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An Efficient One-Pot Three-Component Reaction for Synthesis of Spirooxindole Derivatives in Water Media under Catalyst-Free Condition

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ABSTRACT: *An efficient, clean, and environmentally benign synthesis of spirooxindole derivatives by one-pot three-component reaction of isatins, malononitrile, and carbonyl compound in the absence of catalysis in water was described. A variety of spirooxindole derivatives were obtained with excellent yields within short reaction time. This novel protocol has the advantages of convenient operation, low cost, and environmental benign.* © 2011 Wiley Periodicals, Inc. Heteroatom Chem 22:673–677, 2011; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.20723

INTRODUCTION

Spirooxindoles are well known to exhibit a wide range of biological properties [1], such as coerulescine, the simplest spirooxindole found in nature, displays a local anesthetic effect [2], spirotryprostatin A, a natural alkaloid isolated from the fermentation broth of *Aspergillus fumigatus*, has been shown as a novel inhibitor of the mammalian cell cycle [3], and polycyclic alkaloid pteropodine and isopteropodine have a long history for its medicinal applications in modulating the function of muscarinic serotonin receptors [4] (Fig. 1).

A literature survey reveals several multicomponent reactions (MCRs) procedures using $InCl_3$ [5], triethylbenzylammonium chloride (TEBA) [6], tris(2–8 hydroxyethyl)amine [7], tetrabutylammonium fluoride (TBAF) [8], *L*-Proline [9], and ethylenediamine diacetate(EDDA) [10] as catalyst, as well as using electrocatalytic method [11] to prepare them. However, few attempts have been done on reducing prolonged reaction time, toxic solvents, and moderate yields of the product. Their studies may be more reasonable if they had considered the essence of facile and convenient MCR methodology.

The increasing attention during the last decades for environmental protection has led both modern academic and industrial groups to develop chemical processes with maximum yield and minimum cost, while using nontoxic reagents, solvents, and catalysts or solvent-free condition. Water, when used as a reaction media, could strongly enhance the rate of many organic reactions due to its hydrophobic effects [12]. Thus, there has been a growing recognition that water is an attractive medium for many organic reactions [13] and many MCRs in aqueous medium have been reported [14].

We aim to extend the method of aqueous medium organic synthesis according to our incessant research efforts with MCR chemistry [15]. It is hoped that the above questions will be resolved with our proposed approach. This paper reports an efficient green approach for the syntheses of spirooxindole derivatives via a one-pot three-component

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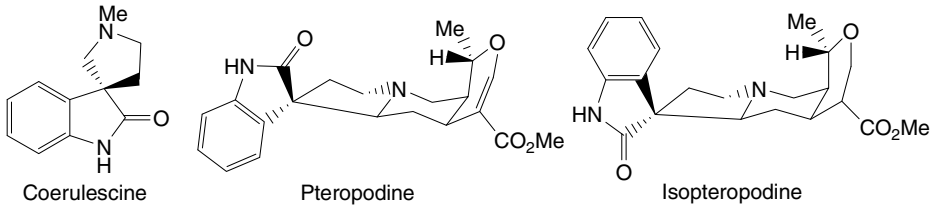


FIGURE 1 Representatives of bioactive spirocyclic oxindoles.

TABLE 1 Optimization of Reaction Temperature

Entry	*Temperature (°C)*	*Time (min)*	*Yield (%)*[a]
1	20	90	84
2	40	60	80
3	50	60	86
4	60	20	89
5	70	20	85
6	80	20	84
7	90	20	86

Reaction condition: isatin **1** (1.0 mmol), malononitrile **2** (1.0 mmol), and carbonyl compound **3** (1.0 mmol) in H_2O (5.0 mL).
[a]Isolated yields.

reaction of isatins, malononitrile, and carbonyl compounds in the absence of any catalyst in water (Scheme 1). To the author's knowledge, there is little information in literature about the synthesis of spirooxindole derivatives in water medium under the catalyst-free conditions.

RESULTS AND DISCUSSION

The model reaction of isatin, malononitrile, and 5,5-dimethylcyclohexane-1,3-dione (dimedone) was carried out at 60°C under water media in the absence of any catalyst. It was found that the model reaction proceeded very smoothly and gave the corresponding product **4a** in 89% yield (Table 1, entry 4). Encouraged by this result, we further demonstrated the reaction of various isatin **1** with malononitrile **2** and carbonyl compounds **3** (Scheme 1). These results agreed well with the findings of the model reaction.

Furthermore, the reactions were carried out at different temperatures ranging from 20 to 90°C. It is clear that the yield was increased with the increasing temperature, and the optimal temperature was 60°C (Table 1, entry 6). Higher temperatures could not, obviously, improve the yield.

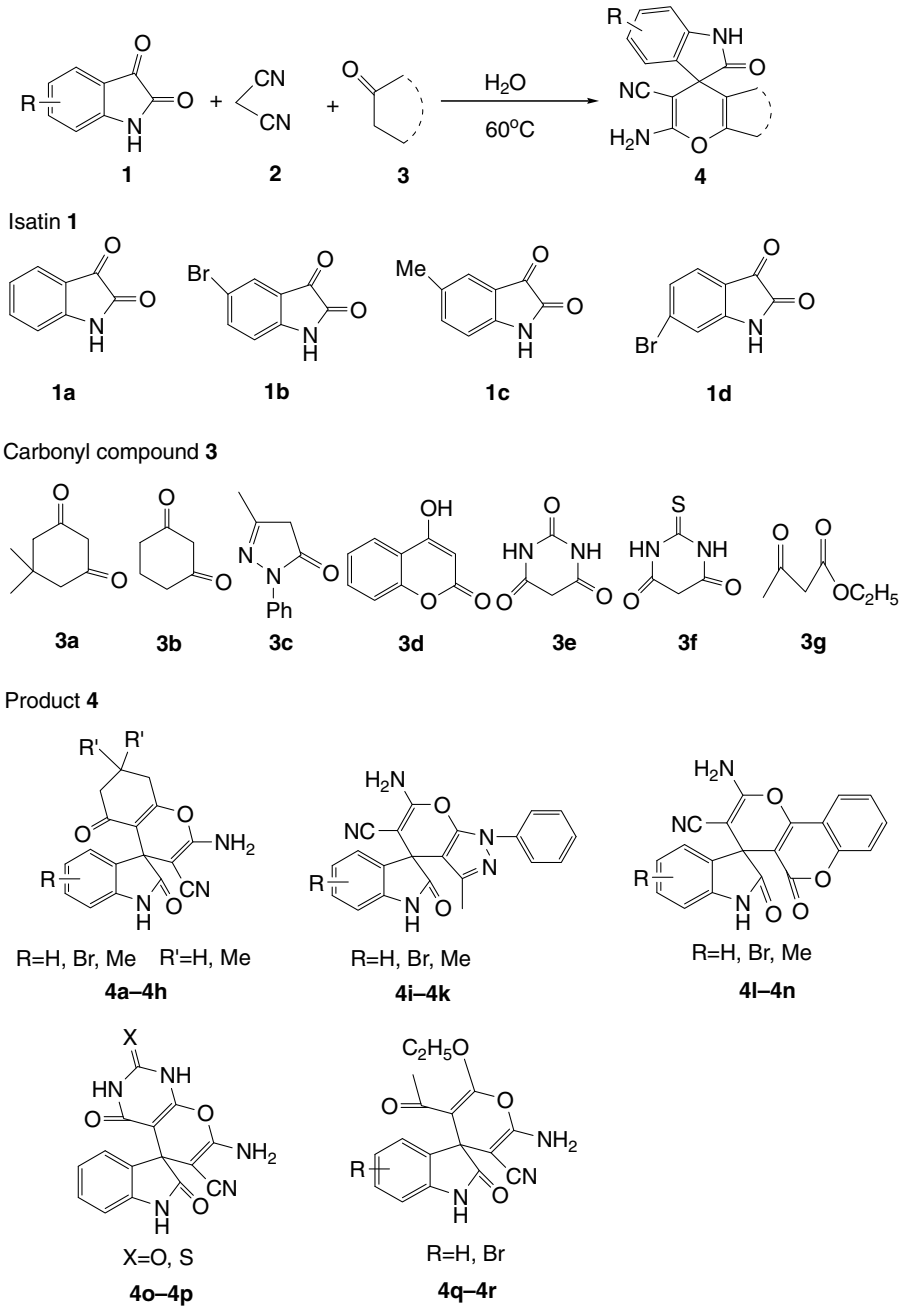
In addition, a series of syntheses of various isatins **1** with malononitrile **2** and carbonyl compounds **3** were carried out under optimal temperature conditions. In all cases, excellent yields with good selectivity were obtained (Table 2).

As can be seen from Table 2, isatins with either electron-donating or electron-withdrawing groups on the aromatic ring underwent smoothly and gave the products in good yields (Table 2).

TABLE 2 Synthesis of Spirooxindole Derivatives in Water Medium

Entry	*Isatin (**1**)*	*Carbonyl Compound (**3**)*	*Product (**4**)*	*Time (min)*	*Yield (%)*[a]
1	**1a**	**3a**	**4a**	20	89
2	**1b**	**3a**	**4b**	20	94
3	**1c**	**3a**	**4c**	60	90
4	**1d**	**3a**	**4d**	120	82
5	**1a**	**3b**	**4e**	15	88
6	**1b**	**3b**	**4f**	20	95
7	**1c**	**3b**	**4g**	30	90
8	**1d**	**3b**	**4h**	120	82
9	**1a**	**3c**	**4i**	120	84
10	**1b**	**3c**	**4j**	110	95
11	**1c**	**3c**	**4k**	60	92
12	**1a**	**3d**	**4l**	120	92
13	**1b**	**3d**	**4m**	110	95
14	**1c**	**3d**	**4n**	120	85
15	**1a**	**3e**	**4o**	30	75
16	**1a**	**3f**	**4p**	30	83
17	**1a**	**3g**	**4q**	30	80
18	**1b**	**3g**	**4r**	30	88

Reaction condition: isatin **1** (1.0 mmol), malononitrile **2** (1.0 mmol), and carbonyl compound **3** (1.0 mmol) in H_2O (5.0 mL) at 60°C°
[a]Isolated yields.



SCHEME 1

CONCLUSION

In summary, a practical and efficient procedure for the synthesis of spirooxindole derivatives was investigated via the one-pot three-component reaction at 60°C under water media in the absence of any catalyst. This procedure offers several advantages including higher yields, mild reaction conditions, shorter reaction time, convenient procedure, and environmental friendliness. Further research on aqueous medium organic synthesis will continue in our next study.

EXPERIMENTAL

Melting points are measured on an Electrothemal X6 microscopy digital melting point apparatus (Beijing Tech Instrument Co. Ltd., Beijing, China) and are uncorrected. Infrared (IR) spectra were recorded on

a Nicolet 6700 FT-IR (Thermo Electron Corporation, USA) spectrometer in KBr pellets. ^{1}H NMR spectra were recorded in DMSO-d_6 on a Bruker Avance 300 (300 MHz; Swiss Bruker Corporation, Switzerland) instrument with the TMS at δ0.00 ppm as an internal standard. Chemicals used are of commercial grade, without further purification.

Typical Procedure for Preparation of Spirooxindole Derivatives

A mixture of isatin **1** (1.0 mmol), malononitrile **2** (1.0 mmol), and carbonyl compound **3** (1.0 mmol) in H_2O (5.0 mL) was stirred at 60°C for 15–120 min. The reaction was monitored by thin layer chromatography (TLC). Upon completion, the reaction mixture was allowed to cool to room temperature. Then, the precipitated product was filtered and washed with water and the crude product was purified by cooled ethanol to afford the pure product **4**.

2-Amino-7,7-dimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carbonitrile **(4a**, $C_{19}H_{17}N_3O_3$**)** mp > 300°C (lit. [13] > 300°C); IR (KBr) ν: 3377, 3312, 3144, 2192, 1723, 1683, 1655, 1472, 1349, 1223, 1055 cm^{-1}. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 0.98 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 2.10 (d, J = 16.0 Hz, 1H, CH_2), 2.18 (d, J = 16.0 Hz, 1H, CH_2), 2.48 (d, J = 18.0 Hz, 1H, CH_2), 2.54 (d, J = 18.0 Hz, 1H, CH_2), 6.78 (d, J = 7.6 Hz, 1H, ArH), 6.88 (t, J = 7.2 Hz, 1H, ArH), 6.95 (d, J = 7.2 Hz, 1H, ArH), 7.13 (t, J = 7.6 Hz, 1H, ArH), 7.23 (s, 2H, NH_2).

2-Amino-5′-methyl-2′,5-dioxo-1′,2′,5,6,7,8-hexahydrospiro[chromene-4,3′-indole]-3-carbonitrile (**4g**, $C_{18}H_{15}N_3O_3$) mp 288°C (lit. [11] 287°C); IR (KBr) ν: 3362, 3145, 2195, 1658, 1603, 1351, 1213, 1075, 1009 cm^{-1}. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.90 (t, J = 6.0 Hz, 2H, CH_2), 2.19–2.21 (m, 5H, CH_2, CH_3), 2.64 (t, J = 5.9 Hz, 2H, CH_2), 6.65 (d, J = 7.8 Hz, 1H, ArH), 6.80 (s, 1H, ArH), 6.92 (d, J = 7.8 Hz, 1H, ArH), 7.19 (s, 2H, NH_2).

6′-Amino-3′-methyl-2-oxo-1′-phenyl-1′H-spiro[indoline-3,4′-pyrano[2,3-c]pyrazole]-5′-carbonitrile (**4i**, $C_{21}H_{15}N_5O_2$) mp 238–240°C (lit. [13] 236–237°C); IR (KBr) ν: 3461, 3296, 3178, 2196, 1701, 1655, 1595, 1470, 1392, 1331, 1221, 1127, 1070 cm^{-1}. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.53 (s, 3H, CH_3), 6.94 (d, J = 7.3 Hz, 1H, ArH), 7.02 (t, J = 7.3 Hz, 1H, ArH), 7.17 (d, J = 7.1 Hz, 1H, ArH), 7.27 (t, J = 7.3 Hz, 1H, ArH), 7.35 (d, J = 7.3 Hz, 1H, ArH), 7.50 (t, J = 7.0 Hz, 2H, ArH), 7.57 (s, 2H, NH_2), 7.78 (d, J = 7.3 Hz, 2H, ArH), 10.74 (s, 1H, NH).

2′-Amino-5-bromo-2,5′-dioxo-5′H-spiro[indoline-3,4′-pyrano[3,2-c]chromene]-3′-carbonitrile (**4m**, $C_{20}H_{10}N_3O_4$) mp > 300°C (lit. [13] > 300°C); IR (KBr) ν: 3323, 3208, 2202, 1739, 1672, 1608, 1473, 1361, 1221, 1113, 1087, 976, 922, 868, 764, 578 cm^{-1}. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 6.81 (d, J = 7.9 Hz, 1H, ArH), 7.38 (d, J = 7.9 Hz, 1H, ArH), 7.48–7.54 (m, 3H, ArH), 7.74 (s, 2H, NH_2), 7.79 (d, J = 7.9 Hz, 1H, ArH), 7.92 (d, J = 7.5 Hz, 1H, ArH).

2-Amino-5-oxo-7-thioxo-spiro[(3′H)-indol-3′,4,4(H)-5,6,7,8-tetrahydropyrano(2,3-d)pyramidine]-(1′H)-2′-one-3-carbonitrile (**4p**, $C_{15}H_9N_5O_3S$) mp 240–242°C (lit. [10] 238–242°C); IR (KBr) ν: 3508, 3427, 3308, 3160, 2202, 1693, 1656, 1569, 1470, 1400, 1343, 1185, 1133, 919, 868, 768, 580 cm^{-1}. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 6.79 (d, J = 7.1 Hz, 1H, ArH), 6.90 (t, J = 7.1 Hz, 1H, ArH), 7.16 (t, J = 8.1 Hz, 2H, ArH), 7.42 (s, 2H, NH_2), 10.54 (s, 1H, NH), 12.51 (s, 1H, NH).

Ethyl 2′-Amino-3′-cyano-6′-methyl-2-oxospiro[indoline-3,4′-pyran]-5′-carboxylate (**8q**, $C_{17}H_{15}N_3O_4$) mp 259–260°C (lit. [13] 258–260°C); IR (KBr) ν: 3484, 3160, 2188, 1713, 1620, 1472, 1380, 1288, 1212, 1072 cm^{-1}. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 0.76 (t, J = 7.1 Hz, 3H, CH_3), 2.30 (s, 3H, CH_3), 3.34 (s, 2H, NH_2), 3.73–3.77 (m, 2H, CH_2), 6.76 (d, J = 7.6 Hz, 1H, ArH), 6.92 (t, J = 7.2 Hz, 1H, ArH), 7.08 (d, J = 7.2 Hz, 1H, ArH), 7.20 (t, J = 7.6 Hz, 1H, ArH), 10.39 (s, 1H, NH).

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