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Iodine-Catalyzed Synthesis of 12-Aryl-8,9,10,12tetrahydro-benzo[*a*]xanthen-11-one Derivatives via Multicomponent Reaction

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Abstract: Iodine efficiently catalyzes the one-pot, three-component reaction of aryl aldehyde, 2-naphthol, and cyclic 1,3-dicarbonyl compound under solvent-free conventional heating conditions to afford the corresponding 12-aryl-8,9,10,12-tetrahydro-benzo[*a*]xanthen-11-one derivatives. The present approach offers several advantages such as shorter reaction times, good yields, low cost, and mild reaction conditions.

Keywords: Aldehyde, iodine, multicomponent reaction, β -naphthol, solvent-free conditions, xanthene

INTRODUCTION

Multicomponent reactions (MCRs) have attracted much attention as a result of their synthetic efficiency, simplicity of operation, reduction of isolation and purification steps, and minimization of costs, energy, time, and waste production.^[1–3]

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Scheme 1. Synthesis of 12-aryl-8,9,10,12-tetrahydro-benzo[*a*]xanthen-11-one derivatives catalyzed by iodine.

Compounds containing a xanthene skeleton exhibit good biological and pharmaceutical activities such as antibacterial, antiviral, and antiinflammatory activities. They have found application in industries such as dyes, laser technologies, and pH-sensitive fluorescent material to monitor changes in intracellular pH.^[4–7] Therefore, several approaches have been reported for their synthesis.^[8] Despite the available methods, little attention has been paid to synthesis of 12-aryl-8,9,10,12-tetrahydro-benzo[*a*]xanthen-11-one derivatives. To the best of our knowledge, only one procedure was reported in the literature,^[9] in which NaHSO₄· SiO₂ was used as a catalyst and the reaction was carried out in refluxing 1,2-dichloreethane. However, this procedure involves the use of harmful volatile organic solvent and extended reaction times. Thus, it is necessary to further develop an efficient and convenient method to construct this type of heterocyclic compounds.

In recent years, molecular iodine has emerged as an inexpensive and easily available catalyst for various organic transformations.^[10–18] It is therefore of interest to examine the behavior of molecular iodine as catalyst in the synthesis of xanthene-based compounds. Herein, we report a new method for the synthesis of 12-aryl-8,9,10,12-tetrahydro-benzo[*a*]-xanthen-11-one derivatives via a one-pot, three-component reaction of aldehydes with β -naphthol and cyclic 1,3-dicarbonyl compound by use of molecular iodine as catalyst under solvent-free conditions (Scheme 1).

RESULTS AND DISCUSSION

In an initial endeavor, a mixture of 2-naphthol (1 mmol), 4-chlorobenzaldehyde (1 mmol), and 5,5-dimethyl-1,3-cyclohexanedione (1.2 mmol) in the presence of iodine (0.1 mmol) was stirred in 1,2-dichloroethane under reflux conditions. After 3 h, only 38% of the expected product **4e** was obtained. This is probably because the use of solvent decreases the catalytic efficiency of iodine. It has been shown that many reactions proceed efficiently under solvent-free conditions.^[19] To improve the yield, the same reaction was carried out under solvent-free conditions at 60 °C. A significant improvement was observed, and the yield of **4e** was increased to 95%. The effect of amount of catalyst on the yield and rate was

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also investigated. It was found that 10 mmol% of catalyst was enough for a fairly good yield. Lesser amounts gave a poor yield even after a long reaction time, and greater amounts did not obviously increase the yield of the product. Meanwhile, we also tested the effect of reaction temperature on the catalyzed reaction. When the reaction was carried out at 60 °C, the maximum yield was obtained in a short reaction period (1 h).

To extend the scope of the reaction and to generalize the procedure, a variety of electronically divergent aromatic aldehydes, 5,5-dimethyl-1,3-cyclohexanedione, and β -naphthol were examined, and the results are summarized in Table 1. In all cases, aromatic aldehydes carrying either an electron-withdrawing group or an electron-donating group reacted successfully and gave the products in good to excellent yields. The results proved that this methods is superior to previously reported methods in terms of yields and reaction times.^[9] It is observed that substituents in the aromatic ring of aldehydes have a delicate effect on the reaction process. Aromatic aldehydes with electron-withdrawing groups reacted faster than those with electron-donating groups. To further expand the scope of the present method, the replacement of 5,5-dimethyl-1,3-cyclohexanedione with 1,3-cyclohexanedione was examined. To our delight, under the same conditions, the reactions proceeded steadily to afford a series of xanthene-based compounds in good yields.

A plausible mechanism was proposed in Scheme 2. After reviewing the literature,^[20] we think that iodine catalyzes the reaction as a mild

Entry	Aldehydes	R	Time (min)	Yield (%) ^a	Mp (°C)
a	PhCHO	Me	75	90	149-150 ^[21]
b	4-MeC ₆ H ₄ CHO	Me	85	89	175-176
c	4-MeOC ₆ H ₄ CHO	Me	90	88	208-209 ^[9]
d	4-OHC ₆ H ₄ CHO	Me	65	82	150–151 ^[9]
e	4-ClC ₆ H ₄ CHO	Me	60	95	187–188 ^[9]
f	4-BrC ₆ H ₄ CHO	Me	60	95	186–187
g	4-NO ₂ C ₆ H ₄ CHO	Me	45	90	175-176 ^[21]
ĥ	PhCHO	Н	70	88	188–189 ^[9]
i	4-MeC ₆ H ₄ CHO	Н	90	87	205-206
i	4-MeOC ₆ H₄CHO	Н	95	86	181-182 ^[21]
k	4-ClC ₆ H ₄ CHO	Н	60	94	205-206 ^[21]
1	3-NO ₂ C ₆ H ₄ CHO	Н	50	92	235-236 ^[21]
m	$4-NO_2C_6H_4CHO$	Н	55	91	234-235 ^[21]

Table 1. Iodine-catalyzed preparation of 12-aryl-8,9,10,12-tetrahydro-benzo[*a*] xanthen-11-one derivatives under solvent-free conditions

^aIsolated yield.



Scheme 2. Hypothetical mechanism for the synthesis of xanthene-based compounds.

Lewis acid. First, the condensation of 2-naphthol with aldehydes produced *ortho*-quinone methides (*o*-QMs) in the presence of molecular iodine. Then, the trapping of *o*-QMs with dimedone formed intermediates **5**, which were cyclized and then dehydrated to give the corresponding products **4**.

In conclusion, molecular iodine has proved to be a useful and novel catalyst for the synthesis of 12-aryl-8,9,10,12-tetrahydro-benzo[*a*]-xanthen-11-one derivatives in good yields and short reaction times. The use of inexpensive and readily available molecular iodine made this procedure simple, convenient, and practical.

EXPERIMENTAL

Melting points were recorded on an X-4 apparatus and are uncorrected. Infrared (IR) spectra were obtained using a Shimadzu Fourier transform (FT)IR–8900 spectrometer using KBr optics. ¹H NMR spectra were recorded with a Varain Mercury Plus 400 spectrometer in CDCl₃ using tetramethylsilane (TMS) as internal standard. Mass spectra (MS) were recorded on a VG-7070E mass spectrophotometer. Elemental analyses were performed on Vario EL III CHNOS elemental analyzer.

General Procedure for the Preparation of 14-Aryl-14 Hdibenzo[*a*,*j*]xanthene Derivatives

A mixture of aldehydes (1 mmol), β -naphthol (1 mmol), cyclic 1,3dicarbonyl compound (1.2 mmol), and I₂ (0.1 mmol) was ground and heated at 60 °C for a specified time. After completion of the reaction as indicated by thin-layer chromatography (TLC), the system was cooled to room temperature. The mixture was treated with aqueous Na₂S₂O₃ and then extracted with ethyl acetate (2 × 10 mL). The combined organic

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layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by silica-gel column chromatography using ethyl acetate–hexane (1:10) as eluent to afford pure products. The identification and characterization of the products were carried out by comparing their physical and spectroscopic data with those of known samples.^[9] The purity of the presently synthesized compounds was demonstrated by TLC and ¹H NMR.

Spectral Data for Selected Compounds

9,9-Dimethyl-12-*p*-tolyl-8,9,10,12-tetrahydro-benzo[*a*] xanthen-11-one (**4b**)

White solid; mp 175–176 °C; IR (KBr): 2947, 2869, 1647, 1596, 1508, 1400, 1371, 1226, 1186, 827, 812 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ : 0.97 (s, 3H), 1.12 (s, 3H), 2.19 (s, 3H), 2.25 and 2.30 (AB system, J = 16.0 Hz, 2H, CH_aCH_bCO), 2.57 (s, 2H), 5.67 (s, 1H), 6.98 (d, J = 7.6 Hz, 2H), 7.21–7.38 (m, 4H), 7.43 (t, J = 8.0 Hz, 1H), 7.76 (t, J = 7.6 Hz, 2H), 8.01 (d, J = 8.4 Hz, 1H) ppm; MS (EI, 70 eV) m/z (%): 368 (M⁺, 88), 277 (100), 221 (26), 193 (18), 165 (16), 55 (8). Anal. calcd. for C₂₆H₂₄O₂: C, 84.75; H, 6.57. Found: C, 84.66; H, 6.42.

12-(4-Bromophenyl)-9,9-dimethyl-8,9,10,12-tetrahydro-benzo[*a*] xanthen-11-one (**4f**)

White solid; mp 186–187 °C; IR (KBr): 2962, 2868, 1643, 1593, 1483, 1400, 1375, 1220, 1174, 1145, 1008, 837 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ : 0.97 (s, 3H), 1.12 (s, 3H), 2.25 and 2.30 (AB system, J = 16.4 Hz, 2H, CH_aCH_bCO), 2.57 (s, 2H), 5.67 (s, 1H), 7.20–7.46 (m, 7H), 7.78 (t, J = 7.6 Hz, 2H), 7.89 (d, J = 8.4 Hz, 1H) ppm; MS (EI, 70 eV) m/z (%): 434 (M + 2, 42), 432 (M⁺, 40), 277 (100), 221 (23), 193 (12), 165 (16), 55 (8). Anal. calcd. for C₂₅H₂₁BrO₂: C, 69.29; H, 4.88. Found: C, 69.12; H, 4.93.

12-p-Tolyl-8,9,10,12-tetrahydro-benzo[a]xanthen-11-one (4i)

White solid; mp 205–206 °C; IR (KBr): 2950, 2871, 1651, 1595, 1508, 1402, 1373, 1226, 1188, 1176, 1126, 1137, 954, 817 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ : 1.91–1.94 (m, 2H), 2.20 (s, 3H), 2.31–2.48 (m, 2H), 2.55–2.76 (m, 2H), 5.70 (s, 1H), 6.98 (d, J=8.0 Hz, 1H), 7.03 (d, J=8.0 Hz, 1H), 7.19 (d, J=8.0 Hz, 1H), 7.24 (d, J=8.0 Hz, 1H),

7.31–7.44 (m, 3H), 7.76 (d, J = 8.0 Hz, 2H), 7.97 (d, J = 8.4 Hz, 1H) ppm; MS (EI, 70 eV) m/z (%): 340 (M⁺, 42), 325 (8), 308 (28), 277 (124), 249 (100), 216 (40), 165 (10), 55 (12). Anal. calcd. for C₂₄H₂₀O₂: C, 84.68; H, 5.92. Found: C, 84.79; H, 6.06.

12-(4-Methoxyphenyl)-8,9,10,12-tetrahydro-benzo[*a*] xanthen-11-one (**4j**)

White solid, mp 181–182°C; IR (KBr): 2945, 2875, 1651, 1595, 1460, 1377, 1251, 1226, 1188, 1174, 1033, 952, 748 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ : 1.91–2.08 (m, 2H), 2.31–2.48 (m, 2H), 2.57–2.76 (m, 2H), 3.69 (s, 3H), 5.69 (s, 1H), 6.70 (d, J = 8.0 Hz, 2H), 7.23–7.44 (m, 5H), 7.76 (t, J = 8.4 Hz, 2H), 7.95 (d, J = 8.0 Hz, 1H) ppm; MS (EI, 70 eV) m/z (%): 356 (M⁺, 65), 355 (95), 324 (28), 299 (22), 249 (100), 216 (8), 165 (20), 55 (12). Anal. calcd. for C₂₄H₂₀O₃: C, 80.88; H, 5.66. Found: C, 80.74; H, 5.81.

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