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Bleaching earth clay (pH 12.5): A novel and reusable catalyst for rapid synthesis of 7-Hydroxy 4-Styryl coumarin derivatives and their antihelmintic activity

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Abstract: 7-hydroxy 4-styryl coumarin derivatives were synthesized by Knovengel condensation of 7-hydroxy 4-methyl coumarin with aldehydes by using novel and reusable catalyst bleaching earth clay (pH12.5) in PEG-400 as green reaction solvent, followed by the Mannich reaction. The synthesized compounds were evaluated for their *in vitro* antihelmintic activity and it was found that the synthesized compounds showed good antihelmintic activity.

Keywords: 7-hydroxy 4-styryl coumarin derivatives; bleaching earth clay (pH12.5); PEG-400; antihelmintic activity; albendazole.

1. Introduction

The global burden of both human and domestic animal parasitic diseases coupled with the emergence of drug resistance has made the development of new chemotherapeutic agents, a critical need. Albendazole are still extensively used for the treatment of human pinworm infection[1].Some antihelmintic drugs such as Praziquantel and Albendazole are avoided for certain groups of patients like pregnant and lactating women.

Many natural products and their synthetic analogue have been reported for their biological applications. Coumarin is the naturally occurring compounds, which are widely distributed in the plantae kingdom and has also been produced synthetically[2]. Members of this group shows a wide range of applications, as fragrances, pharmaceuticals [3], food additives, anti-inflammatory activity[4], biological activities like antihelmintic[5], antitumor[6], hypnotic[7], insecticidal[8], anticoagulant[9] and antimicrobial activity[10]. The reported significance of coumarin derivatives generated the interest to exploit this valuable nucleus in the design and synthesis of 7-hydroxy 4-styryl coumarin derivatives via a green approach.

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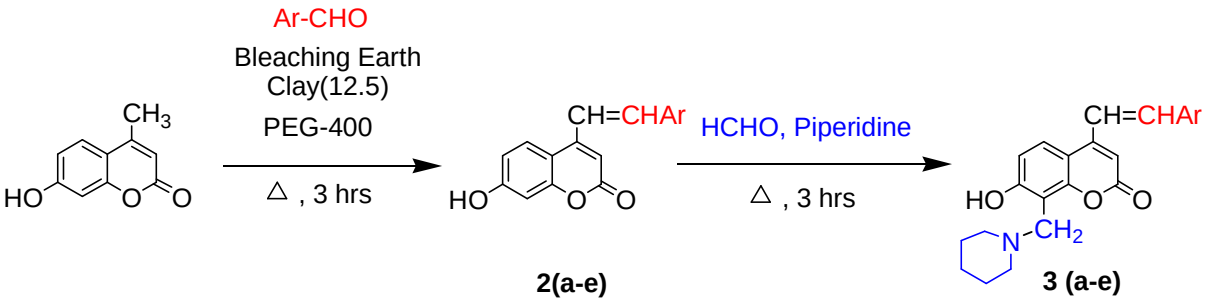
The recovery of heterogeneous catalysts from the reaction mixture is simply by filtration posses advantageous over the conventional homogeneous catalysts. Moreover, it can be reused after activation, thereby making the process economically viable. Naturally occurring clay has unique physical and chemical properties such as shape selectivity, acidic, basic nature and thermal stability. The bleaching earth clay (pH 12.5) a highly efficient heterogeneous base catalyst is used for several base-catalyzed organic transformations[11-12]. Use of green solvent is one of the aspects of green synthesis. Liquid polymers or low melting polymers have recently emerged as alternative green solvent with unique properties such as thermal stability, commercial availability, non-volatility, miscibility with a number of organic solvents and recyclability. Poly ethylene glycols (PEGs) [13-15] are among the one of green solvents to overcome the toxic solvent effect on environment. Most of reported methods for synthesis of 7-hydroxy 4-styryl coumarin derivatives suffer from different drawbacks such as longer reaction times and/or the application of expensive toxic catalysts and solvents.

2. Results and discussion

With our recent success on the development of environmentally friendly methodologies using polyethylene glycol (PEG-400)[11-15] as a solvent for the preparation of biologically active compounds, herein we report the synthesis of some 7-hydroxy 4-styryl coumarin **(2 a-e)** derivatives by the reaction of 7-hydroxy 4-methyl coumarin with different substituted aromatic aldehydes using bleaching earth clay (12.5) in PEG-400 as green reaction solvent (**scheme 1**) were synthesized by modifications of reported method[16] followed by the Mannich reaction yielding product **(3 a-e)**.



Scheme 1. Synthesis of 7-hydroxy 4-styryl coumarin derivatives

Initially, we attempted the condensation of 7-hydroxy 4-methyl coumarin with aromatic aldehydes using bleaching earth clay (pH 12.5) in polyethylene glycol (PEG-400) as reaction solvent. The reaction went to completion within 25 min and corresponding product **2(a-e)** was obtained in 90% yield. In order to optimize the reaction conditions, we carried out the above reaction in different solvents such as ethanol, acetic acid, dioxane, DMF and polyethylene glycol-400 **(Table 1**). We found that polyethylene glycol-400 as an efficient reaction medium in terms of reaction time as well as yields (above 80 %). Encouraged by the results, we turned our attention to variety of substituted aromatic aldehydes. In all cases, the reaction proceeded efficiently in high yields at 60- 80 ^{0}C using PEG-400 as an alternative reaction solvent. Further styrene derivatives undergo Mannich reaction with piperidine, formaldehyde in methanol with few drop of acetic acid to yield **3(a-e)** the physical data of synthesized 7-hydroxy4-styryl coumarin derivatives is shown in **Table 2**.

Table 1. Effect of solvent on the reaction of 7-hydroxy 4-methyl coumarin with aromatic aldehydes

Entry	Solvent	Time (h)	Yield (%)
1	EtOH	6	65
2	CH_3COOH	5	72
3	Dioxane	5	62
4	DMF	5	68
5	PEG-400	25 min	94

Table 2. Physical data of synthesized 7-hydroxy 4-styryl coumarin derivatives

Entry	Ar	m.p. (^oC)	Yield (%)
2 a	2-chlorophenyl	158	91
2 b	4-chlorophenyl	176	90
2 c	4-bromophenyl	135	89
2 d	4-methylphenyl	139	93
2 e	4-fluorophenyl	147	88
3 a	2-chlorophenyl	162	72
3 b	4-chlorophenyl	168	82
3 c	4-bromophenyl	172	78
3 d	4-methylphenyl	178	75
3 e	4-fluorophenyl	170	80

All synthesized compounds are well confirmed on the basis of spectral data. The absences of characteristic signals due to three protons of methyl of 4-methyl coumarin in ^1H NMR spectrum of compound **2 (a-e)** confirms the formation of styryl derivatives of coumarin, further the presence of -OH proton resonates between δ 10-11 ppm. The aromatic protons are observed at the expected chemical shift and integral values. 7-Hydroxy 4-styryl coumarin **(2 a-e)** derivatives was further supported by IR spectral data, picks due to (C-H aliphatic) stretching in (2930 cm^{-1}–2960 cm^{-1}) of 7-hydroxy 4-methyl coumarin get disappeared and new pick observed at 3023 cm^{-1} due to (C=C-H) stretching moreover the MS (EI) spectrum value corresponds to its an M + 1 peak of expected mass. Yield and melting point are summarized in **Table 2**. These newly synthesized compounds were screened for their antihelmintic activity.

3. Antihelmintic activity

The antihelmintic activity was performed according to the method reported by Ghosh et al, on adult Indian earth worm *Eisinea fetida* (family: Lumbricidae) as it has anatomical and physiological resemblance with the intestinal round worm parasites of human beings[17]. The worms were collected from the Agricultural Science Center Pokharni, Nanded (MS) India. The worms were placed in fecal mass before *in vitro* screening so as to prior use. *Eisinea fetida* (earth worms) were placed in petridish containing three different concentrations (0.1, 0.5, 1%), one petridish was kept as a control (distilled water) and one petridish contain standard drug Albendazole (1%) in distilled water. Each petridish contains six worms (approximately equal length and diameter) and observed for paralysis and death time. The mean time for paralysis was noted when no movement of any sort is observed, except when the worm was shaken vigorously; the death time of worm (min) was recorded after ascertaining that worms neither moved when shaken nor given external stimuli. The Test results were compared with reference compound Albendazole (10mg/ml) treated samples.

The antihelmintic screening of the 7-hydroxy 4-styryl coumarin derivatives and Albendazole showed in **Table 3.** A closer inspection of data from tables indicates that compounds **3e** and **3c** showed promising paralytic activity compared with standard Albendazole. Compound **3b** showed moderate paralysis activity with standard Albendazole. The transformation order of screened compounds for paralysis time is **3e>3c>3b>3d>3a**. Compounds **3e** and **3c** showed a moderate antihelmintic activity with respect to death of worms than standard Albendazole. The transformation order of screened compounds for death time is **3e>3c>3b>3a>3d**.

Table 3. *In vitro* antihelmintic activity of various styrene derivatives

Sr. No.	Treatment	Concentration (%)	Paralysis time	Death time (min)
1	Albendazole (Std)	1	7.45± 0.22	30±0.30
2	Control	---	---	---
3	**3a**	0.1	62.54±0.58	92±2.48
		0.5	48.24±1.32	75±3.32
		1	32.20±1.20	58±2.20
4	**3b**	0.1	58.20±0.16	73±0.42
		0.5	37.40±0.26	57±0.52
		1	24.00±0.40	43±0.58
5	**3c**	0.1	48.56±0.22	68±0.22
		0.5	25.08±0.30	53±0.44
		1	**10.20±0.42**	**36±0.74**
6	**3d**	0.1	62.40±0.80	91±0.72
		0.5	48.56±0.56	76±1.10
		1	28.80±1.20	62±3.20
7	**3e**	0.1	46.52±0.20	62±0.32
		0.5	28±0.26	45±0.40
		1	**9.10±0.34**	**32±0.46**

All Values represent Mean+ SD; n=6 in each group.

4. Conclusion

In summary, we have developed a novel, efficient and environmentally benign methodology towards the synthesis of 7-hydroxy 4-styryl coumarin derivatives by the condensation reaction of 7-hydroxy 4-methyl coumarin derivatives with aldehydes using bleaching earth clay (pH: 12.5) as an efficient heterogeneous catalyst in polyethylene glycol (PEG-400) as a green reaction solvent is described. The advantages of the present protocol are the simplicity of operation, the high yields of products, and the recyclability of PEG-400, avoidance of expensive and toxic catalyst and usage of volatile organic solvents. The synthesized compounds exhibited moderate antihelmintic activity compared with standard Albendazole. From the present research work it is concluded that these 7-hydroxy 4-styryl coumarin derivatives can be the promising antihelmintic candidates for *in vivo* studies in future.

5. Experimental

All the melting points were uncorrected and determined in an open capillary tube. The chemicals and solvents used were of laboratory grade and were purified. Completion of the reaction was monitored by thin layer chromatography on precoated sheets of silica gel-G (Merck, Germany) using iodine vapour for detection. IR spectra were recorded in KBr pallets on FTIR Schimadzu spectrophotometer. ^{1}H NMR and ^{13}C NMR (70 MHz) spectra were recorded in DMSO-*d6* with an Avance spectrometer (Bruker, Germany) at 400-MHz frequency using TMS as an internal standard. Mass spectra were recorded on an EI-Shimadzu QP 2010 PLUS GC-MS system (Shimadzu, Japan). Elemental analyses were performed on a Carlo Erba 106 Perkin-Elmer model 240 analyzer (Perkin-Elmer, USA).

General procedure for the preparation of compounds 2(a-e):

A mixture of 7-hydroxy-4-methyl-2-oxo-2H-chromene (**1a)** (10 mmol) and substituted aromatic aldehydes (1.24 gm, 10 mmol) were dissolved in minimum quantity of PEG-400 along with catalytic amount of bleaching earth clay (12.5). The reaction mixture was heated with stirred at 45^{o}C temperature. The progress and completion of the reaction was monitored by TLC. At the end of reaction the solid product precipitated. It was filtered and thoroughly washed with chilled methanol and crystallized from chloroform to give 7-hydroxy 4-styryl coumarin derivatives **2(a-e)**.

4-(2-chlorostyryl)-7-hydroxy-2H-chromen-2-one (**2a)**: Colour (pale yellow); Purity by TLC >90% ; IR (KBr) 3338 cm^{-1}, 2944 cm^{-1}, 1745 cm^{-1}; ^{1}H NMR (DMSO d_6); δ 6.71(d,1H, J=7.5Hz), δ 6.86 (d,1H, J=6.5 Hz), δ 6.91 (s 1H, J=6.2Hz) δ 7.11-7.82 (m, 8 H-Ar proton), δ 10.68 (s, 1H, OH); EIMS=298 (M+).
4-(4-chlorostyryl)-7-hydroxy-2H-chromen-2-one (**2b)**: Colour (white); Purity by TLC >90% ; IR (KBr) 3332 cm^{-1}, 2934 cm^{-1}, 1739 cm^{-1}; ^{1}H NMR (DMSO d_6); δ 6.70 (d, 1H, J=7.4Hz), δ 6.82 (d,1H, J=6.5Hz), δ6.90 (s, 1H), δ 6.96-7.61 (m, 7H-Ar proton), δ 10.87 (s, 1H, OH); EIMS=298 (M+).
4-(4-bromostyryl)-7-hydroxy-2H-chromen-2-one (**2c)**: Colour (pale yellow); Purity by TLC >90% ; IR (KBr) 3338 cm^{-1}, 2944 cm^{-1}, 1745 cm^{-1}; ^{1}H NMR (DMSO d_6); δ 6.76 (d,1H, J=7.6 Hz), δ 6.91 (d,1H, J=6.4Hz), δ 6.99 (s, 1H) δ 7.19-7.81 (m, 7H-Ar proton), δ 10.67 (s, 1H, OH); EIMS=342 (M+).
7-hydroxy-4-(4-methylstyryl)-2H-chromen-2-one (**2d)**: Colour (pale brown); Purity by TLC >90% ; IR (KBr) 3328 cm^{-1}, 2929 cm^{-1}, 1749 cm^{-1}; ^{1}H NMR (DMSO d_6) δ 1.32 (s, 3H), 6.69 (d,1H, J=7.5Hz) , δ 6.72 (d,1H, J=6.8 Hz) , δ 6.92-7.512 (m, 8H-Ar proton), δ 10.321 (s, 1H, OH); EIMS=278 (M+).
4-(4-flurostyryl)-7-hydroxy-2H-chromen-2-one (**2a)**: Colour (yellow); Purity by TLC >90% ; IR (KBr) 3348 cm^{-1}, 2941 cm^{-1}, 1748 cm^{-1}; ^{1}H NMR (DMSO d_6); δ 6.81(d, 1H, J=7.5Hz), δ 6.92 (d,1H, J=7.5Hz), δ7.21(s, 1H) δ 7.29-7.81 (m, 7H-Ar proton), δ 10.36 (s, 1H, OH); EIMS=282 (M+).

General procedure for the preparation of compounds 3:

Mixture of **2(a-e)**, formaldehyde and piperidine taken in an RBF containing methanol and few drop of AcOH was refluxed for 3 hrs. After completion of reaction (monitored by TLC), the reaction mixture was poured in ice cold water the precipitate obtained were filter and recrystalised from methanol to obtain **3(a-e).**
4-[2-(2-Chloro-phenyl)-vinyl]-7-hydroxy-8-piperidin-1-yl-methyl-chromen-2-one (**3a)**: Colour (White); Purity by TLC >95 % ; IR (KBr) 3358 cm^{-1}, 3118 cm^{-1}, 2940 cm^{-1}, 1755 cm^{-1}; ^{1}H NMR (DMSO d_6); δ 1.81 (m, 4H, piperidine), δ 2.13 (m ,6H, piperidine), δ 4.15 (s, 2H), δ 6.71 (d,1H, J=7.2Hz), δ 6.91 (d,1H, J=6.6Hz), δ 6.93-7.19 (m, 7H, Ar proton), δ 10.68 (s, 1H, OH); ^{13}C NMR; 24.1(CH_2), 26.3 (CH_2 × 2), 51.4 (CH_2), 57.1 (CH_2× 2), 104.5 (CH × 2),115.2 (CH),125.7 (CH), 127.4 (CH × 2), 129.2 (CH × 3), 131.3 (CH), 133.6 (CH × 2), 155.2 (C-O × 2), 159.8 (C=O), 162.4 (C); EIMS=396 (M+).
4-[2-(4-Chloro-phenyl)-vinyl]-7-hydroxy-8-piperidin-1-yl-methyl-chromen-2-one (3b): Colour (pale brown); Purity by TLC >95 % ; IR (KBr) 3328 cm^{-1}, 3120 cm^{-1}, 2929 cm^{-1}, 1749 cm^{-1}; ^{1}H NMR (DMSO d_6); δ 1.71 (m, 4H, piperidine), δ 2.41 (m ,6H), δ 4.32 (s,2H), δ 6.69 (d,1H, J=7.5Hz) , δ 6.72 (d,1H, J=6.3Hz) , δ 6.92-7.58 (m, 7H, Ar proton), δ 10.21 (s, 1H, OH); ^{13}C NMR; 23.9 (CH_2), 27.1 (CH_2 × 2), 50.8 (CH_2), 56.4 (CH_2× 2), 102.9 (CH × 2),116.0 (CH),123.7 (CH), 128.4 (CH × 2), 129.1 (CH × 3), 132.6(CH), 135.7 (CH × 2), 156.2 (C-O × 2), 161.1 (C=O), 163.4 (C); EIMS=396 (M+).
4-[2-(4-Bromo-phenyl)-vinyl]-7-hydroxy-8-piperidin-1-yl-methyl-chromen-2-one (3c): Colour (pale brown); Purity by TLC >95 % ; IR (KBr) 3309 cm^{-1}, 3109 cm^{-1}, 2972 cm^{-1}, 1748 cm^{-1}; ^{1}H NMR (DMSO d_6); δ 1.90 (m, 4H, piperidine), δ 2.32 (m,6H), δ 4.23 (s,2H), δ 6.70 (d,1H), δ 6.72 (d,1H) δ 6.91-7.74 (m, 7H, Ar proton), δ 10.64 (s, 1H, OH); ^{13}C NMR; 23.9 (CH_2), 26.8 (CH_2 × 2), 51.3 (CH_2), 56.8 (CH_2× 2), 103.4 (CH × 2),116.1 (CH),123.5 (CH), 128.2 (CH × 2), 129.2 (CH × 3), 132.8 (CH), 135.4 (CH × 2), 155.2 (C-O × 2), 161.5 (C=O), 162.0 (C); EIMS=440 (M+).
4-[2-(4-Methyl-phenyl)-vinyl]-7-hydroxy-8-piperidin-1-yl-methyl-chromen-2-one (**3d)**: Colour (pale yellow); Purity by TLC >95 % ; IR (KBr) 3328 cm^{-1}, 3123 cm^{-1}, 2929 cm^{-1}, 1749 cm^{-1}; ^{1}H NMR

(DMSO d_6); δ 1.43 (s, 3H), δ 1.69 (m, 4H, piperidine), δ 2.24 (m ,6H), δ 4.32 (s,2H), δ 6.69 (d,1H, J=7.5Hz) , δ 6.72 (d,1H, J=6.8Hz) , δ 6.92-7.52 (m, 7H, Ar proton), δ 10.61 (s, 1H, OH); ^{13}C NMR; 20.3(CH_3), 24.9 (CH_2), 27.2 (CH_2 × 2), 51.1 (CH_2), 55.8 (CH_2× 2), 104.4 (CH × 2),115.8 (CH),124.5 (CH), 127.2 (CH × 2), 128.8 (CH × 3), 131.8 (CH), 134.4 (CH × 2), 155.3 (C-O × 2), 160.5 (C=O), 162.1 (C); EIMS=375 (M+).

4-[2-(4-Fluro-phenyl)-vinyl]-7-hydroxy-8-piperidin-1-yl-methyl-chromen-2-one (3e): Colour (pale yellow); Purity by TLC >95 % ; IR (KBr) 3315 cm^{-1}, 3118 cm^{-1}, 2985 cm^{-1}, 1739 cm^{-1}; ^{1}H NMR (DMSO d_6); δ 1.82 (m, 4H, piperidine), δ 2.16 (m ,6H), δ 4.23 (s,2H), δ 6.52 (d,1H, J=7.8Hz), δ 6.86 (d,1H, J=6.2Hz), δ 6.10-7.60 (m, 7H, Ar proton), δ 10.54 (s, 1H, OH); ^{13}C NMR; 24.3(CH_2), 27.3 (CH_2 × 2), 51.7 (CH_2), 57.0 (CH_2× 2), 104.1 (CH × 2),116.2 (CH),125.2 (CH), 126.4 (CH × 2), 128.2 (CH × 3), 138.3 (CH), 139.6 (CH × 2), 155.2 (C-O × 2), 159.8 (C=O), 162.4 (C);EIMS=379 (M+).

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