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Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/lsyc20

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To cite this article: Ahmed F. Darweesh , Soad K. Salama , Ismail A. Abdelhamid & Ahmed H. M. Elwahy (2020): Green synthesis of novel bis(hexahydro-1*H*-xanthene-1,8(2*H*)-diones) employing *p*-toluenesulfonic acid (*p*-TSA) as a solid acid catalyst, Synthetic Communications, DOI: 10.1080/00397911.2020.1837170

To link to this article: https://doi.org/10.1080/00397911.2020.1837170

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https://doi.org/10.1080/00397911.2020.1837170

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Green synthesis of novel bis(hexahydro-1*H*-xanthene-1,8(2*H*)-diones) employing *p*-toluenesulfonic acid (*p*-TSA) as a solid acid catalyst

Ahmed F. Darweesh, Soad K. Salama, Ismail A. Abdelhamid, and Ahmed H. M. Elwahy

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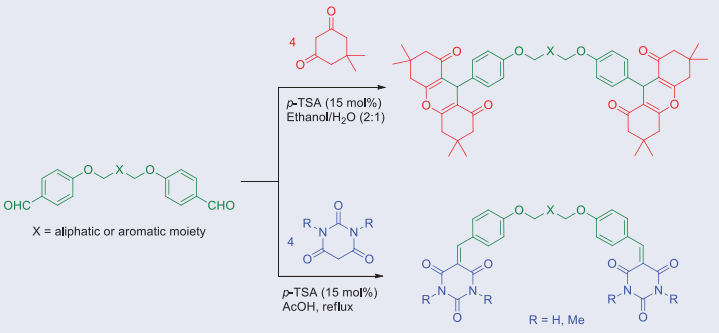
ABSTRACT

Green synthesis of novel *bis*(hexahydro-1*H*-xanthene-1,8(2*H*)-diones) which are linked to aliphatic or aromatic spacers *via* ether or ester linkages were performed in good to excellent yields by the reaction of 5,5-dimethyl-1,3-cyclohexanedione with the appropriate *bis*-aldehydes using *p*-TSA as an organic acid solid catalyst. The reaction of the *bis*-aldehydes with barbituric acid or 1,3-dimethylbarbituric acid instead of 5,5-dimethyl-1,3-cyclohexanedione afforded the corresponding Knoevenagel condensation adducts in good yield.

GRAPHICAL ABSTRACT



ARTICLE HISTORY
Received 31 August 2020

KEYWORDS
Bis(aldehydes); 55-dimethyl-13-cyclohexanedione; p-TSA bis(hexahydro-1H-xanthene-18(2H)-diones); bis(pyrimidine-246(1H3H5H)-trione)

Introduction

Xanthene derivatives are an important class of heterocyclic compounds containing a pyran nucleus. Due to their wide variety of medicinal and biological properties such as anti-inflammatory,[1,2] antibacterial,[3] antiviral,[4] antifungal,[5] antitumor[6] and anti-proliferative[7] activities, these compounds attracted the attention of organic chemists. Some derivatives of xanthene have also been found to show promising leishmanicidal activity while other derivatives have been reported to act as potential α-glucosidase inhibitors.[8]

Many well-known xanthene-containing medications such as Ro67-4853 (a positive allosteric modulator of metabotropic glutamate 1 receptors), propantheline bromide (an

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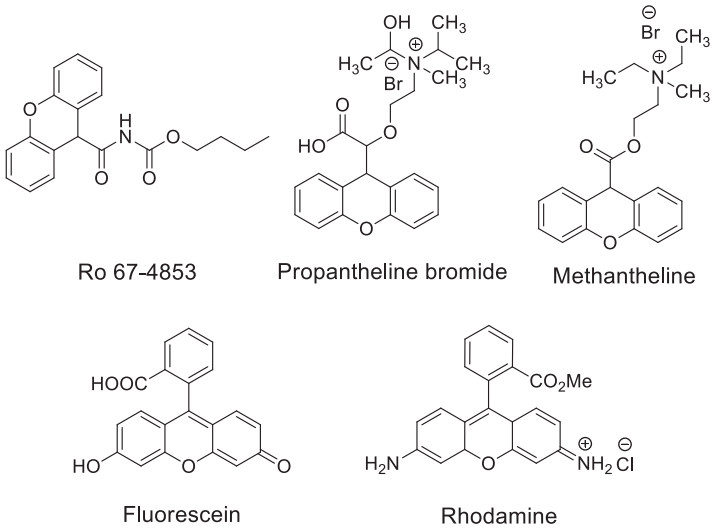


Figure 1. Structures of some pharmacologically active xanthenes as well as some xanthene dyes.

antimuscarinic agent used to treat excessive sweating [hyperhidrosis]), and methantheline (antispasmodic drug) are outlined in Figure 1.[9] Besides, some xanthene derivatives are used as sensitizers in photodynamic therapy (PDT).[10] They can also be used as dyes,[11] as pH-sensitive fluorescent materials[12] and can be used in laser technology[13] as well. Fluorescein and rhodamine are among the most commonly known xanthene dyes (Figure 1). Recently, xanthene synthesis and applications have been reviewed.[14]

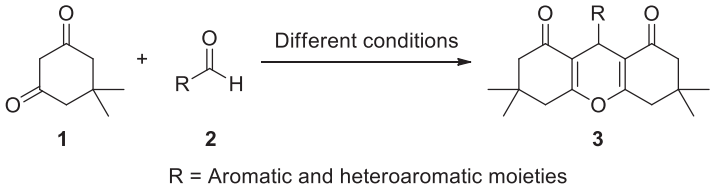
Recently the synthesis of bis(heterocycles) has attracted great attention.[15–17] A combination of several multiple heterocyclic cores as symmetrical or unsymmetrical bis-heterocycles in a single molecular system was found to exploit the pharmacological and altered physical properties of the resulting multivalent ligands. In this regard, several bis(heterocyclic) derivatives have been reported to exhibit bioactivity that includes anticancer,[18–20] fungicidal[21] and antibacterial[22] properties. They also have diverse applications as metal ligands,[23] chelating agents,[24] and electrically conducting materials.[25]

Moreover, the employment of homogenous catalysts, heterogeneous catalysts or nano-catalysts in organic synthesis has recently attracted much attention.[26–31]

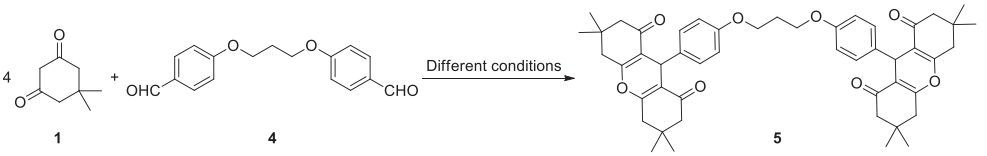
Motivated by these findings and as a part of our increasing interest in searching for environmentally friendly methods for synthesis of heterocyclic as well as bis(heterocyclic) compounds,[32–50] we report here on the green synthesis of new, structurally diverse bis(xanthenes) libraries as to the best of our knowledge, very little is known about this class of compounds.

Results and discussion

Many strategies have been reported for the synthesis of xanthenes, among them, the condensation of aldehydes with β-cyclic 1,3-dicarbonyl compounds was found to be the simplest one for the synthesis of symmetric xanthenes. Various catalysts have been reported for the preparation of these types of xanthenes including homogeneous[2,51,52] or reusable heterogeneous nanocatalysts.[53,54] The reactions were carried out in the



Scheme 1. Reported methods for the synthesis of symmetric xanthenes.



Scheme 2. Synthesis of bis(hexahydro-1*H*-xanthene-1,8(2*H*)-dione) **5.**

Table 1. Effect of the solvent on the synthesis of compound **5**.

Entry	Solvent	Yield[a,b] (%)
1	Ethanol	66
2	Ethanol/ H_2O (1:1)	88
3	H_2O	56
4	THF	36
5	DMF	42
6	AcOH	43
7	Neat	19

[a]The reaction was performed at refluxing temperature of solvents for 6 h. (monitored by TLC).
[b]The reaction was carried out in the presence of 15 mol% of *p*-TSA.

Table 2. Effect of the amount of *p*-TSA catalyst and reaction time on the synthesis of compound **5**.

Entry	*p*-TSA (mol%)	Time (h)	Yield[a] (%)
1	5	2	61
2	5	4	69
3	5	6	75
4	10	4	77
5	10	6	83
6	15	4	84
7	15	6	88
8	15	10	Nil[b]

[a]The reaction was performed in Ethanol/H_2O (1:1) at reflux.
[b]The reaction was performed in Ethanol/H_2O (1:1) at room temperature.

presence of solvents or under solvent-free conditions.[13,55,56] They were also performed under conventional heating as well as under microwave[57,58] or ultrasound irradiation (Scheme 1).[59,60]

Firstly, we studied the synthesis of bis(hexahydro-1*H*-xanthene-1,8(2*H*)-dione) **5** by investigating the reaction of one equivalent of 4,4′-(propane-1,3-diylbis(oxy))dibenzaldehyde (**4**) with four equivalents of 5,5-dimethyl-1,3-cyclohexanedione (**1**) as a model reaction at different conditions (Scheme 2). The results are summarized in Tables 1 and 2.

The reaction was carried out in the absence as well as in the presence of *p*-TSA as a cheap and readily available organic acid catalyst with excellent catalytic property, especially as a

proton donor.[61,62] We studied the effect of various solvents (EtOH, H_2O, Ethanol/H_2O (1:1), THF, AcOH, and DMF) on the yield of the reaction. The reaction was also performed under solvent-free conditions. The best results were obtained when the reaction mixture was performed in the presence of 15 mol% of *p*-TSA in a mixture of Ethanol/H_2O (1:1) as a solvent (Table 1, entry 2). The reaction proceeded also under solvent-free conditions to give the target molecule but in very low yields (Table 1, entry 7).

To evaluate the effect of the catalyst under the reaction conditions, the reaction was performed in the presence of different amounts of catalyst loading. As outlined in Table 2, the reaction did not proceed successfully in the absence of the catalyst and the desired product could not be obtained even after prolonged heating. *p*-TSA (15 mol%) was found to be the optimum amount of catalyst (Table 2, entry 6&7). Larger amounts of the catalyst did not improve the yields while decreasing the amount of catalyst decreased the yields.

The reaction was attempted at room temperature and also under heating. The reactions afforded good yields of the products at the refluxing temperature of solvents (Table 2, entry 1–7). On the other hand, no traces of the products were obtained at room temperature even after a prolonged time (Table 2, entry 8). The influence of the reaction time on the yield was also investigated. It was found that higher yield occurred when the reaction time was 6 h. (Table 2, entry 7).

The structure of target compound **5** was established based on spectral data. Thus, its IR spectra revealed the carbonyl group at 1666 cm^{-1}. In the ^1H NMR spectrum, the hydrogen atom of the pyran ring was observed at 4.45 ppm. Moreover, the ^{13}C NMR spectrum of **5** was found to be in agreement with the proposed structure, it showed the pyran C-4 at 30.2 ppm and the carbonyl group at 195.9 ppm. Further structural verification was obtained from its mass spectroscopy, which showed the correct molecular ion peak at m/z 772.

To explore the scope and limitations of this reaction, a range of *bis*-aldehydes **6–9** were allowed to react with 5,5-dimethyl-1,3-cyclohexanedione (**1**) under the above-mentioned conditions to give the corresponding *bis*(hexahydro-1*H*-xanthene-1,8(2*H*)-diones) **10–13** which are linked to aliphatic spacers *via* ether linkages in good to excellent yields (Scheme 3).

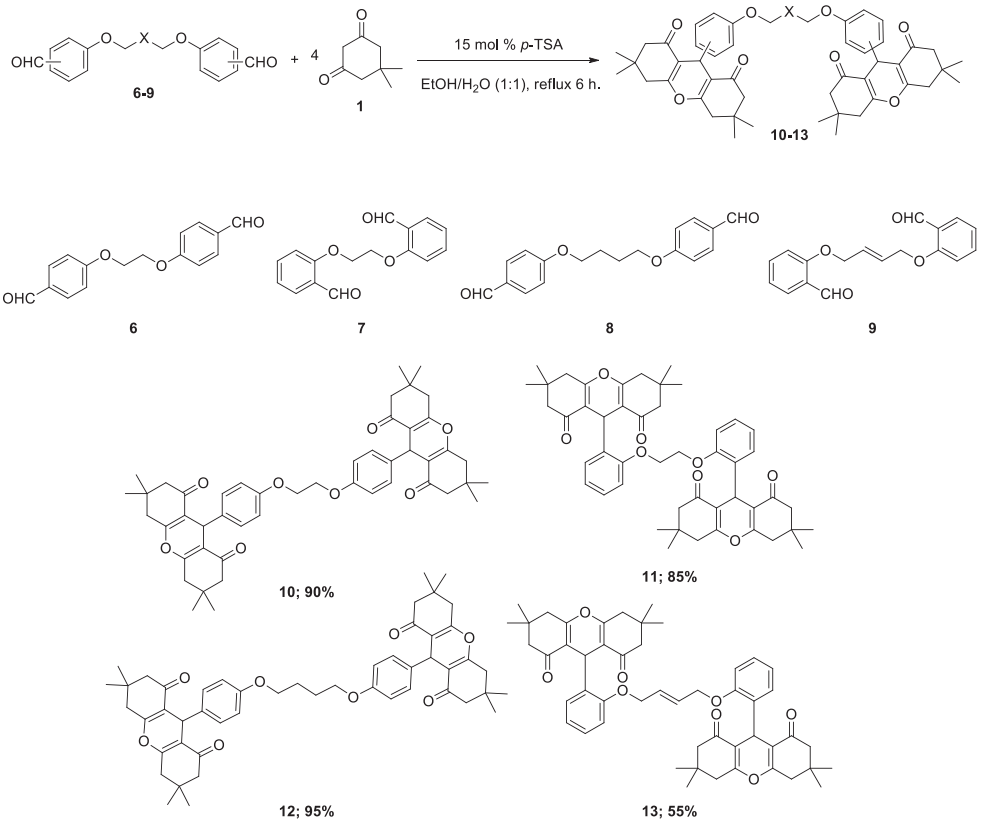
Similarly, the reaction of 5,5-dimethyl-1,3-cyclohexanedione (**1**) with *bis*-aldehydes **14–16** under similar reaction conditions afforded *bis*(hexahydro-1*H*-xanthene-1,8(2*H*)-diones) **17–19** which are linked to aromatic spacers *via* ether linkages (Scheme 4).

Likewise, the *bis*-aldehydes **20–22** were utilized as versatile precursors to a variety of novel *bis*(hexahydro-1*H*-xanthene-1,8(2*H*)-dione) derivatives **23–25** containing carboxylate ester linkages (Scheme 5).

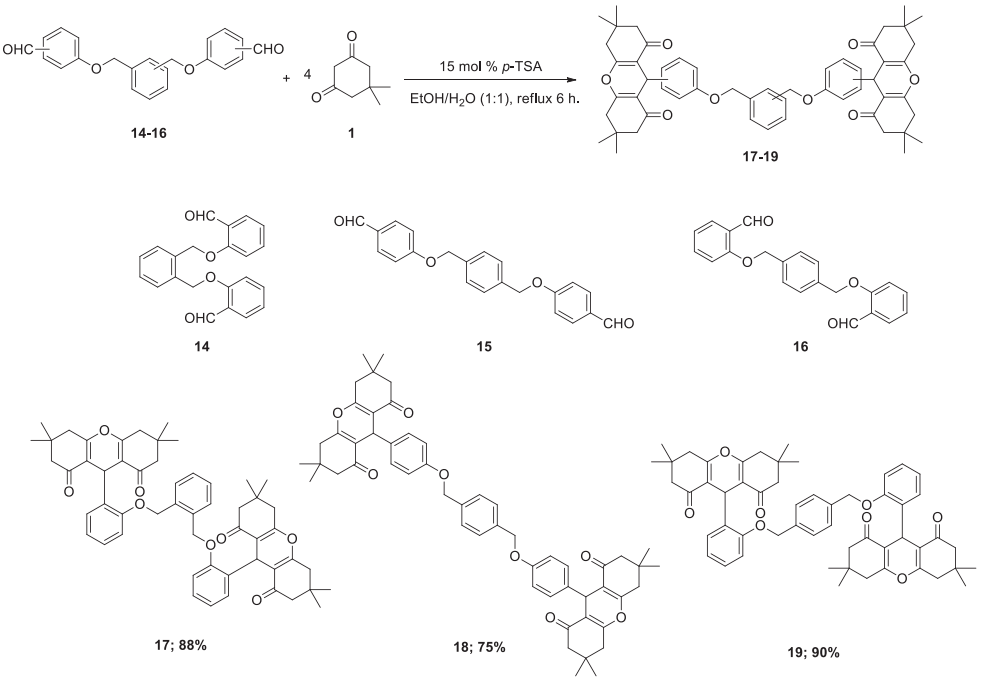
Bis-aldehydes **4, 6–9** and **14–16** were prepared in good yields as previously reported by the reaction of the potassium salt of the appropriate hydroxybenzaldehyde with the corresponding bis(bromomethyl) derivatives in boiling DMF.[49,50,63–65]

The *bis*-aldehydes **20–22** were prepared by the reaction of 4-formylbenzoic acid with the appropriate dihalo compounds in DMF at reflux.[66,67]

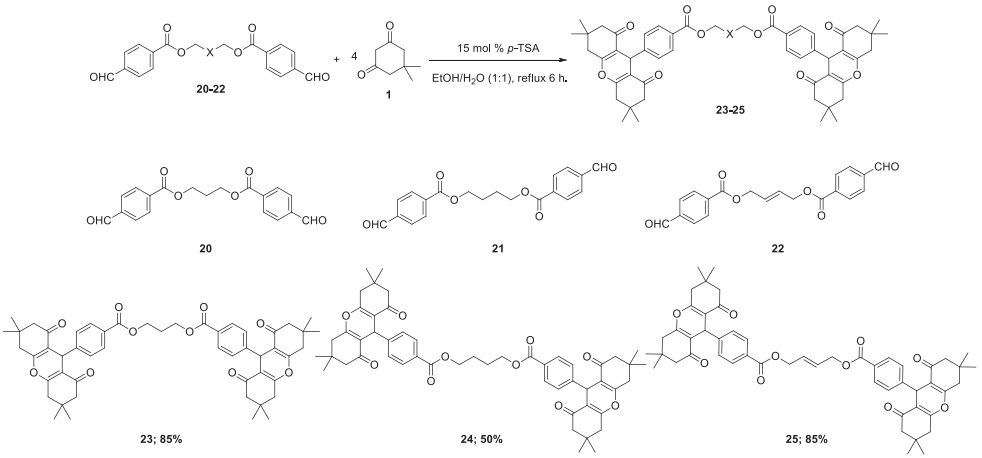
Generally, the employment of bis-aldehyde with formyl substituents either at the *ortho*- or *para*- positions of the ether linkages showed no remarkable effect on product



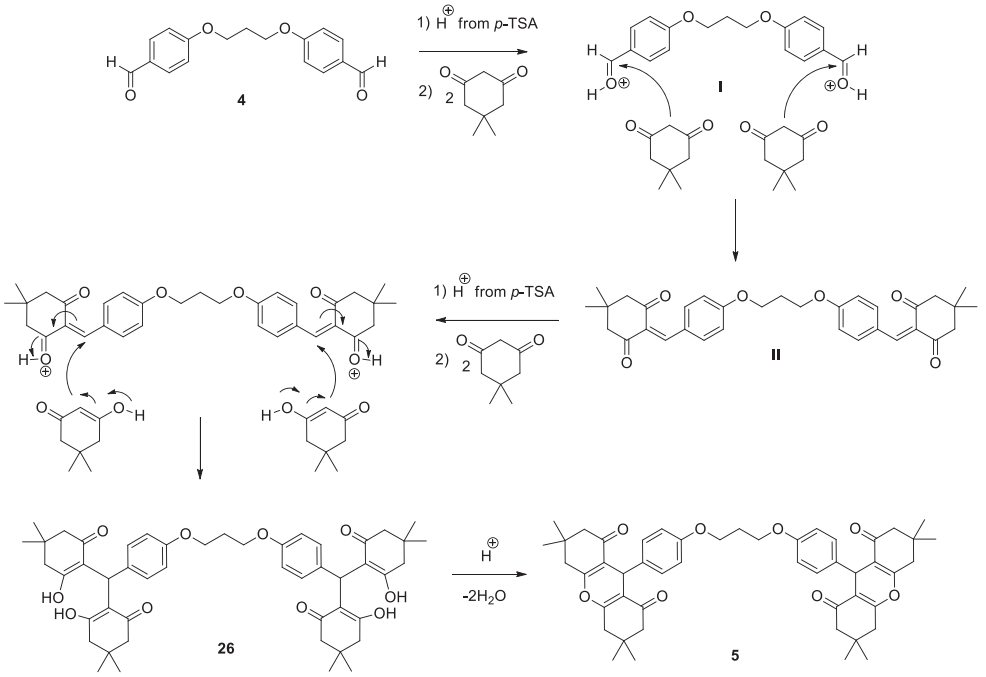
Scheme 3. Synthesis of *bis*(hexahydro-1*H*-xanthene-1,8-diones) **10–13.**



Scheme 4. Synthesis of bis(hexahydro-1*H*-xanthene-1,8-diones) linked to aromatic spacers **17–19.**



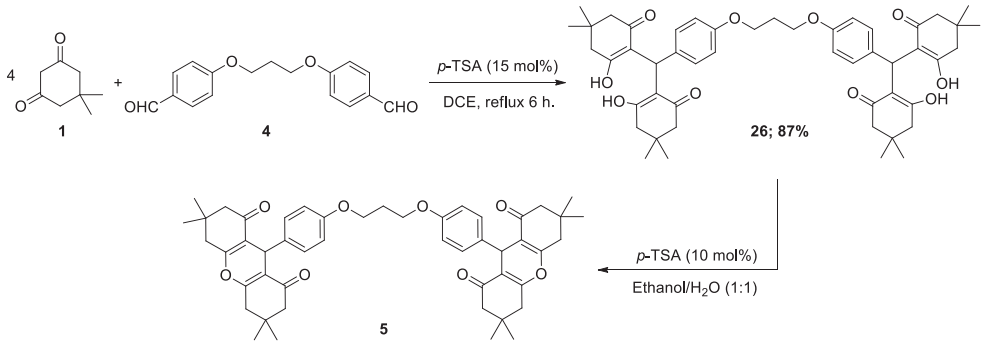
Scheme 5. Synthesis of bis(hexahydro-1*H*-xanthene-1,8-diones containing carboxylate ester linkages **23–25**.



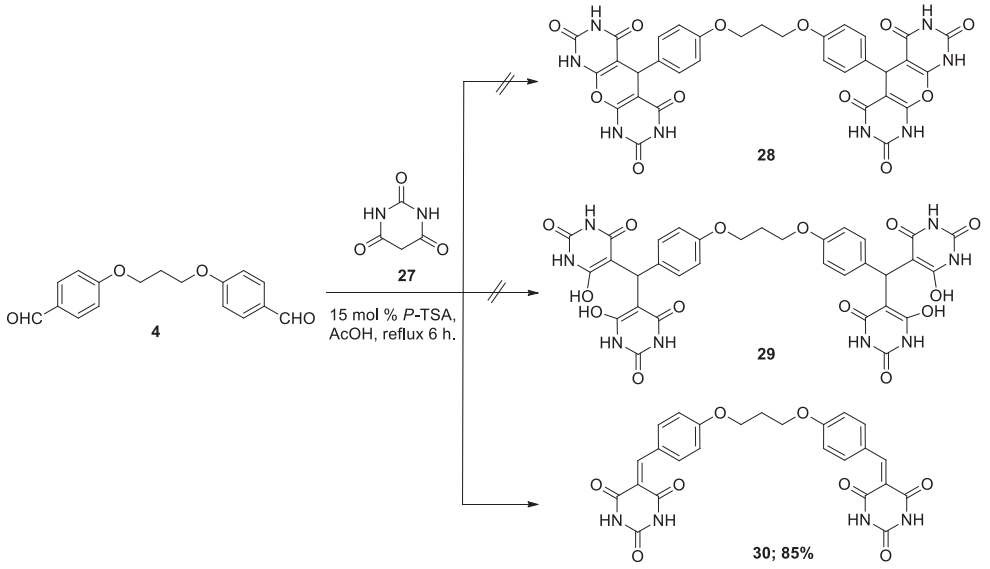
Scheme 6. Plausible mechanism for the formation of **5.**

yield and reaction time. Moreover, the length of the spacers was found to have no significant improving effect on reaction yields.

The plausible mechanism for the formation of **5** from the reaction of 5,5-dimethyl-1,3-cyclohexanedione with the corresponding aldehyde **4** is illustrated in Scheme 6. The mechanism includes one-pot Knoevenagel condensation, Michael addition, and cyclodehydration reaction. At first, the electrophilicity of the carbonyl carbon of the bis-aldehyde could have been activated by the H^+ from *p*-TSA followed by attack of two moles



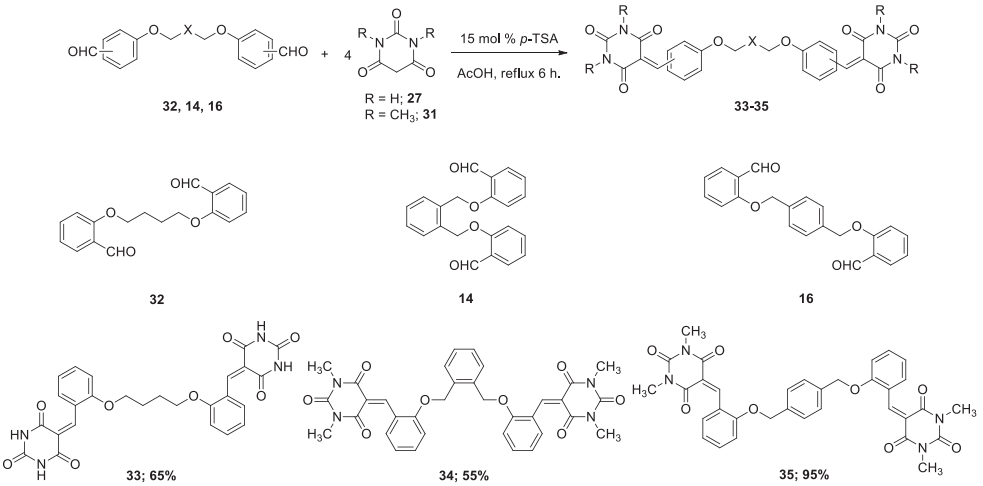
Scheme 7. Synthesis of tetrakis(3-hydroxy-5,5-dimethylcyclohex-2-en-1-one) **26** and bis(hexahydro-1*H*-xanthene-1,8(2*H*)-dione) **5.**



Scheme 8. Reactivity of bis-aldehyde **4** toward barbituric acid.

of the nucleophilic cyclohexanedione derivatives on the carbonyl carbons to form the Knoevenagel product **II**. Subsequent addition of this fragment to another two moles of 5,5-dimethyl-1,3-cyclohexanedione gives the acyclic adduct intermediate **26**. Subsequent intramolecular dehydrative cyclization with the participation of four hydroxyl groups affords the xanthene derivative **5** (Scheme 6).

In support of this mechanism, we managed to separate the tetrakis(3-hydroxy-5,5-dimethylcyclohex-2-en-1-one) **26.** Thus, performing the same reaction in DCE at refluxing temperature afforded the corresponding tetraketone **26** as a sole product in excellent yield (Scheme 7). Ring closure of **26** to the corresponding **5** was successfully achieved by heating of **26** in ethanol/water mixture (1:1) in the presence of *p*-TSA (15 mol%). Tetraketones are considered not only as an important class of biologically active compounds but also as significant precursors for the synthesis of various fused heterocyclic.[68]



Scheme 9. Synthesis of bis(pyrimidine-2,4,6-triones) **33–35.**

The structure of the compound **26** was confirmed spectroscopically. In the IR spectrum, the carbonyl and the hydroxyl stretching frequencies were noticed at 1651 and 3224–3502 cm^{-1}, respectively. The ^{1}H NMR spectrum of **26** displayed a broad at 3.85 ppm characteristic for the OH protons in addition to the pyran C-4 at 4.45 ppm. Its mass spectroscopy showed the correct molecular ion peak at m/z 808.

In order to broaden the scope of this protocol, we explored the reaction of the *bis*-aldehyde **4** with barbituric acid (**27**) or 1,3-dimethylbarbituric acid (**31**) instead of 5,5-dimethyl-1,3-cyclohexanedione (**1**) aiming at synthesizing the corresponding *bis*(1*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8(3*H*,5H,7H,9*H*)-tetraone) **28**. The reaction was carried out in the absence as well as in the presence of *p*-TSA in acetic acid at reflux. In both cases, the reaction did not afford compound **28** or the corresponding *bis*(methanetriyl))tetrakis(6-hydroxypyrimidine-2,4(1*H*,3*H*)dione) **29**. Instead, the corresponding Knoevenagel adducts **30** were obtained in excellent yield (Scheme 8).

The IR spectrum of compound **30** indicated the presence of the NH and the carbonyl groups at 3328, 1751, and 1666 cm^{-1}. The ^{1}H NMR spectra of compound **30** exhibited a singlet signal at 8.24 ppm and two singlet signals at 11.13 and 11.26 ppm belonging to the olefinic CH and -NH groups, respectively. The molecular formula of **30** was confirmed by mass spectrometry which showed the correct molecular ion peak at m/z 504.

Using a similar approach, the corresponding Knoevenagel adducts **33–35** were obtained in excellent yields upon treatment of the appropriate *bis*-aldehydes **32**, **14** and **16** with barbituric acid (**27**) or 1,3-dimethylbarbituric (**31**), respectively (Scheme 9).

Conclusion

We developed a simple one-pot green protocol for the preparation of symmetrical bis-xanthenes by condensation of various bis-aldehydes, with 5,5-dimethyl-1,3-cyclohexanedione using various reaction conditions. Operational simplicity, easy work-up, mild reaction conditions, clean production of the products in high isolated yields from readily available starting materials are significant advantages of the used protocol. Despite

the remarkable achievements in this area, the synthesis of novel structures of these interesting molecules using an inexpensive, easily available and metal-free catalyst is still in demand.

Experimental

General

Melting points were determined in open glass capillaries with a Gallenkamp apparatus. The infrared spectra were recorded in potassium bromide disks on a Pye Unicam SP 3-300 and Shimaduz FTIR 8101 PC infrared spectrophotometer. NMR spectra were recorded with a Varian Mercury VXR-300 NMR spectrometer at 300 MHz (^{1}H NMR) and 75 MHz (^{13}C NMR). Mass spectra (EI) were obtained at 70 eV with a type Shimadzu GCMQP 1000 EX spectrometer. Analytical thin-layer chromatography was performed using pre-coated silica gel 60,778 plates (Fluka), and the spots were visualized with UV light at 254 nm. Elemental analyses were performed on a Perkin-Elmer 240 micoanalyser at the Micro analytical Center of Cairo University. All chemicals were purchased from Sigma-Aldrich and used without further purification.

General procedure for the synthesis of compounds 5, 10–13, 17–19 and 23–25

A mixture of bis-aldehydes **4**, **6–9**, **14–16** or **20–22** (1 mmol), 5,5-dimethyl-1,3-cyclohexanedione (**1**) (4 mmol), *p*-TSA (15 mol%) in ethanol/H_2O (15 mL, 1:1) was heated at reflux for 6 h. The crude solid was isolated and recrystallized from the proper solvent.

9,9′-((Propane-1,3-diylbis(oxy))bis(4,1-phenylene))bis(3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione) (5)

Yield (88%), colorless powder (ethanol), mp 220–224 °C, IR (KBr): ν = 1666 (CO) cm^{-1}, ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.89 (s, 12H, 4CH_3), 1.02 (s, 12H, 4CH_3), 2.03–2.52 (m, 18H, dimedone H2, H7, H4, H5 & –OCH_2–$\underline{CH_2}$–OCH_2–), 4.01 (t, 4H, 2-OCH_2, J = 6.3 Hz), 4.45 (s, 2H, H9), 6.76 (d, 4H, ArH, J = 8.7 Hz), 7.04 (d, 4H, ArH, J = 8.4 Hz); ^{13}C NMR (DMSO-d_6) δ 26.4, 28.5, 30.2, 31.7, 50.0, 64.0, 113.6, 114.5, 128.9, 131.7, 136.4, 156.7, 162.5, 195.9. MS (EI, 70 eV): m/z (%) = 772 [M$^+$, 6.45%], 500 (4.65%), 365 (3.68%), 274 (100%). Anal. Calcd. for $C_{49}H_{56}O_8$: C, 76.14; H, 7.30. Found: C, 76.37; H, 7.49%.

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