

Oxalic acid dihydrate: proline as a new recyclable designer solvent: a sustainable, green avenue for the synthesis of spirooxindole

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Abstract The quest to develop an environmentally friendly, sustainable protocol for immensely bioactive spirooxindole derivatives has encouraged to explore oxalic acid dihydrate: proline low transition temperature mixture as a new designer solvent for the said synthesis at room temperature. It has been successfully applied for the three component reaction of isatin, malononitrile or ethyl cyanoacetate and 1,3–dicarbonyl compounds for the first time. Moderate to good yield of the products, shorter reaction time, energy efficiency, chromatography-free purification process, recyclability and high atom economy are the captivating feature of this protocol which will find applications in multi-component, diversity-oriented synthesis.

Graphical Abstract



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Introduction

In the development of environmentally friendly synthetic routes for drug discovery processes, multi-component reactions (MCRs) have been recognized as a powerful tool during last ten years. These reactions comprises the formation of several bonds in a single operation with remarkable advantages such as operational simplicity, reduction of tedious workup, extraction and purification processes, a high degree of atom economy and a shorter reaction time [1–4]. Furthermore, the quest to develop an ecologically sustainable protocol for immensely bioactive molecules has provoked the scientific community to adopt a "green" chemistry principle. In this esteem, to meet the fundamental scientific challenges of protecting human health and environment, significant attention has been paid to MCRs for their use in ecocompatible reactions promoting a benign solvent rather than a toxic organic solvent.

In recent years, low transition temperature mixtures (LTTMs) or deep eutectic solvents (DESs) have been found to be powerful, greener and cleaner alternatives to conventional molecular solvents. Since inception [5], they have been considered as designer solvents, as their properties are solely dependent on the natures of the hydrogen bond donor and hydrogen bond acceptors. In comparison with ionic liquids, LTTMs can be prepared with 100 % atom economy from easily accessible chemicals. They are found to be non-toxic to the environment, biodegradable and inexpensive. As LTTMs consist mainly of ionic species, they have a strong ability to dissolve CO₂ [6]. Recently, they have been successfully applied as extraction media for proteins and potential lubricants [7, 8]. Various organic transformations like acid-catalyzed reactions, base-catalyzed reactions, Suzuki coupling and Heck coupling have been reported using a DES or LTTM as a catalyst [9-13]. Additionally, numerous MCRs have been investigated using a DES or LTTM as a solvent [14, 15]. The use of LTTMs in MCRs has opened a new green avenue for synthetic organic chemistry. For this reason, MCRs in LTTMs are of having outstanding value in organic synthesis and green chemistry.

Among N-heterocycle skeletons, the indole moiety, being a "privileged scaffold", is an important active feature and structural unit of variety of natural products [16]. Furthermore, an enhancement in biological activity was observed in spirooxindole derivatives due to the presence of a sterically constrained spiro structure at the C3 position [17–20]. For example, some cytostatic alkaloids, like spirotryprostatins and pteropodines, are effective inhibitors of microtubule activity and modulators of muscarinic serotonin receptor functions (Fig. 1). Spirooxindole compounds with substituted, fused 4H chromenes at the C3 position have immense importance because of their diuretic, anticoagulant, anticancer and spasmolitic activities [21–23].

A variety of protocols [24–39] have been reported for the synthesis of spiro [4Hpyran-3,3-oxindole] derivatives. Most of the reported methods are associated with



Fig. 1 Bioactive molecules of spirooxindole

the use of either carcinogenic organic solvents, high temperatures, expensive and non-commercially available catalysts, or are lacking catalyst reusability. Therefore, there is still need for versatile, simple and environmentally friendly sustainable protocols. Considering the above subjects and our continuing efforts to develop new environmentally benign synthetic methodologies [40–44], herein, we explored the role of oxalic acid dihydrate: proline LTTM as a reaction-promoting medium for the first time for the synthesis of diverse spirooxindole derivatives at room temperature (Scheme 1).

Experimental

General

All chemicals and solvents were reagent grade. Analytical thin-layer chromatography (TLC) was performed using percolated silica gel 60-F254 plates. Infrared (IR) spectra on potassium bromide (KBr) disks were recorded on a Shimadzu IR-470 FT-IR spectrophotometer. Routine nuclear magnetic resonance (NMR) spectra were taken in DMSO d6 (dimethyl sulfoxide-d6) using a Bruker 300 and a 400-MHz spectrophotometer with tetramethylsilane (TMS) as an internal standard. Elemental analysis was done using an Euro elemental analyzer.

Typical procedure for preparation of an LTTM

The LTTM was synthesized according to the method reported in the literature [45]. The mixture of oxalic acid dihydrate (12.6 g, 100 mmol) and proline (11.5 g, 100 mmol) at a ratio of 1:1, when heated slowly at 80 °C for 1 h, resulted in the formation of a yellowish viscous liquid (i.e., LTTM) with 100 % atom economy (Scheme 2).

Typical procedure for an LTTM promoted reaction

A mixture of dimedone (0.140 g, 1 mmol), isatin (0.147 g, 1 mmol) and malononitrile (0.066 g, 1 mmol) was stirred in round bottom flask containing 5 mL of oxalic acid dihydrate: proline LTTM at room temperature for an appropriate time. After completion of the reaction, as indicated by TLC, 10 mL of water was added to the reaction mixture



Scheme 1 Synthesis of spirooxindole derivatives in an oxalic acid dihydrate: proline LTTM at room temperature



Scheme 2 Preparation of an oxalic acid dihydrate: proline LTTM

and the insoluble crude product was filtered off. The aqueous layer was evaporated under vacuum to recover the LTTM. The crude product was washed with distilled water (5 mL) and recrystallized from ethanol (10 mL).

Recyclability of an oxalic acid dihydrate: proline LTTM

Recyclability of LTTM was studied using the reaction of 1 mmol of isatin, 1 mmol of dimedone, 1 mmol of malononitrile and the oxalic acid dihydrate: proline LTTM under optimized conditions. After completion of the reaction, as indicated by TLC, 10 mL of water was added to the reaction mixture and the crude product was separated by filtration. The LTTM was recovered by evaporating the water at 80 °C under vacuum. The recycled LTTM was reused for the next batch and recycled again. No observable differences were found between the ¹H NMR spectra of fresh and recovered LTTM after four successive runs. Fresh LTTM: ¹H NMR (300 MHz, DMSO d₆): $\delta_{\rm H}$ (ppm) 1.84–1.99 (m, 3H), 2.17–2.23 (m, 1H), 3.16–3.24 (m, 2H), 4.11–4.16 (t, 1H), 7.60 (bs, 9H).

Recovered LTTM: ¹H NMR (300 MHz, DMSO d₆): $\delta_{\rm H}$ (ppm) 1.83–1.96 (m, 3H), 2.16–2.21 (m, 1H), 3.16–3.22 (m, 2H), 4.10–4.15 (t, 1H), 7.22 (bs, 9H).

Selected spectral data

2-amino-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile (4a)

Colorless Powder, M.P. 269–271 °C, IR (KBr) (Vmax/cm⁻¹): 3399, 3322, 3196, 2202, 1706, 1672. ¹H NMR (300 MHz, DMSO d₆): δ_H (ppm) 1.01–1.04 (d, 6H,

2CH₃), 2.12–2.05 (dd, 2H, CH₂), 2.50–2.56 (d, 2H, CH₂), 6.78–6.80 (d, 1H, Ar-H), 6.86–6.91 (t, 1H, Ar-H), 6.96–6.98 (t, 1H, Ar-H), 7.11–7.14 (1H, m, Ar-H), 7.17 (s, 2H, NH₂), 10.35 (s, 1H, NH). ¹³C NMR (75 MHz, DMSO d₆): d (ppm) 27.52, 28.04, 32.37, 47.32, 50.52, 58.13, 109.71, 111.29, 117.72, 122.14, 123.45, 128.61, 134.87, 142.54, 159.25, 164.58, 178.47, 195.29 Anal. Calcd for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 14.31 %. Found: C, 68.09; H, 5.08; N, 14.28 %.

2-Amino-5-oxo-7,7-dimethyl-spiro[(4H)-5,6,7,8-tetrahydrochromene-4,3'-(3'H)-1'- methyl-indol]-(1'H)-2'-one-3-carbonitrile (4e)

Colorless Powder, M.P. 255–258 °C, IR (KBr) (Vmax/cm⁻¹): 3472, 3315, 2189, 1715, 1654.¹H NMR (400 MHz, DMSO d₆): $\delta_{\rm H}$ (ppm) 0.99 (s, 3H, CH₃), 1.05 (s, 3H, CH₃), 2.14–2.02 (2H, AB system, ²J_{HH} = 16.4 Hz), 2.43 (dd, 2H, CH₂), 3.18 (s, 3H, N-CH₃), 6.38 (s, 2H, NH₂), 6.81–6.79 (1H, d, Ar), 6.95–6.94 (2H, d, Ar), 7.21–7.17 (1H, m, Ar). ¹³C NMR (100 MHz, DMSO d₆): d (ppm) 26.66, 27.63, 28.41, 32.21, 46.85, 50.56, 108.17, 111.54, 117.20, 122.77, 122.95, 128.75, 133.38, 143.70, 159.17, 164.09, 176.95, 194.95. Anal. Calcd for C₂₀H₁₉N₃O₃: C, 68.75; H, 5.48; N, 12.03 %. Found: C, 68.69; H, 5.53; N, 12.08 %.

2-Amino-5-oxo-7,7-dimethyl-spiro[(4H)-5,6,7,8-tetrahydrochromene-4,3'-(3'H)-1'-phenyl-indol]-(1'H)-2'-one-3-carbonitrile (4f)

Colorless Powder, M.P. > 300 °C, IR (KBr) (Vmax/cm⁻¹): 3595, 3376, 3294, 2192, 1682, 1602.¹H NMR (300 MHz, DMSO d₆): $\delta_{\rm H}$ (ppm) 1.03 (s, 3H, CH₃), 1.05 (s, 3H, CH₃), 2.26–2.12 (2H, AB system, ²J_{HH} = 16.2 Hz), 2.62 (s, 2H, CH₂), 6.67–6.65 (2H, d, NH₂), 7.06–7.01 (2H, t, Ar), 7.22–7.14 (2H, m, Ar), 7.40–7.34 (2H, m, Ar), 7.50–7.45 (1H, m, Ar), 7.63–7.58 (2H, m, Ar). ¹³C NMR (100 MHz, DMSO d₆): d (ppm) 27.53, 28.10, 32.50, 47.14, 50.35, 52.74, 109.04, 111.36, 117.62, 123.52, 123.87, 127.10, 128.56, 128.94, 130.12, 133.72, 135.27, 143.77, 159.32, 164.94, 176.59, 194.64. Anal. Calcd for C₂₅H₂₁N₃O₃: C, 72.98; H, 5.14; N, 10.21 %. Found: C, 73.03; H, 5.11; N, 10.18 %.

Ethyl-2-amino-5-oxo-spiro[(4H)-5,6,7,8-tetrahydrochromene-4,3'-(3'H)-5'-nitro-indol]-(1'H)-2'-one-3-carboxylate (4j)

Colorless powder, M.P. 277–279 °C, IR (KBr) (Vmax/cm⁻¹): 3290, 3187, 2959, 1732, 1686, 1644. ¹H NMR (300 MHz, DMSO d₆): $\delta_{\rm H}$ (ppm) 0.845–0.798 (t, 3H, CH₃), 0.97 (s, 3H, CH₃), 1.01 (s, 3H, CH₃), 2.11 (s, 2H, CH₂), 2.65–2.50 (2H, AB system, ²J_{HH} = 17.4 Hz), 3.77–3.72 (q, 2H, CH₂), 6.885–6.91 (d, 2H, NH₂), 7.75 (1H, s, Ar), 8.10–7.98 (m, 3H, Ar), ¹³C NMR (100 MHz, DMSO d₆): d (ppm) 26.66, 27.63, 28.41, 32.21, 46.85, 50.56, 108.17, 111.54, 117.20, 122.77, 122.95, 128.75, 133.38, 143.70, 159.17, 164.09, 176.95, 194.95. Anal. Calcd for C₂₁H₂₁N₃O₇: C, 59.01 %; H, 4.95 %; N, 9.83 %. Found: C, 58.95 %; H, 4.93 %; N, 9.88 %.

7-Amino-2,2',4-trioxo-1,1',2,2',3,4-hexahydrospiro[indole-3',5-pyrano[2,3-d] pyrimidine]-6-carbonitrile (**4***k*)

Colorless powder, M.P. 274–276 °C, IR (KBr) (Vmax/cm⁻¹): 3306, 3145, 2204, 1714, 1393.¹H NMR (300 MHz, DMSO d₆): $\delta_{\rm H}$ (ppm) 6.80–6.78 (1H, d, Ar), 6.94–6.91 (1H, dd, Ar), 7.18–7.11 (1H, m, Ar), 7.32 (s, NH₂). 10.44 (s, NH), 11.08 (s, NH), ¹³C NMR (75 MHz, DMSO d₆): $\delta_{\rm c}$ (ppm) 47.15, 58.49, 87.31, 109.73, 117.29, 122.22, 124.17, 128.86, 133.95, 142.61, 149.66, 153.79, 158.72, 161.83, 178.05. Anal. Calcd for C₁₅H₉N₅O₄: C, 55.73 %; H, 2.81 %; N, 21.66 %. Found: C, 55.69 %; H, 2.85 %; N, 21.60 %.

7-Amino-2,2',4-trioxo-1,1',2,2',3,4-hexahydrospiro[5'nitroindole-3',5-pyrano[2,3d]pyrimidine]-6-carbonitrile (**4n**)

Colorless powder, M.P. > 300 °C, IR (KBr) (Vmax/cm⁻¹): 3444, 3299, 3182, 2200, 1750, 1698 ¹H NMR (300 MHz, DMSO d₆): δ H (ppm) 7.00–7.02 (1H, d, Ar), 7.55 (2H, s, NH₂), 8.14–8.18 (1H, dd, Ar), 8.24–8.25 (1H, d, Ar), 11.18 (1H, s, NH), 11.22 (1H, s, NH), 12.40 (1H, s, NH), 13C NMR (75 MHz, DMSO d₆): δ c (ppm) 56.70, 86.28, 109.88, 117.19, 120.45, 126.35, 135.09, 143.05, 149.10, 149.73, 154.36, 159.12, 162.11, 178.83. Anal. Calcd for C₁₅H₈N₆O₆: C, 48.92 %; H, 2.19 %; N, 22.82 %. Found: C, 48.85 %; H, 2.24 %; N, 22.80 %.

7-Amino-2,2',4-trioxo-1,1',2,2',3,4-hexahydrospiro[5'iodoindole-3',5-pyrano[2,3-d] pyrimidine]-6-carbonitrile (**40**)

Reddish powder, M.P. 276–278 °C (dec.), IR (KBr) (Vmax/cm⁻¹): 3291, 3146, 2198, 1689, 1643 ¹H NMR (300 MHz, DMSO d₆): δ H (ppm) 6.62–6.65 (1H, d, Ar), 7.46–7.51 (2H, m, Ar), 7.55 (2H, s, NH₂), 10.62 (1H, s, NH), 11.17 (1H, s, NH), 12.33 (1H, s, NH), ¹³C NMR (75 MHz, DMSO d₆): δ c (ppm) 47.09, 57.47, 85.22, 86.69, 112.29, 117.34, 132.60, 136.55, 137.48, 142.30, 149.70, 154.01, 158.84, 161.99, 177.72. Anal. Calcd for C₁₅H₈IN₅O₄: C, 40.11 %; H, 1.80 %; N, 15.59 %. Found: C, 40.05 %; H, 1.78 %; N, 15.66 %.

7'-Amino-1',3'-dimethyl-2,2',4'-trioxo-1,1',2,2',3',4'-hexahydrospiro [5'bromoindole-3,5'-pyrano[2,3-d]pyrimidine]-6'-carbonitrile (**4r**)

Colorless powder, M.P. > 300 °C, IR (KBr) (Vmax/cm⁻¹): 3375, 3305, 3202, 2197, 1683, 1653. ¹H NMR (300 MHz, DMSO d₆): $\delta_{\rm H}$ (ppm) 3.05 (3H, s, N-CH₃), 3.38 (3H, s, N-CH₃), 6.79–6.77 (1H, d, Ar), 7.39–7.36 (2H, d, J = 10.8 Hz), 7.61–7.52 (2H, bs, NH₂), 10.61 (s, NH). ¹³C NMR (75 MHz, DMSO d₆): $\delta_{\rm c}$ (ppm) 28.10, 29.80, 48.08, 57.67, 87.04, 117.63, 113.94, 117.09, 127.19, 131.64, 136.54, 141.98, 150.14, 152.72, 158.65, 159.98, 177.63. Anal. Calcd for C₁₇H₁₂N₅O₄: C, 47.46 %; H, 2.81 %; N, 16.28 %. Found: C, 47.50 %; H, 2.78 %; N, 16.22 %.

7'-Amino-1',3'-dimethyl-2,2',4'-trioxo-1,1',2,2',3',4'-hexahydrospiro[5'iodoindole-3,5'-pyrano[2,3-d]pyrimidine]-6'-carbonitrile (**4s**)

Colorless powder, M.P. = 265–267 °C (dec.), IR (KBr) (Vmax/cm⁻¹): 3369, 3301, 2196, 1705, 1679 ¹H NMR (300 MHz, DMSO d₆): $\delta_{\rm H}$ (ppm) 3.37 (6H, s, 2 N-CH₃), 6.64–6.67 (1H, d, Ar), 7.49–7.51 (2H, d, Ar), 7.61 (2H, s, NH₂), 10.64 (1H, s, NH). ¹³C NMR (75 MHz, DMSO d₆): $\delta_{\rm c}$ (ppm) 28.13, 29.81, 47.83, 57.43, 85.22, 86.94, 112.34, 117.20, 132.54, 136.70, 137.53, 142.28, 150.16, 152.72, 158.65, 160.02, 177.69. Anal. Calcd for C₁₇H₁₂IN₅O₄: C, 42.79 %; H, 2.53 %; N, 14.68 %. Found: C, 42.84 %; H, 2.50 %; N, 14.71 %.

7'-Amino-5-chloro-2,4'-dioxo-2'-thioxo-1',2',3',4'-tetrahydrospiro[indoline-3,5'pyrano [2,3-d] pyrimidine]-6'-carbonitrile (**4u**)

Colorless powder, M.P. 224–226 °C, IR (KBr) (Vmax/cm⁻¹): 3359, 3282, 3148, 2197, 1686, 1575. ¹H NMR (300 MHz, DMSO d₆): $\delta_{\rm H}$ (ppm) 6.83–6.80 (1H, d, Ar), 7.21–7.24 (1H, d, Ar), 7.40 (1H, s, Ar), 7.53 (2H, s, NH₂), 10.71 (1H, s, NH), 12.55 (1H, s, NH). ¹³C NMR (75 MHz, DMSO d₆): $\delta_{\rm c}$ (ppm) 57.32, 91.48, 111.13, 117.14, 124.85, 126.37, 128.93, 135.47, 141.53, 153.46, 158.69, 159.68, 174.47, 177.51. Anal. Calcd for C₁₅H₁₁N₅O₃SCI: C, 48.20 %; H, 2.16 %; N, 18.74 %; S, 8.58 %. Found: C, 48.25 %; H, 2.18 %; N, 18.70 %; S, 8.55 %.

7'-Amino-1-methyl-2,4'-dioxo-2'-thioxo-1',2',3',4'-tetrahydrospiro[indoline-3,5'pyrano[2,3-d]pyrimidine]-6'-carbonitrile (**4x**)

Colorless powder, M.P. > 300 °C, IR (KBr) (Vmax/cm⁻¹): 3344, 3175, 2848, 2206, 1682, 1647, 1593. ¹H NMR (300 MHz, DMSO d₆): $\delta_{\rm H}$ (ppm) 3.14 (3H, s, N-CH₃), 6.98–7.03 (2H, t, Ar), 7.24–7.28 (2H, t, Ar J = 10.8 Hz), 7.315 (1H, s, NH), 7.46 (2H, s, NH₂), 12.50 (1H, s, NH). ¹³C NMR (75 MHz, DMSO d₆): $\delta_{\rm c}$ (ppm) 26.94, 56.65, 91.96, 108.55, 110.96, 123.11, 125.95, 129.31, 132.83, 138.16, 144.02, 158.70, 160.01, 161.27, 174.41, 176.16. Anal. Calcd for C₁₆H₁₁N₅O₃S: C, 54.38 %; H, 3.14 %; N, 19.82 %; S, 9.07 %. Found: C, 54.32 %; H, 3.11 %; N, 19.87 %; S, 9.11 %.

7'-Amino-5-iodo-2,4'-dioxo-2'-thioxo-1',2',3',4'-tetrahydrospiro[indoline-3,5'pyrano[2,3-d] pyrimidine]-6'-carbonitrile (**4y**)

Colorless powder, M.P. = 250–253 °C (dec.), IR (KBr) (Vmax/cm⁻¹): 3275, 3156, 2194, 1681, 1615, 1570. ¹H NMR (300 MHz, DMSO d₆): $\delta_{\rm H}$ (ppm) 6.63–6.66 (1H, d, Ar), 7.49–7.52 (3H, m, 2Ar and 1NH), 7.63 (2H, s, NH₂), 10.67 (1H, s, NH), 12.54 (1H, s, NH). ¹³C NMR (75 MHz, DMSO d₆): $\delta_{\rm c}$ (ppm) 46.95, 57.23, 85.33, 112.31, 132.89, 135.96, 137.65, 142.33, 153.37, 158.69, 159.71, 174.32, 177.27. Anal. Calcd for C₁₅H₈IN₅O₃S: C, 38.73 %; H, 1.73 %; N, 15.05 %; S, 6.89 %. Found: C, 38.78 %; H, 1.69 %; N, 15.01 %; S, 6.95 %.

Result and discussion

In view of the important applications of bioactive spirooxindole derivatives, our current focus has been targeted on the facile synthesis of these moieties at room temperature. As a part of the endeavor, the reaction of isatin (1 mmol), malononitrile (1 mmol) and dimedone (1 mmol) was selected as a template reaction. The model reaction was carried out in different DESs or LTTMs at room temperature (Table 1, entries 1–8). In the absence of solvent, the reaction afforded traces of the product (Table 1, entry 1). A comparison of efficiency of the LTTM revealed that oxalic acid dihydrate: proline LTTM (Table 1, entry 6) as a superior solvent.

With these interesting results in our hand, we then explored the scope of the present method with various isatins, malononitrile or ethyl cyanoacetate, and various 1,3-dicarbonyl compounds; results are depicted in Table 2. As shown in Table 2, it was observed that this protocol works well with a wide array of substrates. A series of 5-substituted and N-substituted isatins and various dicarbonyl compounds were used in the reaction. Although the reaction of isatin and dimedone with malononitrile or ethyl cyanoacetate proceeded smoothly, the reaction time with ethyl cyanoacetate was longer than that with malononitrile (Table 2, entry 7–10), which is possibly due to lower reactivity of ethyl cyanoacetate.



Table 1	Screening	of	various	LTTMs	and	optimum	conditions	for	the	synthesis	of	spirooxindolea
derivative	es in differe	ent	conditio	ns								

d (%) ⁶
ces

^a Reaction condition: all three reactants in equimolar ratio, solvent, RT

^b Isolated yield



Table 2 Synthesis of spirooxindole derivatives a $(\mathbf{5a}-\mathbf{5j})$ with varying reactants over LTTMs at room temperature

Entry	Isatin	Alkyl malonate	1,3-dicarbonyl compound	Product	Time (min)	Yield ^b (%)	Atom economy ^d
1	1a	2a	3a	4 a	30	94	89.13
2	1b	2a	3a	4b	35	89	85.09
3	1c	2a	3a	4c	35	89	85.29
4	1d	2a	3a	4d	40	87	83.06
5	1e	2a	3a	4 e	32	91	86.53
6	1f	2a	3a	4f	30	90	86.22
7	1 a	2b	3a	4g	55	86	82.13
8	1b	2b	3a	4h	58	84	80.52
9	1c	2b	3a	4 i	62	85	81.80
10	1d	2b	3a	4j	65	83	79.64
11	1 a	2a	3b	4k	55	90	85.25
12	1b	2a	3b	41	56	87	82.23
13	1c	2a	3b	4m	60	88	84.22
14	1d	2a	3b	4n	70	82 ^c	78.17
15	1g	2a	3b	40	65	89 ^c	85.56
16	1 a	2a	3c	4p	60	86	81.80
17	1b	2a	3c	4 q	60	85	81.21
18	1c	2a	3c	4r	59	86	82.54
19	1g	2a	3c	4 s	55	88 ^c	84.80
20	1a	2a	3d	4t	60	84	79.76
21	1b	2a	3d	4u	62	82	78.22
22	1c	2a	3d	4 v	65	83	79.61
23	1d	2a	3d	4 w	70	78	74.50
24	1e	2a	3d	4x	60	80 ^c	76.11

Entry	Isatin	Alkyl malonate	1,3-dicarbonyl compound	Product	Time (min)	Yield ^b (%)	Atom economy ^d
25	1g	2a	3d	4y	60	81 ^c	77.98

Table 2 continued

^a Reaction condition: All three reactants in equimolar ratio, oxalic acid dihydrate: proline RT

^b Isolated yield

^c Repared for first time

 $^{\rm d}$ Atom economy = molecular weight of desired product/sum of molecular weight of all reactants \times 100 %



Scheme 3 Plausible mechanism for spirooxindole synthesis showing electrophilic activation of isatin through hydrogen bonding

The selectivity of an LTTM is due to the hydrogen bonding nature of the LTTM enhancing the electrophilicity of carbonyl groups which substantially promotes the reaction. Though the role of an LTTM is yet to be confirmed, we explore the probable mechanism of LTTM promoted one-pot synthesis of spirooxindole involving initial formation of a Knoevenagel adduct with subsequent Michael addition and cyclization via hydrogen bonding, as depicted in Scheme 3.

Next, recyclability is an essential aspect in view of green chemistry. The possibility of recyclability of LTTM was examined by using the reaction of isatin, malononitrile and dimedone as model substrates under optimized conditions. After

Run	Fresh	Ι	II	III	IV
LTTM	94	92	90	87	80











Fig. 3 Percent atom economy of product (4a-4v)

completion of the reaction, water (10 mL) was added to the reaction mixture and crude product was separated by filtration. Finally, the LTTM was recovered by evaporating the water at 80 °C under vacuum and was reused for the next batch and recycled again. It was found that the LTTM could be used for four successive runs without a noticeable decrease in its activity (Table 3, Fig. 2). In addition, a group-assistant-purification (GAP) chemistry process [46] was used for purification of crude product. All the products were obtained as pure by just washing the solid crude products with ethanol, avoiding traditional chromatography and recrystallization purification processes. The products were characterized by spectroscopic analysis (¹HNMR, ¹³CNMR, CHNS) and confirmed by comparison of the spectroscopic data

Entry	Reaction condition	Time (min)	Yield (%)	Reference
1	Nano-MgO/H ₂ O/80 °C	120	93	[26]
2	L-proline/H ₂ O/80 °C	15	92	[30]
3	SBNPTT/H ₂ O/reflux	20	97	[31]
4	PEG-400/50 °C	60	92	[35]
5	TEBA/H ₂ O/60 °C	180	90	[36]
6	InCl ₃ /MW or reflux	3 or 90	93 or 75	[37]
7	Magnetic catalyst/H ₂ O/30 °C	20	75	[38]
8	Oxalic acid dihydrate: proline LTTM/RT	30	94	Present work

 Table 4
 Comparison of efficiency of oxalic acid dihydrate: proline with several catalysts in the literature for the synthesis of spirooxindole (4a)

and melting points with authentic literature data. Moreover, the sustainability and greenness of the protocol was proven by its atom economy. Higher atom economy values were found to support the greenness of the methodology (Fig. 3).

The proficiency of this protocol has been compared with some of the previously reported methods and results are compiled in Table 4. It is clear from Table 4 that oxalic acid dihydrate: proline is an environmentally benign and efficient reaction promoting medium for the synthesis of a series of spirooxindole derivatives.

Conclusion

An efficient and simple method for the synthesis of spirooxindole derivatives was developed via one-pot, three component reaction of isatin, malononitrile or ethyl cyanoacetate and 1,3-dicarbonyl compounds. Most of the reported methods involve an expensive catalyst which requires tedious preparation, involve harmful organic solvents and lack recyclability. The present method offers several advantages, such as simple LTTM preparation with 100 % atom efficiency, good product yield, shorter reaction times, LTTM recyclability enabling avoidance of hazardous organic solvents, and a GAP chemistry procedure. Owing to the advantages of this protocol over other methods, we expect that it will find extensive application in combinatorial chemistry as well as multi-component green synthesis as it involves green, three component, LTTM prompted reaction that afford different types of spirooxindole fused heterocycles.

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References

- 1. J. Zhu, H. Bienayme, Multi-component Reactions (Wiley-VCH, Weinheim Germany, 2005)
- 2. R.A. Sheldon, Pure Appl. Chem. 72, 1233-1246 (2000)
- 3. B.M. Trost, Science 254, 1471-1477 (1991)

- 4. M.S. Singh, S. Chowdhury, RSC Adv. 2, 4547-4592 (2012)
- 5. A.P. Abbott, G. Capper, D.L. Davies, R.K. Rasheed, V. Tambyrajah, Chem. Commun. 70-71 (2003)
- 6. X. Li, M. Hou, B. Han, X. Wang, L. Zou, J. Chem. Eng. Data 53, 548-550 (2008)
- 7. Q. Zeng, Y. Wang, Y. Huang, X. Ding, J. Chen, K. Xu, Analyst 139, 2565 (2014)
- 8. A.P. Abbott, E.I. Ahmed, R.C. Harris, K.S. Ryder, Green Chem. 16, 4156 (2014)
- 9. N. Azizi, S. Dezfooli, M.M. Hashemi, J. Mol. Liq. 194, 62-67 (2014)
- D.R. Chandam, A.G. Mulik, P.P. Patil, S.D. Jagdale, D.R. Patil, S.A. Sankpal, M.B. Deshmukh, J. Mol. Liq. 207, 14–20 (2015)
- 11. S.B. Phadtare, G.S. Shankarling, Green Chem. 12, 458-462 (2010)
- 12. G. Imperato, S. Hoger, D. Lenoir, B. Konig, Green Chem. 8, 1051-1055 (2006)
- 13. F. Ilgen, B. Konig, Green Chem. 11, 848-854 (2009)
- 14. S. Gore, S. Baskaran, B. Konig, Green Chem. 13, 1009–1013 (2011)
- 15. Z.-H. Zhang, X.-N. Zhang, L.-P. Mo, Y.-X. Li, F.P. Ma, Green Chem. 14, 1502–1506 (2012)
- 16. W.J. Houlihan, W.A. Remers, R.K. Brown, Indoles, Part I (Wiley, New York, 1992)
- T.H. Kang, K. Matsumoto, Y. Murakami, H. Takayama, M. Kitajima, N. Aimi, H. Watanabe, Eur. J. Pharmacol. 444, 39–45 (2002)
- 18. J. Ma, S.M. Hecht, Chem. Commun. 1190-1191 (2004)
- 19. M.M. Khafagy, A.H. El-Wahas, F.A. Eid, A.M. El, Farmaco 57, 715-722 (2002)
- 20. J. Skommer, D. Wlodkowic, M.M. Matto, P. Eray, J. Leuk. Res. 30, 322-331 (2006)
- 21. W.P. Smith, L.S. Sollis, D.P. Howes, C.P. Cherry, D.I. Starkey, N.K. Cobley, J. Med. Chem. 41, 787–797 (1998)
- 22. L. Bonsignore, G. Loy, D. Secci, A. Calignano, Eur. J. Med. Chem. 28, 517 (1993)
- 23. L. Andreani, E. Lapi, Bol. Chim. Farm. 99, 583 (1960)
- 24. M. Seyed, T. Mahmood, F. Maryam, C. R. Chimie 17, 1160-1164 (2014)
- 25. D.S. Raghuvanshi, K.N. Singh, J. Heterocycl. Chem. 47, 1323 (2010)
- 26. B. Karmakar, A. Nayak, J. Banerji, Tetrahedron Lett. 53, 5004–5007 (2012)
- 27. S.P. Satasia, P.N. Kalaria, J.R. Avalani, D.K. Raval, Tetrahedron 70, 5763-5767 (2014)
- 28. Y. Li, H. Chen, C. Shi, D. Shi, S. Ji, J. Comb. Chem. 12, 231 (2010)
- 29. K. Niknam, P. Abolpour, Monatsh. Chem. 4, 683-690 (2015)
- 30. G.S. Hari, Y.R. Lee, Synthesis 3, 453 (2010)
- 31. S.J. Chai, Y.F. Lai, J.C. Zu, H. Zheng, Q. Zhu, P.F. Zhang, Adv. Synth. Catal. 353, 371 (2011)
- 32. R.M. Kurosh, Y.M. Leila, Tetrahedron 67, 5693 (2011)
- 33. M. Dabiri, M. Bahramnejad, M. Baghbanzadeh, Tetrahedron 65, 9443-9447 (2009)
- 34. S. Gao, C.H. Tsai, C. Tseng, C. Yao, Tetrahedron 64, 9143 (2008)
- 35. H.M. Meshram, D.A. Kumar, B.R.V. Prasad, P.V. Goud, Helv. Chim. Acta 93, 648 (2010)
- 36. S.L. Zhu, S.J. Ji, Y. Zhang, Tetrahedron 63, 9365 (2007)
- 37. G. Shanthi, G. Subbulakshmi, P.T. Perumal, Tetrahedron 63, 2057 (2007)
- L. Jalili-Baleh, M. Narges, K. Mehdi, L. Mamani, A. Foroumadi, A. Shafiee, Helv. Chim. Acta 96, 1601 (2013)
- 39. Y.L. Gu, Green Chem. 14, 2091-2128 (2012)
- 40. D.R. Chandam, A.G. Mulik, P.P. Patil, S.D. Jagdale, D.R. Patil, M.B. Deshmukh, Res. Chem. Intermed. 41, 761–771 (2015)
- 41. A.G. Mulik, D.R. Chandam, P.P. Patil, S.D. Jagdale, D.R. Patil, M.B. Deshmukh, J. Mol. Liq. **179**, 104–109 (2013)
- 42. D.R. Patil, D.R. Chandam, A.G. Mulik, P.P. Patil, S.D. Jagdale, M.B. Deshmukh, Res. Chem. Intermed (2014). doi:10.1007/s11164-014-1782-7
- D.R. Patil, D.R. Chandam, A.G. Mulik, P.P. Patil, S.D. Jagdale, R. Kant, V. Gupta, M.B. Deshmukh, Catal. Lett. 144, 949–958 (2014)
- 44. A.A. Patravale, A.H. Gore, D.R. Patil, G.B. Kolekar, M.B. Deshmukh, P.V. Anbhule, Ind. Eng. Chem. Res. 53, 16568–16578 (2014)
- 45. M. Francisco, M.C. Kroon, Angew. Chem. Int. Ed. 52, 3074–3085 (2013)
- 46. P. Kaur, S. Pindi, W. Wever, T. Rajale, G. Li, Chem. Commun. 46, 4330-4332 (2010)