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Synthesis of some new indeno[1′,2′:3,4]fluoreno[1,2-d]oxonine-5,11,16,21-tetraones and oxocyclohex-1-en-1-yl-hydro-1H-xanthen-1-ones

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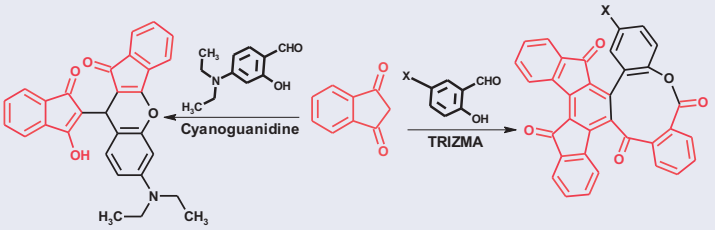
ABSTRACT

The novel oxonine **2**, **4** have been synthesized by the reaction of 1,3-indandione with 4-bromo-2-hydroxybenzaldehyde and/or 2-hydroxy-1-naphthaldehyde in the presence of 1,3-diaminopropan-2-ol as green basic catalyst. On the other hand, the reaction of 1,3-cyclohexanediones with 2-hydroxy aromatic aldehydes under the same reaction condition afforded xanthenone derivatives **9-11**.

GRAPHICAL ABSTRACT



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1,3-Indandione; 2-hydroxy aromatic aldehyde; oxonine; tetrahydroxanthenones; xanthenones

Introduction

Reports on the synthesis of oxonine derivatives are quite rare due to their infrequent occurrence and because of the challenges associated with their stereoselective assembly.[1] Hence, the creation of new method for the synthesis of new oxonenes, which is present in marine natural products[2–4] from available material is an important goal of synthetic chemists.[5] On the other hand, xanthenes exhibit a range of important biological activities such as anti-inflammatory,[6] anti-viral,[7] anti-bacterial,[8] anti-cancer[9,10] antileukemic,[11] and antimalarial[12] properties. Moreover, they are being used as laser dyes[13] and fluorescent materials for visualization of biomolecules.[14] Xanthenones, especially tetrahydroxanthenones, are also an important class of compounds for their distinct structural features and a great potential for further

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transformations.[15,16] Therefore, the development of new practical methods to construct oxonine or xanthenone derivatives is of great importance.

Results and discussion

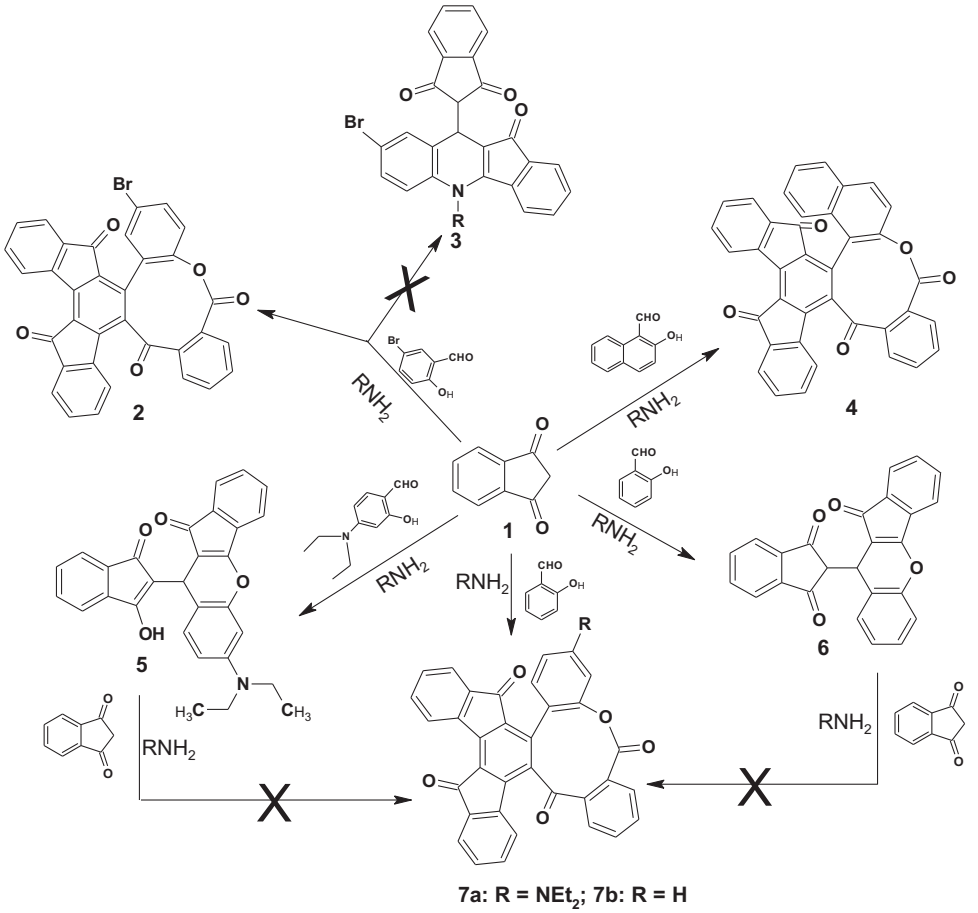
Herein, we present a new, mild, efficient, and facile method for the synthesis of new oxonines and we discuss the possible reaction mechanisms for the formation of these products. As an introductory test, we run a model reaction by refluxing 1,3-indandione (4.0 mmol) with 4-bromo-2-hydroxybenzaldehyde (1.0 mmol) and 1,3-diaminopropan-2-ol (1.0 mmol) in ethanol for 6 h that resulted in the production of dibenzo[*b*,*g*]indeno-[1′,2′:3,4]fluoreno[1,2-*d*]oxonine-5,11,16,21-tetraone (**2**) in 86% yield instead the expected product **3** may be due to the very high activity of indandione (as reported in our previous work for the reaction between 2-hydroxybenzaldehyde and three molecules of indandione in the presence of 1,3-diaminopropan-2-ol as a basic catalyst).[17] In the same manner, 1,3-indandione reacts with 2-hydroxy-1-naphthaldehyde under the same reaction condition to give the corresponding oxonine **4**. Also, the same products **2** and **4** had been separated when we used either (4-aminophenyl)methanol or TRIZMA (tris(hydroxymethyl)-aminomethane) as a green Lewis base catalyst instead of 1,3-diaminopropan-2-ol.

In other manner, the reaction of 1,3-indandione (1.0 mmol) with 4-(diethylamino)-2-hydroxybenzaldehyde (1.0 mmol) and cyanoguanidine (1 mmol) in 60 ml ethanol for 6 h yielded diethylamino-2-(11-oxo-10H,11H-indeno[1,2-b]chromen-10-yl)-2,3-dihydro-1H-indene-1,3-dione (**5**), which did not react with 1,3-indandione to give oxonine **7a**. Also, treatment of 1,3-indandione with salicylaldehyde in the presence of a guanidine hydrochloride as a Lewis acid catalyst afforded chromen-10-yl)-2,3-dihydro-1H-indene-1,3-dione **6**.[18] All attempts failed to convert product **6** to oxonine **7 b**[16] (Scheme 1).

The chemical structures of the newly synthesized products **2–7** were confirmed by their spectral (IR, ^{1}H, ^{13}C NMR) and elemental analyses data. For example, the IR spectra of **2** showed absorption bands assignable for the four C = O groups at 1762, 1714, 1702, 1664 cm^{-1}. The ^{1}H-NMR spectra of **2** illustrated the presence of five signals in the range of 9.01–7.09 ppm characteristic for the aromatic protons. Its ^{13}C NMR spectrum showed 4 signals at δ 192.02, 190.92, 189.99, 172.22 attributed to four carbonyl carbons and 16 signals which are assigned to aromatic carbons at δ 167.08, 148.19, 136.16, 136.08, 135.99, 134.28, 134.14, 132.17, 131.48, 131.16, 129.00, 128.12, 127.57, 125.04, 123.40, 123.31.

The formation of oxonines **2**, **4, 7** and xanthenone **5** were assumed to take place through a Knoevenagel condensation between 1,3-indandione **1** and 2-hydroxy aromatic aldehyde to produce arylidene **8**, which underwent Michael addition with third mole of 1,3-indandione to give intermediate **I**, which cyclized through path **A** to give xanthenones **5**, **6** or react with other mole of 1,3-indandione to give intermediate **III**. Subsequently, cyclization took place to give intermediate **V**, which undergoes ring expansion[19,20] via oxidation to yield oxonine **2, 4,** and **7** via path **B** (Scheme 2).

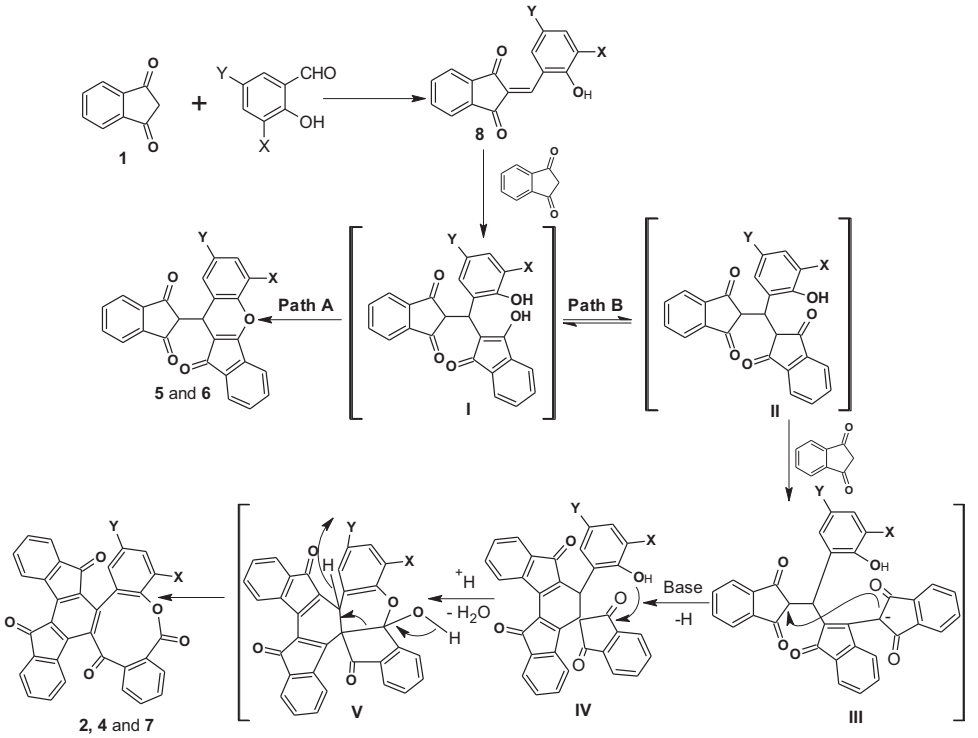
In a further extension of these optimized reaction conditions, we continued to examine the substrate scope of the reaction using a range 1,3-cyclohexanedione derivatives to synthesise other oxonines. We found that reaction between salicylaldehyde derivatives and 1,3-cyclohexanediones yielded xanthenones **9a–c** instead of desired oxonines (Scheme 3). It is clear from previous data that the formation of oxonine depends on the



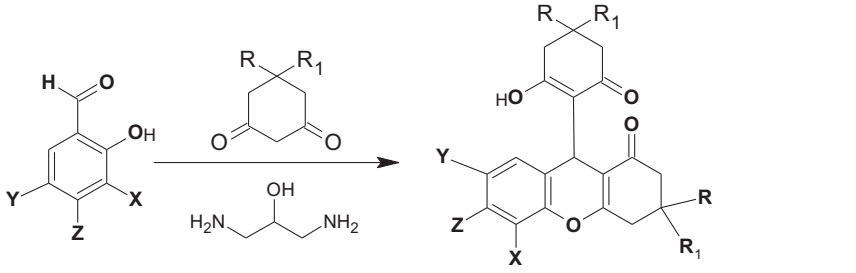
Scheme 1. Synthesis of oxonine and xanthenone derivatives.

activity of 1,3-cyclodiones and the type of catalyst. However, only indandione can react with salicylaldehydes to give the corresponding oxonine. Also, we found that using middle base such as;(4-aminophenyl)methanol, TRIZMA or1,3-diaminopropan-2-ol as a basic catalyst for this reaction leads to the formation of oxonine while using a very weak basic catalyst such as cyanoguanidine or acidic catalyst as guanidine hydrochloride afforded xanthenone derivatives.

The structures of the newly synthesized compounds **9a–c** were confirmed by their spectral IR, ^{1}H, ^{13}C NMR and elemental analyses. For example, IR spectrum of compound **9 b** exhibited characteristic absorption bands at 3359 cm^{-1} (OH); 3032 cm^{-1} (C–H aromatic); 2968 and 2876 cm^{-1} (C–H aliphatic) and 1640 cm^{-1} for C = O. Its ^{1}HNMR spectrum showed singlet signal at δ 10.64 ppm for OH, in addition to two singlet signals at δ 7.36 and 7.00 for aromatic protons and other singlet signals at δ 5.07 for H-pyran, also it exhibited three multiplet and two singlet signals in aliphatic region at δ 2.89, 2.58, 2.00, 1.06, 0.92 attributed to CH_2, CH_2, $2CH_2$, 2 CH_3, 2 CH_3, respectively. Its ^{13}C NMR spectrum showed one signal δ 197.39 for carbonyl carbon and eight signals which are assigned to aromatic carbons at δ 154.76, 149.33, 136.02, 129.85,



Scheme 2. Reaction mechanism for synthesis of oxonines and xanthenones.



9a,b

9a: R = R_1 = Y = X = H; Z = Cl

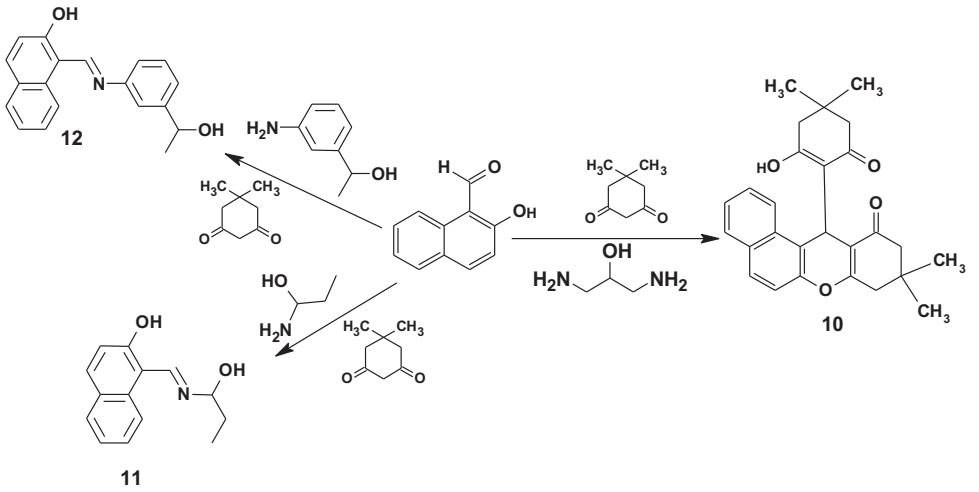
9b: R = R_1 = CH_3, X = Br, Y = Cl, Z = H

9c: R = H, R_1 = Ph, X = Br, Y = Cl, Z = H

Scheme 3. Reaction od salicylaldehyde derivatives with 1,3-cyclohexadiones.

127.44, 124.13, 112.75, 111.61, in addition to seven signals appears at δ 60.80, 48.87, 46.75, 39.08, 32.19, 28.69, 26.67 for sp^3 carbons.

Similar to salicylaldehydes 2-hydroxy-1-naphthaldehyde react with 5,5-dimethylcyclohexane-1,3-dione in the presence of 1,3-diaminopropan-2-ol as a basic catalyst to give the corresponding xanthenones **10** (Scheme 4). On the other hand, when we used other primary aliphatic or aromatic amine as a basic catalyst, the reaction afforded Schiff bases **11** and **12**



Scheme 4. Synthesis of Schiff bases and xanthenones from naphthaldehyde.

instead of expected product **10**. The chemical structures of the new products **10–12** were confirmed by their spectral (IR, ^{1}H, ^{13}C NMR) and elemental analyses data.

Complete experimental procedures and characterization data of compounds **2–12** are given in supplemental material.

Experimental

All commercially available reagents were purchased from Merck, Aldrich, and Fluka and were used without further purification. Melting points were detected with a Kofler melting points apparatus and uncorrected. Melting points were detected with a Kofler melting points apparatus and uncorrected. A SHIMADZU FT-IR-8400s spectrometer was used to record IR spectra using KBr pellets. ^{1}H– and ^{13}C-NMR spectra (400 MHz for 1 H, 100 MHz for ^{13}C) were observed in DMSO-d_6 on DELTA2-NMR spectrometer (DELTA2, Manchester Metropolitan University, United Kingdom) with tetramethylsilane as the internal standard. The ^{13}C-NMR signals were assigned with the aid of DEPT 135/90 experiments.

General procedure for the synthesis of oxonine-5,11,16,21-tetraone derivatives 2, 4

A reaction mixture of 4 mmol (576 mg) indandione and 2 mmol of aromatic aldehydes namely: p-bromosalicylaldehyde and 2-hydroxynaphthaldehyde in presence of 1 mmol of 3-aminopropane-1,2-diol or 1,3-diaminopropan-2-ol as a Lewise base catalyst in 60 ml ethanol was refluxed for 6 h. The excess solvent was evaporated under vacuum and the obtained solid was recrystallized from acetic acid to afford oxonine-5,11,16,21-tetraone derivatives **2** and **4**, respectively.

9-Bromo-dibenzo[b,g]indeno[10,20:3,4]fluoreno-[1,2-d]oxonine-5,11,16,21-tetraone (2)

Yield (86%); mp. 294–295 °C; FTIR (cm^{-1}) 1762, 1714, 1702, 1664;^{1}H NMR (400 MHz, DMSO-d_6) δ 9.01 (d, $J = 7.2$ Hz, 1 H, CHarom), 8.23 (d, $J = 8.4$ Hz, 1 H, CHarom), 7.87 (m, 3H, CHarom), 7.65 (m, 8H, CHarom), 7.09 (m, 2 H, CHarom); ^{13}C NMR (100 MHz, DMSO-d_6) δ 192.02, 190.92, 189.99, 172.22, 167.08, 148.19, 136.16, 136.08, 135.99, 134.28, 134.14, 132.17, 131.48, 131.16, 129.00, 128.12, 127.57, 125.04, 123.40, 123.31; Anal. Calcd. for $C_{34}H_{15}BrO_5$ (583): C, 70.00; H, 2.59. Found: C, 69.96; H, 2.38.

Synthesis of 8-diethylamino-2-(11-oxo-10H,11Hindeno[1,2-b]chromen-10-yl)-2,3-dihydro-1H-indene-1,3-dione (5)

In 60 ml of ethanol, a mixture of 1 mmol of 4-(diethylamino)-2-hydroxybenzaldehyde and 2 mmol (292 mg) of 1 *H*-indene-1,3(2*H*)-dione has been refluxed in the presence of a **c**yanoguanidine as a Lewis base catalyst for 5 h. On cooling, the solid product was collected by filtration, dried under vacuum, and recrystallized from ethanol to give **5**.

Yield (75%); mp. 246–247 °C; FTIR (cm^{-1}) 3423, 3047, 1680, 1623; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.82 (s, 1H, OH), 9.23 (d, $J = 9.2$ Hz, 1 H, CHarom), 8.22 (s, 1H, CHarom), 7.81–7.42 (m, 8H, CHarom), 6.45 (d, $J = 9.4$ Hz, 1H, CHarom), 6.19 (s, 1H, CH-pyran), 1.19–1.04 (m, 10H, $2CH_2$+$2CH_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.92, 183.62, 163.61, 155.10, 139.66, 136.36, 134.57, 134.29, 121.79, 110.83, 105.50, 95.78, 44.56, 12.76; Anal. Calcd. for $C_{29}H_{23}NO_4$ (449): C, 77.49; H, 5.16; N, 3.12. Found: C, 77.45; H, 5.17; N, 3.00.

General method for synthesis of xanthen-1-one (9a-c and 10)

A mixture of 1 mmol 2-hydroxyaromaticaldehyde, 2 mmol cyclohexane-1,3-diones and 1 mmol either 3-aminopropane-1,2-diol or 1,3-diaminopropan-2-ol as a basic catalyst in 50 ml ethanol was refluxed. The reaction progress was monitored by TLC till completion after about 6 h. Excess solvent was evaporated under vacuum and the resulted solid was filtered and recrystallized from ethanol.

7-Chloro-9-(2-hydroxy-6-oxocyclohex-1-en-1-yl)-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (9a)

Yield (83%); mp. 251–252 °C; FTIR (cm^{-1}) 3361, 3020, 2967, 2915, 1632, 1618; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.73 (br. s, 1H, OH), 7.24 (d, $J = 8.8$ Hz, 1 H, CHarom), 7.02 (s, 1H, CHarom), 6.92 (d, $J = 8.4$ Hz, 1H, CHarom), 5.02 (s, 1H, CH-pyran), 2.46 (m, 4H, $2CH_2$), 2.20 (m, 4H, $2CH_2$), 1.79 (m, 4H, $2CH_2$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 197.82, 167.84, 149.87, 134.10, 131.05, 130.26, 129.07, 126.30, 123.98, 118.22, 114.57, 112.09, 40.48, 37.13, 27.64, 20.87; Anal. Calcd. for $C_{19}H_{17}ClO_4$ (344.5): C, 66.19; H, 4.97. Found: C, 66.29; H, 4.95.

General method for synthesis of Schiff bases 11 and 12

A mixture of 1 mmol 2-hydroxynaphthaldehyde, 2 mmol 5,5-dimethylcyclohexane-1,3-dione and 1 mmol either 1-aminopropan-1-ol or 1-(3-aminophenyl)ethanol as a basic catalyst in 60 ml ethanol was refluxed for 6 h. Excess solvent was evaporated under vacuum and the resulted solid was filtered, washed with cold ethanol, and recrystallized from ethanol to give **11** or **12**, respectively.

1-(1-hydroxypropyl)iminomethyl-2-naphthol (11)

Yield (91%); mp. 107 °C; FTIR (cm^{-1}) 3418, 3245, 3027, 2967, 2892, 1625; ^1H NMR (400 MHz, DMSO-d_6) δ 9.02 (s, 1H, CH = N), 8.03 (m, 1H, CHarom), 7.69 (m, 2H, CHarom), 7.43 (m, 1 H, CHarom), 7.19 (m, 1H, CHarom), 6.70 (m, 1H, CHarom), 5.00 (s, 1H, OH), 3.86 (m, 1H, CHaliphatic), 3.92 (m, 1H, CHaliphatic), 3.46 (m, 2H, OH + CHaliphatic), 1.12 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 178.97, 159.80, 137.71, 135.06, 129.39, 128.38, 126.60. 122.48, 118.75, 105.92, 65.83, 58.05, 21.34; Anal. Calcd. for $C_{14}H_{15}NO_2$ (229): C, 73.34; H, 6.59; N, 6.11. Found: C, 73.41; H, 6.50; N, 6.04.

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