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Gold(III) chloride ($HAuCl_4 \cdot 3H_2O$) in PEG: A new and efficient catalytic system for the synthesis of functionalized spirochromenes

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ABSTRACT

Gold(III) chloride ($HAuCl_4 \cdot 3H_2O$) in PEG 400 was found to be an efficient catalytic system for the synthesis of biologically important functionalized spirochromene derivatives *via* one-pot three-component reaction of isatins/acenaphthoquinone, active methylene compounds and cyclic 1,3-diketones/4-hydroxycoumarin. A new catalytic system, recyclability of reaction medium, little reaction times and excellent yields with easy workup render this protocol more attractive and economically viable.

1. Introduction

The evaluation of eco-friendly synthetic methodologies to facilitate the preparation of compound libraries is a pivotal focal point of research activity in the field of modern medicinal and combinatorial chemistry [1]. One approach to address this challenge involves the development of multicomponent reactions (MCRs) in which at least three easily accessible components react to each other to form a single product in a one-pot reaction flask, incorporating essentially all atoms of the starting materials [2]. As one-pot reaction, MCRs show high atom-economy, high selectivity and procedural simplicity due to the formation of C–C and C-heteroatom bonds [3]. The growing interest for an environmentally benign multicomponent procedure is closely related to the development for the synthesis of combinatorial small-molecule heterocyclic libraries which is becoming an important and promising area of current organic synthesis [4].

Compounds containing indole moiety exhibit antibacterial and antifungal activities [5]. Furthermore, it has been reported that using of the indole 3-carbon in the formation of spiroindoline derivatives highly enhances biological activity [6]. The heterocyclic spirooxindole ring system is a widely distributed structural framework of many pharmaceuticals and natural products [7]. For example, spirotryprostatins A, B are a natural alkaloids isolated from the fermentation broth of *Aspergillus fumigates* in which spirotryprostatins B has been shown to completely inhibit the G2/M progression of mammalian tsFT210 cells at concentrations over 12.5 μg/mL [8] and polycyclic alkaloids pteropodine and isopteropodine have a long history for its medicinal applications in modulating the function of muscarinic serotonin receptors [9] (Fig. 1). Among them oxygen-containing heterocycles fused with spirooxindole ring system, functionally substituted 4*H*-chromenes have been received considerable attention due to a wide range of biological properties like anticoagulant, diuretic, anticancer and antianaphylactic activities [10].

There are several methods have been reported for the synthesis of spirooxindoles with fused chromenes in which conventional synthesis involves one-pot, three-component condensation of isatin with cyclic 1,3-diketones and malononitrile or 2-aminobenzothiazole [11]. Shanthi et al. has reported a three-component reaction for the synthesis of spirooxindole derivatives catalyzed by $InCl_3$ with 70–90% yields [12]. This reaction was also carried out in the presence of *p*-TSA within 1 h under reflux conditions [13]. Other more effective procedure for the synthesis of spirooxindoles employed quaternary cationics [14], and electrochemical methods [15]. Thus, each of the known procedures for the synthesis of corresponding spiro[(4*H*-chromene)-4,3′-oxindole] has its merits, however, further studies are still necessary for the

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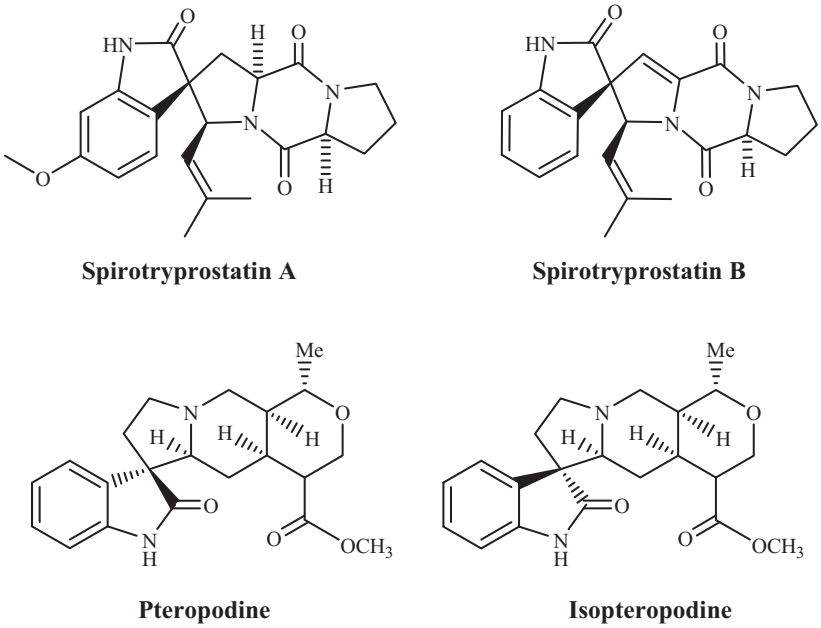


Fig. 1. Biologically active spirooxindole containing compounds.

essence of a new facile, efficient, environmental and economical multicomponent methodology for the synthesis of these heterocyclic compounds.

In recent years, gold catalyzed reactions have focused not only on the development of new processes, but also on improving the sustainability of existing transformations such as cycloaddition, isomerisation, hydroamination or nucleophilic cyclization of allenes [16]. In transition metal catalysis, cationic gold(I) and gold(III) salts are soft carbophilic Lewis acids, have shown extraordinary capability of activating C–C double and triple bond for an inter or intra molecular nucleophilic attack to form a new C–C and C–X bond forming reactions [17]. On the other hand, the versatility of homogeneous mixture of PEG and gold(III) chloride ($HAuCl_4{\cdot}3H_2O$) encouraged us to couple them together to evaluate their utility as a novel and highly efficient catalytic system for the synthesis of spirooxindole derivatives.

Due to increasing awareness of environmental problems for the synthetic chemists in chemical research and industry, efforts have been made to develop an environmentally benign chemical synthesis both in academia and chemical research. In this situation, the search for an alternative reaction media which replace toxic and traditional volatile organic compounds (VOCs) with various aqueous solutions have been attracted much attention in organic synthesis and industrial research [18]. Meanwhile, water used as environmentally benign solvent has been well documented for organic reactions [19] but the practical utilization is limited due to the hydrophobic nature of organic compounds and the sensitivity of catalysts towards moisture. So we decided to use polyethylene glycol (PEG) as the reaction media, as it may stand in comparison to other currently favoured systems such as ionic liquids, super critical carbon dioxide and micellar systems [20]. Recently, PEGs have been explored as a novel, powerful, eco-friendly solvent medium and supporter for various organic transformations due to their relatively inexpensive, thermal stable, recyclable and biodegradable material [21].

In this continuation to our ongoing endeavor and aimed to developed an environmentally benign synthetic methods for pharmacologically important skeletons [22]. Herein, we wish to report a new and efficient protocol for one-pot three-component reaction of isatins with active methylene compounds and cyclic 1,3-diketones to afford a series of spirooxindole derivatives in polyethylene glycol (PEG) as recyclable solvent media catalyzed by gold(III) chloride ($HAuCl_4{\cdot}3H_2O$) at 70 °C.

2. Experimental

2.1. General Information

All of the chemicals were purchased from Sigma-Aldrich and used without further purification. Most of the synthesized compounds are reportedly known and were identified by comparison of spectral and physical data with the literature. IR spectra were recorded on Perkin Elmer FTIR spectrophotometer using KBr pellets. IR frequency, $^{\nu}$max is measured in cm^{-1}. ^1H NMR and ^{13}C NMR (400 and 100 MHz, respectively) spectra were recorded on Jeol JNM ECX-400P Spectrometer using TMS as an internal standard. The chemical shift values are recorded on δ scale and the coupling constants *(J)* are in hertz. Mass spectral data were recorded on a Waters micromass LCT Mass Spectrometer. Temperature of the reaction mixture was measured through AZ, Mini Gun Type, Non-Contact IR thermometer, Model No. 8868. The melting points were determined on Thomas Hoover melting point apparatus. The purity of the compounds was checked on TLC (silica gel coated aluminium sheets, Silica gel 60 F254, E. Merck, Germany).

2.2. General procedure for the synthesis of functionalized spirochromenes derivatives

In a 50 mL round bottom flask, a mixture of isatin **1a–1d** or acenaphthoquinone **6** (1 mmol), active methylene compounds **2a** and **2b** (1 mmol) and $HAuCl_4{\cdot}3H_2O$ (5 mol%) in polyethylene glycol (PEG 400) (5 mL) were placed over a magnetic stirrer and the contents were stirred. To this stirred mixture, cyclic 1,3-diketones **3a–3c**/4-hydroxycoumarin **3d** (1 mmol) was added. The reaction mixture was heated at 70 °C for 30 min. The progress of the reaction mixture was monitored by TLC using hexane-ethyl acetate (2:1) as an eluent. After completion of the reaction, the reaction mixture was allowed to cool in dry ice-bath to precipitate the PEG 400 and extracted with ether (PEG being insoluble in ether). The combined ether layer was filtered in order to recover the PEG. The

filtrate was mixed with water and dried over anhydrous sodium sulfate (Na_2SO_4) and concentrated under reduced pressure. The crude product was washed with cool ethanol (3 × 10 mL) and dried. Further, the product was purified by silica-gel column chromatography using 20% ethylacetate and 80% hexane as an eluent to yield the desired products. The recovered PEG 400 can be reused for further reactions. The structures of all the products were unambiguously established on the basis of their spectral analysis (IR, ^{1}H NMR, ^{13}C NMR and ESI-MS mass spectral data). The melting points of the known synthesized products are identical with those reported previously [11a,14,15a,23].

2.3. Spectral data of synthesized functionalized spirochromenes (*4a–4n, 4a–4d and 7a–7f*)

2-Amino-7,7-dimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carbonitrile (4a): White solid; mp: 288–289 °C; IR (KBr): $^{\nu}$max = 3377, 3314, 3142, 2960, 2192, 1720, 1659, 1605, 1472, 1348, 1227, 1055, 924 cm^{-1}; ^{1}H NMR (DMSO-d$_6$, 400 MHz): δ = 10.32 (s, 1H, NH), 7.14 (br s, 2H, NH_2), 7.06 (t, *J* = 7.8 Hz, 1H, ArH), 6.89 (d, *J* = 7.3 Hz, 1H, ArH), 6.81 (t, *J* = 7.7 Hz, 1H, ArH), 6.70 (d, *J* = 7.8 Hz, 1H, ArH), 2.49 (d, *J* = 3.7 Hz, 2H, CH_2), 2.12 (d, *J* = 16.1 Hz, 1H, CH), 2.04 (d, *J* = 16.1 Hz, 1H, CH), 0.95 (s, 3H, CH_3), 0.92 (s, 3H, CH_3); ^{13}C NMR (DMSO-d$_6$, 100 MHz): *δ* = 194.91, 178.05, 164.16, 158.78, 142.06, 134.42, 128.19, 123.02, 121.70, 117.34, 110.79, 109.26, 57.52, 50.01, 46.83, 31.95, 27.61, 27.04; *m/z* 335.3566 (M + 1, $C_{19}H_{17}N_3O_3$ requires 335.1270).

2-Amino-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carbonitrile (4b): White solid; mp: > 300 °C; IR (KBr): $^{\nu}$max = 3462, 3291, 3169, 2933, 2194, 1714, 1666,1612, 1468, 1392, 1214, 1064, 1012, 931 cm^{-1}; ^{1}H NMR (DMSO-d$_6$, 400 MHz): *δ* = 10.37 (s, 1H, NH), 7.17 (br s, 2H, NH_2), 7.08 (t, *J* = 8.6 Hz, 1H, ArH), 6.94 (d, *J* = 7.8 Hz, 1H, ArH), 6.83 (t, *J* = 7.3 Hz, 1H, ArH), 6.74 (d, *J* = 7.3 Hz, 1H, ArH), 2.43–2.60 (m, 2H, CH_2), 2.18–2.24 (m, 2H, CH_2), 1.85–1.90 (m, 2H, CH_2); ^{13}C NMR (DMSO-d$_6$, 100 MHz): *δ* = 194.74, 178.34, 166.38, 158.60, 141.92, 134.41, 128.17, 123.99, 121.67, 117.45, 111.61, 109.18, 57.68, 47.84, 36.28, 26.82, 19.31; *m/z* 307.3034 (M + 1, $C_{17}H_{13}N_3O_3$ requires 307.0957).

2-Amino-2′,5-dioxo-6,7-dihydro-5*H*-spiro[cyclopenta[*b*]pyran-4,3′-indoline]-3-carbonitrile (4c): White solid; mp: > 300 °C; IR (KBr): $^{\nu}$max = 3352, 3240, 3165, 2917, 2223, 1713, 1649, 1592, 1469, 1337, 1214, 1013, 907, 749, 620 cm^{-1}; ^{1}H NMR (DMSO-d$_6$, 400 MHz): *δ* = 10.54 (s, 1H, NH), 7.47 (br s, 2H, NH_2), 7.18 (t, *J* = 7.6 Hz, 1H, ArH), 7.04 (d, *J* = 6.6 Hz, 1H, ArH), 6.91 (t, *J* = 7.3 Hz, 1H, ArH), 6.80 (d, *J* = 7.3 Hz, 1H, ArH), 2.79 (t, *J* = 4.0 Hz, 2H, CH_2), 2.33–2.35 (m, 2H, CH_2); ^{13}C NMR (DMSO-d$_6$, 100 MHz): *δ* = 199.79, 177.57, 176.56, 160.57, 141.97, 132.12, 128.83, 124.08, 122.87, 117.55, 114.83, 109.51, 56.45, 46.58, 33.19, 24.85; *m/z* 293.0800 (M + 1, $C_{16}H_{11}N_3O_3$ requires 293.2768).

2-Amino-1′,7,7-trimethyl-2′5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carbonitrile (4d): White solid; mp: 254–255 °C; IR (KBr): $^{\nu}$max = 3459, 3234, 3139, 2933, 2193, 1708, 1667, 1605, 1496, 1391, 1256, 1142, 1063, 912 cm^{-1}; ^{1}H NMR (DMSO-d$_6$, 400 MHz): *δ* = 7.21–7.26 (m, 3H, NH_2, ArH), 7.05 (d, *J* = 7.8 Hz, 1H, ArH), 7.00–6.96 (m, 2H, ArH), 3.35 (s, 3H, CH_3), 2.49–2.56 (m, 2H, CH_2), 2.04–2.16 (m, 2H, CH_2), 1.01 (s, 3H, CH_3), 0.97 (s, 3H, CH_3); ^{13}C NMR (DMSO-d$_6$, 100 MHz): *δ* = 195.06, 176.69, 164.26, 158.93, 143.53, 133.56, 128.54, 122.88, 122.27, 117.24, 110.67, 108.31, 57.53, 50.43, 46.82, 32.09, 27.08, 27.09, 25.97; *m/z* 349.3832 (M + 1, $C_{20}H_{19}N_3O_3$ requires 349.1426).

2-Amino-1′-methyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carbonitrile (4e): White solid; mp: 248–249 °C; IR (KBr): $^{\nu}$max = 3565, 3466, 3355, 3145, 2962, 2195, 1702, 1676, 1331, 1216, 1196, 1075,1013, 757; ^{1}H NMR (400 MHz, DMSO-d$_6$) *δ* = 7.19–7.24 (m, 3H, NH_2, ArH), 7.06 (d, *J* = 7.6 Hz, 1H, ArH), 6.94–6.98 (m, 2H, ArH), 3.20 (s, 3H, CH_3), 2.63–2.66 (m, 2H, CH_2), 2.18–2.22 (m, 2H, CH_2), 1.89–1.92 (m, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d$_6$) *δ* = 194.98, 176.55, 166.15, 158.64, 143.60, 133.82, 128.57, 123.11, 122.49, 117.34, 111.99, 108.08, 56.82, 47.52, 37.32, 27.07, 26.23, 19.84; *m/z* 321.3300 (M + 1, $C_{18}H_{15}N_3O_3$ requires 321.1113).

2-Amino-1′-methyl-2′,5-dioxo-6,7-dihydro-5*H*-spiro[cyclopenta[*b*]pyran-4,3′-indoline]-3-carbonitrile (4f): White solid; mp: 279–280 °C; IR (KBr): $^{\nu}$max = 3566, 3456, 3345, 3140, 2960, 2195, 1706, 1675, 1498, 1350, 1216, 1190, 1078,1016, 756; ^{1}H NMR (400 MHz, DMSO-d$_6$) *δ* = 7.29–7.45 (m, 3H, NH_2, ArH), 7.10 (d, *J* = 7.1 Hz, 1H, ArH), 7.01–7.03 (m, 2H, ArH), 3.18 (s, 3H, CH_3), 2.85 (t, *J* = 4.0 Hz, 2H, CH_2), 2.28–2.32 (m, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ = 199.72, 177.56, 176.15, 160.82, 142.62, 132.24, 128.23, 124.12, 122.54, 117.30, 115.26, 108.10, 56.38, 47.51, 36.30, 27.23, 26.36; *m/z* 307.3034 (M + 1, $C_{17}H_{13}N_3O_3$ requires 307.0957).

1′-Acetyl-2-amino-7,7-dimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carbonitrile (4g): White Solid; mp: 230–232 °C; IR (KBr): $^{\nu}$max = 3462, 3194, 2933, 2193, 1757, 1726, 1663, 1354, 1256, 1099 cm^{-1}; ^{1}H NMR (DMSO-d$_6$, 400 MHz): *δ* = 8.07 (d, *J* = 8.1 Hz, 1H, ArH), 7.52 (br s, 2H, NH_2), 7.27–7.36 (m, 1H, ArH), 7.18–7.22 (m, 2H, ArH), 2.66 (s, 3H, CH_3CO), 2.55 (s, 2H, CH_2), 2.48–2.49 (m, 2H, CH_2), 1.03 (s, 3H, CH_3), 0.99 (s, 3H, CH_3); ^{13}C NMR (DMSO-d$_6$, 100 MHz): *δ* = 195.41, 177.84, 170.24, 164.93, 158.74, 139.17, 132.71, 128.67, 125.50, 123.30, 116.93, 115.30, 110.75, 56.96, 49.47, 47.39, 39.91, 32.12, 27.53, 27.02, 25.95; *m/z* 377.3933 (M + 1, $C_{21}H_{19}N_3O_4$ requires 377.1376).

1′-Acetyl-2-amino-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carbonitrile (4h): White Solid; mp: 253–255 °C; IR (KBr): $^{\nu}$max = 3462, 3326, 2933, 2194, 1756, 1725, 1667, 1336, 1256, 1166, 1064; ^{1}H NMR (DMSO-d$_6$, 400 MHz): *δ* = 8.01 (d, *J* = 8.0 Hz, 1H, ArH), 7.44 (br s, 2H, NH_2), 7.23–7.26 (m, 1H, ArH), 7.03–7.16 (m, 2H, ArH), 2.54–2.64 (m, 2H, CH_2), 2.24–2.39 (m, 2H, CH_2), 2.49 (s, 3H, CH_3CO), 2.13–2.21 (m, 2H, CH_2); ^{13}C NMR (DMSO-d$_6$, 100 MHz): *δ* = 195.44, 178.08, 170.25, 166.66, 158.52, 139.12, 133.02, 128.64, 125.51, 123.48, 117.06, 115.03, 111.74, 56.98, 47.44, 35.91, 26.60, 25.95, 19.70; *m/z* 349.1063 (M + 1, $C_{19}H_{15}N_3O_4$ requires 349.0880).

1′-Acetyl-2-amino-2′,5-dioxo-6,7-dihydro-5*H*-spiro[cyclopenta[*b*]pyran-4,3′-indoline]-3-carbonitrile (4i): White Solid; mp: 282–284 °C; IR (KBr): $^{\nu}$max = 3463, 3324, 2919, 2198, 1752, 1721, 1665, 1324, 1253, 1168, 1071, 910, 757; ^{1}H NMR (DMSO-d$_6$, 400 MHz): *δ* = 8.02 (d, *J* = 8.1 Hz, 1H, ArH), 7.70 (br s, 2H, NH_2), 7.27–7.31 (m, 1H, ArH), 7.13–7.20 (m, 2H, ArH), 2.77 (t, *J* = 4.7 Hz, 2H, CH_2), 2.49 (s, 3H, CH_3CO), 2.31 (t, *J* = 5.0 Hz, 2H, CH_2); ^{13}C NMR (DMSO-d$_6$, 100 MHz): *δ* = 200.13, 177.98, 170.32, 163.15, 160.50, 139.44, 130.51, 129.39, 125.85, 124.53, 117.33, 115.57, 112.96, 56.03, 47.44, 34.62, 26.12, 25.18; *m/z* 335.3135 (M + 1, $C_{18}H_{13}N_3O_4$ requires 335.0906).

2-Amino-5′-chloro-2′,5-dioxo-7,7-dimethyl-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carbonitrile (4j): White solid; mp: 288–290 °C; IR (KBr): $^{\nu}$max = 3445, 3285, 3146, 2932, 2194, 1725, 1663, 1605, 1479, 1392, 1256, 1164, 1063, 905 cm^{-1}; ^{1}H NMR (DMSO-d$_6$, 400 MHz): *δ* = 10.39 (s, 1H, NH), 7.24 (br s, 2H, NH_2), 7.12 (d, *J* = 8.0 Hz, 1H, ArH), 7.02 (s, 1H, ArH), 6.71 (d, *J* = 8.8 Hz, 1H, ArH), 2.41–2.53 (m, 2H, CH_2), 2.03–2.11 (m, 2H, CH_2), 0.94 (s, 3H, CH_3), 0.90 (s, 3H, CH_3); ^{13}C NMR (DMSO-d$_6$, 100 MHz): δ = 195.01, 177.77, 164.51, 158.86, 141.02, 136.43, 128.15, 125.72, 123.18, 117.14, 110.70, 110.12, 56.33, 50.48, 46.80, 32.00, 27.52, 27.23; *m/z* 369.8016 (M + 1, $C_{19}H_{16}ClN_3O_3$ requires 369.0880).

2-Amino-5′-chloro-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carbonitrile (4k): White solid; mp: 293–295 °C; IR (KBr): $^{\nu}$max = 3468, 3287, 3142, 2932, 2116, 1722, 1668,1608, 1497, 1391, 1256, 1162, 1063, 908 cm^{-1}; ^{1}HNMR (DMSO-d$_6$, 400 MHz): *δ* = 10.49 (s, 1H, NH),

7.26 (br s, 2H, NH_2), 7.15 (d, J = 7.9 Hz, 1H, ArH), 7.10 (s, 1H, ArH), 6.74 (d, J = 8.0 Hz, 1H, ArH), 2.45–2.60 (m, 2H, CH_2), 2.00–2.20 (m, 2H, CH_2), 1.85–1.91 (m, 2H, CH_2); ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 195.24, 177.97, 166.66, 158.78, 140.96, 136.53, 128.02, 125.58, 123.42, 117.17, 111.29, 110.48, 56.79, 47.06, 32.01, 26.86, 19.56; *m/z* 341.7485 (M + 1, $C_{17}H_{12}ClN_3O_3$ requires 341.0567).

2-Amino-5′-chloro-2′,5-dioxo-6,7-dihydro-5*H*-spiro[cyclopenta[*b*]pyran-4,3′-indoline]-3-carbonitrile (4l): White solid; mp: > 300 °C; IR (KBr): $^{\nu}$max = 3465, 3282, 3135, 2915, 2191, 1720, 1671, 1466, 1213, 1158, 1098, 1010, 912, 753 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 10.70 (s, 1H, NH), 7.57 (br s, 2H, NH_2), 7.20–7.24 (m, 2H, ArH), 6.84 (d, J = 7.8 Hz, 1H, ArH), 2.78–2.80 (m, 2H, CH_2), 2.36–2.49 (m, 2H, CH_2); ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 199.95, 178.00, 176.57, 160.73, 141.73, 136.94, 134.09, 128.81, 124.52, 117.43, 114.22, 110.98, 55.88, 46.79, 33.20, 25.01; *m/z* 327.7219 (M + 1, $C_{16}H_{10}ClN_3O_3$ requires 327.0413).

Ethyl 2-Amino-7,7-dimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carboxylate (4m): White solid; mp: 256–257 °C, IR (KBr): $^{\nu}$max = 3429, 2997, 2128, 1686, 1620, 1473, 1222, 1027, 952, 762 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 10.24 (s, 1H, NH), 7.72 (br s, 2H, NH_2), 6.71–7.08 (m, 4H, ArH), 3.64 (q, J = 5.1 Hz, 2H, CH_2), 2.51 (d, J = 3.5 Hz, 2H, CH_2), 2.13 (d, J = 15.2 Hz, 1H, CH), 2.06 (d, J = 15.2 Hz, 1H, CH), 1.03 (s, 3H, CH_3), 0.94 (s, 3H, CH_3), 0.82 (t, J = 6.6 Hz, 3H, CH_3); ^{13}C NMR (DMSO-d6, 100 MHz): δ = 195.18, 179.80, 168.23, 162.81, 159.65, 143.32, 134.12, 127.41, 123.01, 121.62, 114.36, 109.12, 78.58, 59.61, 52.32, 46.85, 34.09, 27.39, 27.11, 13.65; *m/z* 382.4098 (M + 1, $C_{21}H_{22}N_2O_5$ requires 382.1529).

Ethyl 2-Amino-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carboxylate (4n): White solid; mp: 262–263 °C; IR (KBr): $^{\nu}$max = 3465, 3289, 2932, 1656, 1642, 1532, 1469, 1212, 1065, 1015, 934, 740 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 10.37 (s, 1H, NH), 7.69 (br s, 2H, NH_2), 7.02–7.43 (m, 4H, ArH), 3.66 (q, J = 5.8 Hz, 2H, CH_2), 1.95–2.83 (m, 6H, CH_2), 0.76 (t, J = 6.9 Hz, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 195.40, 178.43, 169.65, 165.12, 159.56, 141.93, 134.42, 127.18, 123.94, 121.65, 115.84, 108.46, 77.95, 59.17, 47.36, 38.22, 27.62, 19.30, 13.51; *m/z* 354.3566 (M + 1, $C_{19}H_{18}N_2O_5$requires 354.1216).

2′-Amino-2,5′-dioxo-5′*H*-spiro[indoline-3,4′-pyrano[3,2-*c*]chromene]-3′-carbonitrile (5a): White solid; mp: 284–286 °C; IR (KBr): $^{\nu}$max = 3467, 3294, 3197, 2932, 2275, 1727, 1660, 1602, 1543, 1496, 1391, 1256, 1172, 1099, 970 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 10.68 (s, 1H, NH), 7.94 (d, J = 7.8 Hz, 1H, ArH), 7.75 (t, J = 7.3 Hz, 1H, ArH), 7.66 (br s, 2H, NH_2), 7.40 (t, J = 7.8 Hz, 1H, ArH), 7.34 (d, J = 8.7 Hz, 1H, ArH), 7.20 (t, J = 7.8 Hz, 2H, ArH), 6.92 (t, J = 7.8 Hz, 1H, ArH), 6.85 (d, J = 7.4 Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 177.26, 159.66, 158.49, 155.24, 152.13, 142.19, 133.69, 132.91, 129.92, 125.05, 124.13, 123.09, 122.71, 117.11, 117.05, 112.57, 109.78, 101.51, 56.91, 47.63; *m/z* 357.3190 (M + 1, $C_{20}H_{11}N_3O_4$ requires 357.0750).

Ethyl 2′-Amino-2,5′-dioxo-5′*H*-spiro[indoline-3,4′-pyrano[3,2-*c*]chromene]-3′-carboxylate (5b): White Solid; mp: 252–253 °C; IR (KBr): $^{\nu}$max = 3455, 3282, 3015, 2920, 1725, 1658, 1563, 1473, 1434, 1315, 1274, 1184, 1027, 949, 754 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 10.40 (s, 1H, NH), 9.80 (br s, 2H, NH_2), 7.50–7.41 (m, 2H, ArH), 7.34 (t, J = 8.1 Hz, 1H, ArH), 7.26 (d, J = 8.04 Hz, 1H, ArH), 7.01–7.10 ((m, 2H, ArH), 6.77–6.83 (m, 2H, ArH), 3.69–3.75 (m, 2H, CH_2O), 0.81 (t, J = 6.9 Hz, 3H, CH_3); ^{13}CNMR (DMSO-d_6, 100 MHz): δ = 170.24, 167.98, 166.06, 163.21, 159.85, 152.10, 142.43, 131.86, 128.57, 127.73, 126.86, 126.21, 125.35, 124.99, 124.23, 121.87, 120.29, 77.38, 59.62, 48.60, 13.85; ^{13}CNMR (DMSO-d_6, 100 MHz): δ = 177.28, 159.68, 158.53, 155.29, 152.17, 142.16, 133.68, 132.986, 129.95, 125.08, 124.16, 123.15, 122.75, 117.18, 117.10, 112.58, 109.72, 101.49, 62.34, 56.95, 47.64, 14.45; *m/z* 404.3722 (M + 1, $C_{22}H_{16}N_2O_6$ requires 404.1008).

2′-Amino-1-methyl-2,5′-dioxo-5′*H*-spiro[indoline-3,4′-pyrano[3,2-*c*]chromene]-3′-carbonitrile (5c): White solid; mp: 283–285 °C; IR (KBr): $^{\nu}$max = 3456, 3291, 3168, 2915, 2227, 1719,1664, 1607, 1465, 1373, 1223, 1127, 1099, 949 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.91 (d, J = 7.8 Hz, 1H, ArH), 7.64 (t, J = 8.5 Hz, 1H, ArH), 7.57 (br s, 2H, NH_2), 7.53 (t, J = 7.8 Hz, 1H, ArH), 7.33 (d, J = 8.0 Hz, 1H, ArH), 7.31 (t, J = 7.8 Hz, 1H, ArH), 7.29 (d, J = 6.6 Hz, 1H, ArH), 7.05 (d, J = 7.8 Hz, 1H, ArH), 7.0 (t, J = 6.6 Hz, 1H, ArH), 3.14 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 171.75, 162.38, 158.62, 155.69, 149.78, 147.31, 137.63, 132.28, 128.56, 125.54, 124.25, 123.45, 118.05, 117.96, 112.95, 111.58, 110.53, 57.12, 47.62, 26.11; *m/z* 371.3456 (M + 1, $C_{21}H_{13}N_3O_4$ requires 371.0906).

2′-Amino-5-chloro-2,5′-dioxo-5′*H*-spiro[indoline-3,4′-pyrano[3,2-*c*]chromene]-3′-carbonitrile (5d): White solid; mp: >300 °C; IR (KBr): $^{\nu}$max = 3459, 3322, 3210, 2932, 2196,1713,1667, 1605, 1440, 1391, 1256, 1171, 1098, 971 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 10.80 (s, 1H, NH), 7.93 (d, J = 7.6 Hz, 1H, ArH), 7.72–7.77 (m, 3H, ArH, NH_2), 7.53 (t, J = 7.3 Hz, 1H, ArH), 7.47 (d, J = 8.1 Hz, 1H, ArH), 7.41 (s, 1H, ArH), 7.26 (d, J = 8.1 Hz, 1H, ArH), 6.84 (d, J = 7.3 Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 176.91, 159.02, 158.39, 155.43, 152.30, 141.01, 134.92, 133.71, 128.74, 126.10, 124.97, 124.50, 122.65, 116.88, 116.64, 112.71,110.79, 100.69, 56.36, 47.85; *m/z* 391.7641 (M + 1, $C_{20}H_{10}ClN_3O_4$ requires 391.0360).

2′-Amino-7′,7′-dimethyl-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-2*H*-spiro[acenaphthylene-1,4′-chromene]-3′-carbonitrile (7a): Light yellow solid; mp: 261–263 °C; IR (KBr): $^{\nu}$max = 3468, 3186, 2932, 2192, 1718, 1663, 1497, 1256, 1098 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 8.41–8.44 (m, 1H. ArH), 8.24 (d, J = 7.4 Hz, 1H, ArH), 8.17 (d, J = 7.6 Hz, 1H, ArH), 7.91–8.01 (m, 3H, ArH), 7.31 (br s, 2H, NH_2), 2.47–2.49 (m, 2H, CH_2), 2.11 (d, J = 16.1 Hz, 1H, CH), 2.06 (d, J = 16.0 Hz, 1H, CH), 1.02 (s, 3H, CH_3), 1.4 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 203.61, 195.34, 164.62, 158.65, 143.20, 140.48, 132.17, 131.52, 130.14, 129.84, 128.93, 124.51, 121.40, 119.84, 117.45, 112.05, 57.92, 51.04, 49.73, 32.09, 27.52, 27.20; *m/z* 370.4006 (M + 1, $C_{23}H_{18}N_2O_3$ requires 370.1317).

2′-Amino-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-2*H*-spiro[acenaphthylene-1,4′-chromene]-3′-carbonitrile (7b): Orange solid; mp: 244–246 °C; IR (KBr): $^{\nu}$max = 3490, 3072, 2931, 2116, 1720, 1672, 1498, 1389, 1256, 1064 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 8.40–8.44 (t, J = 8.0 Hz, 1H, ArH), 8.25 (d, J = 7.3 Hz, 1H, ArH), 8.18 (d, J = 7.3 Hz, 1H, ArH), 7.93–8.01 (m, 3H, ArH), 7.29 (br s, 2H, NH_2), 2.48–2.49 (m, 2H, CH_2) 2.13–2.18 (m, 2H, CH_2), 1.89–1.95 (m, 2H, CH_2); ^{13}CNMR (DMSO-d_6, 100 MHz): δ = 203.72, 198.34, 168.30, 156.06, 143.39, 140.79, 132.20, 130.13, 129.43, 128.54, 123.66, 123.15, 122.86, 117.35, 113.19, 57.25, 51.30, 36.81, 27.14, 21.32; *m/z* 342.3475 (M + 1, $C_{21}H_{14}N_2O_3$ requires 342.1004).

2′-Amino-2,5′-dioxo-6′,7′-dihydro-2*H*,5′*H*-spiro[acenaphthylene-1,4′-cyclopenta[*b*]pyran]-3′-carbonitrile (7c): Orange solid; mp: > 300 °C; IR (KBr): $^{\nu}$max = 3440, 3072, 2933, 2117, 1722, 1613, 1495, 1385, 1223, 1026, 983, 780 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 8.43 (t, J = 8.8 Hz, 1H, ArH), 8.34 (d, J = 7.4 Hz, 1H, ArH), 8.17 (d, J = 7.4 Hz, 1H, ArH), 7.92–8.01 (m, 3H, ArH), 7.57 (br s, 2H, NH_2), 2.86–2.87 (m, 2H, CH_2) 2.47–2.49 (m, 2H, CH_2); ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 203.09, 200.16, 177.84, 155.98, 141.31, 140.73, 132.33, 129.40, 129.09, 128.74, 125.08, 123.27, 122.05, 121.08, 117.70, 111.72, 56.99, 50.92, 33.10, 25.06; *m/z* 328.3209 (M + 1, $C_{20}H_{12}N_2O_3$ requires 328.0848).

Ethyl 2′-Amino-7′,7′-dimethyl-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-2*H*-spiro[acenaphthylene-1,4′-chromene]-3′-carboxylate (7d): White solid; mp: 263–264 °C; IR (KBr): $^{\nu}$max = 3421, 3185, 2939, 2182, 1717, 1602, 1487, 1277, 1014 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.52–8.41 (m, 6H. ArH), 7.90 (s, 2H, NH_2), 4.48 (q, J = 6.1 Hz, 2H, CH_2), 2.48–2.49 (m, 2H, CH_2), 1.35–1.38 (m, 2H, CH_2), 1.09 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 0.45

Table 1
Optimization of reaction conditions.[a]

Entry	Catalyst	Amount (mol%)	Time (min)	Yield (%)[b]
1	–	–	600	24
2	$ZnCl_2$	5	210	43
3	$BiCl_3$	5	360	38
4	$InCl_3$	5	120	73
5	$FeCl_3{\cdot}6H_2O$	5	450	25
6	$SnCl_2{\cdot}2H_2O$	5	270	47
7	*p*-TSA	5	300	50
8	AuCl	5	180	30
9	Ph_3PAuCl	5	180	30
10	$HAuCl_4{\cdot}3H_2O$	3	30	93
11	$HAuCl_4{\cdot}3H_2O$	5	30	96
12	$HAuCl_4{\cdot}3H_2O$	10	30	95

[a] Reaction conditions: Isatin **1a** (1 mmol), malononitrile **2a** (1 mmol), dimedone **3a** (1 mmol); solvent: PEG 400 (5 mL); different catalysts (5 mol%); temperature: 70 °C.
[b] Isolated yields.

Table 2
Screening of solvent and temperature.[a]

Entry	Solvent	Temp (°C)	Time (min)	Yield (%)[b]
1	C_2H_5OH	Reflux	355	76
2	CH_3CN	Reflux	240	<35
3	H_2O	Reflux	240	<35
4	DMSO	Reflux	650	Trace
5	DMF	Reflux	650	Trace
6	Solvent-free	70	650	Trace
7	PEG 200	70	30	94
8	PEG 400	70	30	96
9	PEG 600	70	30	96
10	PEG 400	80	30	96
11	PEG 400	rt	120	60
12	PEG 400	40	120	70

[a] Reaction conditions: isatin **1a** (1 mmol), malononitrile **2a** (1 mmol) dimedone **3a** (1 mmol); catalyst: gold(III) chloride (5 mol%); different solvents: (5 mL); at different temperature.
[b] Isolated yields.

(t, J = 6.8 Hz, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 196.42, 195.25, 167.60, 164.98, 159.73, 145.26, 134.18, 132.41, 130.63, 129.79, 128.35, 128.09, 124.45, 121.66, 118.70, 114.30, 78.01, 58.61, 51.13, 50.15, 35.29, 29.22, 28.85, 13.56; *m/z* 418.2110 (M + 1, $C_{25}H_{23}NO_5$ requires 417.1576).

Ethyl 2′-Amino-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-2*H*-spiro[acenaphthylene-1,4′-chromene]-3′-carboxylate (7e): Yellow solid; mp: 224–226 °C; IR (KBr): $^{\nu}$max = 3486, 3280, 2986, 1717, 1675, 1586, 1362, 1276, 1013, 755 cm^{-1}; ^{1}HNMR (DMSO-d_6, 400 MHz): δ = 7.86–8.59 (m, 6H, ArH), 7.32 (s, 2H, NH_2), 4.48 (q, J = 7.3 Hz, 2H, CH_2), 2.30–2.31 (m, 2H, CH_2) 1.35–1.37 (m, 2H, CH_2), 1.20–1.22 (m, 2H, CH_2), 0.34 (t, J = 6.8 Hz, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 196.88, 195.41, 168.16, 165.43, 144.10, 132.30, 129.22, 128.62, 128.32, 128.16, 127.98, 124.34, 121.23, 116.11, 78.79, 62.41, 59.32, 39.70, 33.14, 27.84, 13.82; *m/z* 389.1263 (M + 1, $C_{23}H_{19}NO_5$ requires 389.4007).

2′-Amino-2,5′-dioxo-2*H*,5′*H*-spiro[acenaphthylene-1,4′-pyran[3,2-*c*]chromene]-3′-carbonitrile (7f): Brown solid; mp: 255–256 °C; IR (KBr): $^{\nu}$max = 3414, 3062, 2129, 1725, 1659, 1486, 1379, 1230, 1026 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 8.32–8.39 (m, 2H, ArH), 8.13 (d, J = 7.3 Hz, 1H, ArH), 7.82–8.00 (m, 3H, ArH), 7.77 (br s, 2H, NH_2), 7.42–7.66 (m, 4H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 195.35, 176.87, 158.49, 156.11, 152.24, 142.11, 133.84, 132.34, 131.38, 129.97, 129.36, 128.87, 128.56, 127.85, 127.11, 126.43, 125.28, 123.75, 121.21, 117.26, 100.25, 57.75, 55.36; *m/z* 392.7026 (M + 1, $C_{24}H_{12}N_2O_4$ requires 392.0797).

3. Results and discussion

Initially, the synthesis of spirooxindole *via* one-pot three-component reaction was carried out using 1 equiv. each of isatin, malononitrile and dimedone as a model substrate (Scheme 1). The reaction mixture was stirred at 70 °C in PEG (5 mL). During the reaction, it was observed that the yield of product was 93% in the presence of 3 mol% of $HAuCl_4{\cdot}3H_2O$ after 30 min (Table 1, Entry 10). In contrast to this, the yield of product was very low in absence of catalyst even after longer reaction time (Table 1, Entry 1).

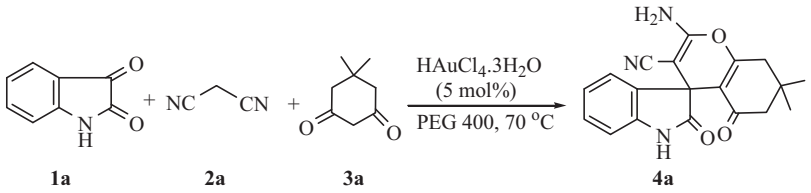
The effect of catalyst loading for this transformation was also studied. Interestingly, when increasing the amount of gold(III) chloride could improve the product yields significantly. Inspired by the result, when we increased the concentration of catalyst from 3 mol% to 10 mol%, increased the yield of product from 93% to 96%, respectively (Table 1, Entries 10–12). It shows that using 5 mol% of gold(III) chloride in PEG 400 is sufficient to push this reaction forward. More amount of catalyst did not improve the product yields.

To evaluate the catalytic activity of catalyst, the same reaction was carried out in the presence of various Lewis acid catalysts such as $ZnCl_2$, $BiCl_3$, $InCl_3$, $FeCl_3{\cdot}3H_2O$, $SnCl_2{\cdot}2H_2O$, *p*-TSA, AuCl, Ph_3PAuCl and $HAuCl_4{\cdot}3H_2O$, among them $HAuCl_4{\cdot}3H_2O$ was found to be best choice for this multicomponent reaction (MCRs) (Table 1, Entry 11). On the basis of above observations, we choose gold(III) chloride ($HAuCl_4{\cdot}3H_2O$) as a potential catalyst for the synthesis of spirooxindole derivatives under similar conditions.

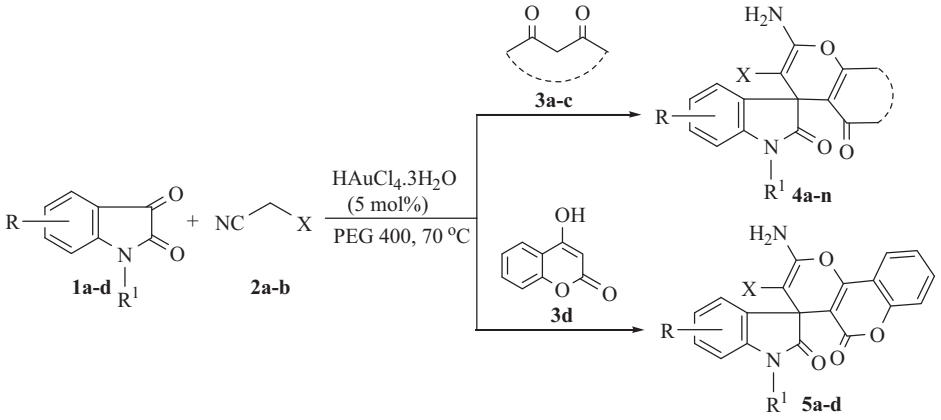
A screening of solvents was also carried out under similar reaction conditions. There are several solvents such as C_2H_5OH, CH_3CN, H_2O, DMSO, DMF and PEGs were used and it turned out that PEG 400 was found to be a best choice as a solvent for this reaction with excellent yield of product and less reaction time (Table 2, Entry 8). PEG 400 is well known solvent which may increase the solubility of the substrates and other reagents. Moreover, PEG 400 is able to extract the hydrogen atom from active methylene groups (malononitrile or 1,3-dicarbonyl compounds) and is also able to retain it by chelation through several lone pairs of electrons in its oxygen containing chain. This may be due to the attraction between the PEG hydroxyl group oxygen and hydrogen of the methylene (CH_2) of malononitrile. That makes the C–H bond weaker, enhancing the nucleophilicity of the carbon and the catalytic activity of PEG 400 as a solvent was increased. Lower molecular weight PEG 200 was also tested as solvent, to give the low yield of product under same reaction conditions. These results showed that PEG not only acted as recyclable solvent but could also accelerate the three component reaction. In addition, when the reaction was performed under solvent-free conditions to give only trace amount of product (Table 2, Entry 6). The results show that the catalytic performance is strongly affected by the type of solvent but a direct correlation between solvent properties and their efficiency could not be established in any case as summarized in Table 2.

The effect of temperature was also studied. The reaction was carried out at different temperature, increasing from room temperature to 80 °C. We observed that the yield of product was improved and the reaction time was shortened as the temperature was increased from room temperature to 70 °C. The product yields plateaued when temperature was further increased up to 80 °C (Table 2, Entry 10). Consequently, 70 °C was found to be the most suitable reaction temperature for an optimum yield of desired product (Table 2, Entry 8).

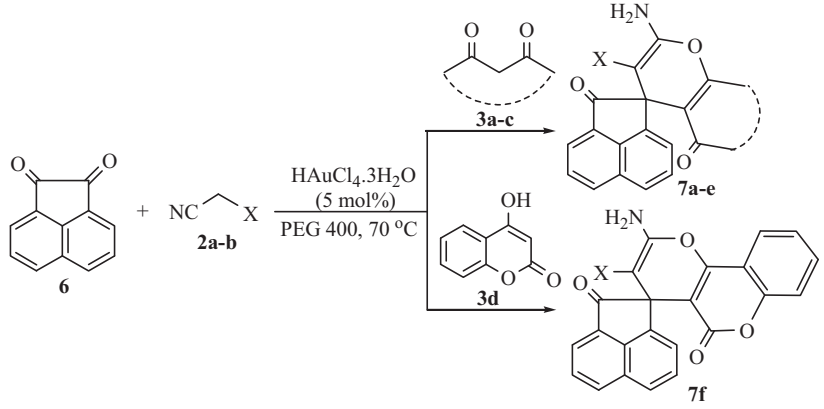
In order to prove that the use of polyethylene glycol as environmentally benign solvent is also practical, it must be conveniently recycled with minimum loss and decomposition. The reaction mixture was cooled in dry ice-bath to precipitate the PEG 400 and extracted with ether (PEG being insoluble in ether) and the retained PEG phase may be reused. The recycled PEG does not change in its reactivity but approximately 5% weight loss of PEG was observed from cycle to cycle (Table 3). Therefore, we also examined the



Scheme 1. $HAuCl_4{\cdot}3H_2O$ catalyzed Model reaction.



Scheme 2. $HAuCl_4{\cdot}3H_2O$ catalyzed one-pot three-component reaction of isatins, active methylene compounds and cyclic 1,3-diketones or 4-hydroxycoumarin.



Scheme 3. $HAuCl_4{\cdot}3H_2O$ catalyzed one-pot three-component reaction of acenaphthoquinone, active methylene compounds and cyclic 1,3-diketones or 4-hydroxycoumarin.

recyclability of the catalyst after the extraction of product with an organic solvent (diethyl ether) was accompanied by considering leaching of the catalyst, so the recyclability of the gold(III) chloride is not possible.

After optimization of reaction conditions, to delineate this approach, especially in regard to library construction, this methodology was evaluated by using different isatins, active methylene compounds and cyclic 1,3-diketones for the synthesis of a series of tetrahydrospiro[chromene-4,3′-indoline] derivatives **4a–4n** and **5a–5d** (Scheme 2 and Table 4). We used several types of isatins including either electron withdrawing or electron donating groups, malononitrile **2a** or cyanoacetic ester **2b** and cyclic 1,3-diketones **3a–3c** or 4-hydroxycoumarin **3d** were used in this reaction. It was observed that all these cyclic 1,3-diketones or 4-hydroxycoumarin as well as active methylene compounds were suitable for this reaction which gives a satisfactory yield of desired products.

Encouraged by these remarkable results, further to extend this protocol and in order to explore the scope of the $HAuCl_4{\cdot}3H_2O$ catalyst, we also examined one-pot three-component reaction using another reactant acenaphthoquinone **6** inplace of isatins under similar reaction conditions. We first used the optimized reaction conditions of Entry 11, Table 1 and Entry 8, Table 2 to convert the model reactant acenaphthoquinone **6**, malononitrile **2a** and dimedone **3a** in to the corresponding product spiro acenaphthyleneones **7a**. After apply the same reaction conditions, we were prepared a variety of spiro acenaphthyleneone derivatives **7a–7f** with excellent yields (Scheme 3 and Table 5).

Mechanistically, we have proposed two plausible pathways [24] for the synthesis of spirooxindole derivatives, Scheme 4 (path A and

Table 3
Recyclability of PEG 400.[a]

No. of cycles[a]	Fresh	Run 1	Run 2	Run 3
Yield (%)[b]	96	94	93	90
Time (min)	30	30	30	30

[a] Reaction conditions: isatin **1a** (1 mmol), malononitrile **2a** (1 mmol); dimedone **3a** (1 mmol), catalyst: gold(III) chloride (5 mol%); solvent: PEG 400 (5 mL); temperature: 70 °C.
[b] Isolated yields.

Table 4
Synthesis of spirooxindole derivatives (**4a–4n** and **5a–5d**).[a]

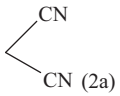
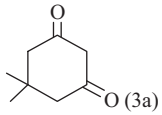
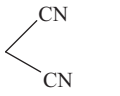
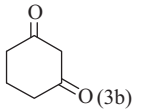
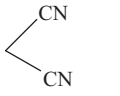
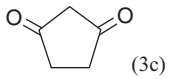
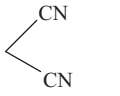
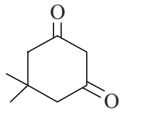
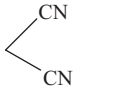
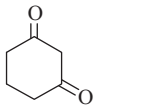
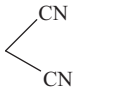
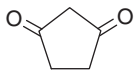
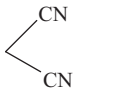
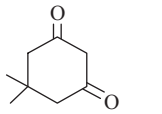
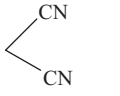
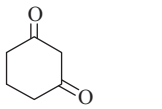
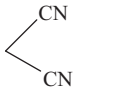
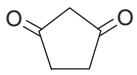
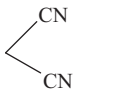
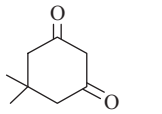
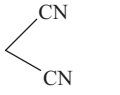
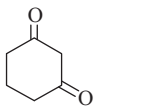
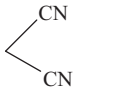
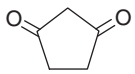
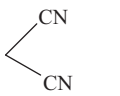
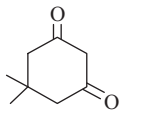
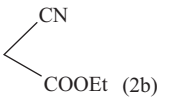
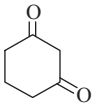
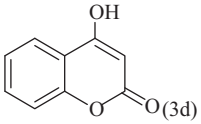
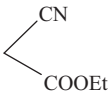
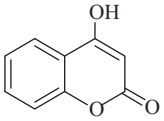
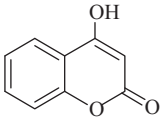
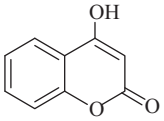
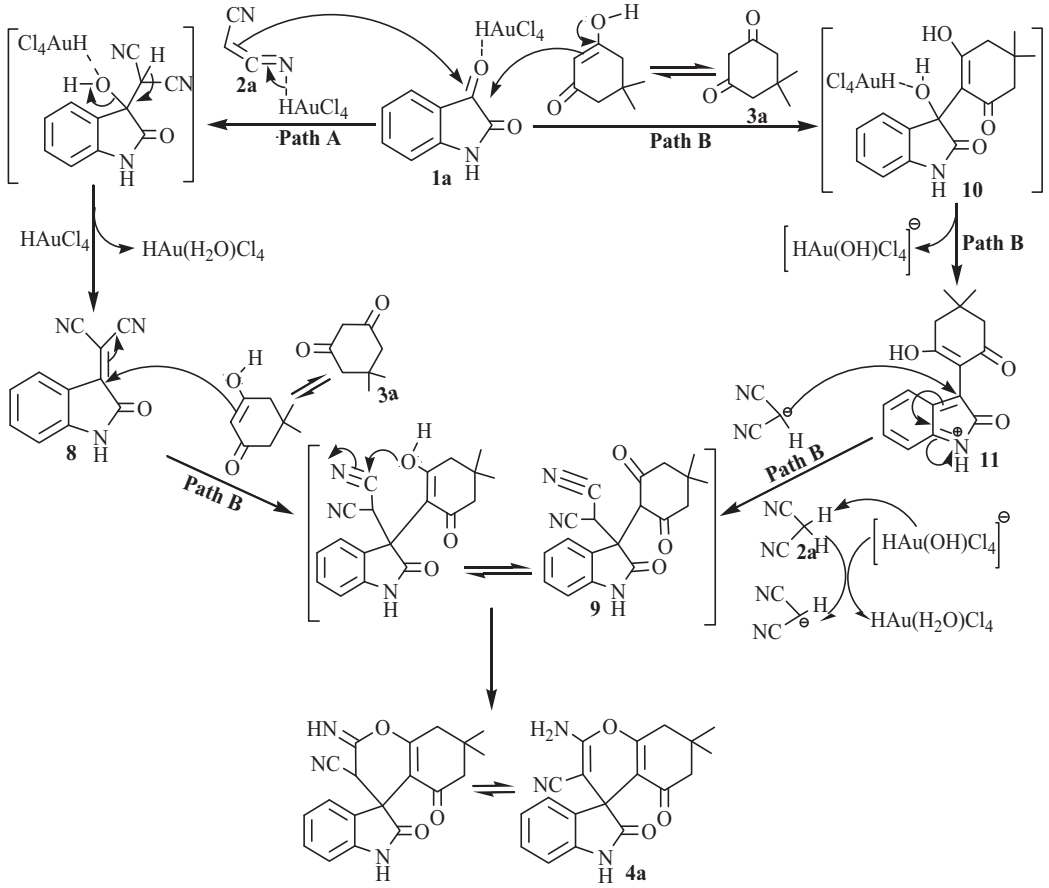
Entry	R	R^1	Active methylene compounds	Cyclic 1,3-diketones/4-hydroxycoumarin	Product	Yield (%)[b]
1	H	H	 (2a)	 (3a)	**4a**	96
2	H	H		 (3b)	**4b**	94
3	H	H		 (3c)	**4c**	92
4	H	CH_3			**4d**	93
5	H	CH_3			**4e**	94
6	H	CH_3			**4f**	90
7	H	$COCH_3$			**4g**	91
8	H	$COCH_3$			**4h**	88
9	H	$COCH_3$			**4i**	83
10	5-Cl	H			**4j**	92
11	5-Cl	H			**4k**	85
12	5-Cl	H			**4l**	92
13	H	H			**4m**	88

Table 4 (*Continued*)

Entry	R	R^1	Active methylene compounds	Cyclic 1,3-diketones/4-hydroxycoumarin	Product	Yield (%)[b]
14	H	H	 (2b)		**4n**	84
15	H	H		 (3d)	**5a**	94
16	H	H			**5b**	84
17	H	CH_3			**5c**	92
18	5-Cl	H			**5d**	93

[a] Reaction conditions: isatins **1a–1d** (1 mmol), active methylene compounds **2a** and **2b** (1 mmol); cyclic 1,3-diketones **3a–3c** or 4-hydroxycoumarin **3d** (1 mmol); catalyst: gold(III) chloride (5 mol%); solvent: PEG 400 (5 mL); temperature: 70 °C.
[b] Isolated yields.



Scheme 4. Plausible mechanism for the synthesis of spirooxindole **4a** *via* path A and path B.

Table 5
Synthesis of spiro acenaphthyleneone derivatives (**7a–7f**).[a]

Entry	Active methylene compounds	Cyclic 1,3-diketones/4-hydroxycoumarin	Product	Yield (%)[b]
1	2a	3a	**7a**	91
2	2a	3b	**7b**	76
3	2a	3c	**7c**	85
4	2b	3a	**7d**	82
5	2b	3b	**7e**	88
6	2a	3d	**7f**	90

[a] Reaction conditions: acenaphthoquinone **6** (1 mmol), active methylene compounds **2a** and **2b** (1 mmol), cyclic 1,3-diketones **3a–3c** or 4-hydroxycoumarin **3d** (1 mmol); catalyst: gold(III) chloride (5 mol%); solvent: PEG 400 (5 mL); temperature: 70 °C.
[b] Isolated yields.

path B). To check the mechanistic way for the formation of desired products, we have also made the reaction of isatin with dimedone followed by the addition with malononitrile (path B) and we found that the product was same as the formation of desired product *via* path A (Scheme 4). Typically, in the first step isatin **1a** may coordinate with $HAuCl_4$ and react with malononitrile **2a** to produce the isatylidene malononitrile **8** by the removal of $HAu(H_2O)Cl_4$. The step can be regarded as Knoevenagel condensation. Further in the second step, the electron deficient Knoevenagel adduct **8** may be subsequently attacked *via* Michael addition of dimedone **3a** to give the intermediate **9** (path A). Alternatively, the mechanistic detail of path B can be understood by assuming that in the first step isatin **1a** may coordinate with $HAuCl_4$ and react with dimedone **3a** to afford the aldol adduct **10** followed by dehydration of **10** and nucleophilic attack of **2a** to afford the intermediate **9** with the removal of $HAu(H_2O)Cl_4$. In both paths, the intermediate **9** involves the cycloaddition of hydroxyl group (from enolic form of 1,3-diketone) to the cyano moiety to form the desired product **4a** (Scheme 4, path A and path B). Moreover, the formation of quaternary nitrogen containing intermediate (**11**) is not possible in path A (step I) due to highly withdrawing nature of malononitrile.

4. Conclusion

In conclusion, we have successfully developed a novel and more environmentally friendly procedure for the preparation of spirochromene derivatives of potential synthetic and pharmacological interest. The use of gold(III) chloride ($HAuCl_4{\cdot}3H_2O$) in PEG 400 as a non-toxic, and low loading of catalytic system with little reaction times and excellent product yields are the main advantages of this methodology appears to have a broad scope to represent a straightforward procedure for the synthesis of functionalized spirochromene derivatives.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.apcata.2012.02.043.

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