mild reaction conditions, cleaner reactions, high yield of the products, lower catalytic loading *etc.* Moreover, this catalyst could be recovered and recycled easily for several cycles without losing its activity. This study can provide a road map to design new green synthetic methodologies for single step cyclo-condensation reaction through MCRs with better yields.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's website along with the published article.

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