Expedient Synthesis of Diverse Spirooxindoles via Multicomponent Approach in Presence of Green Catalyst

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Abstract An efficient, convenient and environmentally benign procedure for the construction of various bioactive spirooxindoles has been developed by condensation reactions of isatins, malononitrile and α-methylene carbonyl compounds/enols in the presence of starch solution as expedient, eco-friendly and biodegradable catalyst at 60 °C. The prominent features of the above protocol are short reaction time, high atom economy, simple work-up, cost-effectiveness, avoidance of toxic chemicals.

Keywords Spirooxindoles · Green synthesis · Multicomponent synthesis Starch

1 Introduction

Spirooxindole based compounds possess wide array of activities such as antitumuor [1], antimicrobial [2, 3], antitubercular [4], antimycobacterial [5], antiproliferative properties [6]. The unique structure of spirooxindoles and their highly pronounced biological activity has attracted the interest among various researchers [7–9].

Moreover design and development of methods to access biologically relevant complex molecules has become increasingly popular at the forefront of contemporary organic synthesis. Multicomponent reactions (MCRs), provide one of the most dominant platforms for the sustainable synthesis of polyfunctionalized heterocyclic compounds owing to their atom economy, operational simplicity, environmental friendliness and green chemistry characteristics [10–13].

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As a part of our research interest toward the development of environmentally benevolent, efficient and economically viable protocol for the synthesis of heterocycles [14–20], we envisaged on the synthesis of spiropyran annulated heterocycles through one pot condensation of isatins with malononitrile and α-methylene carbonyl compounds/enols. Starch solution which is easily available, inexpensive, biodegradable as well as non-toxic in nature was used as catalyst for the synthesis of aforementioned heterocycles.

2 Results

In the present work, a novel, proficient and green protocol for the synthesis of spirooxindoles has been described via one pot condensation reactions of isatins, malononitrile and α-methylene carbonyl compounds/enols namely 5,5-dimethylcyclohexane-1,3-dione (dimedone), cyclohexane-1,3-dione, 4-hydroxycoumarin, 2,4-dihydro-5-methyl-pyrazol-3-one in presence of starch solution at 60 °C.

In order to optimise the reaction conditions isatin, malononitrile and cyclohexane-1,3-dione were selected as model substrates. Various reactions of isatin (1.0 mmol) with malononitrile (1.5 mmol) and cyclohexane-1,3-dione (1.0 mmol) were attempted in presence of varying amount of starch solution which serve as dual role of catalyst as well as reaction media at different temperature. The impact of different amounts of catalyst load as well as reaction temperature on the yield of desired product i.e. 2-amino-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carbonitrile (**Ia**) and reaction time is shown in Table 1. The best result was obtained using 5.0 mL starch solution at 60 °C. The reaction was complete in 10 min. and gave 93% of **Ia**.

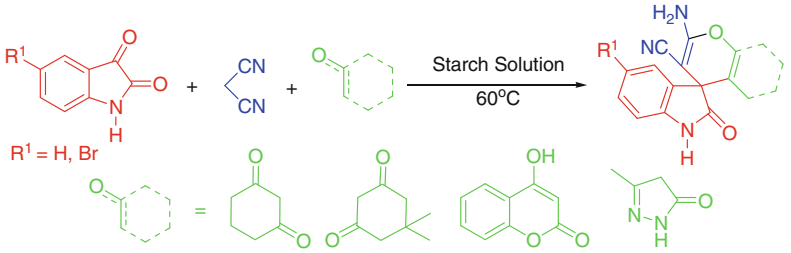
Table 1 Optimization of reaction conditions for the formation of **Ia**

Entry	Starch solution (mL)	Temperature (°C)	Time (min)	Yield (%)
1	5.0	r.t.	60	55
2	5.0	50	60	75
3	**5.0**	**60**	**10**	**93**
4	5.0	70	10	93
5	4.0	60	25	70
6	6.0	60	10	93
7	8.0	60	10	93

[1]Reactions were carried out in 1.0 mmol scale with 1:1.5:1 ratio of isatin, malononitrile and 1,3-cyclohexane-1,3-dione in starch solution

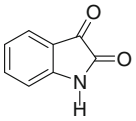
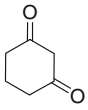
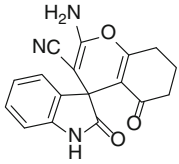
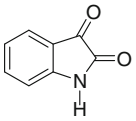
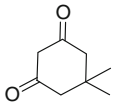
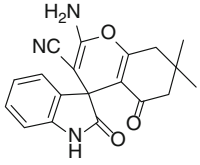
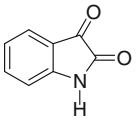
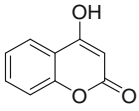
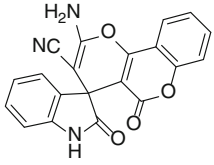
Using these optimised reaction conditions, reactions of isatin, malononitrile with 3,3-dimethylcyclohexane-1,3-dione/4-hydroxycoumarin/2,4-dihydro-5-methyl-pyrazol-3-one were also performed. All the reactions underwent completion in 10–15 min and afforded the corresponding spirooxindoles (**Ib-d**).

The scope of the above condensation reaction was also examined by using 5-bromoisatin for reactions with malononitrile and 1,3-dicarbonyl compounds (dimedone, cyclohexane-1,3-dione) under otherwise identical conditions and 2-amino-5′-bromo-7,7-dimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carbonitrile (**Ie**), 2-amino-5′-bromo-2′,5-dioxo-5,6,7,8-tetrahydrospiro [chromene-4,3′-indoline]-3-carbonitrile (**If**) were obtained respectively. All these results have been shown in Table 2 and represented in Eq. 1.



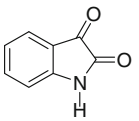
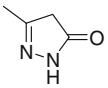
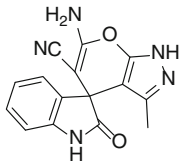
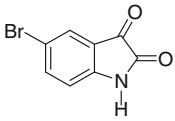
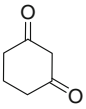
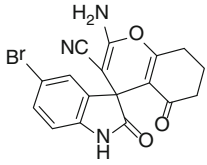
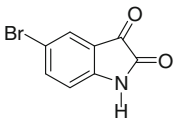
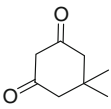
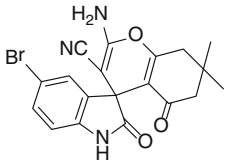
(1)

Table 2 Synthesis of spirooxindoles (I) via reaction of isatins, malononitrile and α-methylene carbonyl compounds/enols in starch solution at 60 °C

Entry	Isatin	α-methylene carbonyl compounds/enols	Product (I)	Time (min)	Yield (%)
1.			 **Ia**	10	93
2.			 **Ib**	10	94
3.			 **Ic**	10	95

(continued)

Table 2 (continued)

Entry	Isatin	α-methylene carbonyl compounds/enols	Product (I)	Time (min)	Yield (%)
4.			 **Id**	15	92
5.			 **Ie**	10	91
6.			 **If**	10	90

[1]Reaction conditions: Isatin/5-bromoisatin (1.0 mmol), 3,3-dimethylcyclohexane-1,3-dione/cyclohexane-1,3-dione/4-hydroxycoumarin/2,4-dihydro-5-methyl-pyrazol-3-one (1.0 mmol) and malononitrile (1.5 mmol) in presence of starch solution (5.0 mL) at 60 °C

3 Discussion

The proposed mechanism for the synthesis of spirooxindoles is shown in Fig. 1. The starch is expected to form micelle-like structure, which is capable of holding the molecules and thereby catalysing the reaction. Initially, Knoevenagel condensation of isatin with malononitrile takes place to give an intermediate. The intermediate so formed underwent Michael addition with α-methylene carbonyl compounds/enol to furnish an intermediate. The hydroxyl group of this intermediate underwent cycloaddition to cyano group to yield **I.**

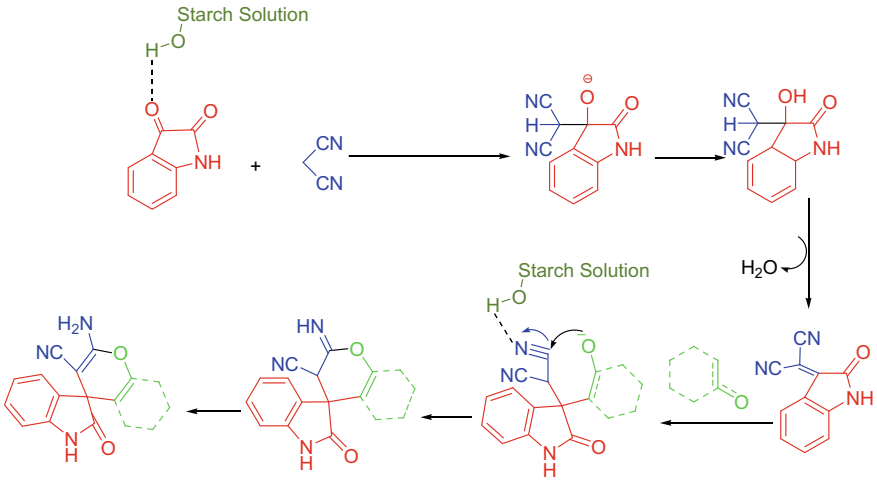


Fig. 1 Mechanism for the formation of spirooxindoles

4 Materials and Methods

All the melting points were measured using Buchi melting point 545 apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer FTIR spectrophotometer using KBr pellets. The ^{1}H NMR spectra were recorded on Jeol JNM ECX-400P (at 400 MHz) with DMSO-d_6 as solvent and using TMS as internal reference. Thin Layer Chromatography (TLC) was performed on precoated silica gel plates (Merck).

General procedure for preparation of starch solution: The starch solution employed for carrying out synthesis of spirooxindoles was prepared by stirring a mixture of solid starch (1.5 g) in water (15.0 mL) at 25 °C for 30 min. After 30 min. the solution was filtered and the filtrate was used for synthesis of **I**.

Procedure for synthesis of spirooxindoles: To a 50 mL round-bottomed flask isatins (1.0 mmol), malononitrile (1.5 mmol), α-methylene carbonyl compounds/enols (1.0 mmol) and starch solution (5.0 mL) were added. The contents were stirred vigorously at 60 °C for the appropriate times as mentioned in Table 2. After completion of reaction (monitored by TLC), the content was cooled to room temperature. The precipitate so obtained was filtered, washed with water and subsequently with ethanol. All the synthesised products were known compounds and were characterized by FT-IR, ^{1}H NMR and comparison of their melting points with known compounds [21–24].

Spectral Data of Representative Spirooxindoles:

2-Amino-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carbonitrile (Ib): White solid; Yield = 94%; M.pt.: 300 °C IR (KBr) υ_{max}-/cm^{-1} = 3377, 3314, 3145, 2960, 2192, 1722, 1682, 1656, 1471, 1348,

1327, 1223; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.32 (1H, s, NH), 7.15 (2H, s, NH_2), 7.09-7.04 (1H, m, Ar-H), 6.91-6.80 (2H, m, Ar-H), 6.73-6.71 (1H, m, Ar-H), 2.44-2.43 (2H, m, CH_2), 2.10 and 2.08 (AB system, 2H, J = 16 Hz, $CH_aH_bC(CH_3)_2$), 0.96 (3H, s, CCH_3), 0.93 (3H, s, CCH_3).

2′-Amino-2,5′-dioxo-5′*H*-spiro[indoline-3,4′-pyrano[3,2-*c*]chromene]-3′-carbonitrile (Ic): White solid; Yield = 95%; M.pt.: 294–296 °C; IR (KBr) υ_{max}-/cm^{-1} = 3350, 3297, 3196, 2955, 2206, 1736, 1673, 1604, 1541, 1471, 1359, 1219, 1169; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.69 (1H, s, NH), 7.94 (1H, d, Ar-H, J = 7.8 Hz), 7.77 (1H, t, Ar-H, J = 7.7 Hz), 7.66 (2H, s, NH_2), 7.56 (1H, t, Ar- H, J = 7.6 Hz), 7.49 (1H, d, Ar-H, J = 8.4 Hz), 7.22 (2H, t, Ar-H, J = 7.6 Hz), 6.93 (1H, t, Ar-H, J = 7.6 Hz), 6.86 (1H, d, Ar-H, J = 7.9 Hz).

5 Conclusion

In this work, we report a rapid and green synthesis of spirooxindoles via multi-component approach in the presence of starch solution. The benefits of this novel environmentally benign protocol are excellent yields, short reaction time, ease of product isolation and purification, use of environment-friendly catalyst.

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