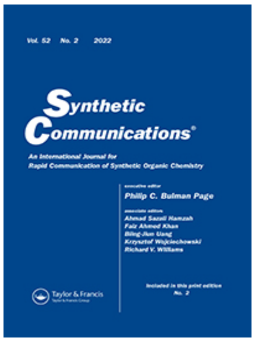


Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

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

A concise metal-free synthesis of xanthene derivatives mediated by achiral 2-aminophenol under solvent-free conditions

Mohinuddin Khan Imon, Readul Islam, Pran G. Karmaker, Pijush K. Roy, Kee-In Lee & Harendra N. Roy

To cite this article: Mohinuddin Khan Imon, Readul Islam, Pran G. Karmaker, Pijush K. Roy, Kee-In Lee & Harendra N. Roy (2022): A concise metal-free synthesis of xanthene derivatives mediated by achiral 2-aminophenol under solvent-free conditions, Synthetic Communications, DOI: 10.1080/00397911.2022.2047730

To link to this article: https://doi.org/10.1080/00397911.2022.2047730

SYNTHETIC COMMUNICATIONS®
https://doi.org/10.1080/00397911.2022.2047730

A concise metal-free synthesis of xanthene derivatives mediated by achiral 2-aminophenol under solvent-free conditions

Mohinuddin Khan Imon[a], Readul Islam[a], Pran G. Karmaker[a], Pijush K. Roy[a], Kee-In Lee[b], and Harendra N. Roy[a]

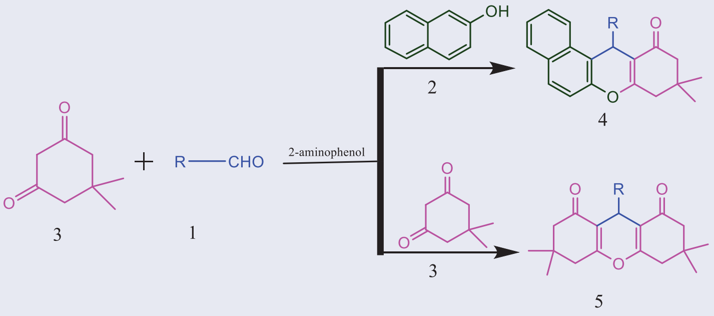
[a]Department of Chemistry, University of Rajshahi, Rajshahi, Bangladesh; [b]Korea Research Institute of Chemical Technology, Daejeon, South Korea

ABSTRACT
An efficient green technique has been developed for the synthesis of some biologically active 12-aryl or 12-alkyl 8,9,10,12-tetrahydrobenzo[*a*]xanthenes-11-one and 3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione derivatives have been described. This process arranged a three-component one-pot condensation of aldehydes, 2-naphthol, and dimedone mediated by 2-aminophenol and has offered an excellent scope of tailoring a large number of xanthene derivatives with good to charming yields. Short reaction time, straightforward, easy product isolation technique, non-toxic catalyst, and above all metal-free process are noteworthy advantages of this method.

ARTICLE HISTORY
Received 20 December 2021

KEYWORDS
Xanthene; multicomponent reaction; organo-catalyst; dimedone; *β*-naphthol; 2-aminophenol; solvent-free

GRAPHICAL ABSTRACT



Introduction

Recently synthesis of xanthene and benzoxanthene derivatives has attracted considerable attention in organic synthesis owing to their wide spectrum of therapeutic and biological properties, such as antiviral,[1] ant-inflammatory,[2] and agricultural bactericidal activity.[3] They have also been utilized in the preparation of dyes[4] in laser technologies,[5] for visualization of biomolecules,[6] and pH-sensitive fluorescent materials. Moreover, fused pyran ring systems especially pyranopyrimidines have immense

---

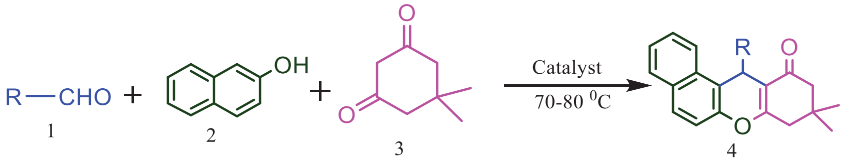
CONTACT Harendra N. Roy ✉ hnroy01@yahoo.com Department of Chemistry, University of Rajshahi, Rajshahi, Bangladesh.

Supplemental data for this article can be accessed on the publisher's website.

biological activities including antimicrobial,[7] anticonvulsant,[8] antiplatelet,[9] antibacterial,[10] antiphlogistic,[11] analgesic,[2] antigenotoxic,[12] anticancer,[13] antifungal activities,[14] and antioxidant.[15] This unusual property led to intensive research on the synthesis of xanthenes and naphthopyrano pyrimidine derivatives and thereby accelerating the need of developing newer synthetic routes for scaffold manipulation. Now various methods are available in tailoring xanthenes and benzoxanthene involving trapping of benzyne by phenols,[16] cyclo-condensation reaction between 2-hydroxyaromatic aldehydes and β-tetralone,[17] intramolecular phenyl carbonyl coupling reactions of benzaldehydes and acetophenone,[18] and the reaction of β-naphthol with β-naphthol-1-methanol,[19] and carbon monoxide.[20] However, all these methods are not free from restraints, such as low yields, requirements of longer reaction time, use of injurious solvents, excess use of reagents, toxic metal catalysts, and harsh reaction conditions. To avoid these numerous drawbacks, the reaction pattern has been largely replaced by mixing aldehydes with β-naphthol or dimedone in the presence of catalysts, such as *p*-TSA,[21] p-TSA/ionic liquid ([bmim]BF4),[22] Na-montmorillonite sulfonic acid,[23] amberlyst-15,[24] molecular iodine,[25] silica-sulfonic acid,[26] wet cyanuric chloride,[27] $K_{12}[As_2W_{18}Cu_3O_{68}]\cdot 30H_2O$, $K_{12}[As_2W_{18}U_3O_{74}]\cdot 21H_2O$,[28] boric acid,[29] PVPP-BF_3,[30] CAN,[31] and $InCl_3$.[32] Some nanoparticle catalyzed methods are available, such as nano-TiO_2,[33] ZnO-NPs,[34] brønsted ionic liquid,[35] perlite-SO_3H,[36] phosphoric acid supported on alumina[37] are notable. Most recently aluminized polyborate,[38] potassium fluoride impregnated on clinoptilolite nanoparticles (KF/CP NPs),[39] immobilization of Lewis acidic ionic liquid on perlite nanoparticle surfaces[40] were also employed to synthesize xanthene derivatives. Today some organic reactions were carried out in absence of solvents[41,42] in a regio-specific manner mediated by the metal-free catalyst,[43,44] especially organo-catalysts[45–47] recently proved as a powerful catalyst to such transformations, with high regio-and chemo-selectivity.[48,49] Furthermore, organo-catalyst has been found to be moisture tolerant, easy to handle, sub-stoichiometric, and environmentally friendly, and in the true sense, a few multi-component condensation reactions have been carried out by organo-catalyst to date. We previously found that L-proline, amino alcohol, and 3-picolinic acid are effective organo-catalysts for condensing three or four-component coupling reactions.[50–52] Up till now, in xanthene derivative synthesis, a few pure organo-catalysts driven method has been deployed.[53–55] The procedures described in the literature have some limitations and hence, it is necessary to develop more advantageous methods to eliminate those shortcomings. Observing the efficacy of organo-catalyst, we wish to report here a remarkable catalytic activity of 2-aminophenol to a one-pot, three-component condensation of β-naphthol, aldehyde, and dimedone without any solvent.

Results and discussion

To investigate the synthesis of some biologically active molecules by a more convenient method, a multicomponent scaffold mediated by organo-catalysts is a major concern to our current work. Viewing to combat the present challenge in green chemistry, initially, we opted to use some small molecules which are well-recognized as harmless to the environment, readily available, and cheap. In coordination with our earlier work for the



Scheme 1. Reaction strategy for xanthene derivatives **4**.

Table 1. Effects of catalysts, solvents, and reaction temperature.

Entry	Catalyst	Amount (mol%)	Solvent	Temperature (°C)	Time (h)	Yield (%)
01	1,1,2-Triphenylethanediamine	5–10	EtOH	80	48	No
02	1,1,2-Triphenylethane diamine	5–10	No solvent	80	48	No
03	L-Cystine	5–10	EtOH	80	48	No
04	L-Cystine	5–10	No solvent	80	48	No
05	L-Proline	5–10	EtOH	80	48	35
06	L-Proline	5–10	No solvent	105–110	1	20
07	Aspartic Acid	5–10	No solvent	80	48	10
08	Aspartic Acid	5	EtOH	RT, Reflux	48	15
09	p-Aminobenzoic Acid	5	EtOH	RT, Reflux	48	10
10	L-Glutamic acid	5,10	EtOH	RT, Reflux	48	20
12	2-Picolinic Acid	5,10	EtOH	RT, Reflux	48	40
13	Nicotinic Acid	5,10	No solvent	110	2	
14	Nicotinic Acid	5,10	EtOH	75	2	
15	4-Amino-phenol	5,10	EtOH	80	2	50
16	4-Amino-phenol	5,10	No solvent	80	4	5
17	2-Amino-phenol	5,10	EtOH	RT, Reflux	30 min	75
18	2-Amino-phenol	5,10	No solvent		25 min	85
19	Without Catalyst	–	EtOH	RT, Reflux	48	No

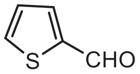
development of a new and environmentally feasible method, we attempted to prepare 8,9,10,12-tetrahydrobenzo[*a*]xanthenes-11-one **4** derivatives from the condensation of 2-naphthol, aldehyde, and dimedone mediated by some small molecules. The working equation of our reaction strategy has given in Scheme 1.

As an effort to select a suitable organo-catalyst for the above reaction (Scheme 1) initially we conducted a series of experiments with 2-naphthol, aldehydes, and dimedone mediated by 1,1,2-triphenylethanediamine in ethanol at different catalysts loadings over reflux temperature, but in TLC monitoring no noticeable changes were observed. Later, we used L-cysteine to the same reaction both with or without a solvent but the reaction did not proceed at all except for the formation of some unwanted products. For a succinct representation, all catalytic trial reactions are arranged in Table 1.

In continuation of the catalyst screening program, we employed aspartic acid, 4-amino-benzoic acid, L-glutamic acid, and in all the cases we discovered little or no conversion, and for a few cases, two or more side products were resulted in, which were impossible to isolate. Later, we utilized pure L-proline to ethanol, and we were enabled to isolate the products by usual work-ups, although the yield was not satisfactory. With this glimmer of optimism, we attempted to improve the yield by modifying catalyst loadings, changing solvents, without solvents, and temperature adjustment, but no progress was seen in each trial. So, we think pure L-proline catalyzation is not appropriate for this transformation, and thereby the work has been postponed. Based on our earlier trials, 2-picolinic acid[56] seemed to have a lot of potentials, and to our amazement, it has been successful in producing the target product up to 40% yield, but changing of reaction settings failed to increase the yield. The intramolecular H-bonding tendency of 2-picolinic acid may be the real cause of its inertness to this reaction. As a trend, nicotinic acid (5 mol%) was utilized in this reaction, and it was examined in different ways but TLC monitoring revealed a minor conversion of the starting materials. Finally, 4-Amino phenols were exploited in EtOH, and in this case, moderate success was seen in the solution phase. The yield after product recovery is not as high as we had hoped during TLC checking, perhaps a fraction of the products was soluble in ethanol. Then, to attain a greater yield, we decided to perform the same reaction without any solvent, however, no conversion was discovered in this trial. Later, 2-amino phenol (10 mol%) was added to this reaction in EtOH, and full conversion was detected in TLC at refluxing temperature with only a few percentages of a side product. To prevent the formation of the side product, the reaction temperature was set to 80 °C, and by this tricky way, we eliminated this cumbersome. However, because of the product's higher solubility in ethanol, we faced the same problems during the product isolation. Finally, we chose to continue the reaction without any solvents, and to our amazement, a full conversion of the starting materials was achieved at 75 °C without producing any side products. By adding ice-cold water to the reaction mixture, the product was seen to float over the water layer, and thus it was easily collected by filtration. For a few cases, ethanol recrystallization was done instead of chromatographic purification to obtain NMR grade samples. All these data firmly supported the formation of xanthene derivatives **4** and completely agreed with the given structures. A series of experiments were conducted to establish the amount of catalyst required, and it was found that 5 mol% is sufficient to speed up the process. Furthermore, it was determined without catalyst this reaction did not proceed at all, and introducing excess catalyst has no additional benefits in improving the yields.

After establishing the optimal conditions, we explored the generality of this method to synthesize different tetrahydrobenzo[*a*]xanthenes-11-one derivatives **4** (Table 2) by varying the aldehydes. Aromatic aldehydes with electron-withdrawing groups, electron-donating groups, and hetero-aromatic aldehydes reacted easily with β-naphthol and dimedone under these experimental circumstances. But we noticed that electron-withdrawing groups in aldehydes speed up the reaction whereas electron pushing groups in aldehydes slightly slow the process down. To our

Table 2. Synthesis of xanthene derivatives **4** catalyzed by 2-aminophenol.

Entry	*R*	Time/min	Products	Yield/%
01	4-(Cl)-C_6H_4-	20	4a	88
02	2-(Cl)-C_6H_4-	20	4b	87
03	4-(NO_2)-C_6H_4-	20	4c	85
04	3-(NO_2)-C_6H_4-	20	4d	90
05	3-(Br)-C_6H_4-	20	4e	92
06	Ph-	25	4f	90
07	4-(OMe)-C_6H_4-	30	4g	91
08	3-(OMe)-C_6H_4-	30	4h	90
09	4-(OH)-C_6H_4-	30	4i	88
10	2-(OH)-C_6H_4-	30	4j	86
11	4-(Me)-C_6H_4-	30	4k	90
12	Naphthaldehyde	25	4l	85
13	4-(F)-C_6H_4-	20	4m	90
14		30	4n	88
15		25	4o	85

Reaction conditions: β-naphthol (1.0 mmol), aldehyde (1.0 mmol), dimedone (1.0 mmol), 2-aminophenol (5 mol%), and reactions temperature (70–80) °C.

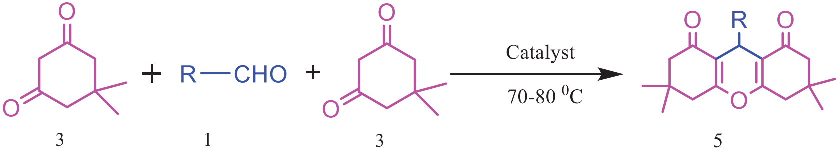
Table 3. Synthesis of xanthene derivatives **5** catalyzed by 2-aminophenol.

Entry	*R*	Time/min	Product	Yield/%
01	Ph-	30	5a	88
02	4-(NO$_2$)-C$_6$H$_4$-	25	5b	90
03	3-(NO$_2$)-C$_6$H$_4$-	25	5c	90
04	4-(Cl)-C$_6$H$_4$-	35	5d	88
05	4-(Me)-C$_6$H$_4$-	35	5e	86
06	4-(OMe)-C$_6$H$_4$-	35	5f	87
07	4-(OH)-C$_6$H$_4$-	35	5g	88
08	2-(Cl)-C$_6$H$_4$-	35	5h	82
09	2-(Br)-C$_6$H$_4$-	35	5i	86
10	3-(OMe),4-(OH)-C$_6$H$_3$-	35	5j	82
11	3,4-Di-(OMe)-C$_6$H$_3$-	35	5k	75
12	3,4,5-tri-(OMe)-C$_6$H$_2$-	35	5l	70
13	2-(NO$_2$)-C$_6$H$_4$-	35	5m	82

Reaction conditions: Dimedone (2.0 mmol), aromatic aldehyde (1.0 mmol), 2-aminophenol (5 mol%), and reaction temperature (70–80) °C.

delight butyraldehyde (entry-15) underwent a clean conversion, which was the key objection to some reported works.[39,40,53–55] As a result, the proposed approach has provided a great deal of flexibility in terms of designing various xanthene derivatives. Later, we wished to engage methyl ketone instead of aldehydes without changing other starting materials and in this case, we did not find any conversion in TLC. Therefore, 2-aminophenol failed to catalyze this reaction with the ketone.

To extend the applicability of this method we then attempted to synthesize 3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione **5** from the usual condensation of 2 mol of dimedone and 1 mol of aromatic aldehyde. With the previous reaction techniques within 30 min, a white color product was seen to float over the reaction mixture. The working equation of this reaction has given below:



By this short-cut technique, we also synthesized 13 more xanthene derivatives from different substituted aromatic aldehydes without any conspicuous difficulties (Table 3). In terms of yields, the product generation in both cases is similar, although aliphatic aldehydes are uninterested in the second condensation process. Another key finding during the second condensation phase (entry-11 and 12) was a steric hindrance, which made the process slow and resulted in lower yields.

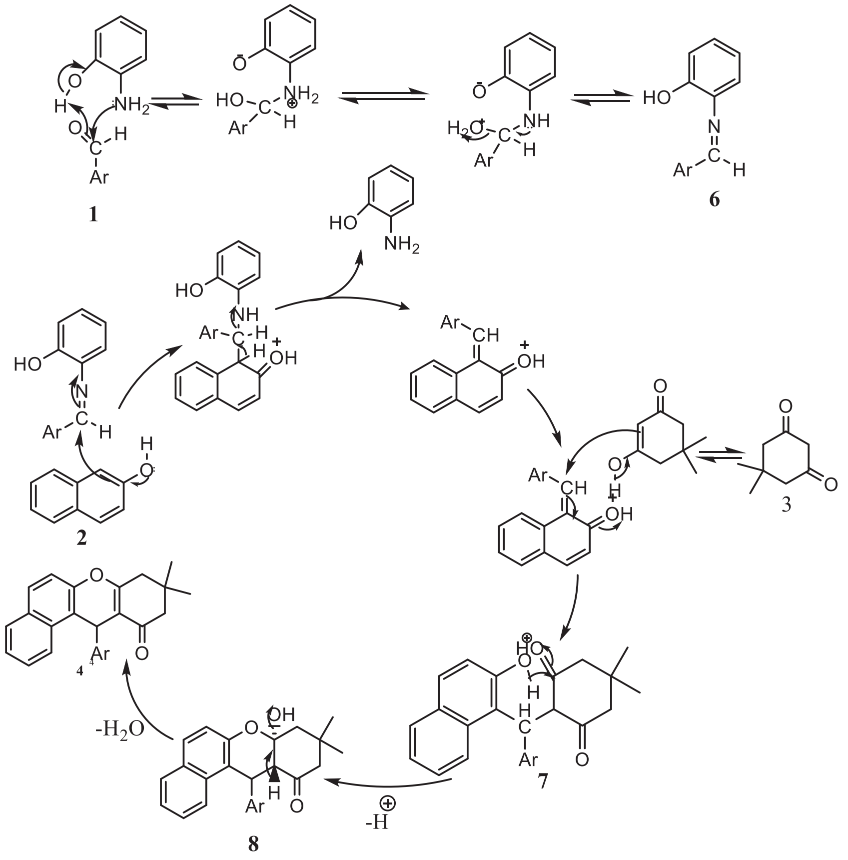
A comparison of our method with the previous literature has set in Table 4. By this current technique and with 2-amino phenol, we have synthesized 28 xanthene derivatives in a very short reaction time and faced no difficulties in the products separation process. Moreover, both of 12-aryl or 12-alkyl 8,9,10,12-tetrahydrobenzo[*a*]xanthenes-11-one and 3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione derivatives could be synthesized in high yields mediated by a single catalyst 2-amino phenol, and most importantly only two other literature[37,40] are available where a single catalyst was exploited for such transformations with a few examples.

Although the catalytic activity of 2-aminophenol in multicomponent reactions was not known, its soft dual behavior, frugal H-donating capacity to aldehyde molecule, and

Table 4. Comparison of different catalytic methods in the synthesis of xanthene derivatives.

Entry	Catalyst	Conditions	Reaction time	Yield/%	References
01	*p*-TSA	80 °C/[bmim]BF_4/Neat	(2–3.5) h	84–92	[22]
02	KF impregnated on nanoparticles (KF/CP NPs)	80 °C/solvent-free	(1–1.3) h	88–92 with only 9 examples	[39]
03	Ionic liquids	120 °C/solvent-free	(60–120) min	70–90	[35]
04	$InCl_3$	120 °C/solvent-free	(30–75) min	63–68	[32]
05	Cyanuric chloride	80 °C/solvent-free	(30–70) min	84–93	[27]
06	Imidazole	80 °C/solvent-free	20 min	84–95	[53]
07	Molecular I_2	AcOH at reflux temp.	(2–3.5) h	70–88	[25]
08	ZnO nano particle	EtOH at reflux temp.	(1–2.5) h	78–98	[34]
09	Silica sulfuric acid	80 °C/solvent-free	(1–2.5) h	88–97 with 8 examples	[26]
10	Aluminized polyborate	100–110 °C/ solvent-free	(15–25) min	85–93	[38]
11	Perlite NPs@IL/ZrC$_{l4}$	80 °C/solvent-free	(1.5–2) h	88–91 with only 10 examples	[40]
12	(H_3PO_4/Al_2O_3) (50% w/w)	120 °C/solvent-free	(20–30) min	82–90 with only 6 examples	[37]
13	2-Aminophenol	70–80 °C/solvent free	(20–30) min	75–92 with 28 examples	Our method

enolizability power over dimedone may have increased its potential as a catalyst in the current reaction. A plausible reaction mechanism has given below:



Reaction mechanism for the formation of 8,9,10,12-tetrahydrobenzo[*a*]xanthenes-11-one derivatives.

Our assumption may be erroneous; however, 2-aminophenol first encapsulated the aldehyde molecule resulting in an imine intermediate **6**. At the same time, 2-aminophenol promotes the enolization of dimedone more quickly. After that, β-naphthol condensed with the imine to form an intermediate adduct **7**, which was then transformed to a tetracycle **8** by a typical condensation process. By heating, this tetracycle will eliminate one molecule of water instantly, yielding the final product **4**. In the second part of the work, 2-aminophenol plays the same role as it has done for the synthesis of 8,9,10,12-tetrahydrobenzo[*a*]xanthenes-11-one derivatives **4**.

Whatever the mechanism, this short-cut method offers a wide range of applications, such as yields are high, simple product separations process, uses of an organo-catalyst, costly chromatographic techniques were avoided resulting in an environmentally friendly process.

Conclusion

From aldehydes, 2-naphthol, and dimedone, we developed a novel and highly efficient process for the synthesis of 12-aryl or 12-alkyl-8, 9, 10, 12-tetrahydrobezo[*a*]xanthenes-11-one and 3,3,6,6-tetramethyl-9-aryl-3,4,5,6,7,9-hexahydro-2*H*-xanthene-1,8-dione derivatives with good to high yields. Although 2-aminophenol is not a popular organocatalyst but it has demonstrated its full capability in customizing a large number of xanthene derivatives in this work. Moreover, this catalyst is inexpensive, readily available, biodegradable, and its lower concentrations (5–10%) can drive reactants into the product channel. For the first time, we have used 2-aminophenol to synthesize xanthene derivatives, which is a significant accomplishment of this methodology. We believe that our solvent-free, time-saving, environmentally friendly, and economically viable technique will find use in the one-pot multicomponent synthesis of new xanthene derivatives.

Experimental section

General information

The melting points were determined on a capillary melting point apparatus and are uncorrected. Infrared spectra were recorded using KBr pellets for solids and neat for liquids on FT-IR 8400 Perkin-Elmer 883 grating spectrometers. ^{1}H NMR spectra were taken on AC-Bruker 500 MHz spectrometer in $CDCl_3$ and containing TMS as internal standard. HRMS (ESI) were taken on Thermo LCQ TM Deca XP plus spectrometer. All J values are given in Hz, chemical shifts in δ-units. Ethanol was simply distilled over CaO and the reaction progress was monitored by TLC.

General procedure for the synthesis of 8,9,10,12-tetrahydrobenzo[a]xanthene-11-one derivatives (4) and 3,3,6,6-tetramethyl-9-aryl-3,4,5,6,7,9-hexahydro-2H-xanthene-1,8-dione derivatives (5)

To a mixture of β-naphthol (1.0 mmol), 4-chloro-benzaldehyde (1.0 mmol), and dimedone (1.0 mmol); 2-aminophenol (5.0 mol%) was added for the synthesis of compound

4a. The reaction mixture was heated at about 80 °C with constant mechanical stirring for a specific time and the progress of the reaction was monitored by TLC. After completion of the reaction, 10 mL of cold distilled water was poured to arrest the reaction and the mixture was further stirred for 10–12 min. The obtained solid product was filtered and recrystallized from hot ethanol to obtain pure xanthene derivatives. The product 4a was synthesized by the above general procedure. Isolated yield 90%, white crystal, m.p. 181–182 °C. (lit. 182–184)[50] ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm); 7.93 (d, $J = 8.4$ Hz, 1H, Ar-H), 7.83–7.95 (m, 2H, Ar-H), 7.48–7.29 (m, 5H, Ar-H), 7.17–7.15 (d, $J = 9.9$ Hz, 2H, Ar-H), 5.71 (s, 1H, Pyran-H), 2.60 (s, 2H, -CH_2), 2.36–2.26 (m, 2H, -CH_2), 1.15 (s, 3H, -CH_3), 0.98 (s, 3H, -CH_3). ^{13}C NMR (300 MHz, $CDCl_3$): δ (ppm); 27.1, 29.3, 32.2, 34.2, 41.4, 50.9, 113.8, 117.0, 117.1, 119.6, 121.5, 123.5, 125.0, 127.1, 128.4, 128.5, 129.1, 129.8, 131.5, 132.0, 143.2, 147.7, 164.1, 196.9. HRMS(ESI): Calcd. for $C_{25}H_{21}O_2Cl$ $[M + H]^+$ 388.8860; found 388.8862.

All the reaction procedures for compound **5** are same except the addition of dimedone 2.0 mmol instead of β-naphthol. Following the given general procedure compound **5j** was synthesized from condensation of dimedone (2.0 mmol) and 4-hydroxy-3-methoxybenzaldehyde. Isolated yield: 85% as a solid. The spectral data of the compound **5j**. m.p. 224–226 °C (new compound). ^{1}H NMR (400 MHz, CDCl3): δ (ppm) = 7.0 (s, 1H, Ar-H), 6.74 (d, $J = 8$ Hz, 1H, Ar-H), 6.58 (d, $J = 8$ Hz, 1H, Ar-H), 5.46 (s, 1H, -OH), 4.66 (s, 1H, -CH), 3.89 (s, 3H, -OCH_3), 2.45 (s, 4H, 2×-CH_2), 2.20 (q, $J = 7.2$ Hz, 4H, 2×-CH_2), 1.10 (s, 6H, 2×-CH_3), 1.00 (s, 6H, 2×-CH_3). ^{13}C NMR (300 MHz, $CDCl_3$): δ (ppm) = 27.28, 29.31, 31.30, 32.20, 40.86, 50.77, 55.88, 112.26, 113.91, 115.81, 120.01, 136.46, 144, 145.87, 162.08. HRMS(ESI): Calcd. for $C_{24}H_{28}O_5$ $[M + H]^+$ 396.4761; found 396.4763.

Experimental details and spectroscopic data are available on the web page of this journal as a Supplementary File.

Acknowledgments

We gratefully acknowledge UGC for research grants and to the Department of Chemistry, the University of Rajshahi, Bangladesh for the facilities given and to the Green Chemistry Laboratory, KRICT for necessary spectral assistance.

References

[1] Lambert, R. W.; Martin, J. A.; Merrett, J. H.; Parkes, K. E. B.; Thomas, G. J. Clean Synthesis of 1,8-Dioxo-Octahydroxanthene Derivatives Using NBS as an Efficient and Almost. PCT IntAppl WO 9706178. *Chem. Abstr.* **1997**, *126*, 212377.

[2] Bruno, O.; Brullo, C.; Schenone, S.; Bondavalli, F.; Ranise, A.; Tognolini, M.; Ballabeni, V.; Barocelli, E. Synthesis and Pharmacological Evaluation of 5H-[1]Benzopyrano[4,3-*d*]Pyrimidines Effective as Antiplatelet/Analgesic Agents. *Bioorg. Med. Chem.* **2004**, *12*, 553–561. DOI: 10.1016/j.bmc.2003.11.018.

[3] Hideu, T. In Jpn. Tokkyo Koho JP 56005480. *Chem. Abstr.* **1981**, *95*, 80922b.

[4] Peters, A. T.; Bide, M. J. Amino Derivatives of 1,8-Naphthalic Anhydride and Derived Dyes for Synthetic-Polymer Fibres. *Dyes Pigments* **1985**, *6*, 349–375. DOI: 10.1016/0143-7208(85)85005-1.

[5] Shinde, P. V.; Kategaonkar, A. H.; Shingate, B. B.; Shingare, M. S. Surfactant Catalyzed Convenient and Greener Synthesis of Tetrahydrobenzo[*a*]xanthene-11-Ones at Ambient Temperature. *Beilstein J. Org. Chem.* **2011**, *7*, 53–58. DOI: 10.3762/bjoc.7.9.

[6] Knight, C. G.; Stephens, T. Xanthene-Dye-Labelled Phosphatidylethanolamines as Probes of Interfacial pH. Studies in Phospholipid Vesicles. *Biochem. J.* **1989**, *258*, 683–687. DOI: 10.1042/bj2580683.

[7] Wang, H.; Lu, L.; Zhu, S.; Li, Y.; Cai, W. The Phototoxicity of Xanthene Derivatives against *Escherichia coli*, *Staphylococcus aureus*, and *Saccharomyces cerevisiae*. *Curr. Microbiol.* **2006**, *52*, 1–5. DOI: 10.1007/s00284-005-0040-z.

[8] Bedair, A. H.; El-Hady, N. A.; El-Latif, M. S. A.; Fakery, A. H.; El-Agrody, A. M. Synthesis of Some New Pyrano[2,3-*d*]Pyrimidine, 2-Substituted[1,2,4]Triazolo[1,5-*c*]Pyrimidine and Pyrimido[1,6-b][1,2,4]Triazine Derivatives. *IL Farmaco* **2000**, *55*, 708–714. DOI: 10.1016/S0014-827X(00)00097-5.

[9] Bruno, O.; Brullo, C.; Schenone, S.; Bondavalli, F.; Ranise, A.; Tognolini, M.; Impicciatore, M.; Ballabeni, V.; Barocelli, E. Synthesis, Antiplatelet and Antithrombotic Activities of New 2-Substituted Benzopyrano [4,3-*d*] Pyrimidin-4-Cycloamines and 4-Amino/Cycloamino-Benzopyrano [4,3-*d*] Pyrimidin-5-Ones. *Bioorg. Med. Chem.* **2006**, *14*, 121–130. DOI: 10.1016/j.bmc.2005.07.066.

[10] Bennett, G. J.; Lee, H. H. Xanthones from Guttiferae. *Phytochemistry* **1989**, *28*, 967–998. DOI: 10.1016/0031-9422(89)80170-0.

[11] Bruno, O.; Brullo, C.; Schenone, S.; Ranise, A.; Bondavalli, F.; Barocelli, E.; Tognolini, M.; Magnanini, F.; Ballabeni, V. Progress in 5*H*[1]Benzopyrano [4,3-*d*]Pyrimidin-5-Amine Series: 2-Methoxy Derivatives Effective as Antiplatelet Agents with Analgesic Activity. *Il Farmaco* **2002**, *57*, 753–758. DOI: 10.1016/S0014-827X(02)01269-7.

[12] Chabchoub, F.; Messaâd, M.; Mansour, H. B.; Chekir-Ghedira, L.; Salem, M. Synthesis and Antigenotoxic Activity of Some Naphtho[2,1-*b*]Pyrano[3,2-*e*][1,2,4]Triazolo[1,5-*c*]Pyrimidine Derivatives. *Eur. J. Med. Chem.* **2007**, *42*, 715–718. DOI: 10.1016/j.ejmech.2006.12.002.

[13] Vijayakurup, V.; Carmela, S.; Carmelo, D.; Corrado, T.; Srinivas, P.; Gopala, S. Phenethyl Caffeate Benzo[kl]Xanthene Lignan with DNA Interacting Properties Induces DNA Damage and Apoptosis in Colon Cancer Cells. *Life Sci.* **2012**, *91*, 1336–1344. DOI: 10.1016/j.lfs.2012.10.013.

[14] Messaád, M.; Chabchoub, F.; Salem, M. Action of Primary Amines and Hydroxylamine on Ethoxymethyleneaminonaphtopyranes: Synthesis of New Naphtopyrano[2,3-*d*]Pyrimidines Derivatives. *Heterocycl. Commun.* **2005**, *11*, 139–144.

[15] Iniyavan, P.; Sarveswari, S.; Vijayakumar, V. Synthesis and Antioxidant Studies of Novel Bi-, Tri-, and Tetrapodal 9-Aryl-1,8-Dioxo-Octahydroxanthenes. *Tetrahedron Lett.* **2015**, *56*, 1401–1406. DOI: 10.1016/j.tetlet.2015.01.162.

[16] Knight, D. W.; Little, P. B. The First High-Yielding Benzyne Cyclisation Using a Phenolic Nucleophile: A New Route to Xanthenes. *Synlett* **1998**, *10*, 1141–1143.

[17] Jha, A.; Beal, J. Convenient Synthesis of 12*H*-Benzo[*a*]Xanthenes from 2-Tetralone. *Tetrahedron Lett.* **2004**, *45*, 8999–9001. DOI: 10.1016/j.tetlet.2004.10.046.

[18] Kuo, C. W.; Fang, J. M. Synthesis of Xanthenes, Indanes, and Tetrahydronaphthalenes via Intramolecular Phenyl–Carbonyl Coupling Reactions. *Synth. Commun.* **2001**, *31*, 877–892. DOI: 10.1081/SCC-100103323.

[19] Sen, R. N.; Sarkar, N. N. The Condensation of Primary Alcohols with Resorcinol and Other Hydroxy Aromatic Compounds. *J. Am. Chem. Soc.* **1925**, *47*, 1079–1091. DOI: 10.1021/ja01681a023.

[20] Ota, K.; Kito, T. An Improved Synthesis of Dibenzoxanthene. *BCSJ.* **1976**, *49*, 1167–1168. DOI: 10.1246/bcsj.49.1167.

[21] Khosropour, A. R.; Khodaei, M. M.; Moghannian, H. A Facile, Simple and Convenient Method for the Synthesis of 14-Alkyl or Aryl-14-*H*-Dibenzo[*a*,*j*]Xanthenes Catalyzed by pTSA in Solution and Solvent-Free Conditions. *Synlett* **2005**, *6*, 955–958.

[22] Khurana, J. M.; Magoo, D. pTSA-Catalyzed One-Pot Synthesis of 12-Aryl-8,9,10,12-Tetrahydrobenzo[*a*]Xanthen-11-Ones in Ionic Liquid and Neat Conditions. *Tetrahedron Lett.* **2009**, *50*, 4777–4780. DOI: 10.1016/j.tetlet.2009.06.029.

[23] Shirini, F.; Mamaghani, M.; Atghia, S. V. Use of Nanoporous Na^+-Montmorillonite Sulfonic Acid (SANM) as an Eco-Benign, Efficient and Reusable Solid Acid Catalyst for the One-Pot Synthesis of 14-Aryl-14-*H*-Dibenzo [*a,j*] Xanthenes and 1,8-Dioxo-Dodecahydroxanthene Derivatives. *J. Iran. Chem. Soc.* **2013**, *10*, 415–420. DOI: 10.1007/s13738-012-0174-4.

[24] Ko, S.; Yao, C. F. Heterogeneous Catalyst: Amberlyst-15 Catalyzes the Synthesis of 14-Substituted-14H-Dibenzo[*a,j*]Xanthenes under Solvent-Free Conditions. *Tedraherdon Lett.* **2006**, *47*, 8827–8829. DOI: 10.1016/j.tetlet.2006.10.072.

[25] Sun, X. J.; Zhou, J. F.; Zhao, P. S. Molecular Iodine-Catalyzed One-Pot Synthesis of Tetrahydrobenzo[*a*]Xanthene-11-One and Diazabenzo[*a*]Anthracene-9,11-Dione Derivatives under Microwave. *J. Heterocyclic Chem.* **2011**, *48*, 1347–1350. DOI: 10.1002/jhet.742.

[26] Seyyedhamzeh, M.; Mirzaei, P.; Bazgir, A. Solvent-Free Synthesis of Aryl-14H-Dibenzo[*a,j*]Xanthenes and 1,8-Dioxo-Octahydro-Xanthenes Using Silica Sulfuric Acid as Catalyst. *Dyes Pigments* **2008**, *76*, 836–839. DOI: 10.1016/j.dyepig.2007.02.001.

[27] Zhang, Z. H.; Zhang, P.; Yang, S. H.; Wang, H. J.; Deng, J. Multicomponent, Solvent-Free Synthesis of 12-Aryl-8,9,10,12-Tetrahydrobenzo[*a*]-Xanthen-11-One Derivatives Catalysed by Cyanuric Chloride. *J. Chem. Sci.* **2010**, *122*, 427–432. DOI: 10.1007/s12039-010-0049-0.

[28] Sheshmani, S. Catalytic Application of Two Novel Sandwich-Type Polyoxometalates in Synthesis of 14-Substituted-14*H*-Dibenzo[*a,j*]Xanthenes. *J. Chem. Sci.* **2013**, *125*, 345–351. DOI: 10.1007/s12039-013-0384-z.

[29] Jaber, Z. K.; Abbasi, S. Z.; Pooladian, B.; Jokar, M. Efficient, One-Pot Synthesis of Tetrahydrobenzo[a]Xanthen-11-Ones and Dibenzo[*a,j*]Xanthenes Using Trichloroacetic Acid as a Solid Heterogeneous Catalyst under Solvent-Free Conditions. *E-J. Chem.* **2011**, *8*, 1895–1899. DOI: 10.1155/2011/359175.

[30] Mokhtary, M.; Langroudi, S. A. M. Polyvinylpolypyrrolidone-Supported Boron Trifluoride: A Mild and Efficient Catalyst for the Synthesis of 1,8-Dioxooctahydroxanthenes and 1,8-Dioxodecahydroacridines. *Monatsh. Chem.* **2014**, *145*, 1489–1494. DOI: 10.1007/s00706-014-1206-9.

[31] Kumar, A.; Sharma, S.; Maurya, R. A.; Sarkar, J. Diversity Oriented Synthesis of Benzoxanthene and Benzochromene Libraries via One-Pot, Three-Component Reactions and Their anti-Proliferative Activity. *J. Comb. Chem.* **2010**, *12*, 20–24. DOI: 10.1021/cc900143h.

[32] Nandi, G. C.; Samai, S.; Kumar, R.; Singh, M. S. An Efficient One-Pot Synthesis of Tetrahydrobenzo[*a*]Xanthene-11-One and Diazabenzo[*a*]Anthracene-9,11-Dione Derivatives under Solvent Free Condition. *Tetrahedron* **2009**, *65*, 7129–7134. DOI: 10.1016/j.tet.2009.06.024.

[33] Mirjalili, B. F.; Bamoniri, A.; Akbari, A.; Taghavinia, N. Nano-TiO_2: An Eco-Friendly and Re-Usable Catalyst for the Synthesis of 14-Aryl or Alkyl-14 H-Dibenzo[*a,j*]Xanthenes. *JICS.* **2011**, *8*, S129–S134. DOI: 10.1007/BF03254289.

[34] Lasemi, Z.; Mehrasbi, E. ZnO Nanoparticles: An Efficient and Reusable Catalyst for One-Pot Synthesis of 1,8-Dioxo-Octahydroxanthenes. *Res. Chem. Intermed.* **2015**, *41*, 2855–2866. DOI: 10.1007/s11164-013-1394-7.

[35] Zakeri, M.; Heravi, M. M.; Saeedi, M.; Karimi, N.; Oskooie, H. A.; Tavakoli-Hoseini, N. One-Pot Green Procedure for Synthesis of Tetrahydrobenzo[*a*]Xanthene-11-One Catalyzed by Brønsted Ionic Liquids under Solvent-Free Conditions. *Chin. J. Chem.* **2011**, *29*, 1441–1445. DOI: 10.1002/cjoc.201180240.

[36] Mirhadi, E.; Ramazani, A.; Rouhani, M.; Joo, S. W. Perlite-SO_3H Nanoparticles: A Novel and Efficient Catalyst for the Synthesis of 14-Aryl 14*H*-Dibenzo[*a,j*]Xanthenes under Microwave Conditions. *CHEMIJA* **2013**, *24*, 320–324.

[37] Shaterian, H. R.; Azizi, K.; Fahimi, N. Phosphoric Acid Supported on Alumina (H_3PO_4/Al_2O_3) as an Efficient and Reusable Catalyst for the One-Pot Synthesis of Benzoxanthene Pigments. *Res. Chem. Intermed.* **2014**, *40*, 1403–1414. DOI: 10.1007/s11164-013-1047-x.

[38] Aute, D.; Kshirsaga, A.; Uphade, B.; Gadhave, A. An Expedient and Straightforward Solvent-Free Synthesis of 1,8-Dioxo-Octahydroxanthenes Using Eco-Friendly Aluminized Polyborate Catalyst. *J. Heterocyclic Chem.* **2020**, *57*, 3691–3702. DOI: 10.1002/jhet.4090.

[39] Balou, J.; Khalilzadeh, M. A.; Zareyee, D. An Efficient and Reusable Nano Catalyst for the Synthesis of Benzoxanthene and Chromene Derivatives. *Sci. Rep.* **2019**, *9*, 3605. DOI: 10.1038/s41598-019-40431-x.

[40] Moradi, L.; Mirzaei, M. Immobilization of Lewis Acidic Ionic Liquid on Perlite Nanoparticle Surfaces as a Highly Efficient Solid Acid Catalyst for the Solvent-Free Synthesis of Xanthene Derivatives. *RSC Adv.* **2019**, *9*, 19940–19948. DOI: 10.1039/C9RA03312B.

[41] Sardarian, A. R.; Inaloo, I. D. 4-Dodecylbenzenesulfonic Acid (DBSA) Promoted Solvent-Free Diversity-Oriented Synthesis of Primary Carbamates, S-Thiocarbamates and Ureas. *RSC Adv.* **2015**, *5*, 76626–76641. DOI: 10.1039/C5RA14528G.

[42] Sardarian, A. R.; Inaloo, I. D.; Modarresi-Alam, A. R. Highly Efficient Synthesis of Alkyl and Aryl Primary Thiocarbamates and Dithiocarbamates under Metal- and Solvent-Free Conditions. *Mol. Divers.* **2018**, *22*, 863–878. DOI: 10.1007/s11030-018-9831-6.

[43] Sardarian, A. R.; Inaloo, I. D.; Modarresi-Alam, A. R.; Kleinpeter, E.; Schilde, U. Metal-Free Regioselective Monocyanation of Hydroxy-, Alkoxy-, and Benzyloxyarenes by Potassium Thiocyanate and Silica Sulfuric Acid as a Cyanating Agent. *J. Org. Chem.* **2019**, *84*, 1748–1756. DOI: 10.1021/acs.joc.8b02191.

[44] Sardarian, A. R.; Inaloo, I. D.; Modarresi-Alam, A. R.; Kleinpeter, E. Synthesis of Primary Thiocarbamates by Silica Sulfuric Acid as Effective Reagent under Solid-State and Solution Conditions. *J. Mol. Struct.* **2012**, *1024*, 156–162. DOI: 10.1016/j.molstruc.2012.05.033.

[45] Suzuki, I.; Iwata, Y.; Takeda, K. Biginelli Reactions Catalyzed by Hydrazine Type Organocatalyst. *Tetrahedron Lett.* **2008**, *49*, 3238–3241. DOI: 10.1016/j.tetlet.2008.03.080.

[46] Vachan, B. S.; Karuppasamy, M.; Vinoth, P.; Vivek Kumar, S.; Perumal, S.; Sridharan, V.; Menéndez, J. C. Proline and Its Derivatives as Organocatalysts for Multi-Component Reactions in Aqueous Media: Synergic Pathways to the Green Synthesis of Heterocycles. *Adv. Synth. Catal.* **2020**, *362*, 87–110. DOI: 10.1002/adsc.201900558.

[47] Sharma, H.; Sharma, S.; Paul, S. 2-(5-phenyl-4*H*-1,2,4-Triazol-3-Ylthio) Acetic Acid: Greener and Efficient Organocatalyst for Multicomponent Reactions under Aqueous Media. *Curr. Res. Green Sustain. Chem.* **2021**, *4*, 100181. DOI: 10.1016/j.crgsc.2021.100181.

[48] Ramachary, D. B.; Shashank, A. B. Organocatalytic Triazole Formation, Followed by Oxidative Aromatization: Regioselective Metal-Free Synthesis of Benzotriazoles. *Chemistry* **2013**, *19*, 13175–13181. DOI: 10.1002/chem.201301412.

[49] Guillena, G.; Ramon, D. J.; Yus, M. Organocatalytic Enantioselective Multicomponent Reactions (OEMCRs). *Tetrahedron* **2007**, *18*, 693–700. DOI: 10.1016/j.tetasy.2007.03.002.

[50] Roy, H. N.; Rana, M.; Munsur, A. Z. A.; Lee, K. I.; Sarker, A. K. Efficient and Convenient Synthesis of 1*H*-Pyrazolo[1,2-*b*]Phthalazine-5,10-Dione Derivatives Mediated by L-Proline. *Syn. Comm.* **2016**, *46*, 1370–1376. DOI: 10.1080/00397911.2016.1192650.

[51] Al-Munsur, A. B. Z.; Roy, H. N.; Imon, M. K. Highly Efficient and Metal-Free Synthesis of Tri- and Tetrasubstituted Imidazole Catalyzed by 3-Picolinic Acid. *Arab. J. Chem.* **2020**, *13*, 8807–8814. DOI: 10.1016/j.arabjc.2020.10.010.

[52] Rana, M.; Rahman, A.; Roy, P. K.; Roy, H. N. Environmentally Benign Synthesis of Tetra-Substituted Imidazoles through 4-Components Strategy Mediated by (S)-3-Methyl-1,1-Diphenylbutane-1,2-Diamine. *J. Sci. Res.* **2018**, *10*, 39–50. DOI: 10.3329/jsr.v10i1.32794.

[53] Heydari, R.; Shahrekipour, F. One-Pot Synthesis of 12-Aryl-8,9,10,12-Tetrahydrobenzo[*a*]Xanthen-11-Ones by Using of Neutral and Efficient Organocatalysts under Solvent-Free Conditions. *Res. Chem. Intermed.* **2015**, *41*, 4581–4586. DOI: 10.1007/s11164-014-1553-5.

[54] Mondal, J.; Nandi, M.; Modak, A.; Bhaumik, A. Functionalized Mesoporous Materials as Efficient Organocatalysts for the Syntheses of Xanthenes. *J. Mol. Catal. A* **2012**, *363–364*, 254–264. DOI: 10.1016/j.molcata.2012.06.017.

[55] Kamalifar, S.; Kiyani, H. Facile and Efficient Synthesis of 9-Aryl-1,8-Dioxo-Octahydroxanthenes Catalyzed by Sulfacetamide. *Polycycl. Aroma. Comp.* **2021**, *41*, 1–19. DOI: 10.1080/10406638.2021.1872656.

[56] Imon, M. K.; Kamma, K. R.; Islam, M. N.; Roy, H. N. A Convenient Metal Free Approach towards the Synthesis of Dihydropyrimidones Mediated by Achiral Nicotinic Acid without Solvent. *Ind. J. Chem.* **2021**, *60B*, 1378–1384.