A Clean Synthesis of Spiro[indoline-3,9′-xanthene]trione Derivatives

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A simple, clean and efficient method for the synthesis of spiro[indoline-3,9′-xanthene]trione derivatives and spiro[acenaphthene-1,9′-xanthene]-1′,2,8′(2′*H*,5′*H*)-trione by condensation reaction of dimedone and isatins or acenaphthene in aqueous media is reported.

Key words isatin; spirooxindole; spiro[indoline-3,9′-xanthene]trione; spiro[acenaphthene-1,9′-xanthene]trione

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 heterocyclic compounds has received significant attention.

Indole fragment is featured widely in a wide variety of pharmacologically and biologically active compounds.[3] Furthermore, it has been reported that sharing of the indole 3-carbon atom in the formation of spiroindoline derivatives highly enhances biological activity.[4—6] The spirooxindole system is the core structure of many pharmacological agents and natural alkaloids.[7—10] For example, spirotryprostatins A and B, two natural alkaloids isolated from the fermentation broth of *Aspergillus fumigatus*, have been identified as two novel inhibitors of microtubule assembly,[8] and pteropodine and isopteropodine have been shown to modulate the function of muscarinic serotonin receptors.[10]

Xanthene derivatives have been reported to possess diverse biological and therapeutic properties such as antibacterial, antiviral, and anti-inflammatory activities, as well as being useful in photodynamic therapy.[11,12] The other useful applications of these heterocycles are as dyes, fluorescent materials for visualization of biomolecules, and in laser technologies.[13,14]

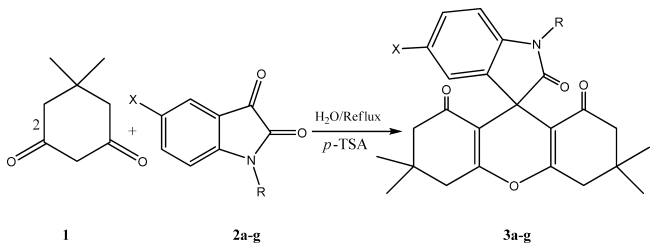
As part of our program aimed at developing new selective and environmentally-friendly methodologies for the preparation of heterocyclic compounds,[15—21] we performed the synthesis of spiro[indoline-3,9′-xanthene]triones through a cyclo-condensation reaction employing water as the reaction medium. In fact, as clearly stated by R. A. Sheldon, it is generally recognized that "the best solvent is no solvent and if a solvent (diluent) is needed it should preferably be water."[22] The use of water as the reaction medium represents a remarkable benefit since this green solvent is highly polar and therefore immiscible with most organic compounds; moreover, the water soluble catalyst resides and operates in the aqueous phase and separation of the organic materials is thus easy.

Results and Discussion

To achieve suitable conditions for the synthesis of spiro[indoline-3,9′-xanthene]triones, we tested the reaction of dimedone **1** and isatin **2a** as a simple model substrate in different solvents in the presence of *p*-toluenesulfonic acid (*p*-TSA) as an inexpensive and available catalyst in reflux conditions (Chart 1). The results are shown in Table 1. It was found that water was a solvent of choice for the reaction and the desired product was obtained in good yield in water (Entry 4).

The general efficiency of this protocol was then studied for the synthesis of a variety of spiro[indoline-3,9′-xanthene]trione derivatives and the results are summarized in Table 2. Various isatins (**2a**—**g**) reacted efficiently with dimedone **1** to afford the desired spiro[indoline-3,9′-xanthene]triones (**3a**—**g**) in good yields (Chart 1, Table 2). The results were good in terms of yields and product purity in the presence of *p*-TSA, while without *p*-TSA and over a long period of time (48 h) the yields of products were low (<30%).

The compounds **3** apparently result from the initial addi-



1 **2a-g** **3a-g**

Chart 1. Synthesis of Spiro[indoline-3,9′-xanthene]triones

Table 1. Solvent Effect on Reaction[a)]

Entry	Solvent	Yield (%)[b)]	Time (h)
1	EtOH (reflux)	60	24
2	MeOH (reflux)	52	24
3	$CHCl_3$ (reflux)	Trace	24
4	H_2O (reflux)	75	24
5	CH_3CN (reflux)	47	24
6	$PhCH_3$ (reflux)	Trace	24

a) Dimedone (2 mmol), isatine (1 mmol), *p*-TSA (0.1 g). *b*) Isolated yield.

Table 1. Synthesis of Spiro[indoline-3,9′-xanthene]triones **3**

Product **3**	X	R	Time (h)	Yield (%)
a	H	H	24	75
b	H	Me	30	67
c	H	Et	30	63
d	Br	H	24	70
e	Br	Me	24	68
f	NO_2	H	24	78
g	H	$PhCH_2$	39	65

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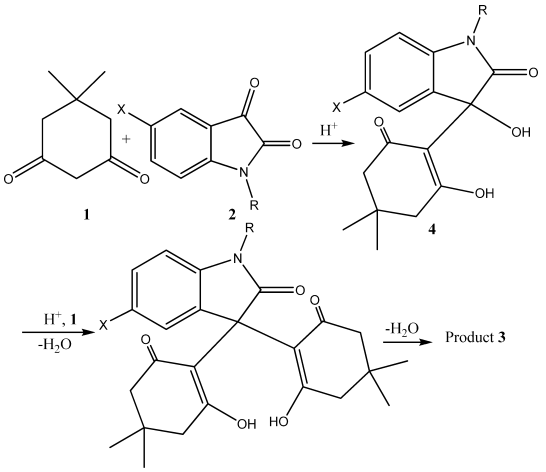

Chart 2. Proposed Mechanism for the Synthesis of Spiro[indoline-3,9′-xanthene]triones

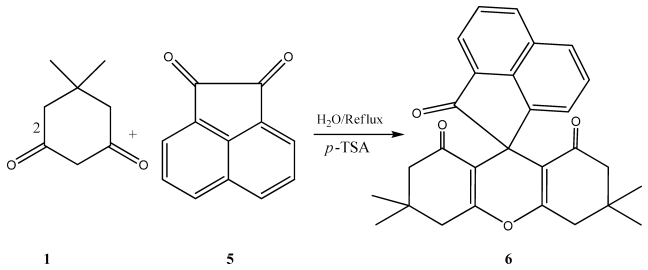

Chart 3. Synthesis of Spiro[acenaphthene-1,9′-xanthene]-1′,2,8′(2′*H*,5′*H*)-trione

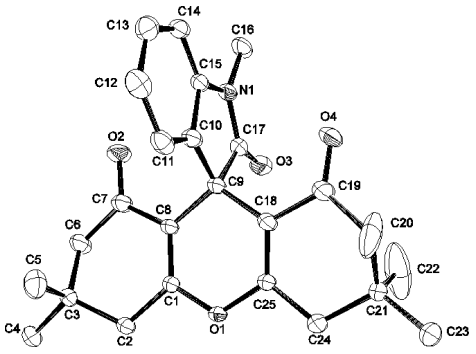

Fig. 1. X-Ray Crystal Structure of **3b**

tion of dimedone **1** to the isatins **2** to yield intermediate **4**, which reacted further with another molecule of dimedone **1** (molar ratio of dimedone to isatins is 2 : 1) and followed by cyclization afforded the corresponding spiro[indoline-3,9′-xanthene]triones **3** (Chart 2).

Finally, to further explore the potential of this protocol for spiro-heterocyclic synthesis, we investigated the reaction involving acenaphthene **5** and obtained 3′,3′,6′,6′-tetramethyl-3′,4′,6′,7′-tetrahydro-2*H*-spiro[acenaphthene-1,9′-xanthene]-1′,2,8′(2′*H*,5′*H*)-trione **6** in a 61% yield (Chart 3). Previously, related acid-catalyzed condensation reactions of indan-1,3-dione with acenaphthene have been reported by Gieta *et al.*[23,24]

Compounds **3a**—**g** and **6** are stable solids whose structures were established by IR, ^{1}H- and ^{13}C-NMR spectroscopy, mass spectrometry and elemental analysis. The structure of **3b** was confirmed by single crystal X-ray analysis (Fig. 1).[25]

Conclusions

In summary, we have described a clean, efficient and simple method for the preparation of spiro[indoline-3,9′-xanthene]trione derivatives in a condensation reaction of dimedone and isatins under reflux in water. Furthermore, a novel synthesis of spiro[acenaphthene-1,9′-xanthene]-1′,2,8′(2′*H*,5′*H*)-trione was reported.

Experimental

Apparatus Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz, respectively. Elemental analyses were performed using a Heracus CHN-O-Rapid analyzer.

Typical Procedure for the Preparation of 3′,3′,6′,6′-Tetramethyl-3′,4′,6′,7′-tetrahydrospiro[indoline-3,9′-xanthene]-1′,2,8′(2′*H*,5′*H*)-trione (3a, $C_{24}H_{25}NO_4$) A mixture of dimedone (2 mmol), isatin (1 mmol) and *p*-TSA (0.1 g) in refluxing water (5 ml) was stirred for 24 h (The reaction progress was monitored by TLC). After completion of the reaction, the reaction mixture was filtered and the precipitate washed with water and residue recrystallized from EtOH/H_2O (1 : 3) to afford the pure product **3a**. White powder (75%); mp 305 °C (decomp.). IR (KBr) cm^{-1}: 3429, 3056, 1733, 1710. MS *m/z*: 391 (M^+, 100), 346 (42), 307 (100). ^{1}H-NMR ($CDCl_3$): δ_H (ppm) 0.91 (6H, s, $2CH_3$), 0.99 (6H, s, $2CH_3$), 2.01 and 2.16 (4H, AB system, J=12.1 Hz, $2CH_2$), 2.55 (4H, m, $2CH_2$), 6.72—7.04 (4H, m, H-Ar), 10.29 (1H, s, NH). ^{13}C-NMR ($CDCl_3$): δ_C (ppm) 26.9, 28.3, 32.0, 40.6, 45.6, 50.9, 108.9, 113.3, 121.2, 122.6, 128.2, 134.4, 144.1, 164.03, 178.9, 195.6. *Anal.* Calcd for $C_{24}H_{25}NO_4$: C, 73.64; H, 6.44; N, 3.58%. Found: C, 73.69; H, 6.38; N, 3.51%.

1,3′,3′,6′,6′-Pentamethyl-3′,4′,6′,7′-tetrahydrospiro[indoline-3,9′-xanthene]-1′,2,8′(2′*H*,5′*H*)-trione (3b, $C_{25}H_{27}NO_4$) White powder (67%); mp 306 °C (decomp.). IR (KBr) cm^{-1}: 3051, 1733, 1703, 1597. MS *m/z*: 405 (M^+, 100), 377 (40), 321 (380). ^{1}H-NMR ($CDCl_3$): δ_H (ppm) 1.02 (6H, s, $2CH_3$), 1.12 (6H, s, $2CH_3$), 2.09 and 2.22 (4H, AB system, J=15.1 Hz, $2CH_2$), 2.44 and 2.56 (4H, AB system, J=15.6 Hz, $2CH_2$), 3.33, (3H, s, CH_3), 6.81—7.25 (4H, m, H-Ar). ^{13}C-NMR ($CDCl_3$): δ_C (ppm) 26.7, 27.1, 29.1, 31.9, 41.2, 45.3, 50.9, 107.6, 113.7, 121.8, 121.9, 128.5, 133.0, 145.2, 163.5, 177.6, 195.3. *Anal.* Calcd for $C_{25}H_{27}NO_4$: C, 74.05; H, 6.71; N, 3.45%. Found: C, 72.99; H, 6.66; N, 3.39%.

1-Ethyl-3′,3′,6′,6′-tetramethyl-3′,4′,6′,7′-tetrahydrospiro[indoline-3,9′-xanthene]-1′,2,8′(2′*H*,5′*H*)-trione (3c, $C_{26}H_{29}NO_4$) White powder (63%); mp 201 °C (decomp.). IR (KBr) cm^{-1}: 3007, 1724, 1702, 1609. MS *m/z*: 419 (M^+, 100), 376 (37), 298 (30). ^{1}H-NMR ($CDCl_3$): δ_H 1.01 (6H, s, $2CH_3$), 1.10 (6H, s, $2CH_3$), 1.40 (3H, t, J=6.8 Hz, CH_3), 2.08 and 2.23 (4H, AB system, J=15.7 Hz, $2CH_2$), 2.43 and 2.57 (4H, AB system, J=15.6 Hz, $2CH_2$), 3.85 (2H, t, J=6.7 Hz, CH_2), 6.84—7.20 (4H, m, H-Ar). ^{13}C-NMR ($CDCl_3$): δ_C (ppm) 11.8, 27.0, 29.1, 31.9, 35.0, 41.2, 45.4, 50.9, 107.8, 113.6, 121.6, 122.2, 128.4, 133.2, 144.3, 163.5, 177.0, 195.3. *Anal.* Calcd for $C_{26}H_{29}NO_4$: C, 74.44; H, 6.97; N, 3.34%. Found: C, 74.38; H, 6.91; N, 3.41%.

5-Bromo-3′,3′,6′,6′-tetramethyl-3′,4′,6′,7′-tetrahydrospiro[indoline-3,9′-xanthene]-1′,2,8′(2′*H*,5′*H*)-trione (3d, $C_{24}H_{24}BrNO_4$) White powder (70%); mp 290 °C (decomp.). IR (KBr) cm^{-1}: 3342, 2957, 1736, 1669, 1616. MS *m/z*: 471 (M^++2, 100), 469 (M^+, 100), 426 (26), 387 (79), 359 (27). ^{1}H-NMR ($CDCl_3$): δ_H (ppm) 1.05 (6H, s, $2CH_3$), 1.12 (6H, s, $2CH_3$), 2.15 and 2.26 (4H, AB system, J=15.3 Hz, $2CH_2$), 2.47 and 2.55 (4H, AB system, J=15.5 Hz, $2CH_2$), 6.70 (1H, d, J=5.2 Hz, H-Ar), 6.95 (1H, s, H-Ar), 7.25 (1H, d, J=5.4 Hz, H-Ar), 8.20 (1H, s, NH). ^{13}C-NMR ($CDCl_3$): δ_C (ppm) 27.5, 28.7, 32.0, 41.2, 45.8, 50.9, 110.9, 113.2, 114.2, 125.4, 131.2, 135.6, 141.7, 163.9, 178.4, 195.6. *Anal.* Calcd for $C_{24}H_{24}BrNO_4$: C, 61.28; H, 5.14; N, 2.98%. Found: C, 61.33; H, 5.19; N, 2.90%.

5-Bromo-1,3′,3′,6′,6′-pentamethyl-3′,4′,6′,7′-tetrahydrospiro[indoline-3,9′-xanthene]-1′,2,8′(2′*H*,5′*H*)-trione (3e, $C_{25}H_{26}BrNO_4$) White powder (68%); mp 310 °C (decomp.). IR (KBr) cm^{-1}: 3064, 2866, 1727, 1674, 1608. MS *m/z*: 485 (M^++2, 100), 483 (M^+, 100), 401 (20), 315 (30). ^{1}H-NMR ($CDCl_3$): δ_H 1.03 (6H, s, $2CH_3$), 1.09 (6H, s, $2CH_3$), 2.15 (4H, m, $2CH_2$), 2.49 (4H, m, $2CH_2$), 3.28 (3H, s, CH_3), 6.70—7.32 (3H, m, H-Ar).

^{13}C-NMR ($CDCl_3$): δ_C 26.77, 27.5, 28.7, 32.0, 41.1, 45.3, 50.9, 109.0, 113.1, 114.2, 125.1, 131.3, 134.9, 144.5, 163.9, 177.1, 195.5. *Anal.* Calcd for $C_{25}H_{26}BrNO_4$: C, 61.99; H, 5.41; N, 2.89%. Found: C, 61.92; H, 5.35; N, 2.82%.

3′,3′,6′,6′-Tetramethyl-5-nitro-3′,4′,6′,7′-tetrahydrospiro[indoline-3,9′-xanthene]-1′,2,8′(2′*H*,5′*H*)-trione (3f, $C_{24}H_{24}N_2O_6$) Yellow powder (78%); mp 278 °C (decomp.). IR (KBr) cm^{-1}: 3359, 2957, 1742, 1661. MS *m/z*: 436 (M^+, 39), 419 (100), 389 (34). ^{1}H-NMR ($CDCl_3$): δ_H 1.07 (6H, s, $2CH_3$), 1.14 (6H, s, $2CH_3$), 2.18 and 2.29 (4H, AB system, J=15.9 Hz, $2CH_2$), 2.54 and 2.60 (4H, AB system, J=16.6 Hz, $2CH_2$), 6.87 (1H, d, J=7.7 Hz, H-Ar), 7.80 (1H, s, H-Ar), 8.11 (1H, d, J=7.1 Hz, H-Ar), 8.85 (1H, s, NH). ^{13}C-NMR ($CDCl_3$): δ_C 27.6, 28.5, 32.1, 41.2, 45.6, 50.8, 109.2, 112.8, 113.1, 125.9, 134.4, 142.9, 148.8, 164.6, 173.9, 195.6. *Anal.* Calcd for $C_{24}H_{24}N_2O_6$: C, 66.04; H, 5.54; N, 6.42%. Found: C, 65.98; H, 5.59; N, 6.37%.

1-Benzyl-3′,3′,6′,6′-tetramethyl-3′,4′,6′,7′-tetrahydrospiro[indoline-3,9′-xanthene]-1′,2,8′(2′*H*,5′*H*)-trione (3g, $C_{31}H_{31}NO_4$) White powder (65%); mp 258 °C (decomp.). IR (KBr) cm^{-1}: 3064, 2955, 1714, 1673. MS *m/z*: 481 (M^+, 100), 453 (100), 436 (40), 390 (80), 91 (98). ^{1}H-NMR ($CDCl_3$): δ_H 1.03 (6H, s, $2CH_3$), 1.13 (6H, s, $2CH_3$), 2.14 and 2.29 (4H, AB system, J=15.8 Hz, $2CH_2$), 2.46 and 2.59 (4H, AB system, J=15.9 Hz, $2CH_2$), 5.07 (2H, br s, CH_2), 6.54—7.67 (9H, m, H-Ar). ^{13}C-NMR ($CDCl_3$): δ_C 26.8, 27.0, 29.2, 32.0, 41.3, 45.3, 50.9, 107.5, 109.1, 113.5, 121.9, 125.2, 127.3, 128.4, 128.6, 128.8, 132.2, 133.1, 145.3, 163.5, 197.2. *Anal.* Calcd for $C_{31}H_{31}NO_4$: C, 77.31; H, 6.49; N, 2.91%. Found: C, 77.36; H, 6.42; N, 2.96%.

Due to very low solubility, ^{13}C-NMR spectra of product **6** are not reported.

3′,3′,6′,6′-Tetramethyl-3′,4′,6′,7′-tetrahydro-2*H*-spiro[acenaphthene-1,9′-xanthene]-1′,2,8′(2′*H*,5′*H*)-trione (6, $C_{28}H_{26}O_4$) White powder (61%); mp 295 °C (decomp.). IR (KBr) cm^{-1}: 2962, 1730, 1669, 1610. MS *m/z*: 426 (M^+, 37), 342 (100), 258 (50). ^{1}H-NMR (DMSO-d_6): δ_H 1.01 (6H, s, $2CH_3$), 1.09 (6H, s, $2CH_3$), 1.62 (4H, br s, $2CH_2$), 2.53 (4H, br s, $2CH_2$), 7.15—7.99 (6H, m, H-Ar). *Anal.* Calcd for $C_{28}H_{26}O_4$: C, 78.85; H, 6.14%. Found: C, 78.80; H, 6.10%.

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25) X-Ray data for **3b**: ($C_{25}H_{27}NO_4$), M=405.48 g/mol, triclinic system, space group $P\bar{1}$, a=11.1462 (12), b=11.9893 (16), c=16.1294 (19) Å, α=94.154 (10), β=90.004 (9)°, γ=90.195 (10), V=2149.8 (4) Å^3, Z=4, D_c=1.253 g·cm^{-3}, μ(Mo$K\alpha$)=0.084 mm^{-1}, crystal dimension of 0.50×0.40×0.25 mm. The structure was solved by using SHELXS. The structure refinement and data reduction was carried out with SHELXL of the X-Step32 suite of programs.[26] The non-hydrogen atoms were refined anisotropically by full matrix least-squares on F^2 values to final $R1$=0.0932, $wR2$=0.1526 and S=1.567 with 551 parameters using 10440 independent reflection (θ range=1.70—29.29°). Hydrogen atoms were located from expected geometry and were not refined. Crystallographic data for **3b** have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, on application to The Director, CCDC 679233, Union Road, Cambridge CB2 1EZ, U.K. Fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk.
26) X-STEP32 Version 1.07b, X-ray structure evaluation package, 2000, Stoe & Cie, Darmstadt, Germany.