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An efficient synthesis of spiro[dibenzo[*b*,*i*]xanthene-13,3′-indoline]-pentaones and 5*H*-dibenzo[*b*,*i*]xanthene-tetraones

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ABSTRACT

Spiro[dibenzo[*b*,*i*]xanthene-13,3′-indoline]-pentaones and 5*H*-dibenzo[*b*,*i*]xanthene-tetraones are synthesized from the condensation of 2-hydroxynaphthalene-1,4-dione with isatins or aldehydes.

1. Introduction

Polyfunctionalized heterocyclic compounds play important roles in the drug discovery process, and analysis of drugs in late development or on the market shows that 68% of them are heterocycles.[1,2] Therefore, it is not surprising that research on the synthesis of polyfunctionalized heterocyclic compounds has received significant attention.

The quinone moiety is involved in a wide variety of biochemical processes including electron transport and oxidative phosphorylation.[3] Various biological properties including enzyme inhibition, antibacterial, antifungal, and anticancer activities have been reported for quinones and quinone derivatives.[4–7] The antitumor activity of the quinone moiety has been studied thoroughly, and it is known that they act as topoisomerase inhibitors via DNA-intercalation.[8,9] Quinone-annulated heterocycles are found in nature, and most of them exhibit interesting biological activities. The chemistry of quinone-annulated heterocycles is dependent largely on the substituent being either on the quinone or on adjacent rings.[10,11] These activities, combined with diverse chemical behavior make quinones attractive targets in organic synthesis.

The indole framework is common in a wide variety of pharmacologically and biologically active compounds.[12] Furthermore, it has been reported that sharing of the indole 3-carbon atom during the formation of spiroindoline derivatives enhances the biological activity highly.[13,14] The spiro-oxindole system is the core structure of some pharmacological agents and natural alkaloids.[15–17] Similarly, xanthenes have been reported to possess diverse biological and therapeutic properties such as antibacterial, antiviral, and anti-inflammatory activities, as well as being used in photodynamic therapy.[18,19] Other useful applications of these heterocycles are as dyes, fluorescent materials for visualization of biomolecules and in laser technologies.[20,21]

Considering the above reports, and as part of our program aimed at developing new selective and environmentally friendly methodologies for the preparation of heterocyclic compounds,[22–28] we undertook the synthesis of spiro[dibenzo[*b*,*i*]xanthene-13,3′-indoline]-pentaone derivatives through a cyclo-condensation reaction employing water as the reaction medium.

Reaction of 2-hydroxynaphthalene-1,4-dione **1** and isatins **2a–f** in the presence of a catalytic amount of *p*-toluenesulfonic acid (*p*-TSA) as an inexpensive and readily available catalyst proceeded smoothly in water at reflux for 24 h to produce spiro[dibenzo[*b*,*i*]-xanthene-13,3′-indoline]-2′,5,7,12,14-pentaones **3a–f** in 75–82% yields (Scheme 1). Without *p*-TSA, for long periods of time (60 h), the yields of products were low (<30%).

It is thought that compounds **3** result from initial addition of 2-hydroxynaphthalene-1,4-dione **1** to the isatin **2** to yield intermediates **4**, which react further with another molecule of **1**. Finally, cyclization afforded the corresponding products **3** (Scheme 2).

To further explore the potential of this protocol for spiro-heterocycle synthesis, we investigated the reaction between ninhydrin **5** and **1**, and obtained spiro[dibenzo[*b*,*i*]xanthene-13,2′-indene]-1′,3′,5,7,12,14-hexaone **6** in 62% yield (Scheme 3).

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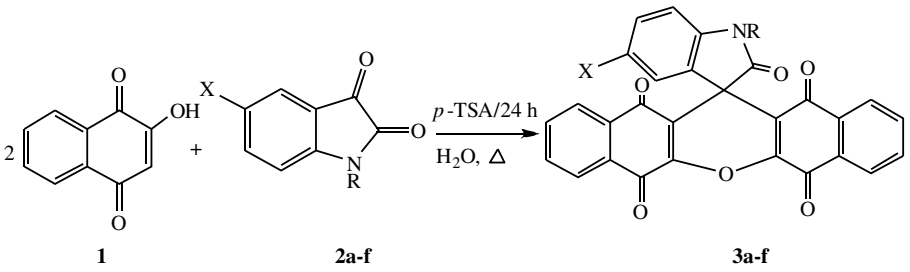
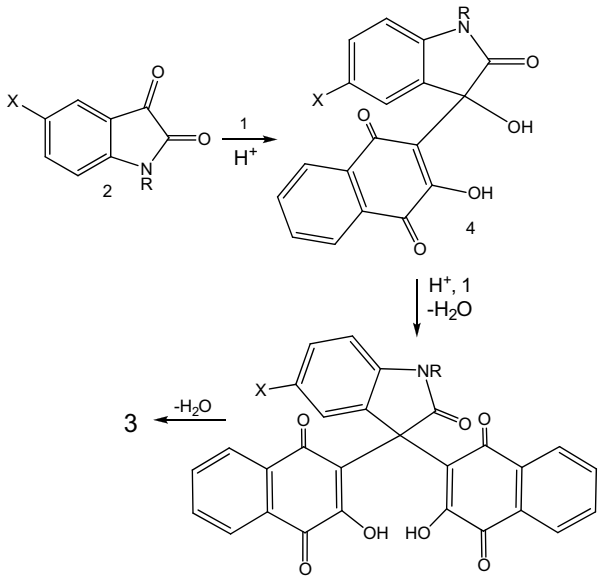


1 2a-f 3a-f

Product **3**	R	X	Yield (%)
a	H	H	80
b	Me	H	79
c	$PhCH_2$	H	81
d	H	Br	82
e	H	NO_2	75
f	Me	Br	77

Scheme 1.



Scheme 2.

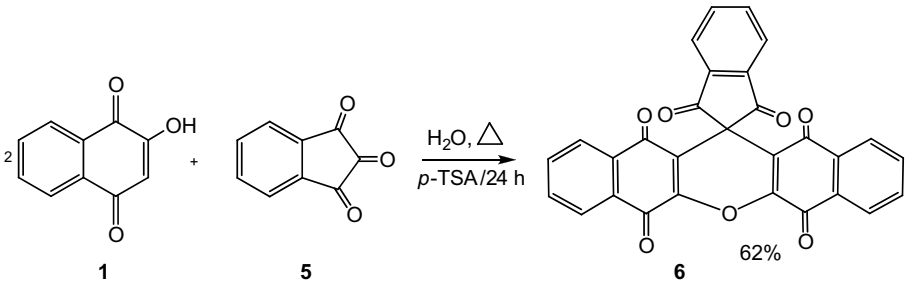
Finally, the feasibility of employing aldehydes for the synthesis of 5*H*-dibenzo[*b*,*i*]xanthene-tetraones was also investigated. When aromatic aldehydes were used, the yields of the expected products were low (<30%). In order to improve the yields of the 5*H*-dibenzo[*b*,*i*]xanthene-ytetraones, we examined the reaction under different conditions including refluxing in various solvents (MeOH, EtOH, THF, CH_3CN, EtOAc, and toluene) and also under solvent-free classical heating conditions. In refluxing solvents, after 48 h, the yields of products were low (<40%). We found that the best results were obtained under solvent-free conditions in the presence of *p*-TSA at 80 °C. Several aromatic aldehydes reacted to give products **8a**–**f** in 70–78% yields in 7 h (Scheme 4). When this reaction was carried out with an aliphatic aldehyde such as propionaldehyde, TLC and ^{1}H NMR spectroscopy of the reaction mixture showed a combination of starting materials and numerous products, the yield of the expected product was very poor.

Compounds **3, 6**, and **8** are stable solids whose structures were established by IR, ^{1}H NMR spectroscopy, mass spectrometry and elemental analysis. The electronic absorption spectra of 10^{-5} M solutions of **3a**–**f** and **8a**–**f** in DMSO were measured, Table 1. The longest wavelength maximum absorption (λ_{max}) of all the compounds was located between 260 and 275 nm. Studies on the fluorescent properties of these compounds were also carried out in DMSO (Table 2).

In summary, we have described efficient and simple methods for the preparation of spiro[dibenzo[*b*,*i*]xanthene-13,3′-indoline]-pentaones yand 5*H*-dibenzo[*b*,*i*]xanthene-tetraones via condensation reactions of 2-hydroxynaphthalene-1,4-dione with isatins or aldehydes.

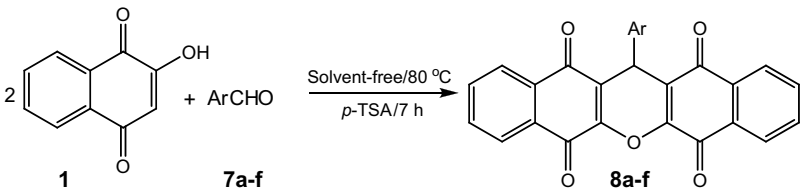
2. Typical procedure for the preparation of spiro[dibenzo[*b*,*i*]xanthene-13,3′-indoline]-pentaone (3a)

A mixture of 2-hydroxynaphthalene-1,4-dione (2 mmol), an isatin (1 mmol) and *p*-TSA (0.1 g) in refluxing water (5 ml) was stirred for 24 h (the progress of the reaction was monitored by TLC). After completion, the reaction mixture was filtered and the obtained precipitate washed with water and recrystallized from



1 5 6

Scheme 3.



Product **8**	Ar	Yield (%)
a	C_6H_5	74
b	4-Cl-C_6H_4	76
c	4-Br-C_6H_4	75
d	4-Me-C_6H_4	70
e	2-Cl-C_6H_4	71
f	3-NO_2-C_6H_4	78

Scheme 4.

Table 1
UV/visible data for compounds **3** and **8** in DMSO

Entry	Compound	λ_{max} (nm)	ε (10^4 L mol^{-1} cm^{-1})
1	**3a**	265	6.55
2	**3b**	267	7.15
3	**3c**	268	7.91
4	**3d**	260	7.46
5	**3e**	264	6.84
6	**3f**	270	7.35
7	**8a**	274	7.25
8	**8b**	272	6.89
9	**8c**	270	6.94
10	**8d**	271	7.11
11	**8e**	275	7.45
12	**8f**	268	6.97

Table 2
Fluorescence properties for compounds **3** and **8** in DMSO

Entry	Compound	λ_{ex} (nm)	λ_{em} (nm)
1	**3a**	355	398
2	**3b**	328	362
3	**3c**	350	397
4	**3d**	315	347
5	**3e**	384	391
6	**3f**	319	359
7	**8a**	310	340
8	**8b**	306	333
9	**8c**	300	321
10	**8d**	314	342
11	**8e**	309	328
12	**8f**	335	374

EtOH/H_2O (1:3) to afford pure **3a**. Orange powder (80%); mp: 350 °C dec. IR (KBr) (ν_{max}/cm^{-1}): 3410, 3090, 1720, 1668, 1603. MS (EI, 70 eV) *m/z* (%): 459 (M^+, 80), 417 (100), 76 (70). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 6.78–8.11 (12H, m, H–Ar), 10.84 (1H, s, NH). Anal. Calcd for $C_{28}H_{13}NO_6$: C, 73.20; H, 2.85; N, 3.05. Found: C, 73.25; H, 2.80; N, 3.12.

Due to the very low solubilities of products **3**, **6**, and **8**, we were unable to obtain ^{13}C NMR spectra for these products.

3. Selected data for products

3.1. 1′-Methylspiro[dibenzo[*b*,*i*]xanthene-13,3′-indoline]-pentaone (3b)

Red powder (79%); mp: 360 °C dec. IR (KBr) (ν_{max}/cm^{-1}): 3064, 1714, 1674, 1602. MS (EI, 70 eV) *m/z* (%): 473 (M^+, 100), 445 (40), 402 (70), 76 (30).^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 3.33 (3H, s, CH_3), 6.86–820 (12H, m, H–Ar). Anal. Calcd for $C_{29}H_{15}NO_6$: C, 73.57; H, 3.19; N, 2.96. Found: C, 73.51; H, 3.15; N, 2.90.

3.2. 1′-Benzylspiro[dibenzo[*b*,*i*]xanthene-13,3′-indoline]-pentaone (3c)

Red powder (81%); mp: 358 °C dec. IR (KBr) (ν_{max}/cm^{-1}): 3013, 1724, 1672, 1610. MS (EI, 70 eV) *m/z* (%): 549 (M^+, 50), 453 (100), 414 (30), 91 (80). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 5.10 and 5.30 (2H, AB system, J = 15.2 Hz, CH_2), 6.74–8.33 (17H, m, H–Ar). Anal. Calcd for $C_{35}H_{19}NO_6$: C, 76.50; H, 3.48; N, 2.55. Found: C, 76.45; H, 3.42; N, 2.62.

3.3. 5′-Bromo-1′-methylspiro[dibenzo[*b*,*i*]xanthene-13,3′-indoline]-pentaone (3f)

Orange powder (77%); mp: 365 °C dec. IR (KBr) (ν_{max}/cm^{-1}): 3015, 1716, 1605. MS (EI, 70 eV) *m/z* (%): 553 (M^+, ^{81}Br, 100), 551 (M^+, ^{79}Br, 100), 525 (26), 480 (30), 76 (40).^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 3.32 (3H, s, CH_3), 7.03–8.18 (11H, m, H–Ar). Anal. Calcd for $C_{29}H_{14}BrNO_6$: C, 63.06; H, 2.55; N, 2.54. Found: C, 63.01; H, 2.60; N, 2.61.

3.4. Spiro[dibenzo[*b*,*i*]xanthene-13,2′-indene]-1′,3′,5,7,12,14-hexaone (6)

Yellow powder (62%); mp: 230 °C dec. IR (KBr) (ν_{max}/cm^{-1}): 3011, 1734, 1725, 1678, 1615. MS (EI, 70 eV) *m/z* (%): 472 (M^+, 15), 444 (10), 290 (30), 104 (100). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 7.26–8.08 (12H, m, H–Ar). Anal. Calcd for $C_{29}H_{12}O_7$: C, 73.73; H, 2.56. Found: C, 73.80; H, 2.60.

3.5. 13-Phenyl-5*H*-dibenzo[*b*,*i*]xanthene-5,7,12,14(13*H*)-tetraone (8a)

Red powder (74%); mp: 305–307 °C; IR (KBr) (ν_{max}/cm^{-1}): 3035, 1660, 1569. MS (EI, 70 eV) *m/z* (%): 418 (M^+, 57), 390 (90), 313 (100). ^{1}H NMR (DMSO-d_6): δ_H 5.09 (1H, s, CH), 7.16–8.08 (13H, m, H–Ar). Anal. Calcd for $C_{27}H_{14}O_5$: C, 77.51; H, 3.37. Found C, 77.64; H, 3.41.

3.6. 13-(4-Chlorophenyl)-5*H*-dibenzo[*b*,*i*]xanthene-5,7,12,14(13*H*)-tetraone (8b)

Orange powder (76%); mp: 330–332 °C; IR (KBr) (ν_{max}/cm^{-1}): 3028, 1663, 1610. MS (EI, 70 eV) *m/z* (%): 452 (M^+, 5), 424 (60),

313 (100). ^{1}H NMR (DMSO-d_6): δ_H 5.10 (1H, s, CH), 7.26–8.07 (12H, m, H–Ar). Anal. Calcd for $C_{27}H_{13}ClO_5$: C, 71.61; H, 2.89. Found C, 71.56; H, 3.93.

3.7. 13-p-Tolyl-5*H*-dibenzo[*b*,*i*]xanthene-5,7,12,14(13*H*)-tetraone (8d)

Brick-red powder (70%); mp: 304–307 °C; IR (KBr) (ν_{max}/cm^{-1}): 3088, 1663, 1608. MS (EI, 70 eV) *m*/*z* (%): 432 (M^+, 45), 404 (100), 313 (65). ^{1}H NMR (DMSO-d_6): δ_H 2.21 (3H, s, CH_3), 5.09 (1H, s, CH), 7.07–8.12 (12H, m, H–Ar). Anal. Calcd for $C_{28}H_{16}O_5$: C, 77.77; H, 3.73. Found C, 77.68; H, 3.66.

3.8. 13-(3-Nitrophenyl)-5*H*-dibenzo[*b*,*i*]xanthene-5,7,12,14(13*H*)-tetraone (8f)

Orange powder (78%); mp: 340–342 °C; IR (KBr) (ν_{max}/cm^{-1}): 3035, 1662, 1605. MS (EI, 70 eV) *m*/*z* (%): 463 (25), 418 (40), 313 (100). ^{1}H NMR (DMSO-d_6): δ_H 5.47 (1H, s, CH), 7.11–8.13 (12H, m, H–Ar). Anal. Calcd for $C_{27}H_{13}NO_7$: C, 69.98; H, 2.83; N, 3.02. Found C, 69.91; H, 2.78; N, 3.09.

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