International Journal of Modern Agriculture, Volume 9, No. 4, 2020
ISSN: 2305-7246

SYNTHESIS AND CHARACTERIZATION OF BIOLOGICAL ACTIVE NOVEL SPIRO[INDOLINE-BENZOCHROMENE] DERIVATIVES

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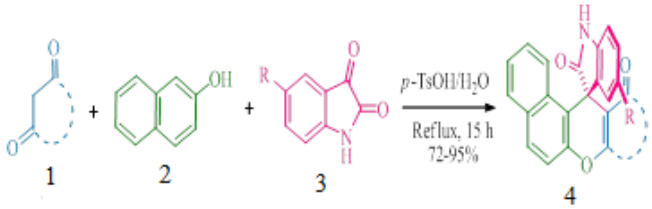
Abstract

A three-component domino reaction of β-naphthol, isatin and cyclic 1,3-dicarbonyl compounds, including cyclohexane-1,3-dione, barbituric acid and 2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione, allowed the construction of novel spiro[indoline-benzochromene] derivatives. This experimentally simple protocol carried out in the presence of *p*-TSA as the only catalyst in aqueous media and allowed the generation of one C-O and two new C-C bonds in a single synthetic operation leading to compounds containing one spiro center and up to six rings.



1. Introduction

In cancer research, multidrug resistance (MDR) is one of the major aspects that causes failure in therapeutic treatment. This phenomenon could occur either via inherited or acquired approaches, which refers to the initial resistance to a specific drug and the development of resistance after successful treatment, respectively. There have been numerous attempts to overcome these obstacles, including applying drug treatment in combination protocols. In the meantime, the development of new materials for drug design continues to be crucial in addressing this phenomenon.

Heterocyclic compounds, in particular oxygen-containing molecules, represent an indispensable class due to their physicochemical properties. The literature reveals that chromenes and benzochromenes are important pharmacophores associated with a broad range of pharmacological activities, such as antimicrobial [1,2,3,4], anticancer agent[5] hypolipidemic[6], antioxidant [7,8], analgesic [9], antileishmanial [10,11], vascular-disrupting activity [12], estrogenic anticoagulant and antispasmolytic [8], and blood platelet antiaggregating [13] effects

2. General aspects

Polycyclic oxygen heterocycles such as chromene, xanthene, and their benzo derivatives have very interesting pharmacological activities[14]. For instance, (–)-clavizepine **1**, a naturally occurring alkaloid with a xanthene core isolated from *Corydalis claviculata*[15] and *Sarcocapnos crassifolia* subsp[16]. *speciosa*, binds to several types of catecholamine and serotonine receptors[17]; its analogue **2** has the highest known pIC_{50} for binding to $5\text{-}HT_7$ receptors. Xanthenes, especially benzoxanthenes, display antiviral antibacterial and anti-inflammatory activities[18], besides being used as sensitizers in photodynamic therapy[19], leuco-dyes[20], and in laser technology. Benzochromenes like mollugin **3** and 3,4-dihydromollugin **4** were isolated from the medicinal plant *Rubia cordifolia* [21](Figure 5.1), which is used as a herbal medicine in the Chinese Pharmacopeia and displays antitumor and anti-inflammatoryactivities. Recently, *cis*- and *trans*-3,4-dihydroxy-3,4-dihydromollugins[22] **5** and **6** were isolated from *Pentas longiflora*, an spiroWe started our investigation by examining the reaction between

International Journal of Modern Agriculture, Volume 9, No. 4, 2020
ISSN: 2305-7246

dimedone, β-naphthol and unsubstituted isatin in the presence of *p*-TSA, a mild Brønsted acid catalyst, which afforded compound **4**. In order to establish the optimal solvent for the reaction, the study summarized in Table 5.1 was carried out. The reaction failed in dichloromethane even at reflux temperature (entry 1), while in 1,2-dichloroethane, acetonitrile,

dimethylformamide and methanol, under reflux conditions, moderate to acceptable yields of the product were obtained along with unreacted starting materials, necessitating column chromatographic purification (entries 2-5). In a subsequent experiment, water emerged as the solvent of choice, furnishing a 92% yield of the product in a pure form after simple filtration (entry 6). In a control experiment, the reaction in water in the absence of *p*-TSA afforded a very low yield of **4** (<30%, entry 7) even after a prolonged reaction time (48 h). The identification of water as the ideal solvent for the present transformation renders it very attractive owing to the null toxicity and eco-friendly nature of this solvent. Water also offers distinctly unique advantages arising from inter- and intramolecular non-covalent interactions, leading to novel solvation and assembly processes that confer unique selectivity and reactivity for the reactions performed in water.

Table 5.1. Solvent-screening for the synthesis of in the presence of *p*-TSA at reflux.

Entry	**Solvent**	**Reaction time (h.)**	**Yield (%)**
1	CH_2Cl_2	24	No reaction
2	CH_3CN	15	65[a]
3	MeOH	15	58[a]
4	DMF	15	60[a]
5	$ClCH_2$-CH_2Cl	24	40[a]
6	Water	15	92[b]
7	Water	48	<30%[b,c]

[a]Isolated yield after purification by column chromatography [b]Isolated yield after filtration and washing with water and methanol

[c]The reaction performed in the absence of *p*-TSA.

After determining the optimal conditions, the scope of the reaction was examined in more detail. As shown in Scheme 5.1, the three-component reactions of β-naphthol, substituted isatins (R = H, Me, Cl, Br and NO_2) and cyclic 1,3-dicarbonyl compounds, *viz.* cyclohexan-1,3-dione, dimedone, barbituric acid and 2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione were carried out in water in the presence of *p*-TSA under reflux conditions for 15 h, which afforded respectively 9,10-dihydrospiro[benzo[*a*]xanthene-12,3'-indoline]-2',11(*8H*)-diones **54a-j**, spiro[benzo[*f*]chromeno-[2,3-*d*]pyrimidine-5,3'-indoline]-2,2',4(1*H*,3*H*)-triones **55a-c** and 2-thioxo-2,3-dihydrospiro[benzo[*f*]chromeno[2,3-*d*]pyrimidine-5,3'-indoline]-2',4(*1H*)-diones **55d-f**.

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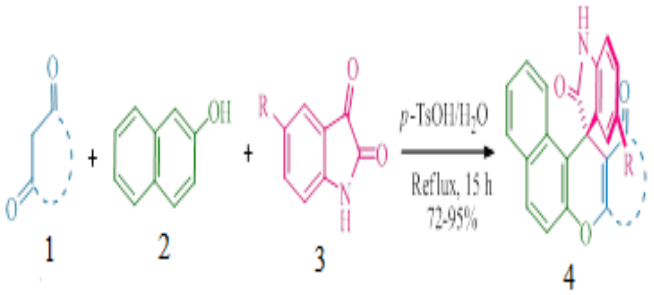

3. Conclusion:

The present work one pot three-component domino reaction of β-naphthol, isatin and cyclic 1,3-dicarbonyl compounds, including cyclohexane-1,3-dione, barbituric acid and 2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione, offords excellent yield. Further researches of building new C–C bond with this green approach are in due course in our laboratory.

3. Experimental section

3.1. General method

The melting points were measured in open capillary tubes and are uncorrected. The ^{1}H NMR, ^{13}C NMR, DEPT, H,H-COSY, C,H-COSY and HMBC spectra were recorded on a Bruker (Avance) 300 MHz NMR instrument using TMS as internal standard and DMSO-d_6 as solvent. Standard Bruker software was used throughout. Chemical shifts are given in parts per million (δ-scale) and the coupling constants are given in Hertz. Silica gel-G plates (Merck) were used for TLC analysis with a mixture of petroleum ether (60–80 ºC) and ethyl acetate as eluent. Elemental analyses were performed on a Perkin Elmer 2400 Series II Elemental CHNS analyzer.

Synthesis of spiro[oxindole-benzochromene] derivatives.

General procedure: A mixture of cyclic 1,3-dicarbonyl compounds **1** (1 mmol), β-naphthol **2** (1 mmol), isatin **3**(1 mmol) and *p*-TSA (0.5 mmol) in refluxing water (10 mL) was stirred for 15 h. After completion of the reaction confirmed by TLC (eluent EtOAc/*n*-hexane, 3:1 v/v), the reaction mixture was cooled to room temperature, the precipitated product was filtered off and washed with water (10 mL) and methanol (10 mL) to afford the pure **4** and **5** as a colourless solid. Spectroscopic data for all the synthesised compounds are given below.

9,9-Dimethyl-9,10-dihydrospiro[benzo[*a*]xanthene-12,3'-indoline]-2',11(*8H*)-dione

Isolated as colorless solid (92%); mp >300 ºC; IR υ_{max} (KBr) 3230, 2947, 2884, 1802, 1719cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 0.98 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 2.11-2.21 (m, 2H, H-10a & H-10b), 250 (s, 1H, H-8), 2.69 (d, 1H, *J* = 12.3 Hz, H-8), 6.79-7.42 (m, 7H, Ar-H), 7.72 (d, 1H, *J* = 8.7 Hz, Ar-H), 7.88 (d, 1H, *J* = 9.0 Hz, Ar-H), 7.95 (d, 1H, *J* = 9.0 Hz, Ar-H), 10.97 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 27.1, 28.3, 32.0, 41.2, 49.5, 51.0, 109.8, 111.6, 114.3, 118.0, 122.4, 123.3, 124.1, 125.3, 127.7, 128.9, 129.7, 131.4, 131.9, 135.3, 143.2, 147.8, 164.4, 179.4, 195.5. Anal. Calcd for $C_{26}H_{21}NO_3$: C, 78.97; H, 5.35; N, 3.54%; found: C, 79.03; H, 5.39; N, 3.59%.

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