Tetrahedron Letters 53 (2012) 1018–1024

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A multicomponent, solvent-free, one-pot synthesis of benzoxanthenones catalyzed by HY zeolite: their anti-microbial and cell imaging studies

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ARTICLE INFO

Article history:
Received 19 September 2011
Revised 22 October 2011
Accepted 26 October 2011
Available online 31 October 2011

Keywords:
HY zeolite
Heterogeneous catalysts
Benzoxanthenones
Multicomponent reaction
Solvent-free conditions

ABSTRACT

An atom-economical, multicomponent condensation of naphthols, aldehydes, and cyclic 1,3-dicarbonyl compounds catalyzed by HY zeolites under solvent-free conditions is reported. This ecofriendly protocol offers several advantages such as a green and cost-effective procedure with excellent yield, shorter reaction time, simpler work-up, recovery, and reusability of metal-free solid acid heterogeneous catalyst and tolerance of a wide range of functional groups. The biological studies such as in vitro anti-microbial activities of the prepared new compounds and cell imaging studies on K562 leukemia cell lines by selected benzoxanthenones are evaluated.

Multicomponent reactions are valuable tools for the preparation of structurally diverse chemical libraries of drug-like heterocyclic compounds.[1] Xanthenes are one of the most widely distributed classes of natural compounds. Multicomponent one-pot strategies to access xanthenes and benzoxanthenones, have attracted considerable attention over the years due to their diverse biological properties, such as antiviral,[2] anti-inflammatory,[3] antibacterial activities, as well as their use as dyes and fluorescent materials.[4] Some of them have been used as antagonists for paralyzing the action of zoxazolamine,[5] in photodynamic therapy (PDT)[6] and as antagonists for drug-resistant leukemia lines.[7] Thus a broad utility range has made xanthenes prime synthetic candidates thereby accentuating the need to develop newer routes for scaffold manipulation of xanthenes derivatives. Recent strategies to synthesize xanthenones scaffolds include palladium-catalyzed cyclization of polycyclic aryl triflate esters,[8] resorcinol, and various analytes, such as phthalic anhydride, acid chloride, ester or aldehyde,[9] intramolecular trapping of benzynes by phenols,[10] reaction of aryloxy magnesium halides with triethyl orthoformate[11] and reaction of 2-tetralones with substituted 2-hydroxyarylaldehydes.[12]

Recently enormous progress has been made in expanding the scope of condensation of β-naphthol, aldehyde with 1,3-dicarbonyl compounds by employing a wide array of acid catalysts, such as $BF_3{\cdot}Et_2O$,[13a] $InCl_3$,[13b] PTSA,[13c] $Zr(HSO_4)_4$,[13d] $Sr(OTf)_2$,[13e] TBAF,[13f] I_2,[13g] sulfamic acid,[13h] $NaHSO_4$–SiO_2,[13i] Caro's acid-SiO_2,[13j] 12-tungstophosphoric acid,[13k] cyanuric acid,[13l] proline triflates,[13m] $HClO_4$–SiO_2,[13n] CAN,[13o] *N*,*N*′-dibromo-*N*,*N*′-1,2-ethanediyl*bis*(*p*-toluenesulfonamide),[13p] and $HClSO_3$.[13q] Many of these synthetic methods, however, have limitations such as longer reaction time, harsher reaction conditions, expensive catalysts, and generation of noticeable amount of side products. These catalysts also suffer from other drawbacks, such as strongly acidic media, high temperature, inert atmosphere, stoichiometric amounts of reaction promoters, moisture sensitiveness of the catalysts, and difficulty in the separation of the products such as tedious work-up or purification. Thus there is ample scope for the development of new greener synthetic protocols to assemble such scaffolds.

Heterogeneous catalysis by zeolites by the virtue of their tunable larger pore sizes and inherent acid/base catalytic properties finds extensive applications as novel catalysts, as they provide greener alternatives to homogeneous catalysis. The success of multicomponent one-pot transformation is centered on the design of highly selective catalysts with well optimized isolated active sites. HY zeolite is an important heterogeneous catalyst used in various chemical transformations such as one-pot synthesis of 2,3-dihydro-2,2-dimethylbenzofurans,[14a] 1,4-dihydropyridines,[14b] methyl *N*-phenyl carbamate,[14c] tetrahydrocarbazole,[14d] bis(indolyl)methanes,[14e] 2-substituted benzimidazoles,[14f] polyhydroquinolines,[14g] substituted quinazolin-4(3*H*)ones,[14h] and tetrasubstituted imidazoles.[14i]

In continuation of our work[15] on the applications of heterogeneous catalysts on organic transformations, we proposed to utilize HY zeolite in the present work as a promising candidate to perform the condensation of naphthols, aldehydes with cyclic 1,3-dicabonyls (Scheme 1). In the search toward eco-compatibility, the solvent-based chemistry has stimulated us to study the reactions

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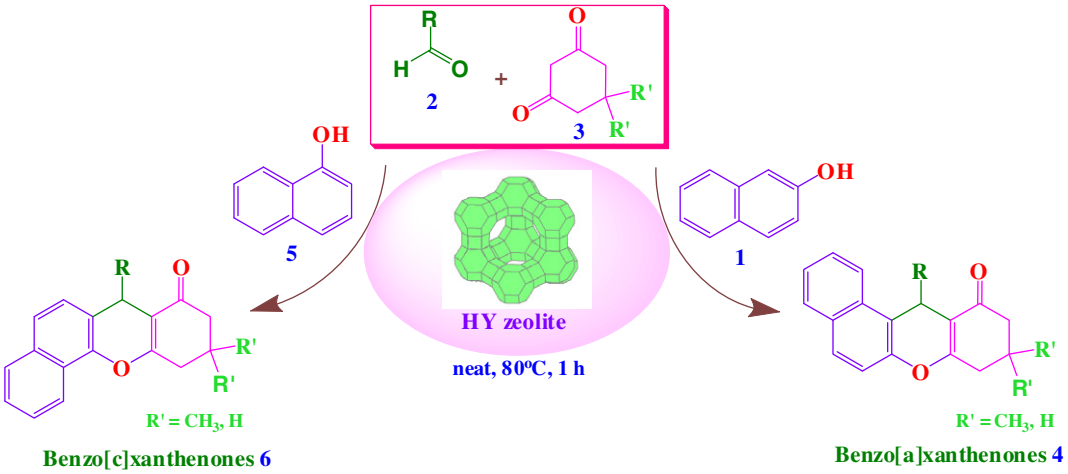
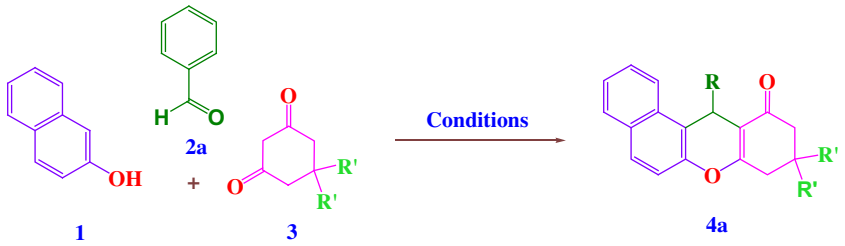
doi:10.1016/j.tetlet.2011.10.143



Scheme 1. HY zeolite catalyzed synthesis of benzoxanthenones by reaction of naphthols, aldehydes and cyclic 1,3-dicarbonyl compounds.

Table 1
Optimization of reaction conditions in synthesis of benzoxanthenones using β-naphthol, benzaldehyde and 5,5-dimethyl-1,3-cyclohexanedione[a]



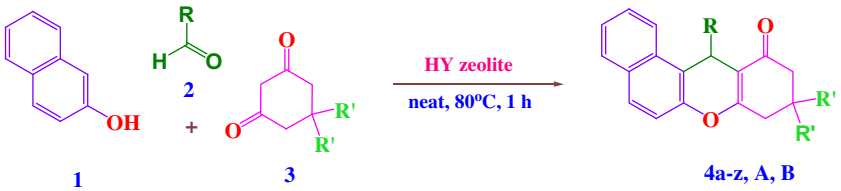
Entry	Catalyst	Solvent	Time (h)	Yield[b] (%)
1	None	Neat	5	0
2	HY	Toluene	5	72
3	HY	DMF	5	60
4	HY	EtOH	5	Trace
5	HY	THF	5	Trace
6	HY	ACN	5	36
7	HY	Bmim	5	25
8	HY	Ethyl acetate	5	58
9	HY	*n*-Hexane	5	65
10	HY	Neat	5	93
11	NaY	Neat	5	40
12	CaY	Neat	5	55
13	FeY	Neat	5	58
14	CoY	Neat	5	43
15	NiY	Neat	5	55
16	CuY	Neat	5	52
17	ZnY	Neat	5	54
18	AlY	Neat	5	65
19[c]	HY	Neat	5	0, 80, 93, 93, 94
20	HY	Neat	5, 4, 3, 2, 1, 0.5	93, 93, 93, 93, 93, 82
21[d]	HY	Neat	1	93, 93, 93,93, 80

[a] Reaction conditions: β-naphthol (1.0 mmol), benzaldehyde (1.0 mmol), and 5,5-dimethyl-1,3-cyclohexanedione (1.0 mmol), catalyst (20 mg), 100 °C for 5 h.
[b] Isolated yield based on **1**.
[c] Reaction carried out at room temperature, 60, 80, 90 and 100 °C, respectively.
[d] Reaction carried out with 30, 25, 20, 15, 10 mg of catalyst, respectively.

under solvent-free conditions.[16] This protocol offers several advantages such as higher yield, shorter reaction time, simpler work-up, recovery, and reusability of catalyst and tolerates a wide range of functional groups with no side products.

At the outset, the reaction parameters such as temperature, time, identification of the best catalyst, quantity, and solvent for the synthesis of benzoxanthenones are examined by choosing β-naphthol **1**, benzaldehyde **2a**, and 5,5-dimethyl-1,3-cyclohexanedione **3** as model substrates (Table 1). Control experiments have shown that no desired product is detected in the absence of catalyst (Table 1, entry 1). The use of organic solvents results in lower conversion (Table 1, entries 2–9), and the reaction proceeds smoothly under solvent-free conditions (Table 1, entry 10). The acidity of zeolites can be finetuned using exchangeable metal

Table 2
Synthesis of substituted benzo[a]xanthenones[25] using β-naphthol, substituted aldehydes and cyclic 1,3-dicarbonyl compounds[a]



Entry	R	R′	Time (h)	Product	Yield[b] (%)	m.p. (°C)
1	C_6H_5–	CH_3	1	**4a**	93	152–154[13i]
2	*p*-$NO_2C_6H_4$–	CH_3	1	**4b**	92	175–177[13i]
3	*p*-FC_6H_4–	CH_3	1	**4c**	95	190–193[13c]
4	*p*-ClC_6H_4–	CH_3	1	**4d**	90	180-182[13i]
5	*m*-ClC_6H_4–	CH_3	1	**4e**	85	172–173
6	*o*-ClC_6H_4–	CH_3	1	**4f**	84	180–182[13b]
7	*p*-HOC_6H_4–	CH_3	1	**4g**	90	207–209[13i]
8	*o*-HOC_6H_4–	CH_3	1	**4h**	85	223–224
9	*p*-$N(CH_3)_2$–C_6H_4–	CH_3	1	**4i**	80	218–220
10	*p*-$CH_3OC_6H_4$–	CH_3	1	**4j**	85	203–205[13i]
11	*m*-$CH_3OC_6H_4$–	CH_3	1	**4k**	82	204–206[13c]
12	*p*-$CH_3C_6H_4$–	CH_3	1	**4l**	89	203–205[13i]
13	*p*-Cl,*m*-$NO_2C_6H_3$–	CH_3	1	**4m**	88	219–220
14	*p*-HO,*m*-$OCH_3C_6H_3$–	CH_3	1	**4n**	80	185–187
15	Cyclohexyl–	CH_3	4	**4o**	78	Oil
16	$C_6H_5CH_2$–	CH_3	24	**4p**	Trace	n.d.
17	$(CH_3)_2CHCH_2$–	CH_3	4	**4q**	78	190–192
18	CH_3CH═CH–	CH_3	4	**4r**	70	Oil
19	C_6H_5CH═CH–	CH_3	24	**4s**	Trace	n.d.
20	2′-Pyridinyl–	CH_3	1	**4t**	80	204–206
21	2′-Thiophenyl–	CH_3	1	**4u**	95	180–182[13i]
22	5′-Methylfurfuryl-	CH_3	1	**4v**	85	208–210
23[c]	H–	CH_3	4	**4w**	80	173–175
24	C_6H_5–	H	4	**4x**	80	202–203[13i]
25	*p*-ClC_6H_4-	H	4	**4y**	78	204–206[13i]
26	*o*-ClC_6H_4–	H	4	**4z**	82	244–246[13k]
27	*p*-$NO_2C_6H_4$–	H	4	**4A**	78	231–234[13i]
28	*p*-HOC_6H_4–	H	4	**4B**	79	270–271[13l]

[a] Reaction conditions: β-naphthol (1.0 mmol), aldehyde (1.0 mmol) and cyclic 1,3-dicarbonyl compound (1.0 mmol), catalyst (20 mg), at 80 °C, neat.
[b] Isolated yield based on **1**.
[c] Formaldehyde (3.0 mmol).

cations.[14,24] HY, NaY, CaY, FeY, CuY, NiY, ZnY, and AlY zeolites are examined for their catalytic activity for the synthesis of benzoxanthenones. However, when compared to HY zeolite, they exhibit reduced activity (Table 1, entries 11–18),[17] which is attributed to the significant reduction in their Bronsted acidity (though they possess considerable Lewis acidic sites).

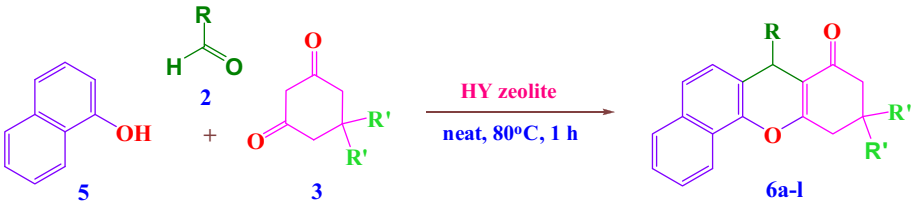
It is thus found that HY zeolite is the best choice of strong solid metal-free catalyst under solvent-free conditions.[25] An increase in the reaction temperature from room temperature to 60 and 80 °C accelerates the reaction to give the desired product in optimum yield, but further increase in the temperature to 90 and 100 °C does not cause any improvement in yield (Table 1, entry 19). When 20 mg of HY zeolite is used, the reaction proceeds smoothly to give the product (Table 1, entry 21) in a 93% yield. Consequently optimum reaction conditions for HY zeolite catalyzed synthesis of benzoxanthenones under solvent-free conditions are at 80 °C for 1 h.

This easy and clean protocol for the synthesis of functionalized benzo[a]xanthenones and benzo[c]xanthenones is extended to various substituted aldehydes and cyclic 1,3-dicarbonyl compounds and the observed results are depicted in Tables 2 and 3. This reaction works very well for a variety of electronically divergent aldehydes, with 5,5-dimethyl-1,3-cyclohexanedione and β-naphthol in very good to excellent isolated yield. The reaction proceeds smoothly with electron-rich, as well as electron-deficient aromatic, aliphatic, cyclic, and heterocyclic aldehydes with moderate to excellent yield. Various functional groups such as NO_2, Cl, OH, OCH_3, and CH_3 are tolerated. When substituents are present in the *para*-position (Table 2, entries 2–4, 7, 9, 10 and 12) higher yield is obtained compared to substituents present in the *meta*- and *ortho*- positions (Table 2, entries 5, 6, 8 and 11). When more than one substituent is present in the phenyl ring, the yield does not change significantly (Table 2, entries 13 and 14). Interestingly, aliphatic aldehydes such as formaldehyde (Table 2, entry 23), 3-methylbutyraldehyde (Table 2, entry 17) crotonaldehyde (Table 2, entry 18), and cyclohexanecarboxaldehyde (Table 2, entry 15) gave the expected products in moderate to good yield. Trace amount of the product is obtained with phenylacetaldehyde (Table 2, entry 16) and cinnamaldehyde (Table 2, entry 19). These results clearly suggested that electronic factors play a limited role and steric factors play a major role in the product formation.

Encouraged by successful condensation of aldehydes, β-naphthol with 5,5-dimethylcyclohexane-1,3-dione, we decided to explore the condensation reaction of cyclohexane-1,3-dione with substituted aldehydes and β-naphthol and products are obtained with very good to excellent isolated yield.

To extend the scope of the reaction with the above optimized conditions, the reactions are also extended to α-naphthol, substituted aldehydes, and cyclic 1,3-dicarbonyl compounds. HY zeolite catalyzes this condensation reaction smoothly and affords the corresponding benzo[c]xanthenones in excellent yield under solvent-free

Table 3
Synthesis substituted benzo[c]xanthenones[25] using α-naphthol, substituted aldehydes and cyclic 1,3-dicarbonyl compounds[a]



Entry	R	R′	Time (h)	Product	Yield[b] (%)	m.p. (°C)
1	C_6H_5–	CH_3	1	**6a**	87	155–157[13m]
2	*m*-$NO_2C_6H_4$–	CH_3	1	**6b**	62	157–158[13m]
3	*p*-FC_6H_4–	CH_3	1	**6c**	93	176–177
4	*p*-ClC_6H_4–	CH_3	1	**6d**	87	178–179[13m]
5	*p*-HOC_6H_4–	CH_3	1	**6e**	77	185–187
6	*p*-$CH_3OC_6H_4$–	CH_3	1	**6f**	92	148–150
7	*m*-$CH_3OC_6H_4$–	CH_3	1	**6g**	84	176–178[13m]
8	C_6H_5CH=CH–	CH_3	1	**6h**	82	61–62[13n]
9	2′-Thiophenyl–	CH_3	1	**6i**	82	163–164[13m]
10	C_6H_5–	H	1	**6j**	82	173–175[13m]
11	*p*-$NO_2C_6H_4$–	H	1	**6k**	90	177–179
12	*p*-ClC_6H_4–	H	1	**6l**	92	175–177

[a] Reaction conditions: α-naphthol (1.0 mmol), aldehyde (1.0 mmol) and cyclic 1,3-dicarbonyl compound (1.0 mmol), catalyst (20 mg), at 80 °C, neat.
[b] Isolated yield based on **5**.

Table 4
Reusability of HY zeolite in synthesis of benzo[a]xanthenones from β-naphthol, benzaldehyde and 5,5-dimethyl-1,3-cyclohexanedione[a]

Run[b]	First	Second	Third	Fourth	Fifth
Yield (%)	93	90	85	82	82

[a] Reactions are performed on a 1 mmol scale of all reactants in solvent-free conditions for 1 h at 80 °C.
[b] After completion of the reaction, catalyst is filtered and washed thrice with ethyl acetate, air dried, activated and reused for successive runs.

conditions, and also tolerates various functional groups such as OCH_3, F, Cl, NO_2, and OH with excellent yield (Table 3). This greener approach provides a mild and general route to synthesize various classes of 7-aryl substituted benzo[c]xanthenones and 12-alkyl/aryl substituted benzo[a]xanthenones. These results clearly prove that this method is more advantageous than the previously reported methods[13a–n] in terms of ecofriendliness in catalyst, much higher yield, reduced reaction time, and above all reusability. Reusability of the catalyst was also tested upto 5 successive runs, with only marginal decrease in catalytic activity (Table 4).

To account for the facile catalysis by HY zeolite in the synthesis of benzoxanthenones, a plausible mechanism is proposed (Scheme 2). The reaction proceeds via the *ortho*-quinone methides intermediate, formed by the nucleophilic addition of 2-naphthol to protonated aldehydes catalyzed by the Bronsted acidic sites of HY zeolite.[18–20] Subsequent Michael addition of this in situ formed *ortho*-quinone methides to 1,3-dicarbonyl compound followed by addition of the phenolic hydroxyl moiety to the carbonyl groups of ketone provides cyclic hemiketal which on dehydration affords the product.

Antimicrobial activity of benzoxanthenones

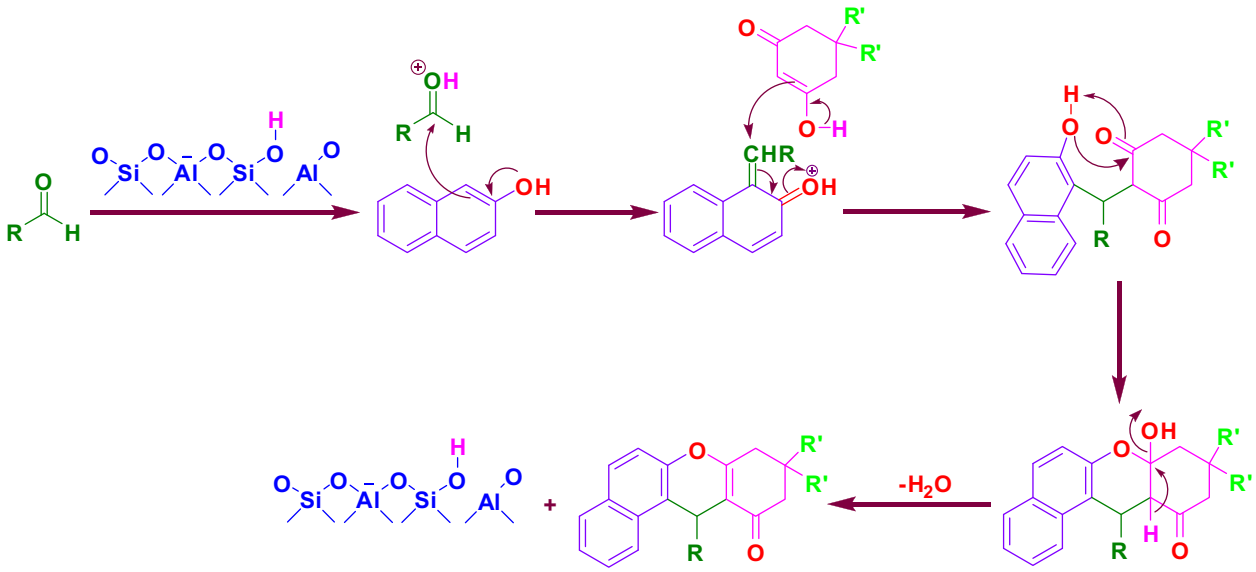
The synthesis of several new derivatives of benzoxanthenones (Fig. 1) by condensation of β-naphthol, various substituted aromatic, aliphatic, cyclic, and heterocyclic aldehydes with cyclic 1,3-dicarbonyl compounds catalyzed by HY zeolite, prompted us to evaluate the antibacterial activity of these synthesized benzoxanthenones.[21]

We tested the strains of *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter sps*, *Proteus mirabilis*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Bacillus coagulase*, *Staphylococcus aureus*, and *Staphylococcus saprophyticus* against the 10 new benzoxanthenones given in Figure 1 (not reported in literature) (Table 5). The results suggest that, products **4e**, **4h**, **4i**, **4m**, **4o**, **4q**, **4r**, **4v**, **4t,** and **4w** exhibited mild to good inhibitory effect against most of the tested microbes. Compounds **4h** and **4i** are found to have good inhibitory effect on the *K. pneumonia* and *S. aureus*, respectively. Compound **4q** is effective against *S. aureus* and *B. coagulase* and **4v** is shown to be effective against *B. subtilis* and *E. coli*. The studies, thus confirm, the potential biological activity and consequent utility of these derivatives as potent drug sources.

Cell imaging studies[26]

Organic fluorophores have found extensive applications in cell imaging.[22] However, their drawbacks, such as narrow excitation, single, wide emission with a long tail, poor photostability, etc., limited their applications in areas such as multiplexing and real-time measurements. Generally benzoxanthenones have wide, long wavelength emission and also exhibit unique properties such as multiple emissions, wide excitation window, low cytotoxicity, and excellent photostability (vide infra) to make them ideal candidates for cellular imaging. Benzo[c]xanthenones were marketed by Molecular Probes (formerly Invitrogen, and now Life Technologies) in the early 1990s. These dyes are long wavelength fluorescent pH_i indicators and have one benzene and a naphthalene component in the fluorophore.[23]

In the present preliminary study, selected benzoxanthenones are tested for cell imaging studies of K562, a human erythromyeloblastoidleukemia cell line. Cellular imaging studies using confocal microscope reveal that benzoxanthenone dye **4h** readily enters **K562** cells whereas the other dyes **4m** and **4t** are not taken by the cells (Fig. 2). Compound **4h** is localized on **K562** cells, and



Scheme 2. Proposed mechanistic pathway for the condensation reaction of aldehyde, β-naphthol, and cyclic 1,3-dicarbonyl compound.

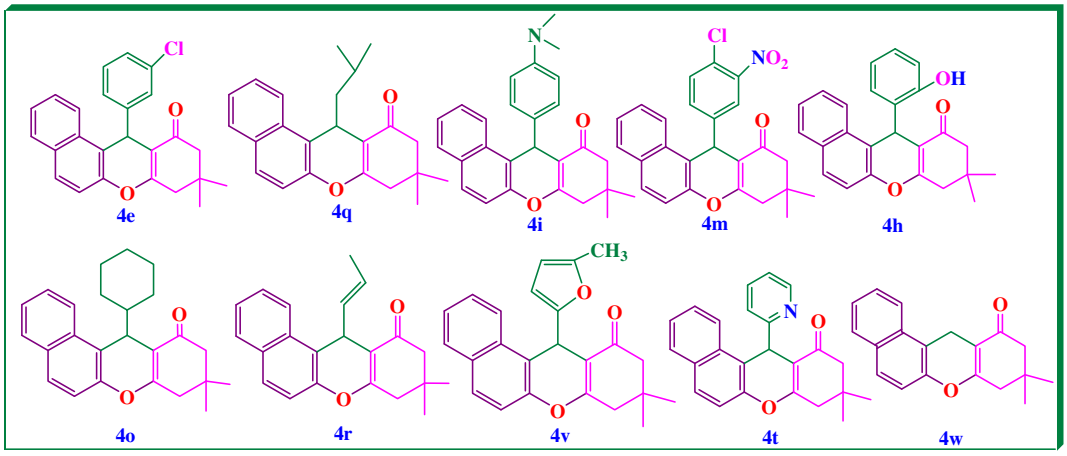


Figure 1. 12-Substituted 8*H*-benzo[a]xanthen-11(12*H*)-one reported for the first time.

Table 5
Antimicrobial activities of 12-substituted benzoxanthenones determined by disk-diffusion method (zone of inhibition in mm) at10 μg/mL in Muller-Hinton Agar

Organisms	Control (ampicillin)	4e	4h	4i	4m	4o	4q	4r	4v	4t	4w
S. aureus	17.5	–	–	18.0	10.2	–	17.5	8.3	–	11.0	10.1
S. saphyrophiticus	15.5	–	–	–	10.0	–	10.5	–	–	–	–
B. subtilis	15.0	11.0	9.8	11.0	12.4	10.5	13.5	9.8	15.0	9.4	–
B. coagulase	18.5	–	10.5	–	10.5	9. 6	18.5	10.5	10.5	10.0	–
E. coli	17.5	13.0	10.5	–	–	10.2	12.0	8.5	17.5	–	14.5
P. aeruginosa	15.0	9.0	–	–	–	–	–	–	11.5	–	–
K. pneumoniae	17.2	8.0	17.5	–	10.2	–	12.5	–	10.0	11.0	13.8
Enterobacter	15.5	10.0	10.5	–	12.2	9.8	12.3	10.5	9.8	10.0	–
P. mirabilis	15.2	10.0	9. 6	–	10.0	10.5	10.5	9. 8	9. 0	9. 0	–
P. vulgatis	17.0	9.2	10.2	10.0	11.0	10.5	11.5	10.0	10.	10.2	13.4

has emitted red and green fluorescence. The intensity profiles are shown in Figure 2 (g).

In conclusion, a mild and efficient method for the synthesis of benzoxanthenones via three-component reaction catalyzed by HY zeolite under solvent-free aerobic conditions is reported. The salient features of this atom economical procedure are its reusability, inexpensiveness environmentally benign nature, use of metal-free heterogeneous solid acid catalyst with good to high yield, shorter reaction times, tolerancy toward wide range of functional groups, operational simplicity, and easy separation. Some of the new compounds exhibit significant biological activity against various microbes. Observations using confocal microscopy in living cells, (K562, a human erythromyeloblastoidleukemia cell lines) by selected substrates, highlight the importance of benzoxanthenone

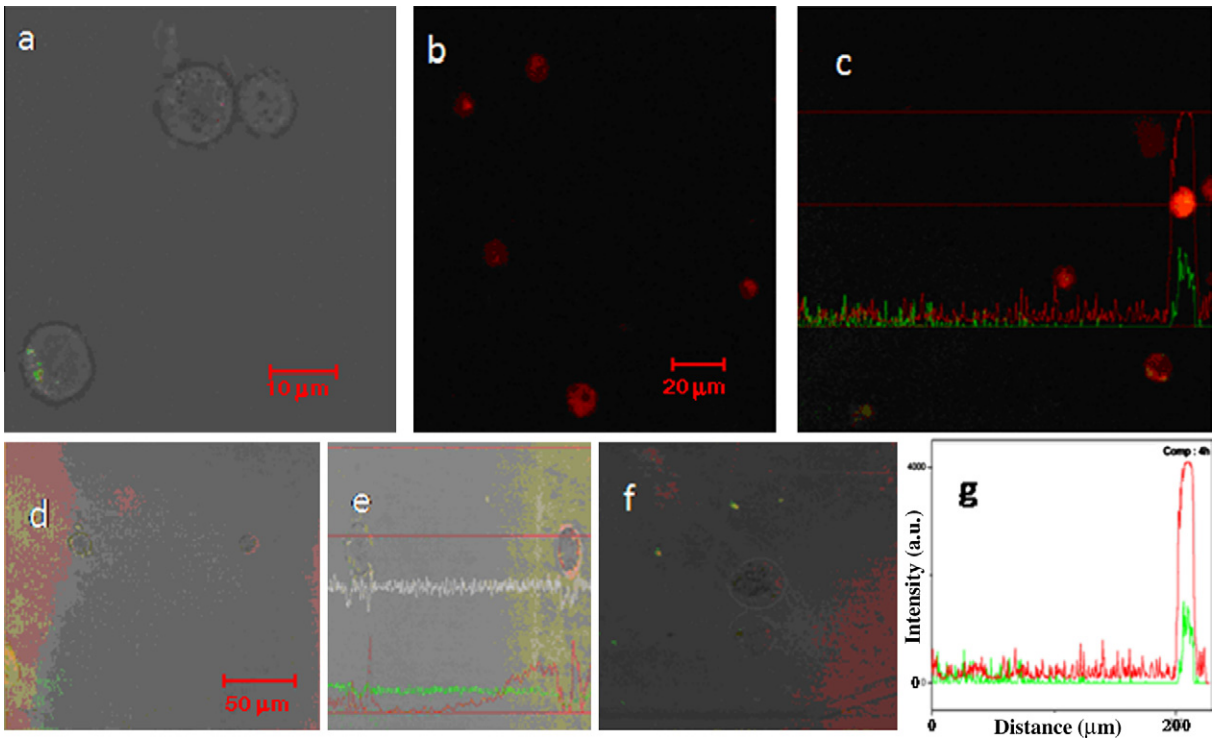


Figure 2. (a) Unstained cells used as control showing no fluorescence; (b) staining of cells by **4h** shows fluorescence emission confirming the uptake of the dye by cells, monitored at 40× magnification; (c) intensity of green and red fluorescence of **4h**, monitored at 40× magnification; (d) and (f) staining of cells with **4m** and **4t** did not show any fluorescence emission.

dyes in cell imaging studies. Further works are in progress for cell imaging and live cell measurement with a wide range of substituted benzoxanthenones.

Acknowledgment

Financial support from UGC Hyderabad, for an award under FDP to V.R. is gratefully acknowledged.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.10.143.

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24. *General method for the preparation of cation-exchanged zeolites:* NaY zeolite powder is purchased from Sigma–Aldrich and used as such. The physicochemical parameters of NaY zeolite are Si/Al ratio 2.43, unit cell size 24.65 Å and surface area, m^2/g: 900 with supercages of a diameter of ca. 1.3 nm. Cation-exchanged zeolites (Ca^{2+}, Fe^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+} and Al^{3+}) are prepared by ion-exchange method.[14j] The cations of interest are exchanged into the NaY zeolite powder (10 g) by stirring with the corresponding nitrate solution (100 ml, 10%) at 90 °C for about 12 h. The exchange is repeated at least four times. Each time, after exchange, the zeolite powder is washed repeatedly with distilled water and then dried. All these cation-exchanged zeolites are activated at 450 °C for about 6 h prior to use.
25. *General procedure for the synthesis of benzoxanthenones over HY zeolite catalyst:* NH_4Y zeolite powder is purchased from Sigma–Aldrich and used as such. The physicochemical parameters of NH_4Y zeolite are Si/Al ratio 2.9, unit cell size 24.68 Å and surface area, m^2/g: 925 with supercages of a diameter of ca. 1.38 nm. Zeolite HY is obtained by the thermal deammonification of NH_4Y zeolite at 450 °C. A heterogeneous mixture of naphthol (1.0 mmol), aldehyde (1.0 mmol), cyclic 1,3-dicarbonyl compound (1.0 mmol) and HY zeolite (20 mg) is heated at 80 °C for 1 h in oil bath under solvent-free condition. The progress of the reaction is monitored by TLC. After completion of the reaction, the product is extracted by ethanol and filtered using Whatmann No. 4 filter paper. The filtered catalyst is washed thrice with ethyl acetate, air dried, activated and reused for successive runs. The filtrate is concentrated and the crude product is recrystalized from ethanol. All the products are well characterized by ^1H & ^{13}C NMR spectra and melting points which are all found to be comparable with the reported ones.[13a–n]
26. *General procedure for the cell imaging studies of benzoxanthenones*[22]*:* The ability of the dye to enter the cells is studied by staining K562 cell lines with the dyes. K562 is a human erythromyeloblastoidleukemia cell line, non-adherent and characterized by round cells, are grown in RPMI 1640 media supplemented with 10% Foetal Bovine Serum in a humidified atmosphere containing 5% CO_2 at 37 °C. Stock solutions containing 10 mM of the dyes **4h**, **4m** and **4t** are prepared in DMSO. The cells are treated with the dyes at a final concentration of 10 μM and are incubated for 1 h. The cells are centrifuged at 2000 rpm for 5 min. The supernatant portion is removed and the pellet is suspended in Phosphate Buffered Saline (PBS). The cells are spotted on the slide and observed for fluorescences using confocal microscope (Zeiss LSM 510 META) by exciting at 514 and 633 nm and the emissions are obtained using emission filters BP 505-550 and LP 585, respectively. Cells without treatment with the dye are used as control.