Study on one-pot four-component synthesis of 9-aryl-hexahydro-acridine-1,8-diones using SiO₂–I as a new heterogeneous catalyst and their anticancer activity

K. B. Ramesh, M. A. Pasha *

Department of Studies in Chemistry, Central College Campus, Palace Road, Bangalore University, Bengaluru 560001, India

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ABSTRACT

A simple, efficient and cost-effective method for the synthesis of 9-aryl-hexahydro-acridine-1,8-diones by a one-pot four-component cyclocondensation of dimedone, aromatic aldehydes and ammonium acetate as a nitrogen source in the presence of a new heterogeneous catalyst silica iodide (SiO_2–I) in EtOH at 80 °C is described. SiO_2–I was subjected to SEM–EDX and found to have iodo group bound to the catalyst. Some of the prepared acridine-diones were found to exhibit promising anti-cancer activity against HepG2 and MCF-7 cell lines.

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Multicomponent reactions (MCRs) have emerged as efficient and powerful strategies in the modern synthetic organic chemistry because synthesis of complex organic molecules from simple and readily available substrates can be achieved in a very fast and efficient manner without the isolation of any intermediates.[1] MCRs contribute to the requirements of an environment friendly process by reducing the number of synthetic steps, energy consumption and waste production.[2] Therefore, developing new MCRs and improvement of known MCRs are popular areas of research in the current synthetic organic chemistry. MCRs play a major role in several biological processes and proliferation of cancer cells.[3] Cancer is one of the lethal diseases which can lead to human death. In most of the cases multi-drug resistance generally leads to the failure of chemotherapy; and most of the drugs used for the treatment of cancer are cytotoxic drugs which lack the site specific activity to cancer cells and lead to damage of the healthy cells. Many research groups have shown anticancer activity of different acridine analogs (Fig. 1), including compounds **1** and **2** on cancer cells.[4]

Derivatives of acridine **3** and **4** (Fig. 2) showed good cytotoxic activity against human leukaemia cells.[5]

Derivative of acridine such as 5 (Fig. 3) was found to be the most potent drug towards the metastatic breast cancer cells.[6]

Acridines are an important class of organic compounds which find use as dyes, fluorescent materials for visualization of biomolecules, and in laser technology due to their useful spectroscopic properties.[7] Acridines have also received significant attention from many pharmaceutical and organic chemists, essentially because of the broad spectrum of their biological and pharmaceutical properties, such as: antiviral,[8] antibacterial,[9] anti-nociceptive activities,[10] as well as efficiency in photodynamic therapy[11] and because of the anti-inflammatory activity.[12] There are a few reports in the literature on the three-component Hantzsch-type condensation of aromatic aldehydes, anilines and dimedone via the traditional heating in organic solvents[13,14] under microwave irradiation[15] and in ionic liquids[16,17] leading to acridines. The main drawback of these methods is the inability to synthesize 9-aryl-hexahydro-acridine-1,8-diones, therefore, the development of simple, efficient, high-yielding and environment friendly methods and use of simple, readily available, recyclable, new heterogeneous catalysts for the preparation of acridines under mild conditions is in demand.

In recent years, the heterogeneous catalysis has developed considerable interest in the various disciplines of science including organic synthesis due to the prime advantage that, in most of the cases the heterogeneous catalysts can be recovered with only minor change in activity and selectivity so that they can be used in continuous flow reactions.[18] Heterogeneous catalysts have many advantages over their homogeneous counterparts. Generally

* Corresponding author. Tel.: +91 80 22961337; fax: +91 80 22961331.
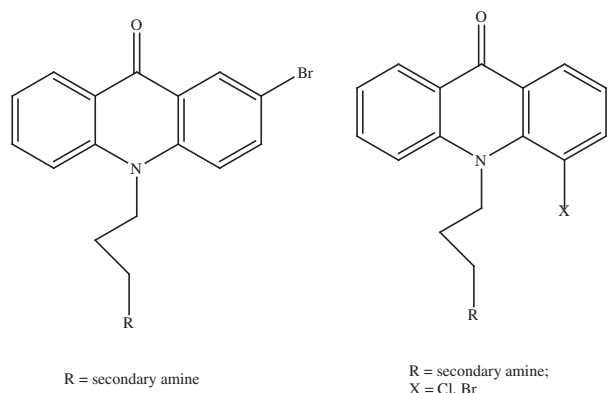*E-mail address:* m_af_pasha@ymail.com (M.A. Pasha).

R = secondary amine

R = secondary amine;
X = Cl, Br
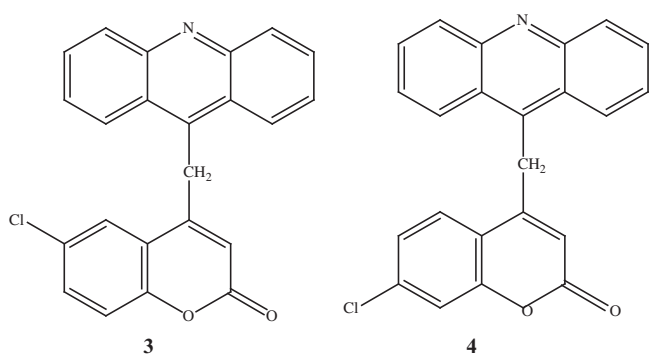
Figure 1.

3　　　　　　　　**4**
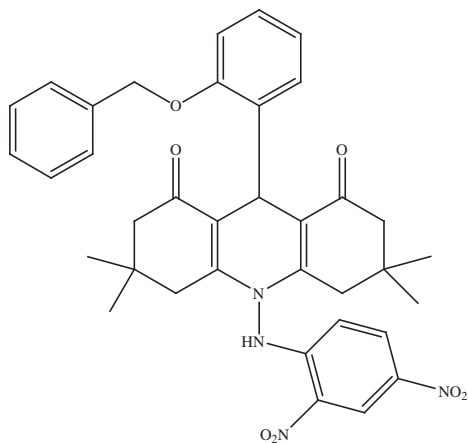
Figure 2.

Figure 3.

heterogeneous catalysts are insoluble in common organic solvents, cause low corrosion, and show environmental acceptability. Also, the products can be easily separated from the reaction mixture and the catalyst is recoverable, and we have prepared a new heterogeneous catalyst-SiO_2–I form silica through its chloride and used successfully in the synthesis of acridines by a one-pot four-component reaction. Due to our interest in the synthesis of heterocyclic compounds,[19–22] and in continuation of our previous work on the application of reusable catalysts in organic reactions,[23] we, herein, report a new and an efficient synthesis of some novel and known 9-aryl-hexahydro-acridine-1,8-diones from two moles of dimedone, one mole of benzaldehyde and one mole of ammonium acetate as shown in the Scheme 1.

We have found that, the prepared acridine analogues show promising effect on cancer cell proliferation.

Materials and methods: All chemicals were commercially available and used without further purification, except liquid aldehydes which were distilled before use. All yields refer to isolated products after purification. Products were characterized by the IR, ^{1}HNMR, ^{13}CNMR, Mass spectral and CHN analyses. Melting points were measured on a Raaga, Indian make melting point apparatus. NMR spectra were obtained on a 400 MHz and 100 MHz Bruker AMX instruments in $CDCl_3$ using TMS as a standard. ESI-MS analysis was carried out using ESI-Q TOF instrument. Silica, silica chloride and silica Iodide were characterised by SIRION high resolution Scanning Electron Microscope–Energy Dispersive X-ray spectroscopic (SEM–EDX) technique.

Preparation of silica iodide: Silica gel (20 g) was suspended in CH_2Cl_2 (50 mL), and $SOCl_2$ (20 mL) was added drop wise with continuous stirring at 26 °C. Evolution of HCl and SO_2 occurred instantaneously; after stirring for 1 h, the solvent was removed by distillation; and the residual solvent was removed under reduced pressure to get a dry solid of silica chloride (26.2 g). The solid SiO_2–Cl was washes with cold water and dried under vacuum. NaI (3 g) was first dissolved in a mixture of EtOH–H_2O (8:2, 10 mL), to this silica chloride (6 g) was added, mixed well and filtered after 15 min, washed with cold water and dried under vacuum to get SiO_2–I (7.5 g).

Detection of the iodide in silica iodide. Qualitative analysis. Test: 1. To detect the presence of iodide in the catalyst, 0.25 mg of silica iodide was transferred to a dry test tube; 0.25 mg of sodium metal was then introduced and heated till the test tube turned red-hot. After cooling the test tube, water (3 mL) was introduced and filtered to get the sodium fusion extract (SFE). SFE (1.5 mL) was then acidified with dil. HNO_3 and treated with $AgNO_3$ solution to get a pale yellow precipitate which was insoluble in aqueous ammonia to confirm the presence of iodide in the heterogeneous catalyst.[24]

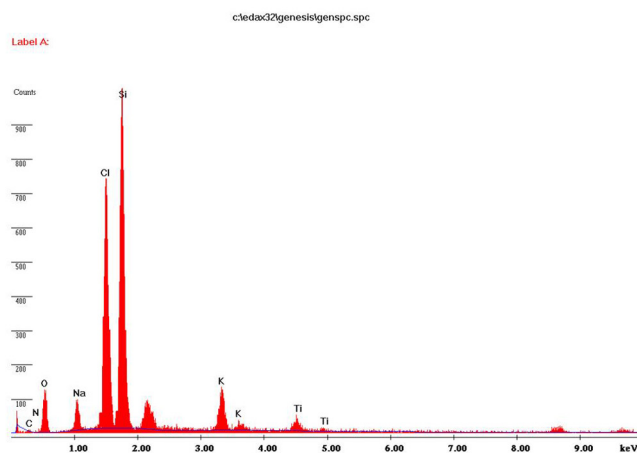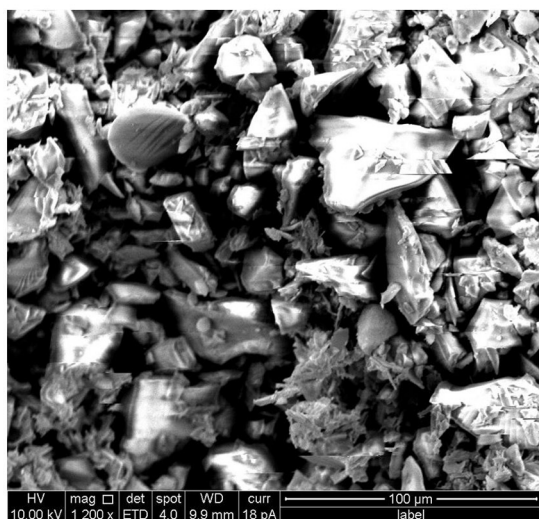*Test: 2.* SFE (1.5 mL) was acidified with dil. HCl, carbon tetrachloride (0.3 mL) was then added and treated with chlorine water (1 mL) to get a violet globule which confirmed the presence of iodide in the heterogeneous catalyst.
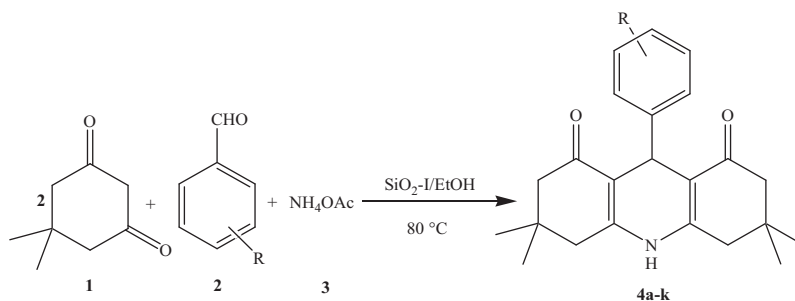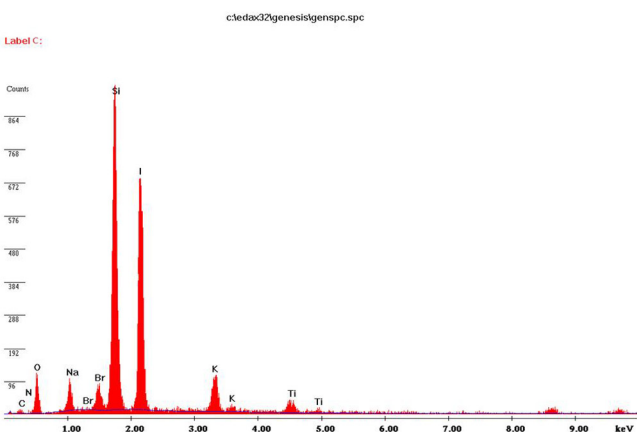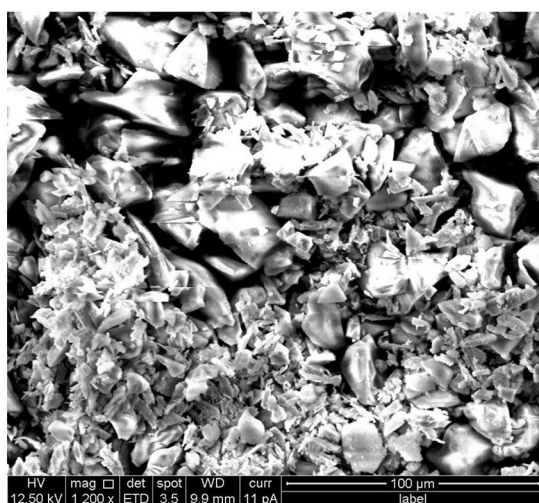

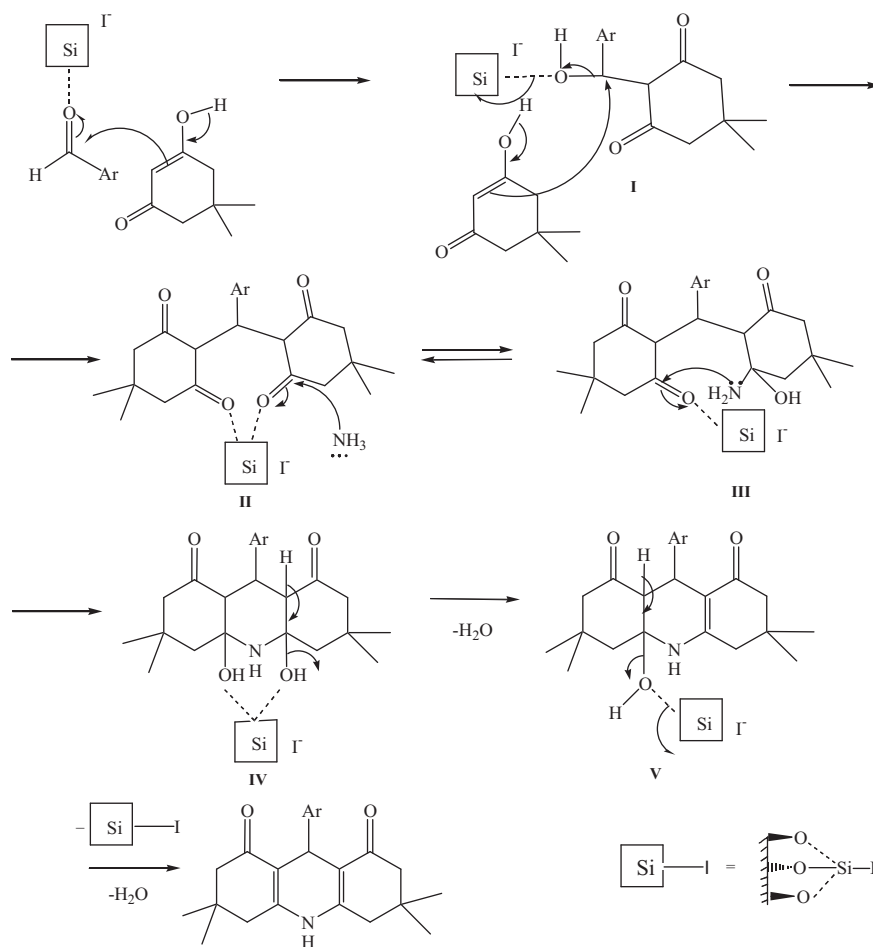**Scheme 1.** Synthesis of 9-aryl-hexahydro-acridine-1,8-diones.
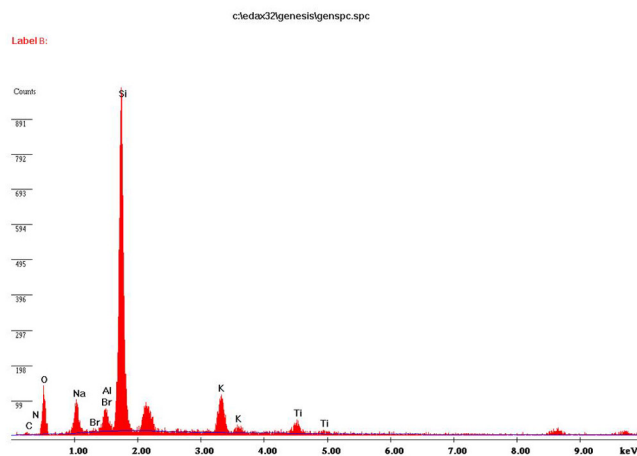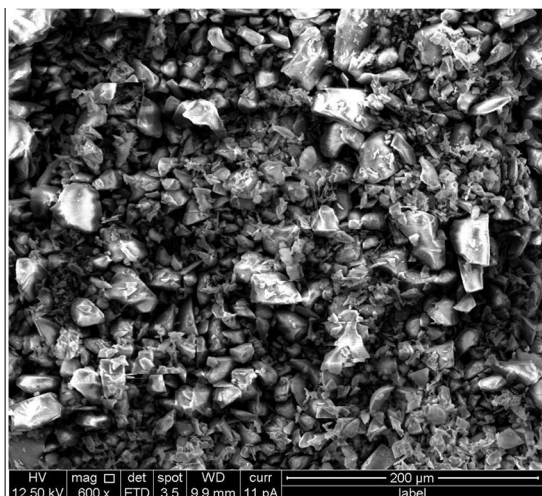
(a) Silica

(b) Silica Chloride

(c) Silica Iodide

Figure 4. SEM–EDX of (a) silica, (b) silica chloride and (c) silica iodide.

Scheme 2. A plausible mechanism for the formation of acridines.

Table 1
Effect of solvent on the synthesis of 9-phenyl-hexahydro-acridine-1,8-diones (**4a**)

Entry	Solvent	Temperature (°C)	Time (h)	Yield[a] (%)
1	CH$_3$CN	83	5	45
2	H$_2$O	98	5	55
3	MeOH	65	4	50
4	EtOH	80	3	60
5	CH$_2$Cl$_2$	40	6	Trace[b]
6	THF	68	5	55
7	Solvent-free	70	6	40

[a] Isolated yield.
[b] TLC.

Table 2
Influence of various catalysts on the synthesis of phenyl-hexahydro-acridine-1,8-diones (**4a**)

Entry	Catalyst[a]	Time (h)	Yield[c] (%)
1	AmberliteIR120H	13	20
2	ZnCl$_2$[b]	11	30
3	CeCl$_3$[b]	12	35
4	K$_2$CO$_3$[b]	10	45
5	NaI[b]	12	–
6	SiO$_2$[a]	10	35
7	SiO$_2$–Cl[a]	5	70
8	SiO$_2$–I[a]	2.5	90

[a] 0.1 g.
[b] 10 mol %.
[c] Isolated yield.

Table 3
Optimization of the amount of SiO$_2$–I

Entry	SiO$_2$–I (g)	Amount of NH$_4$OAc (mmol)	Time (h)	Yield[a] (%)
1	0	2	8	40
2	0.01	2	15	50
3	0.05	2	10	55
4	0.06	2	2	60
5	0.08	2	2.5	70
6	0.10	2	2.5	90
7	0.15	2	2.5	90
8	0.20	2	2.5	90
9	0.25	2	2.5	90

[a] Isolated yield.

From the above mentioned tests it was ascertained that iodide in present in silica iodide.

Quantitative analysis. Test: 1. SiO$_2$–I (1 g) was then taken in a 250 mL conical flask and titrated against 0.04 N Na$_2$S$_2$O$_3$ and found to have 0.33 milli-equivalent of iodide in it by the method developed by McDanlel.[25,26]

Test: 2 (SEM–EDX analysis). The SEM micrographs of silica and silica based catalysts viz., chloride and iodide are shown in Figure 4. SEM micrographs showed both chloride and iodide to have similar texture and that the iodide and chloride in these materials is uniformly dispersed on silica surface and both can be used as heterogeneous catalysts Figure 4(b and c). Also, we have determined the composition of the silica, silica chloride and silica iodide by EDX studies. The EDX plots are shown in Figure 4 (a, b and c) along with the SEM micrographs.

Table 4
SiO$_2$–I catalyzed synthesis of acridines **4a–k** in ethanol at 80 °C

Entry	Aldehydes	Product[a]	Time (h)	Yield[b] (%)	Mp (°C)	
					Found	Reported
1	C$_6$H$_5$CHO	**4a**	2.5	90	249–251	258–260[28]
2	3-CNC$_6$H$_4$CHO	**4b**	2.8	87	215–218†	—
3	4-MeOC$_6$H$_4$CHO	**4c**	2.5	89	271–272	270–272[29]
4	4-ClC$_6$H$_4$CHO	**4d**	1.5	82	298–301	299–301[30]
5	4-NO$_2$C$_6$H$_4$CHO	**4e**	2	86	284–287	286–288[30]
6	3-Br,4-MeOC$_6$H$_3$CHO	**4f**	2	89	238–241†	—
7	3-C$_2$H$_5$OC$_6$H$_4$CHO	**4g**	2.6	79	210–213†	—
8	5-F,2-HOC$_6$H$_3$CHO	**4h**	2	85	210–215†	—
9	2-HOC$_6$H$_4$CHO	**4i**	2.5	74	223–225†	—
10	2,4-(CH$_3$O)$_2$C$_6$H$_3$CHO	**4j**	2.3	83	291–296†	—
11	4-(CH$_3$)$_2$NC$_6$H$_4$CHO	**4k**	2	80	281–283	280–282[31]

[a] Isolated yield. All the synthesized products were characterized from their spectroscopic analytical data (IR, NMR, CHN, ESI-MS), except **4a** which was compared on TLC with the authentic sample.

[b] Isolated yield.

† Novel compounds.

Mechanism: A probable mechanism for the formation of acridines involves the activation of aldehyde followed the attack of enol form of the dimedone to give the intermediate **I**. The intermediate **I** may react with another molecule of dimedone to give **II**. Attach of ammonia formed from ammonium acetate gives **III**, and **III** may cyclise to give the acridine derivative **IV** which after the elimination of a molecule of water may give **V**. In the last step **V** may lose both the catalyst and another molecule of water to give acridines as shown in the Scheme 2.

We studied the effect of several solvents like acetonitrile, water, methanol, dichloromethane, and tetrahydrofuran on the reaction of two moles of dimedone, one mole of benzaldehyde and one mole of ammonium acetate. The reaction in tetrahydrofuran, water, acetonitrile afforded the product but yields were poor. The best results in terms of yield and reaction time were obtained with ethanol as a solvent (Table 1, entry 4). We, then decided to investigate the efficacy of SiO$_2$–I for the synthesis of **4a** under solvent-free condition also, but, ended up getting the product in only 40% yield (entry 7). We studied the effect of different catalysts such as AmberliteIR120H, ZnCl$_2$, CeCl$_3$, K$_2$CO$_3$, NaI, SiO$_2$, SiO$_2$-Cl and SiO$_2$-I also on the preparation of **4a**, and found that, SiO$_2$-I is best in terms of yield and duration of the reaction (Table 2, entry 8).

Further studies were carried out to optimize the amount of catalyst by using different amounts of SiO2–I (0.06, 0.08, 0.10, 0.15, 0.20 and 0.25 g) and the results of this study are presented in the Table 3. From this Table, it is clear that, 0.1 g of SiO$_2$–I afforded the product in 90% isolated yield (Table 3, entry 6). Increasing the amount of catalyst did not improve the yield (entries 7–9).

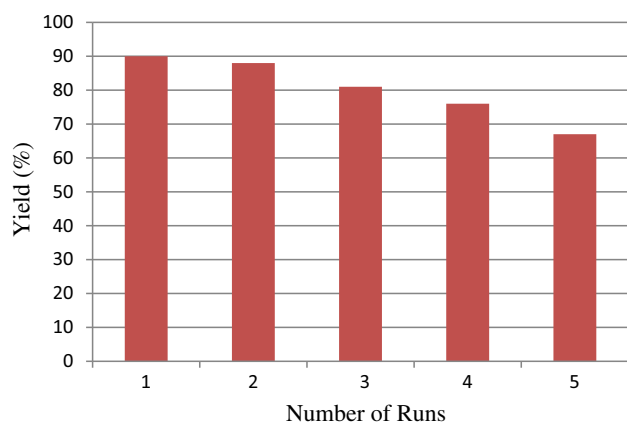We then started our work by examining the possibility of an one-pot four-component reaction involving two molecules of dimedone (**1**, Scheme 1), one molecule of benzaldehyde (**2**) and a molecule of ammonium acetate (**3**) to get 9-phenyl-hexahydro-acridine-1,8-dione (**4a**) in ethanol as a solvent in the presence of SiO$_2$–I.

A mixture of **1**, **2**, and **3** (Scheme 1) in 1.5 mL ethanol was stirred in the presence of SiO$_2$–I for 2–3 h at 80 °C to get **4a** in 90% yield.[27] Encouraged by this result, the reaction of various substituted arylaldehydes was taken up and the results of this study are presented in the Table 4. The data presented in Table 4 indicates that SiO$_2$–I serves as an excellent catalyst for the synthesis different substituted acridines in excellent yield in short reaction duration.

Study on reusability of SiO$_2$–I catalyst: With an effort to make the present reaction much greener, the recovery and reusability of the catalyst was studied. After the completion of the reaction, the solid thus separated was filtered along with the catalyst. The residue containing the catalyst was washed with ether to get the solid SiO$_2$–I which was then dried at 100 °C for 2 h and reused. The results of the study of the reusability of the catalyst are presented in the form of a graph in Figure 5. From Figure 5, it is clear that SiO$_2$–I can be used successively for at least four runs after the first fresh run, after which the yield of the product dropped from 90% in the first fresh run to 67% in the fifth run. The yield of **4a** was found to be 90%, 88%, 81%, 76% and 67%, respectively, for 1–5 cycles, the marginal decrease of yield in the first five cycles may be due to loss of the catalyst during the recovery.

Cell culture: HepG2 (Hepatocellular carcinoma cells) and MCF-7 (Human breast adenocarcinoma cells) cell lines were procured from National Centre for Cell Sciences (NCCS), Pune, India. The cells were cultured in minimum essential medium (MEM) growth medium supplemented with 10% heat inactivated Fetal bovine serum (FBS), penicillin (100 IU/mL), streptomycin (100 µg/mL) and amphotericin-B (5 µg/mL) in a humidified atmosphere of 5% CO$_2$ at 37 °C until confluent. The cells were trypsinized with TPVG solution (0.2% trypsin, 0.02% EDTA, 0.05% glucose in PBS). The cultures were grown in 25 cm^2 flat bottles and the studies were carried out in 96 wells plates.

MTT assay[32]: Cells were plated in 96 wells plate (1 × 10^4 cells/well) and cultured for 24 h at 37 °C in 5% CO$_2$ atmosphere to allow cell adhesion. After 24 h, when partial monolayer was formed, cells were treated with different concentration of standard drug (Doxorubicin) and sample compounds for 48 h. Microscopic examination was carried out and observations recorded every 24 h. After the treatment, the solutions in the wells were discarded and 50 µL of

Figure 5. Reusability of silica iodide in the synthesis of **4a**.

Table 5
In vitro anticancer activity of acridine derivatives on HepG2 and MCF-7 human cancer cell lines

Drug/ formulation	IC$_{50}$value (µg/mL) on HepG2 cells (Hepatocellular carcinoma cells)	IC$_{50}$ value (µg/mL) on MCF-7 cells (Human breast adenocarcinoma cells)
Doxorubicin	1.21 ± 0.05	1.09 ± 0.03
4b[†]	1.4 ± 0.11	4.7 ± 0.09
4c	8.2 ± 0.32	9.6 ± 0.22
4f[†]	2.2 ± 0.09	5.3 ± 0.16
4g	4.8 ± 0.12	4.5 ± 0.10
4h	8.6 ± 0.31	6.2 ± 0.14
4i[†]	2.6 ± 0.11	5.9 ± 0.15
4j[†]	1.6 ± 0.14	5.0 ± 0.18

[†] Active.

freshly prepared MTT (2 mg/mL, prepared in PBS) was added to each well. The plates were shaken gently and incubated for 3 h at 37 °C in 5% CO$_2$ atmosphere. The supernatant was removed and the formazan crystals formed in the cells were solubilised by addition of 50 µL of *iso*-propanol. Finally, the absorbance was recorded using a Micro-plate reader (Bio-Tek, EL$_X$-800 MS) at a wavelength of 540 nm.

$$\% \text{growth inhibition} = \frac{\text{control absorbance} - \text{test absorbance}}{\text{control absorbance}} \times 100$$

The percentage growth was calculated using the standard formula and IC$_{50}$ values are shown in the Table 5.

The data presented in the Table 5 shows the IC$_{50}$ values obtain by the treatment of the prepared acridines with the standard drug (Doxorubicin) on HepG-2 and MCF-7 cells. It is clear from this Table that, compounds **4b**, **4f**, **4i** and **4j** exhibit very good activity towards HepG2 cell lines and **4b**, **4f**, **4g** and **4j** showed comparatively better activity towards MCF-7 cell lines.

In conclusion a reliable, practical procedure and an alternative method for the synthesis of 9-aryl-hexahydro-acridine-1,8-diones has been developed. The method involves the use of silica iodide, a new heterogeneous catalyst which has made this method cost effective, as the catalyst can be recycled for at least five runs without loss of activity and the reaction involves simple workup procedure. The compounds **4b**, **4f**, **4i** and **4j** exhibited very good activity towards HepG2 cell lines and **4b**, **4f**, **4g** and **4j** showed comparatively better activity towards MCF-7 cell lines which can be a plentiful source of potential anti-cancer drugs deserving further study. In our opinion this method is superior to all other previously reported methods[33,34] of synthesis of 9-aryl-hexahydro-acridine-1,8-diones.

Acknowledgments

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2014.06.047.

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26. Mendham, R. C.; Denny, J. D.; Barnes, M. J. K.; Thomas. *Vogel's Quantitative Chemical Analysis*; Prentice Hall: New York, 2000. 6th ed.
27. *General procedure for the synthesis of 9-aryl-hexahydro-acridine-1,8-diones using catalytic SiO$_2$–I:*
    A mixture of dimedone (2 mmol), aromatic aldehyde (1 mmol) and ammonium acetate (1 mmol) was taken in ethanol (1.5 mL), mixed well and then SiO$_2$–I (0.1 g) was added. The reaction mixture was stirred at 80 °C for 2–3 h. The course of the reaction was monitored on TLC (3:7::EtOAc/hexane). After completion of the reaction, water (10 mL) was added and the separated solid was filtered along with the catalyst. The residue was washed with ether and the solid catalyst was recovered and kept aside for reuse. The crude product thus obtained from the ether extract after the evaporation of ether was subjected to silica gel column chromatography (3:7::EtOAc/light petrol) to get the pure products.
    Spectral and analytical data:
    9-(3′-Cyanophenyl)-3,3,6,6-tetramethyl-2,4,5,7,9,10-hexahydro-acridine-1,8-dione(**4b**):
    Colorless solid, mp: 215–218 °C; IR (KBr, v cm^{-1}): 2240 (C–N), 3340 (N–H), 1710 (C=O); ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.10 (s, 6H, 2Me), 1.23 (s, 6H, 2Me), 2.40 (m, 8H, 4CH$_2$), 5.49 (s, 1H, CH), 7.26–7.48 (m, 4H, Ar-H), 11.80 (s, 1H, N–H); ^{13}C NMR (400 MHz, CDCl$_3$): δ 27.9, 29.8, 31.9, 33.1, 46.8, 47.4, 77.1, 77.4, 77.8, 112.8, 115.1, 119.5, 129.4, 130.1, 131.0, 131.8, 140.4, 189.9, 191.4; ESI-MS: [M+H] 375.7;
    Anal. Calcd C$_{24}$H$_{26}$N$_2$O$_2$: C, 76.98; H, 7.00; N, 7.48; Found C, 75.34; H, 7.09; N, 8.29.
    9-(4′-Methoxyphenyl)-3,3,6,6-tetramethyl-2,4,5,7,9,10-hexahydro-acridine-1,8-dione (**4c**):
    Colorless solid, mp: 271–272 °C; IR (KBr, v cm^{-1}): 3320 (N–H), 1720 (C=O); ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.09 (s, 6H, 2Me), 1.22 (s, 6H, 2Me), 2.37 (m, 8H, 4CH$_2$), 3.73 (s, 3H, OCH$_3$), 5.48 (s, 1H, CH), 6.79 (dd, 2H, J = 4.0 Hz, Ar-H), 6.98 (dd, 2H, J = 8.8, 0.8 Hz, Ar- H), 11.91 (s, 1H, N–H); ^{13}C NMR (400 MHz, CDCl$_3$): δ 27.81, 29.72, 30.11, 31.82, 32.46, 32.64, 41.29, 46.87, 47.51, 51.91, 55.54, 55.64, 113.90, 114.08, 116.23,128.23, 129.75, 130.26, 136.91, 158.02, 162.50, 189.80, 190.84, 196.94; ESI-MS: [M+Na] 400.2; Anal. Calcd C$_{24}$H$_{29}$NO$_3$: C, 75.96; H, 7.70; N, 3.69; Found C, 74.43; H, 7.10; N, 3.29.
    9-(4′-Chlorophenyl)-3,3,6,6-tetramethyl-2,4,5,7,9,10-hexahydro-acridine-1,8-dione (**4d**):
    Colorless solid, mp: 299–301 °C; IR (KBr, v cm^{-1}): 3346 (N–H), 1734 (C=O); ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.09 (s, 6H, 2Me), 1.21 (s, 6H, 2Me), 2.18–2.48 (m, 8H, 4CH2), 5.47(s, 1H, CH), 6.99–7.26 (m, 5H, Ar-H), 11.87 (s, 1H, NH); ESI-MS: [M+H] 384.3; Anal. Calcd C$_{23}$H$_{26}$ClNO$_2$: C, 71.96; H, 6.83; N, 3.65; Found C, 71.03; H, 7.02; N, 3.09.
    9-(4′-Nitrophenyl)-3,3,6,6-tetramethyl-2,4,5,7,9,10-hexahydro-acridine-1,8-dione (**4e**):
    Colorless solid, mp: 284–287 °C; IR (KBr, v cm^{-1}): 1550 (NO$_2$), 3343 (N–H), 1716 (C=O); ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.12 (s, 6H, 2Me), 1.27 (s, 6H, 2Me), 2.31 (m, 8H, 4CH$_2$), 5.54(s,1H,CH), 7.39 (dd, 2H, J = 12.4, 8.0 Hz, Ar-H), 8.00 (dd, 2H, J = 11.2, 11.2 Hz, Ar-H), 11.86 (s, 1H, N–H);

ESI-MS: [M+H] 395.1;

Anal. Calcd $C_{23}H_{26}N_2O_4$: C, 70.03; H, 6.64; N, 7.10; Found C, 69.31; H, 6.09; N, 6.29.

9-(3′-Bromo-4′-methoxyphenyl)-3,3,6,6-tetramethyl-2,4,5,7,9,10-hexahydro-acridine-1,8-dione (**4f**):

Colorless solid, mp: 238–241 °C; IR (KBr, v cm^{-1}): 3369 (N–H), 1728 (C=O); ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.93 (s, 6H, 2Me), 1.10 (s, 6H, 2Me), 2.09–2.52 (m, 8H, 4CH$_2$), 3.79 (s, 3H, OMe), 4.78 (1H,CH), 6.71 (d, 1H, J = 8.8 Hz), 7.03 (s, 1H, Ar-H), 7.27 (d, 1H, J = 2.4 Hz), 10.28 (s, 1H, NH);

ESI-MS: [M+H] 458.3;

Anal. Calcd $C_{24}H_{28}BrNO_3$: C, 62.88; H, 6.16; N, 3.06; Found C, 62.46; H, 6.19; N, 3.0.

9-(3′-Ethoxyphenyl)-3,3,6,6-tetramethyl-2,4,5,7,9,10-hexahydro-acridine-1,8-dione (**4g**):

Colorless solid, mp: 210–213 °C; IR (KBr, v cm^{-1}): 3310 (N–H), 1724 (C=O); ^{1}H NMR (400 MHz, CDCl$_3$), δ 1.05 (s, 6H, 2Me),1.16 (s, 6H, 2Me),1.32 (t, 3H, J = 6.8 Hz) 1.95–2.50 (m, 8H, 4CH$_2$), 3.31(s, 1H, NH), 4.01–4.03 (q, 2H, J = 8.8 Hz), 4.84 (s, 1H, CH), 6.81(s, 1H, Ar-H), 6.83 (d, 1H, J = 8.4 Hz), 6.96(d, 1H, J = 7.2 Hz), 7.15 (t, 1H, J = 6.8 Hz);

ESI-MS: [M+H] 394.2;

Anal. Calcd $C_{25}H_{31}NO_3$: C, 76.30; H, 7.94; N, 3.56; Found C, 75.28; H, 7.09; N, 3.29.

9-(5′-Fluoro-2′-hydroxyphenyl)-3,3,6,6-tetramethyl-2,4,5,7,9,10-hexahydro-acridine-1,8-dione (**4h**):

Colorless solid, mp: 210–215 °C; IR (KBr, v cm^{-1}): 3400 (O–H), 3390 (N–H), 1725 (C=O); ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.99 (s, 6H, 2Me),1.12 (s, 6H, 2Me), 1.97–2.49 (m, 8H, 4CH$_2$), 2.55(s, 1H, OH), 4.62 (s, 1H, CH), 6.68 (d, 1H, J = 3.2 Hz, Ar-H), 6.81(d, 1H, J = 3.2 Hz, Ar-H), 6.96 (s, 1H, Ar-H) 10.48 (s, 1H, N–H); ^{13}C NMR (400 MHz, CDCl$_3$): δ 27.6, 28.18, 29.59, 31.40, 32.75, 41.98, 50.35, 111.43, 116.20, 118.75, 124.67, 125.04, 128.00, 128.42, 151.44, 169.64; ESI-MS: [M+H] 384.3;

Anal. Calcd $C_{23}H_{26}FNO_3$: C, 72.04; H, 6.83; N, 3.65; Found C, 71.62; H, 6.05; N, 3.21.

9-(2′-Hydroxyphenyl)-3,3,6,6-tetramethyl-2,4,5,7,9,10-hexahydro-acridine-1,8-dione (**4i**)

Colorless solid, mp: 223–225 °C; IR (KBr, v cm^{-1}): 3412 (O–H), 3356 (N–H),

1789 (C=O); ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.99 (s, 6H, 2Me), 1.02 (s, 6H, 2Me), 2.33–2.58 (m, 8H, 4CH$_2$) 2.62 (s, 1H, OH), 4.68 (s, 1H, CH), 6.99–7.18 (m, 4H, Ar-H), 11.0 (s, 1H, N–H);

ESI-MS: [M+H] 366.1;

Anal. Calcd $C_{23}H_{27}NO_3$: C, 75.59; H, 7.45; N, 3.83; Found C, 75.43; H, 7.07; N, 3.20.

9-(2′,4′-Dimethoxyphenyl)-3,3,6,6-tetramethyl-2,4,5,7,9,10-hexahydro-acridine-1,8-dione (**4j**):

Colorless solid, mp: 291–296 °C; IR (KBr, v cm^{-1}): 3330 (N–H), 1728 (C=O); ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.92 (s, 6H, 2Me), 1.09 (s, 6H, 2Me), 1.95–2.50 (m, 8H, 4CH$_2$), 3.74 (s, 3H,OMe), 3.79 (s, 3H,OMe), 3.95 (s, 1H, NH), 4.73 (s, 1H, CH), 6.34 (d, 1H, J = 2.8 Hz, Ar-H), 6.45 (s, 1H, Ar-H), 6.85 (d, 1H, J = 8.4 Hz);

ESI-MS: [M+H] 410.2;

Anal. Calcd $C_{25}H_{31}NO_4$: C, 73.32; H, 7.63; N, 3.42; Found C, 72.04; H, 7.00; N, 3.19.

9-(4′-N,N-Dimethylaminophenyl)-3,3,6,6-tetramethyl-2,4,5,7,9,10-hexahydro-acridine-1,8-dione (**4k**):

Colorless solid, mp: 281–283 °C; IR (KBr, v cm^{-1}): 3387 (N–H), 1756 (C=O); ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.08 (s, 6H, 2Me), 1.22 (s, 6H, 2Me), 2.31–2.44 (m, 8H, 4CH$_2$), 3.80 [s, 6H, N(CH$_3$)$_2$], 5.54 (s, 1H, CH), 6.54–7.44 (m, 4H, Ar-H), 11.9 (s, 1H, N–H);

ESI-MS: [M+H] 393.2;

Anal. Calcd $C_{25}H_{32}N_2O_2$: C, 76.49; H, 8.22; N, 7.14; Found C, 75.72; H, 7.04; N, 6.29.

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