

SCOLECITE AS NOVEL HETEROGENEOUS CATALYST FOR AN EFFICIENT MICROWAVE ASSISTED SYNTHESIS OF 7-ARYL-6H-BENZO[H][1,3]DIOXOLO[4,5-B]XANTHENE-5,6(7H)-DIONE ANALOGUES VIA MULTI-COMPONENT REACTION


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ABSTRACT: Scolecite is a tectosilicate mineral belonging to the zeolite group, a series of 7-aryl-6H-benzo[h][1,3]dioxolo[4,5-b]xanthene-5,6(7H)-dione have been prepared by aromatic aldehyde, 2-hydroxy-1,4-naphthoquinone and 3,4-methylenedioxyphenol with small quantities of Scolecite as novel heterogeneous catalyst under microwave irradiations using ethanol as a medium which gives consistent yield with shorter reaction time and minimum environmental effects are important features of the reaction.

Key words: Scolecite; Zeolite; Heterogeneous catalyst; Microwave irradiations.

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INTRODUCTION

Microwave irradiated multi component reactions (Hügel H. M. 2009) carried out using heterogeneous catalyst (Lambat T. L. 2016) have gained massive interest in synthetic chemistry over the past few decades so as to avoid extensive decomposition of reactants, unfavorable reaction conditions and hazardous solvents and get environmentally benign conditions of synthesis (Lambat T. L et al, 2014).

Multicomponent reactions (Kappe C.O. 2004, Wannberg J et al, 2005) (MCRs) are attractive progressively due to their improved efficiency, reduced waste, atom economy, simplicity and rapid access for the synthesis of biologically active scaffolds (Sujatha K et al, 2006). Multicomponent reactions are privileged over conventional multistep sequences owing to redeemable in the costs of reagents, solvents and other resources required for purification and isolation (Deshmukh T. B et al, 2015). The greater occurrence of infectious diseases (Lambat T. L et al, 2017) and multi-drug-resistant strains (Jensen A. A et al, 2009) has become a major concern in medicinal area (Liu H et al, 2014, Braak H, Braak E. 1991). Therefore, the development of new potential drugs (Stratmann K et al, 2016, Mino T et al, 2017, Yiannopoulou K. G, Papageorgiou S. G. 2013) to counteract the advancing resistance is one of the key issues and challenges for medicinal chemistry (Lu N et al, 2011) and related disciplines nowadays. The current scenario highlights the need for discovery and development of new drugs (Poljak-Blazi M et al, 2011).

The synthesis of multi-functionalized 7-aryl-6H-benzo[h][1,3]dioxolo[4,5-b]xanthene-5,6(7H)-dione is an important milestone in the history of MCRs. The process consists of three component condensation of an aldehyde, 2-hydroxy-1,4-naphthoquinone and 3,4-methylenedioxyphenol compound in presence of catalytic amount of p-TSA (Qian K et al, 2016) in ethanol at reflux temperature to afford 7-aryl-6H-benzo[h][1,3]dioxolo[4,5-b]xanthene-5,6(7H)-dione which exhibit a wide variety of biological activities (Tu S et al, 2007), the search for new approaches toward the concluding entities with a greater degree of efficiency is of significant importance.

The Naphthoquinone nucleus exhibits a broad spectrum of biological effects such as antibacterial, anti-inflammatory, antiviral, antiproliferative, antifungal, antibiotic and antipyretic (Cui S.L et al, 2005).

According to the literature, a number of strategies for the synthesis of xanthenediones are known. A first approach toward the synthesis by p-TSA were published more than a year ago, In addition to p-TSA, the reaction under acidic conditions gave rise to variable amounts of naphthoquinone as side products.

The literature survey has revealed that there is relatively little number of reports on MCRs reaction using heterogeneous acid catalysis (Lambat T. L, Deo S.S, 2016). Most of the methods are based upon the impregnation of toxic acid such as HCl, H₂SO₄ and KHSO₄ on silica gel (Shinde S. V, 2008). A p-TSA was previously demonstrated for an efficient synthesis, but the reaction time (1–3 h) is relatively longer. Herein, we wish to report an efficient and rapid MCRs reaction using scolecite as a novel heterogeneous acid catalyst (Scheme 1). The Scolecite catalyst is solid, non-corrosive, inexpensive and recyclable. The short reaction time, clean reaction conditions, consistent yields and minimum environmental effects are important features of the reaction.

MATERIALS AND METHOD

Commercially available chemicals with at least 98% purity were used this study. All solvents were reagent grade and freshly distilled. Manually coated glass plates with silica gel were used for thin layer chromatography. STAR-CEM Corporation made microwave was used for the synthesis. IR spectra were recorded on a Shimadzu FTIR-1710 spectrophotometer. The ¹H and ¹³C NMR spectra were recorded on 500 MHz for ¹H and 125 MHz for ¹³C instrument and the chemical shifts were reported with TMS as an internal standard. Mass spectra were recorded in VARIAN 1200. Melting points were measured on a Buchi 510 apparatus in open capillary tubes and were approximate. The representative spectral analysis for few of the products is given below:

General Procedure for synthesis of 7-aryl-6H-benzo[h][1,3]dioxolo[4,5-b]xanthene-5,6(7H)-dione derivatives

The reaction was carried out by microwave method, in which a neat mixture of aromatic aldehydes (1.0 mmol), 2-hydroxy-1,4-naphthoquinone (1.0 mmol) and 3,4-methylenedioxyphenol (1.0 mmol) and catalytic amount of Scolecite (2% weight with respect to all the reactants) in ethanol (4 ml) were added into a reaction tube and irradiated in a microwave reactor under continuous stirring in an open system under inert atmospheric pressure for the time mentioned in Table 1. The reaction was monitored by TLC (petroleum ether/ethyl acetate vol/vol = 1/1). After completion of reaction, the catalyst was filtered under hot conditions and washed with acetone several times. The filtrate was distilled off under vacuum and the residue was recrystallized from methanol to afford product in excellent purity.

Analytical data for selected products

7-(3,4-dimethoxyphenyl)-6H-benzo[h][1,3]dioxolo[4,5-b]xanthene-5,6(7H)-dione (2A):

¹H NMR (500 MHz, DMSO-d₆) δ: 8.20 (d, *J* = 7.6 Hz, 1H), 8.10 (d, *J* = 7.8 Hz, 1H), 8.00 (t, *J* = 7.6 Hz, 1H), 7.80 (t, *J* = 7.7 Hz, 1H), 7.25 (s, 1H), 7.10 (s, 1H), 6.85 (s, 1H), 6.65 (d, *J* = 8.1 Hz, 1H), 6.80 (d, *J* = 8.4 Hz, 1H), 6.15 (s, 1H), 6.10 (s, 1H), 5.15 (s, 1H), 3.64 (s, 3H), 3.72 (s, 3H); ¹³C NMR (125 MHz, DMSO-d₆) δ: 177.93, 175.64, 160.07, 155.04, 146.56, 147.53, 146.77, 142.95, 140.67, 137.86, 135.03, 131.34, 130.29, 128.41, 124.35, 119.40, 115.04, 113.45, 111.06, 110.80, 106.80, 99.80, 98.56, 53.55, 53.52, 36.14; HRMS (ESI) Calcd. for C₂₆H₁₉O₇ ([M+H]⁺): 443.115. Found: 443.112.

7-(4-methoxyphenyl)-6H-benzo[h][1,3]dioxolo[4,5-b]xanthene-5,6(7H)-dione (2B):

¹H NMR (500 MHz, DMSO-d₆) δ: 8.11 (d, *J* = 7.6 Hz, 1H), 7.99 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.88 (td, *J* = 7.6, 1.2 Hz, 1H), 7.69 (td, *J* = 7.5, 1.0 Hz, 1H), 7.29 – 7.22 (m, 2H), 7.16 (s, 1H), 6.87 – 6.76 (m, 3H), 6.06 (d, *J* = 0.9 Hz, 1H), 6.00 (d, *J* = 0.8 Hz, 1H), 5.04 (s, 1H), 3.69 (s, 3H); ¹³C NMR (125 MHz, DMSO-d₆) δ: 176.83, 176.60, 156.90, 155.95, 145.76, 143.98, 141.72, 136.33, 134.02, 130.33, 129.29, 129.21, 127.65, 127.40, 123.33, 116.03, 113.45, 112.83, 106.80, 100.79, 97.54, 54.00, 35.75; HRMS (ESI) Calcd. for C₂₅H₁₇O₆ ([M+H]⁺): 413.100. Found: 413.100.

7-(3-methoxyphenyl)-6H-benzo[h][1,3]dioxolo[4,5-b]xanthene-5,6(7H)-dione (2D):

¹H NMR (500 MHz, DMSO-d₆) δ: 8.15 (d, *J* = 7.3 Hz, 1H), 8.00 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.90 (td, *J* = 7.6, 1.3 Hz, 1H), 7.70 (td, *J* = 7.5, 1.1 Hz, 1H), 7.17 (dd, *J* = 13.0, 4.9 Hz, 2H), 6.90 – 6.88 (m, 1H), 6.86 (s, 1H), 6.82 (d, *J* = 7.7 Hz, 1H), 6.73 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.07 (d, *J* = 0.8 Hz, 1H), 6.00 (d, *J* = 0.9 Hz, 1H), 5.04 (s, 1H), 3.70 (s, 3H); ¹³C NMR (125 MHz, DMSO-d₆) δ: 176.80, 176.56, 158.27, 156.20, 145.88, 145.59, 143.97, 141.71, 133.99, 130.37, 129.29, 129.20, 128.57, 178.39, 123.34, 118.69, 115.59, 113.03, 112.88, 110.48, 106.78, 100.82, 97.58, 53.95, 36.55; HRMS (ESI) Calcd. for C₂₅H₁₇O₆ ([M+H]⁺): 413.100. Found: 413.107.

7-(4-chlorophenyl)-6H-benzo[h][1,3]dioxolo[4,5-b]xanthene-5,6(7H)-dione(2G):

¹H NMR (500 MHz, DMSO-d₆) δ: 8.17 (d, *J* = 7.5 Hz, 1H), 8.03 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.90 (td, *J* = 7.6, 1.2 Hz, 1H), 7.74 (td, *J* = 7.7, 1.0 Hz, 1H), 7.35 – 7.27 (m, 4H), 7.15 (s, 1H), 6.86 (s, 1H), 6.09 (d, *J* = 0.7 Hz, 1H), 6.10 (d, *J* = 0.7 Hz, 1H), 5.15 (s, 1H); ¹³C NMR (125 MHz, DMSO-d₆) δ: 176.74, 176.46, 156.21, 146.00, 144.07, 142.99, 141.73, 133.93, 130.42, 130.18, 129.37, 129.15, 128.58, 127.35, 123.36, 115.12, 112.70, 106.75, 100.87, 97.66, 35.98; HRMS (ESI) Calcd. for C₂₄H₁₄ClO₅ ([M+H]⁺): 417.054. Found: 417.056.

7-(thiophen-2-yl)-6H-benzo[h][1,3]dioxolo[4,5-b]xanthene-5,6(7H)-dione(2K):

¹H NMR (500 MHz, DMSO-d₆) δ: 8.17 (d, *J* = 7.6 Hz, 1H), 8.03 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.90 (td, *J* = 7.8, 1.3 Hz, 1H), 7.70 (td, *J* = 7.7, 1.0 Hz, 1H), 7.26 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.18 (s, 1H), 7.03 (s, 1H), 6.99 (d, *J* = 3.2 Hz, 1H), 6.89 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.10 (d, *J* = 0.9 Hz, 1H), 6.05 (d, *J* = 0.9 Hz, 1H), 5.45 (s, 1H); ¹³C NMR (125 MHz, DMSO-d₆) δ: 176.72, 176.49, 156.26, 147.80, 146.26, 144.11, 142.04, 134.13, 130.61, 129.22, 129.07, 127.56, 125.93, 123.80, 123.76, 123.44, 115.24, 113.11, 106.93, 100.99, 97.67, 31.43; HRMS (ESI) Calcd. for C₂₂H₁₃O₅S ([M+H]⁺): 389.048. Found: 389.041.

RESULT AND DISCUSSION

To estimate the reaction condition, the reaction of 3,4-dimethoxybenzaldehyde (166.2 mg, 1.0 mmol), 3,4-methylenedioxyphenol (138.1 mg, 1.0 mmol), 2-hydroxy-1,4-naphthoquinone (174.1 mg, 1.0 mmol) in Ethanol (4.0 mL) and Scolecite (2% weight with respect to all the reactants) was selected as the model, the results are concise in (Table 1). Therefore, we selected 75^oC to study the effect of reaction time and found that 4 minutes is the optimum reaction time for the achievement of reactants into products.

Similarly, to find the estimate the quantity of scolecite, the above model reaction was carried out under the previously mentioned conditions, using different quantities of catalyst at 75^oC, the use of 2% weight with respect to all the reactants of catalyst resulted in the highest yield, 96% (Entry 4, Table 2).

Scolecite results are far better than other reported catalysts in terms of yield as well and other reaction conditions (Table 3).

To explore the opportunity of our methodology, extensive substituted new aromatic aldehydes were selected to synthesize innovative 7-aryl-6H-benzo[h][1,3]dioxolo[4,5-b]xanthene-5,6(7H)-dione derivatives, According to the investigational results as summarized in (Table 4).

Overall data shown that, all synthesized products give excellent yields (>90%). The yields were not affected by substituents like electron donating group and withdrawing group. The probable role of Scolecite is represented in the proposed mechanism (Scheme 2).

The recyclability potential of the Scolecite catalyst was examined for the model reaction product of 2A. The recycling procedure involved the separation of the catalyst from the reaction mixture simply by usual filtration. The recovered catalyst was purified by washing and activation at 100^oC, followed by drying in an oven. The results shown in (Table 5, Figure 1) show that the catalyst can be used three successive times without significant loss of its activity. The truthfulness of there covered catalyst was detected and proved to be as active as the new catalyst.

Table 1 Optimization of Reaction condition for synthesis of model product 2A

Entry ^b	Temp. (°C)	Time (min)	Yield (%) ^a
1	RT(35)	90	NIL
2	55	4.5	45
3	60	5	54
4	65	4	76
5	70	4	83
6	70	5	89
7	75	4	96
8	75	5	93
9	80	4	81
10	90	4	79

^a Isolated yield; ^b Model reaction: 3,4-dimethoxybenzaldehyde (166.2 mg, 1.0 mmol), 3,4-methylenedioxyphenol (138.1 mg, 1.0 mmol), 2-hydroxy-1,4-naphthoquinone (174.1 mg, 1.0 mmol), Scolecite (2% weight with respect to all the reactants), Ethanol (4.0 mL), NIL- Product not recovered.

Table 2 Optimization of Scolecite (2% weight with respect to all the reactants) catalyst for synthesis of model product 2A

Entry	Amount of Catalyst (% weight)	Time ^{b, c} (min)	Yield (%) ^a
1	0.5	4	68
2	1	4	71
3	1.5	4	86
4	2.0	4	96
5	2.5	4	91
6	3	4	82
7	3.5	4	72

^aIsolated yield; ^bReaction carried out at 75°C; ^cModel reaction: 3,4-dimethoxybenzaldehyde (166.2 mg, 1.0 mmol), 3,4-methylenedioxyphenol (138.1 mg, 1.0 mmol), 2-hydroxy-1,4-naphthoquinone (174.1 mg, 1.0 mmol), solvents (4.0 mL).

Table 3. Comparison results of other reported procedures with the present method in terms of time and yield

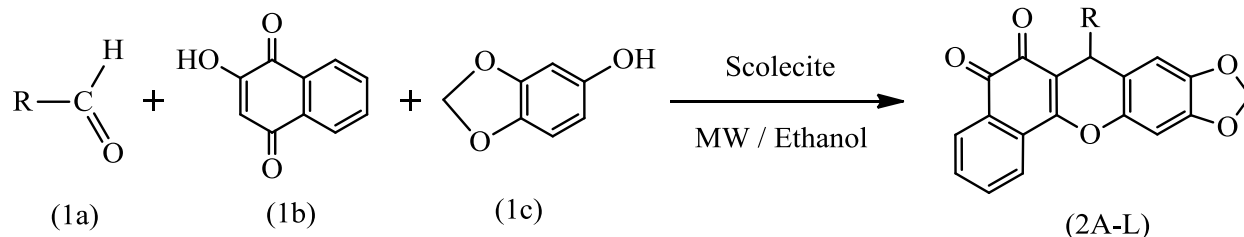
Entry ^b	Solvents	Catalyst (mol %)	Time (min)	Temp. (°C)	Yield (%) ^a
1	Ethanol	Et ₃ N (20)	180	80	Very trace
2	Ethanol	Piperidine (20)	180	80	Trace
3	Ethanol	MgCl ₂ (20)	90	80	81
4	Ethanol	InCl ₃ (20)	120	80	72
5	Ethanol	NiCl ₃ .6H ₂ O (20)	90	80	80
6	Ethanol	Zn(OTf) ₂ (20)	90	80	84
7	Ethanol	CSA (20)	90	80	81
8	Ethanol	CH ₃ COOH (20)	120	80	68
9	Ethanol	NH ₂ SO ₃ H (20)	120	80	76
10	Ethanol	P-TSA (20)	40	100	93
11	Ethanol	Scolecite (2% weight with respect to all the reactants)	4 (MW)	75	96 (Present work)

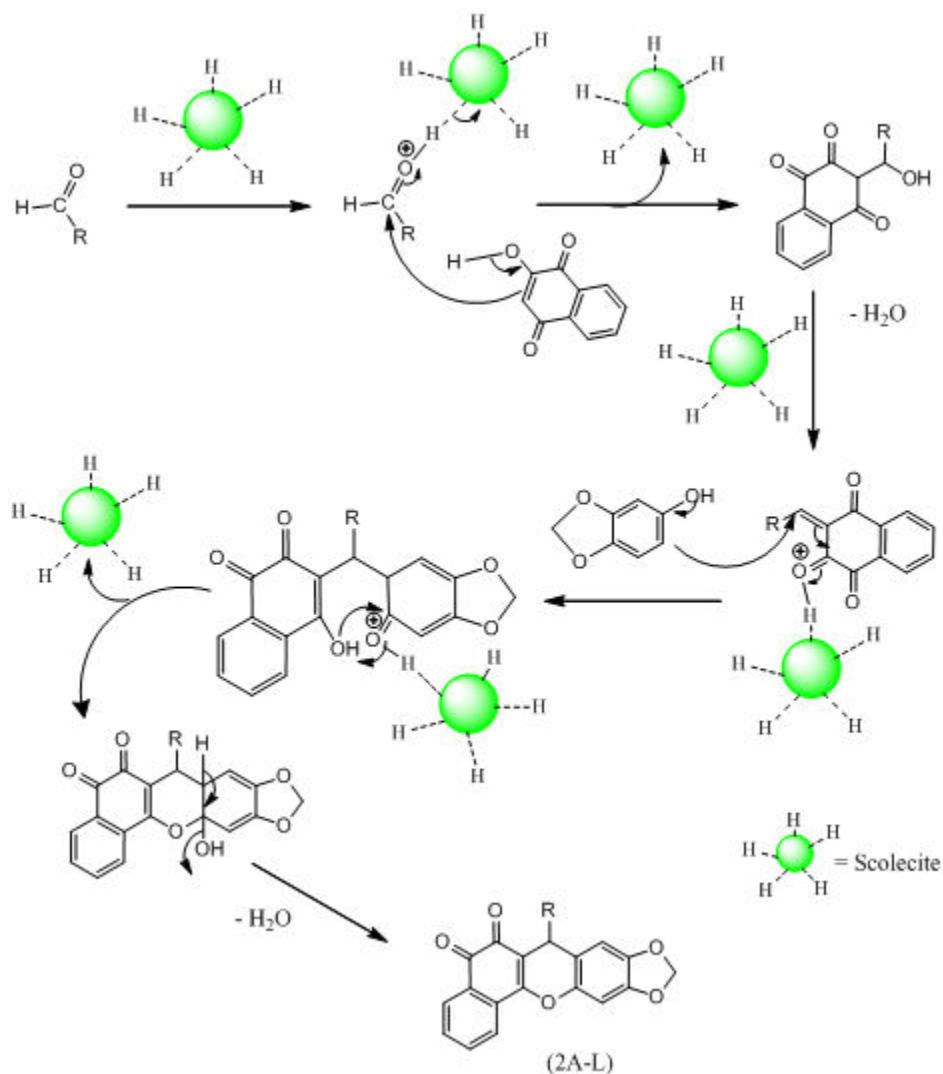
^a Isolated yield; ^b Model reaction: 3,4-dimethoxybenzaldehyde (166.2 mg, 1.0 mmol), 3,4-methylenedioxyphenol (138.1 mg, 1.0 mmol), 2-hydroxy-1,4-naphthoquinone (174.1 mg, 1.0 mmol), solvents (4.0 mL).

Table 5 Recycling of Scolecite (2% weight with respect to all the reactants) for the synthesis of model product 2A.

Sr. no.	Cycle	Yield (%) ^x
1	Fresh	96
2	1 st	91
3	2 nd	86
4	3 rd	79

^x Isolated yield

**Scheme 1.** Synthesis of 7-aryl-6H-benzo[h][1,3]dioxolo[4,5-b]xanthene-5,6(7H)-dione analogues catalyzed by Scolecite as heterogeneous catalysts



Scheme-2: Possible reaction mechanism for the Scolecite catalyzed synthesis of 7-aryl-6H-benzo[h][1,3]dioxolo[4,5-b]xanthene-5,6(7H)-dione analogues.

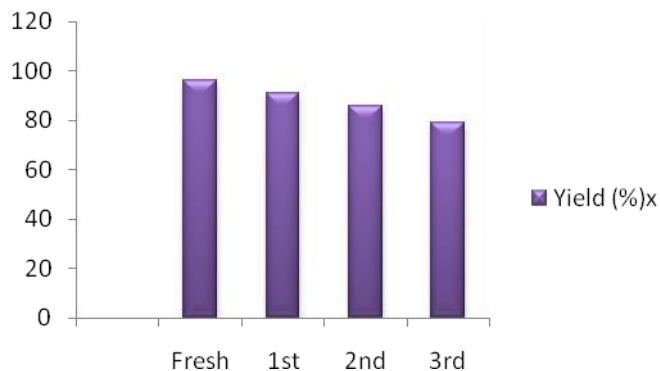
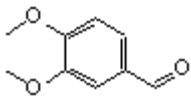
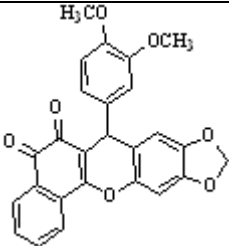
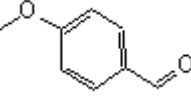
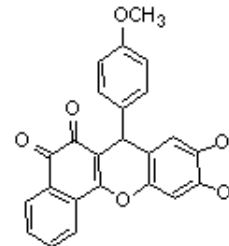
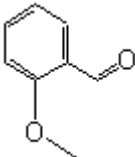
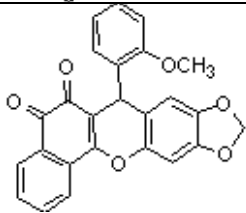
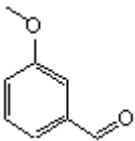
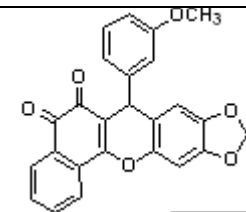
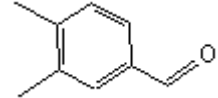
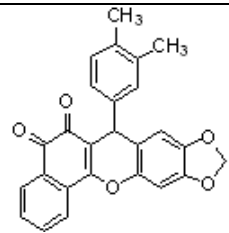
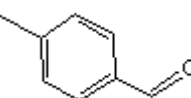
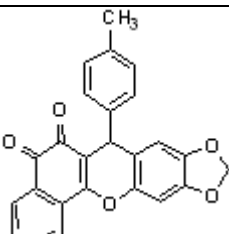
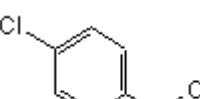
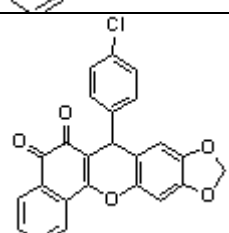
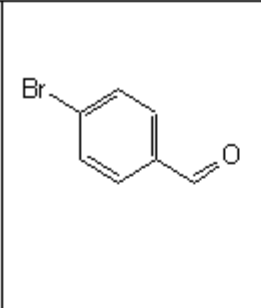
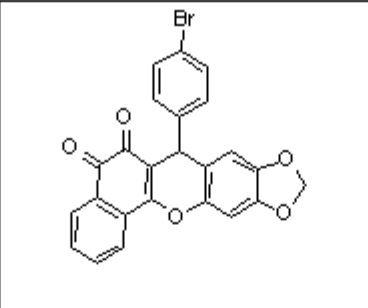
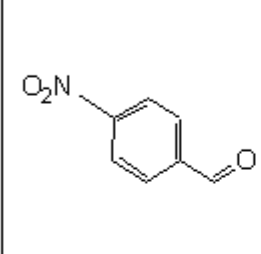
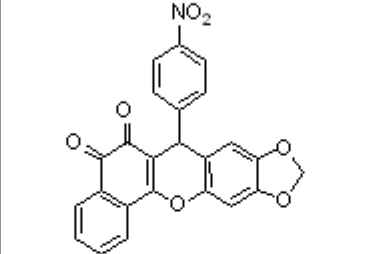
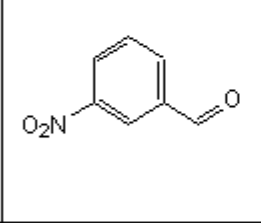
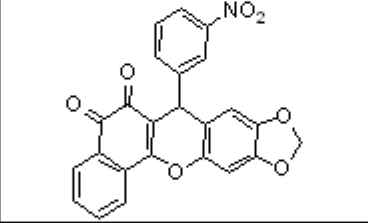
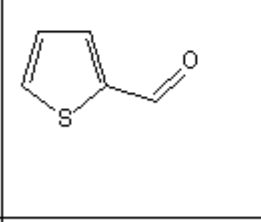
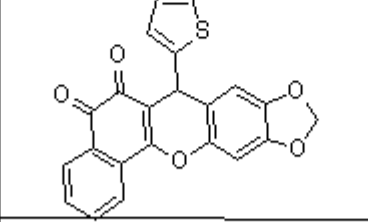
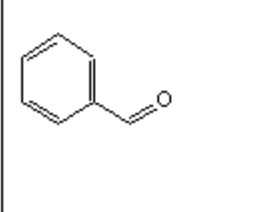
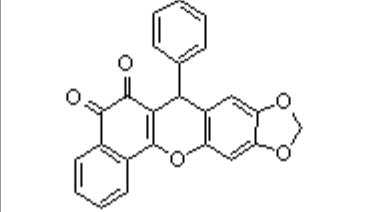


Figure-1: Recyclability potential of the catalyst in the synthesis of 7-aryl-6H-benzo[h][1,3]dioxolo[4,5-b]xanthene-5,6(7H)-dione analogues.

Table 4. Synthesis of 7-aryl-6H-benzo[h][1,3]dioxolo[4,5-b]xanthene-5,6(7H)-dione derivative.

Product	Aldehyde	Product	Time (min)	Yield (%) ^x	MP (°C)
2A			4	96	235-237 [236] ^a
2B			4	89	235-237 [234] ^a
2C			4	91	233-234 [234] ^a
2D			4	94	223-225 [225] ^a
2E			4	92	236-238 [236] ^a
2F			4	93	232-235 [231] ^a
2G			4	89	239-240 [240] ^a

2H			4	90	252-254 [251] ^a
2I			4	82	220-221 [221] ^a
2J			4	84	240-243 [242] ^a
2K			4	91	224-226 [225] ^a
2L			4	94	252-253 [253] ^a

^x Yields refer to those of pure isolated products characterized by ¹H & ¹³C NMR, Mass spectra.

^aKai Qian¹⁷ NIL- Product not recovered

CONCLUSION

In conclusion, we have successfully synthesize 7-aryl-6H-benzo[h][1,3]dioxolo[4,5-b]xanthene-5,6(7H)-dione derivatives using scolecite as a novel heterogeneous acid catalyst. The experimental procedure is quick and simple. Furthermore, this method is advantageous because of clean reaction conditions, consistent yields and minimum environmental effects.

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