Molecular Iodine-Catalyzed One-Pot Synthesis of Tetrahydrobenzo[*a*]xanthene-11-One and Diazabenzo[*a*]anthracene-9,11-Dione Derivatives Under Microwave Irradiation

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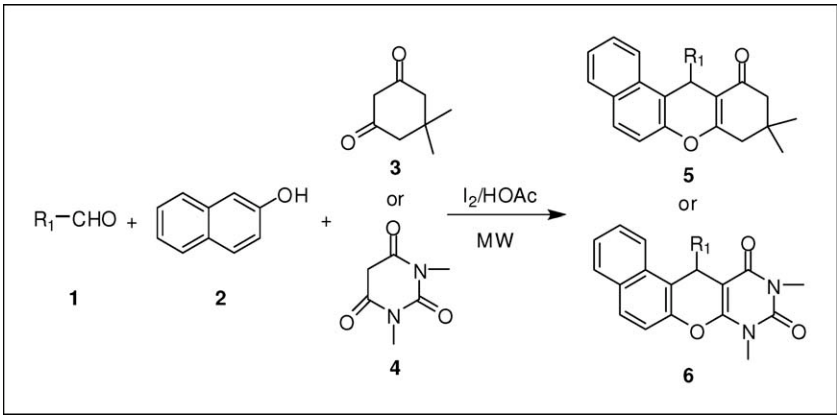

An efficient one-pot condensation of β-naphthol, aldehydes, and cyclic 1,3-dicarbonyl compounds has been achieved with molecular iodine as a catalyst under microwave irradiation, thus a variety of tetrahydrobenzo[*a*]xanthene-11-one and diazabenzo[*a*]anthracene-9,11-dione derivatives were prepared in good yields.

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INTRODUCTION

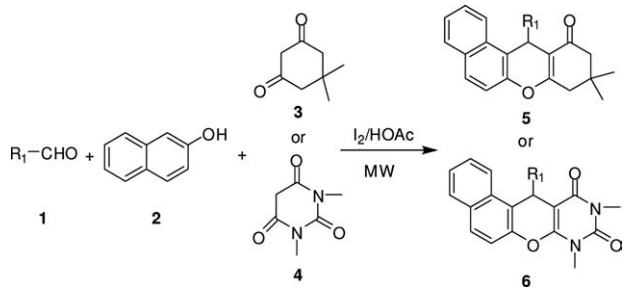
Xanthenes and benzoxanthenes have attracted considerable interest because they possess various biological activities such as antibacterial [1], anti-inflammatory [2], and antiviral [3]. These structural motifs have also found a niche as antagonists for paralyzing the action of zoxazolamine [4] and demonstrate efficacy in photodynamic therapy [5]. In addition, these compounds have been used as dyes [6], and pH-sensitive fluorescent materials for visualization of biomolecular assemblies [7] and used in laser technologies [8]. Thus, a broad utility range has made xanthenes prime synthetic candidates thereby accentuating the need to develop newer synthetic routes for scaffold manipulation of xanthene derivatives. The synthesis of tetrahydrobenzo[*a*]xanthen-11-ones has been reported in the presence of strontium triflate [9] and $NaHSO_4$-SiO_2 under reflux in halogenated solvents for long times [10]. Recent synthetic methods show p-TSA as catalyst in ionic liquid ([bmim]BF_4) or in solvent-free media [11], and $InCl_3$ or P_2O_5 as catalysts under solvent free condition [12]. These synthetic methods afforded good yields however, have limitations of long reaction time, harsh reaction conditions and using expensive catalysts.

Recently, the use of molecular iodine [13] has received considerable attention as an inexpensive, nontoxic, readily available catalyst for various organic transformations to afford the corresponding products in excellent yields. Microwave activation, as a nonconventional energy source, has become an important method in organic synthesis [14]. Here, we report a quick and efficient one-pot method for the three component condensation of a β-naphthol, benzaldehyde, and cyclic-1,3-dicarbonyl compound to synthesis tetrahydrobenzo[*a*]xanthene-11-one and diazabenzo[*a*]anthracene-9,11-dione derivatives using molecular iodine as the catalyst under microwave irradiation (Scheme 1). To the best of our knowledge, this methodology has not been reported in the literature. These catalysts not only make the synthetic process clean, safe and inexpensive, but also afford the products in excellent yield.

RESULTS AND DISCUSSION

The reaction of benzaldehyde **1a**, β-naphthol **2**, 5,5-dimethylcyclohexane-1,3-dione **3** catalyzed by iodine in acetic acid under microwave irradiation has been considered as a standard model reaction.

Scheme 1



We have studied the catalyst loading on model reaction. The amount of catalyst were changed to 5, 10, 15, 20, and 25 mol %, respectively. The results revealed that when the reaction was carried out in the presence of 5 and 10 and 15 mol % of catalyst, it gave lower yield of product even after prolonged reaction time. At the same time, when the amount of catalyst was up to 20 mol %, we got excellent yields of product in a short span. After increasing the catalyst loading at 25 mol %, the yields of the products were found to be constant. So, the use of 20 mol % of catalyst appears to be optimal. The results obtained are summarized in Table 1.

Moreover, we investigated the effect of different microwave temperature settings such as 80, 100, 120, 140, and 160°C when the microwave power sets at 100 W. It was observed that the irradiation at low temperature required longer time and at high temperature suffered from lower yield. This indicates that the irradiation at 120°C gives better result (Table 2, entry 3).

To study the generality of this procedure, a series of aldehydes and 5,5-dimethylcyclohexane-1,3-dione were applied. The results are shown in Table 3. Various aromatic aldehydes containing electron-withdrawing and electron-donating substituent at *ortho*, *meta* or *para*-positions show equal ease towards the product formation in good to high yields.

With the successful condensation of aromatic aldehydes, β-naphthol, and 5,5-dimethylcyclohexane-1,3-dione **3**, we further studied the reaction of aromatic aldehydes, β-naphthol, and 1,3-dimethylbarbituric acid under similar conditions. It was found that the corresponding tetrahydrobenzo[*a*]xanthen-11-one **5** and diazabenzo[*a*]anthracene-9,11-diones **6** could also be obtained in good yields (Table 3).

Table 1

Effect of catalyst concentration on model reaction.[a]

Entry	Catalyst (mol%)	Time (min)	Yield[b] (%)
1	5	6	35
2	10	6	58
3	15	6	73
4	20	6	92
5	25	6	92

[a] Reaction of benzaldehyde, β-naphthol, and 5,5-dimethylcyclohexane-1,3-dione in the presence of iodine in acetic acid under microwave irradiation.
[b] Isolated yield.

Table 2

Effect of microwave-irradiation temperature for the synthesis of tetrahydrobenzo[α]xanthene-11-one derivative **5a**.[a]

Entry	Temperature (°C)	Time (min)	Yield[b] (%)
1	80	10	75
2	100	7	88
3	120	6	92
4	140	5	87
5	160	4	85

[a] Compound **1a** (1 mmol) was treated with β-naphthol (1 mmol) and 5,5-dimethylcyclohexane-1,3-dione (1.2 mmol) in the presence of iodine (20 mol %) in acetic acid under microwave irradiation.
[b] Isolated yield.

A mechanistic rationale portraying the probable sequence of events is given in Scheme 2 [12]. We supposed that the reaction may proceed via the *ortho*-quinone methides (o-QM) intermediate, which was formed by the nucleophilic addition of β-naphthol to aldehyde catalyzed by I_2. Subsequent Michael addition of the o-QM with cyclic 1,3-dicarbonyl and followed by addition of the phenolic hydroxyl moiety to the carbonyl of ketone provides cyclic hemiketal, which on dehydration afforded **5**.

CONCLUSIONS

In summary, we have described an efficient and mild method for the preparation of 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthene-11-ones and 8,10-dimethyl-12-aryl-8,12-dihydro-7-oxa-8,10-diazabenzo[*a*]anthracene-9,11-diones. This process is efficiently promoted by the iodine. Unlike other existing methods, the advantages of this method are reduced reaction times, higher yields, mild reaction condition, easy purification, and economic viability of the catalyst. We believe that this economically viable procedure will find practical utility for the one pot synthesis of novel xanthenes and anthracenes.

EXPERIMENTAL

Melting points were determined in a WRS-1B digital melting-point instrument and are uncorrected. IR spectra were recorded on a Nicolet Avatar 360 FT-IR instrument. ^{1}H NMR and ^{13}C NMR were measured on a Burke 400-MHz spectrometer in $CDCl_3$ with TMS as internal standard. Mass spectra (MS) were recorded on an LCQ Advantage instrument. Reactions under microwaves were performed in a CEM Discover®

Table 3

I_2 catalyzed condensation of aldehydes, β-naphthol and cyclic 1,3-dicarbonyl compounds to give **5** and **6** under microwave irradiation.[a]

Entry	R_1	Time (min)	Yield[b] (%)	Mp (observed/reported[ref])(°C)
5a	C_6H_5	6	92	152–154/151–153 [12]
5b	4-MeC_6H_4	6	93	173–175/176–178 [12]
5c	4-$OMeC_6H_4$	7	80	201–203/204–205 [12]
5d	2-ClC_6H_4	8	94	173–174/179–180 [12]
5e	4-ClC_6H_4	6	92	177–179/180–182 [12]
5f	2,4-$Cl_2C_6H_4$	6	89	175–176/178–180 [12]
5g	3-$NO_2C_6H_4$	6	82	169–171/168–170 [12]
5h	4-$NO_2C_6H_4$	6	90	179–181/178–180 [12]
5i	4-OHC_6H_4	8	75	221–223/223–225 [12]
5j	2-FC_6H_4	6	80	230–232/Not rep.
5k	3,4-$(OCH_2O)C_6H_3$	6	94	203–205/Not rep.
6a	C_6H_5	8	75	227–229/226–228 [12]
6b	4-MeC_6H_4	8	78	199–201/196–198 [12]
6c	4-ClC_6H_4	9	71	274–275/270–272 [12]
6d	2,4-$Cl_2C_6H_4$	8	72	221–223/222–224 [12]
6e	2-ClC_6H_4	9	74	271–273/270–272 [12]
6f	2-$NO_2C_6H_4$	8	75	285–287/288–290 [12]
6g	4-$NO_2C_6H_4$	9	72	283–285/288–290 [12]
6h	2-FC_6H_4	8	70	287–289/Not rep.
6i	3,4-$(OCH_2O)C_6H_3$	8	76	204–206/Not rep.

[a] Reaction condition: **1** (1 mmol), **2** (1 mmol), **3** (1.2 mmol), iodine (20 mol%), under microwave irradiation.
[b] Isolated yield.

monomode microwave reactor. All the reagents are commercially available.

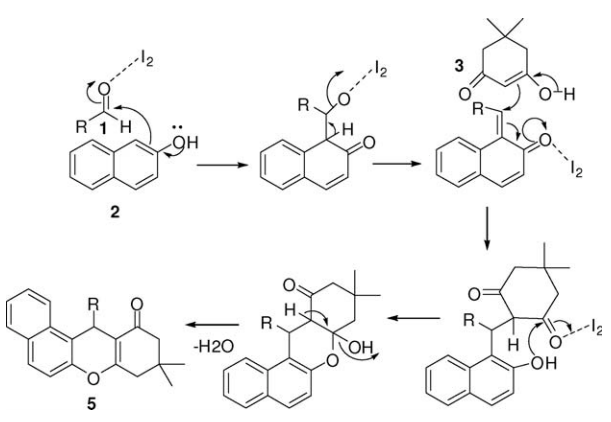
General procedure for synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo[a]xanthene-11-one (5) and 8,10-dimethyl-12-aryl-8,12-dihydro-7-oxa-8,10-diazabenzo[a]anthracene-9,11-dione (6). A 10-mL process vial was charged with a mixture of the aromatic aldehyde (1 mmol), β-naphthol (1 mmol), cyclic-1,3-dicarbonyl compound (1.2 mmol), iodine (0.2 mmol), and acetic acid (3 mL) and sealed with a cap containing a septum. The loaded vial was then placed into the cavity of the microwave reactor and heated at 100 W, 120°C for 6–9 min (as indicated by thin-layer chromatography). After completion of the reaction, the mixture was treated with aq $Na_2S_2O_3$ solution and stirred at room temperature for 10 min. The precipitate formed was collected by vacuum filtration, washed with water, and dried. The crude product was recystallized from methanol.

Spectral data of some representative products are given below. Compound **5j**: ^{1}H NMR(400 MHz, $CDCl_3$): δ 7.81–7.77 (m, 2H), 7.69 (d, J = 8.0 Hz, 1H), 7.44–7.28 (m, 3H), 7.04–7.01 (m, 2H), 6.64–6.61 (m, 2H), 5.79 (s, 1H), 2.63 (s, 1H), 2.44 (d, J = 16.4 Hz, 1H), 2.37 (d, J = 16.4 Hz, 1H), 1.17 (s, 3H), 1.02 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 166.8, 152.9, 147.9, 132.7, 131.6, 131.2, 129.1, 128.7, 128.2, 127.9, 127.5, 125.3, 123.5, 121.5, 118.9, 117.5, 116.6, 50.3, 41.6, 32.4, 29.0, 28.0, 27.2. IR (KBr, cm^{-1}): 3196, 2957, 2891, 1628, 1380, 1229, 1180, 1032, 811. MS(ESI): m/z = 373 $[M+H]^+$. *Anal*. Calcd for $C_{25}H_{21}FO_2$: C 80.62, H 5.68; found C 80.55, H 5.82.

Compound **5k**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, J = 8.4 Hz, 1H), 7.81–7.76 (m, 2H), 7.49–7.28 (m, 3H), 6.88–6.80 (m, 2H), 6.63 (d, J = 8.0 Hz, 1H), 5.81 (s, 2H), 5.65(s, 1H), 2.58 (s, 2H), 2.28 (s, 2H), 1.14 (s, 3H), 1.02 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 196.8, 163.7, 147.7, 147.5, 145.8, 138.9, 131.5, 131.4, 128.8, 128.4, 126.9, 124.9, 123.7, 121.8, 117.7, 117.1, 114.3, 108.9, 107.9, 100.7, 50.7, 41.4, 34.3, 32.3, 29.2, 27.3. IR (KBr, cm^{-1}): 3132, 2959, 2878, 1645, 1399, 1226, 1174, 1034, 823. MS(ESI): m/z = 399 $[M+H]^+$. *Anal*. Calcd for $C_{26}H_{22}O_4$: C 78.37, H 5.57; found C 78.53, H 5.62.

Compound **6h**: ^{1}H NMR(400 MHz, $CDCl_3$): δ 7.89–7.81 (m, 2H), 7.69 (d, J = 7.8 Hz, 1H), 7.45–7.41 (m, 3H), 7.09–7.04 (m, 2H), 6.66–6.58 (m, 2H), 6.02 (s, 1H), 3.64 (s, 3H), 3.41 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 164.9, 153.6, 153.3, 149.9, 147.5, 132.1, 131.8, 130.7, 129.8, 128.4, 128.3, 127.9, 125.8, 123.8, 121.6, 119.5, 117.2, 115.8, 90.9, 29.4, 29.2, 28.7. IR (KBr, cm^{-1}): 3151, 2956, 1710, 1625, 1488, 1231, 1176. MS(ESI): m/z = 389 $[M+H]^+$. *Anal*. Calcd for $C_{23}H_{17}FN_2O_3$: C 71.13, H 4.41, N 7.21; found C 71.36, H 4.65, N 7.05.

Scheme 2



Compound **6i**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.46 (d, J = 8.2Hz, 1H), 7.86–7.83 (m, 2H), 7.50–7.28(m, 4H), 6.93–6.65 (m, 2H), 6.10 (s, 2H), 5.86 (s, 1H), 3.42 (s, 3H), 3.40 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 162.9, 152.7, 150.6, 147.9, 146.3, 137.9, 134.2, 131.8, 129.5, 128.8, 127.5, 125.6, 123.9, 121.6, 116.3, 114.7, 113.2, 108.7, 102.2, 100.9, 91.5, 35.7, 29.1, 28.4. IR (KBr, cm^{-1}): 3128, 2960, 1724, 1671, 1454, 1282, 1151. MS(ESI): m/z = 415 $[M+H]^+$. *Anal*. Calcd for $C_{24}H_{18}N_2O_5$: C 69.56, H 4.38, N 6.76; found C 69.39, H 4.62, N 6.60.

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