



REGULAR ARTICLE

The one-pot four-component eco-friendly synthesis of spirooxindoles in deep eutectic solvent

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MS received 25 July 2019; revised 1 October 2019; accepted 4 October 2019

Abstract. An efficient and facile synthesis of spirooxindole derivatives bearing pyrano[2,3-*c*]pyrazole moiety has been achieved using deep eutectic solvent (DES) promoting a four-component reaction. The protocol avoids the use of costly and toxic catalysts and organic solvents which encounters many side effects on the environment and human beings. The simplicity and versatility of this eco-friendly green method is described.

Keywords. Deep eutectic solvent; spirooxindoles; eco-friendly; hydrazine; isatin.

1. Introduction

The chemistry of indole is one of the most exciting and challenging field for investigative works of synthetic and medicinal chemists.¹ The significant application of indole derivatives in pharmaceuticals, agrochemicals and organic electronics continues to inspire the tireless efforts of synthetic organic chemists since time immemorial.² Among the indole derivatives, the spirooxindole derivatives also occupy a special place in organic and medicinal chemistry since they exhibit diverse biological and pharmacological activities.^{3,4} Representative examples of spirooxindole, spirotryprostatin A and B, isolated from the fermentation broth of *Aspergillus fumigatus*, were found to completely inhibit the G2/M progression of cellular division in mammalian tsFT210 cells (Figure 1).⁵ In the field of synthetic therapeutic agents, compounds containing the spirooxindole core, SOID-8, analogue of spirotryprostatin B, have been described as having anticancer activity against Melanoma cells,⁶ while NITD609 is a promising novel drug for the treatment of malaria (Figure 1).^{7,8} In light of their unique structural features along with the important biological

activities, spirooxindole derivatives have drawn considerable attention to synthetic chemists for their preparation.⁹ In spite of several reports on the synthesis of spirooxindole derivatives involving various application of catalysts and promoters such as β -cyclodextrin,¹⁰ piperidine,^{11,12} *L*-proline,¹³ ZrO_2 ,¹⁴ 4-DMAP,¹⁵ ionic liquid,^{16,17} CeO_2 -NPs,¹⁸ dodecylbenzenesulphonic acid,¹⁹ Fe_3O_4 nanoparticles,²⁰ organometallic nanomagnetic,²¹ SBA-Pr- SO_3H ,²² nanoclay,²³ and $Fe_3O_4@SiO_2-SO_3H$ and $Fe_3O_4@SiO_2-NH$ ^{2,24} the demand for effective and environmentally benign synthetic approaches to spirooxindole derivatives bearing pyrano[2,3-*c*]pyrazoles remains an immense interest to organic chemists.

The challenges in resources and environmental sustainability require more efficient and benign scientific technologies for chemical processes and the manufacture of products. Deep eutectic solvents (DESs) addresses such challenges by bridging as environmentally friendly and acceptable, due to their low vapor pressure, non-toxic properties, reusability, and cheapness.^{25,26} DESs are prepared as mixtures of two or more components, forming a eutectic with a melting point much lower than the starting

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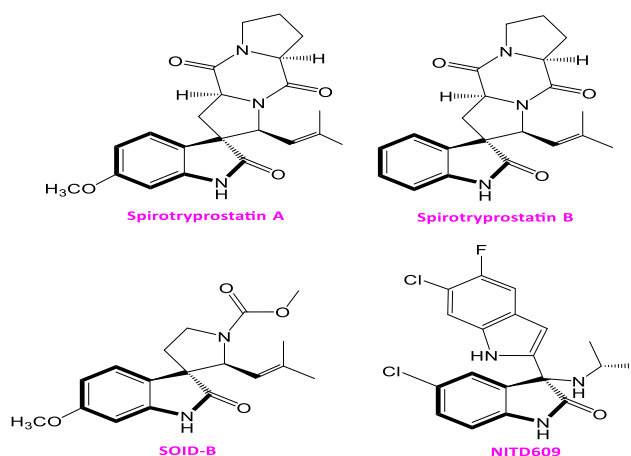


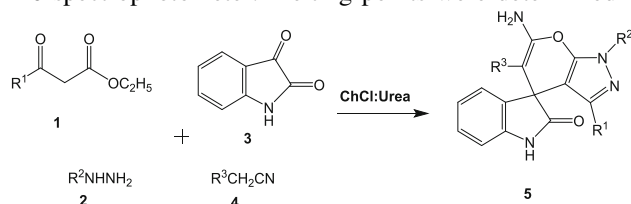
Figure 1. Examples of natural products and synthetic therapeutic agents containing a spirooxindole core.

components. The components of DES are biodegradable and approximately ten-fold less expensive as compared to ionic liquids. Among the DESs, choline chloride: urea-based DES has been successfully used for carboline synthesis,²⁷ coumarin synthesis,²⁸ lipase-catalyzed transesterifications,²⁹ syntheses of dihydropyrimidin-2(1H)-ones,³⁰ etc.

Thus, in continuation of our work in indole chemistry,^{31–34} we are reporting an eco-friendly one-pot synthesis of spiro[indoline-3,4'-pyrano[2,3-*c*]pyrazole derivatives using DES-catalyzed four-component reaction of β -ketoesters, phenylhydrazines, malononitrile, and isatins (Scheme 1).

2. Experimental

All of the commercially available reagents and solvents were used without further purification. The chromatographic purification of compounds was carried out on silica gel (60–200 μm). TLC analysis was performed on pre-coated (0.25 mm) glass supported silica gel plates (Kieselgel 60). All ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker-400 and 100.62 MHz, respectively using CDCl_3 as the solvent with tetramethylsilane (TMS) as an internal standard. The following abbreviations are used to describe peak patterns: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. All coupling constants (J) are given in Hz. FTIR spectra were recorded in FT/IR 410 spectrophotometer. Melting points were determined in



Scheme 1. Synthesis of spirooxindoles in DES.

open capillary tubes and are uncorrected using Buchi melting point apparatus.

2.1 Preparation of deep eutectic solvent

According to literature,²⁶ 50 mmol choline chloride and the required amount of urea were mixed as shown in Table 1, in a round flask and were heated to obtain a clear liquid as DES called urea:ChCl (Figure 2).

The FT-IR spectra of freshly prepared urea:ChCl (2:1) and the 1st and 2nd recycled urea:ChCl (2:1) were recorded in FT-IR Spectrophotometer (Perkin Elmer Spectrum-2). Figure 3 depicts the spectral analysis of bond frequencies for urea:ChCl which indicates a close resemblance with the corresponding peaks from the reported literature.³⁵ From the IR spectra of freshly prepared urea:ChCl Figure 3, the broad absorption bands at 3423 cm^{-1} and 3322 cm^{-1} indicates the stretching mode of $-\text{NH}_2$ ($\nu_{\text{as}} \text{NH}_2$ and $\nu_{\text{s}} \text{NH}_2$). The existence of broad bands results from the formation of hydrogen bonding between urea and choline chloride. The hydrogen bonds formed may be represented as $\text{N-H}\cdots\text{N-H}$, $\text{N-H}\cdots\text{O-H}$, $\text{H-O}\cdots\text{HO}$ and $\text{O-H}\cdots\text{N-H}$. Further, the presence of bending mode of $-\text{NH}_2$ ($\delta_{\text{s}} \text{NH}_2$ and $\delta_{\text{as}} \text{NH}_2$) is attributed by the values at 1653 cm^{-1} and 1615 cm^{-1} . In addition, the bands at 1428 cm^{-1} and 949 cm^{-1} correspond to ρCH_3 and νCCO of ChCl, respectively. These clearly reveal that the structure of Ch^+ in ChCl is not destroyed in Urea:ChCl system. On comparing the spectra of freshly prepared and recycled, similar peaks are obtained which support that the recycled urea:ChCl can be further used for various reaction system.

2.2 General procedure for the synthesis of spirooxindole derivatives (5a–5r)

A mixture of β -ketoester **1** (1 mmol), phenylhydrazine **2** (1 mmol), isatin **3** (1 mmol), active methylene compounds **4** (1 mmol), and Urea:ChCl (10 mol%, 5 mL) was stirred at room temperature for 10 min or until the completion of reaction as indicated by TLC. After completion of the reaction, the reaction mixture was poured to 25 mL water and extracted with 50 mL of ethyl acetate. The separated organic layer was dried over anhydrous Na_2SO_4 , filtered and evaporated. Column chromatography was performed using 10% EtOAc in hexane as eluent to get the desired products, which were further recrystallized from warm ethanol to get pure compounds.

2.3 Spectral data of synthesized compounds

2.3a Entry-5a: 6'-Amino-3'-methyl-2-oxo-1'-phenyl-1'H-spiro[indoline-3,4'-pyrano[2,3-*c*]pyrazole]-5'-carbonitrile: White solid (85%); M.p. $234\text{--}236\text{ }^\circ\text{C}$ (exp), $238\text{--}240\text{ }^\circ\text{C}$ (rep);¹² IR (KBr, ν , cm^{-1}): 3369, 3154, 3031,

Table 1. Optimization of reaction condition^a.

Entry	Solvent	Time (min)	Temp (°C)	Yield ^b (%)
1	Urea:ChCl (2:1)	5	r.t.	85
2	Urea:ChCl (2:1)	10	r.t.	90
3	Urea:ChCl (2:1)	30	r.t.	90
4	Urea:ChCl (2:1)	10	50	90
5	Urea:ChCl (2:1)	10	60	90
6	Urea:ChCl (2:1)	30	4	80
7	Malonic acid:ChCl: (1:1)	10	r.t.	80
8	Oxalic acid:ChCl (2:1)	30	r.t.	70
9	PTSA:ChCl (2:1)	30	r.t.	60
10	Glycerin:ChCl (2:1)	30	r.t.	75
11	N/A	360	r.t.	No reaction

^aReaction condition: methylacetoacetate **1a** (1 mmol), phenyl hydrazine **2a** (1 mmol), isatin **3a** (1 mmol) and malonitrile **4a** (1 mmol), DESs (5 mL).

^bIsolated yield of products.

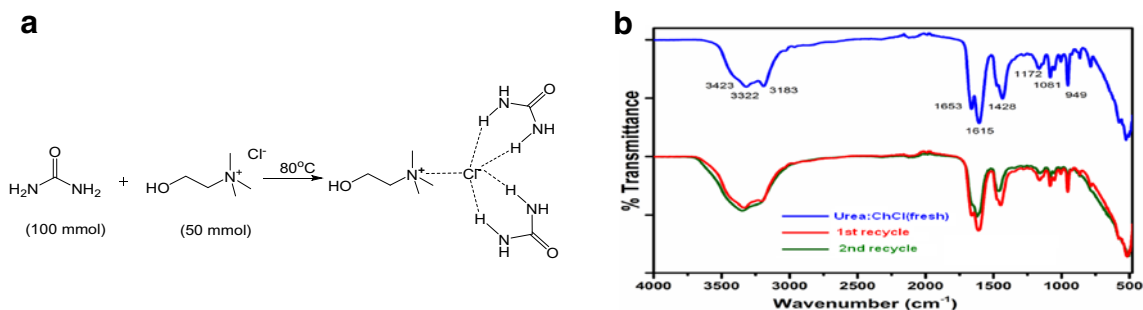


Figure 2. (a) Deep eutectic solvent preparation from urea and ChCl in 2:1 ratio. (b) The FT-IR spectra of freshly prepared Urea:ChCl (2:1) and the 1st recycled and 2nd recycled Urea:ChCl (2:1).

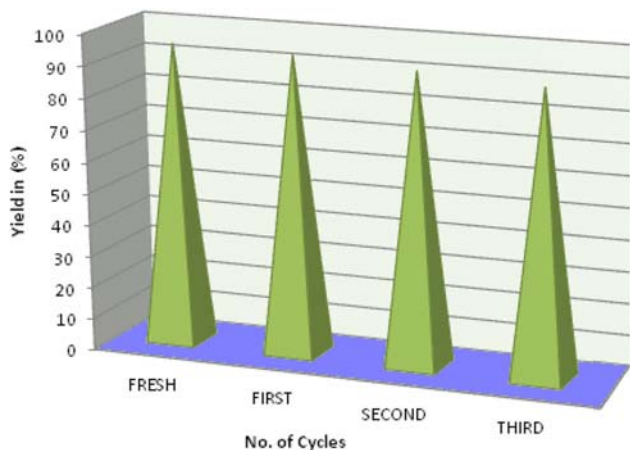


Figure 3. Recycling studies of deep eutectic mixture of (urea:ChCl) in reaction of ethylacetoacetate **1a**, phenyl hydrazine **2a**, isatin **3a** and malonitrile **4a**.

$J = 7.2$ Hz, 1H), 7.38–7.35 (m, 2H), 7.34–7.21 (m, 4H), 7.12–7.04 (m, 2H), 6.92 (d, $J = 8.0$ Hz, 1H), 1.67 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 13.6, 48.8, 58.9, 110.1, 114.4, 119.1, 122.6, 124.8, 126.8, 127.6, 128.0, 129.4, 138.0, 142.5, 147.1, 153.1, 168.0, 177.6; EIMS (m/z): 369 (M^+); Anal. calcd for C₂₁H₁₅N₅O₂: C, 68.28; H, 4.09; N, 18.96; O, 8.66. Found: C, 68.24; H, 4.12; N, 18.91; O, 8.63.

2.3b Entry-5b: 6'-Amino-2-oxo-1'-phenyl-3'-propyl-1'H-spiro[indoline-3,4'-pyrano[2,3-c]pyrazole]-5'-carbonitrile: White solid (83%); M.p. 213–215 °C (exp), 211–213 °C (rep);¹² IR (KBr, ν , cm⁻¹): 3520, 3354, 3305, 3179, 3069, 3031, 2952, 2921, 2862, 2201, 1705, 1653, 1595, 1522, 1468, 1394, 1293, 1213, 1131, 1071, 1026, 929, 741, 681; ¹H NMR (400 MHz, CDCl₃): δ 10.70 (s, 1H), 8.35 (s, 1H), 7.65 (d, $J = 7.6$ Hz, 1H), 7.39–7.35 (m, 2H), 7.34–7.21 (m, 4H), 7.12–7.04 (m, 2H), 6.93 (d, $J = 7.6$ Hz, 1H), 2.64 (t, $J = 6.8$ Hz, 2H), 1.72–1.67 (m, 2H), 1.00 (t, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 13.8, 22.9, 32.0, 48.7, 58.7, 110.3, 114.4, 119.1, 122.0, 122.6, 123.3, 126.8, 128.0, 129.4, 138.1, 142.4, 154.9, 155.4, 168.1, 176.7; EIMS (m/z): 397 (M^+); Anal. calcd for C₂₃H₁₉N₅O₂: C, 69.51; H, 4.82; N, 17.62; O, 8.05. Found: C, 69.51; H, 4.76; N, 17.65; O, 8.01.

2927, 2808, 2093, 1701, 1639, 1611, 1503, 1477, 1401, 1340, 1301, 1217, 1045, 926, 863, 821, 768, 624; ¹H NMR (400 MHz, CDCl₃): δ 10.71 (s, 1H), 7.89 (s, 1H), 7.66 (d,

2.3c Entry-5c: *6'-Amino-3'-isopropyl-2-oxo-1'-phenyl-1'H-spiro[indoline-3,4'-pyrano[2,3-c]pyrazole]-5'-carbonitrile*: White solid (84%); M.p. 200–212 °C (exp), 198–200 °C (rep);¹² IR (KBr, ν , cm^{-1}): 3360, 3318, 3185, 2921, 2893, 2865, 2210, 1708, 1661, 1586, 1518, 1406, 1301, 1217, 1131, 1075, 931, 742, 610; ¹H NMR (400 MHz, CDCl_3): δ 10.72 (s, 1H), 8.55 (s, 1H), 7.63 (d, $J = 6.8$ Hz, 1H), 7.38–7.34 (m, 3H), 7.33–7.20 (m, 3H), 7.09–7.03 (m, 2H), 6.92 (d, $J = 8.0$ Hz, 1H), 3.31–3.23 (m, 1H), 1.31 (d, $J = 7.2$ Hz, 6H); ¹³C NMR (100 MHz, CDCl_3): δ 21.7, 32.3, 48.8, 58.6, 110.2, 114.3, 119.0, 122.0, 122.5, 123.2, 127.3, 128.0, 129.3, 138.2, 142.5, 154.6, 156.3, 168.1, 177.2; EIMS (m/z): 397 (M^+); Anal. calcd for $\text{C}_{23}\text{H}_{19}\text{N}_5\text{O}_2$: C, 69.51; H, 4.82; N, 17.62; O, 8.05. Found: C, 69.50; H, 4.78; N, 17.66; O, 8.02.

2.3d Entry-5d: *6'-Amino-5-chloro-3'-methyl-2-oxo-1'-phenyl-1'H-spiro[indoline-3,4'-pyrano[2,3-c]pyrazole]-5'-carbonitrile*: Light red solid (82%); M.p. 302–304 °C (exp); IR (KBr, ν , cm^{-1}): 3352, 3319, 3195, 2201, 1723, 1658, 1591, 1525, 1448, 1395, 1223, 1128, 1074, 965, 908, 757; ¹H NMR (400 MHz, CDCl_3): δ 10.72 (s, 1H), 7.87 (s, 1H), 7.61 (d, $J = 7.2$ Hz, 1H), 7.36–7.32 (m, 2H), 7.32–7.20 (m, 3H), 7.11–7.05 (m, 2H), 6.91 (d, $J = 8.0$ Hz, 1H), 1.61 (s, 3H); ¹³C NMR (100 MHz, CDCl_3): δ 13.6, 48.8, 58.8, 110.1, 117.4, 119.0, 122.6, 125.8, 126.6, 127.1, 129.0, 129.3, 130.1, 138.1, 142.5, 147.1, 153.1, 168.0; EIMS (m/z): 403 (M^+); Anal. calcd for $\text{C}_{21}\text{H}_{14}\text{ClN}_5\text{O}_2$: C, 62.46; H, 3.49; Cl, 8.78; N, 17.34; O, 7.92. Found: C, 62.41; H, 3.52; Cl, 8.71; N, 17.30; O, 7.95.

2.3e Entry-5e: *Ethyl 6'-Amino-3'-isopropyl-2-oxo-1'-phenyl-1'H-spiro[indoline-3,4'-pyrano[2,3-c]pyrazole]-5'-carboxylate*: White solid (81%); M.p. 254–256 °C (exp), 258–259 °C (rep);¹² IR (KBr, ν , cm^{-1}): 3379, 3203, 3190, 3024, 2938, 1678, 1628, 1523, 1434, 1376, 1285, 1150, 1072, 955, 783, 746, 688, 627; ¹H NMR (400 MHz, CDCl_3): δ 10.71 (s, 1H), 8.13 (s, 1H), 7.66 (d, $J = 7.2$ Hz, 1H), 7.38–7.32 (m, 3H), 7.32–7.20 (m, 3H), 7.12–7.07 (m, 2H), 6.93 (d, $J = 8.0$ Hz, 1H), 4.19 (q, $J = 6.4$ Hz, 2H), 3.38 (m, 1H), 1.33 (d, $J = 8.0$ Hz, 6H), 1.04 (t, $J = 7.2$ Hz, 3H); ¹³C NMR (100 MHz, CDCl_3): δ 14.0, 22.1, 32.2, 50.0, 62.2, 81.0, 110.2, 114.4, 119.1, 122.6, 123.3, 127.3, 128.0, 129.4, 138.0, 142.4, 153.0, 154.5, 158.0, 165.9, 167.1; EIMS (m/z): 444 (M^+); Anal. calcd for $\text{C}_{25}\text{H}_{24}\text{N}_4\text{O}_4$: C, 67.55; H, 5.44; N, 12.60; O, 14.40. Found: C, 67.51; H, 5.48; N, 12.56; O, 14.44.

2.3f Entry-5f: *Ethyl 6'-Amino-2-oxo-1'-phenyl-3'-propyl-1'H-spiro[indoline-3,4'-pyrano[2,3-c]pyrazole]-5'-carboxylate*: White solid (80%); M.p. 252–254 °C (exp), 256–258 °C (rep);¹² IR (KBr, ν , cm^{-1}): 3361, 3258, 3174, 3071, 3029, 2959, 2929, 2869, 2831, 2735, 1689, 1631, 1511, 1467, 1379, 1281, 1165, 1133, 1072, 1039, 935, 785, 760, 747, 682, 617; ¹H NMR (400 MHz, CDCl_3): δ 10.71 (s, 1H), 8.52 (s, 1H), 7.64 (d, $J = 5.2$ Hz, 1H), 7.37–7.34 (m, 2H), 7.25–7.11 (m, 4H), 7.09–7.04 (m, 2H), 6.93 (d, $J = 8.0$ Hz, 1H), 4.08 (q, $J = 5.2$ Hz, 2H), 2.59 (t, $J = 7.6$ Hz, 2H),

1.75 (m, 2H), 1.23 (t, $J = 8.8$ Hz, 3H), 0.97 (t, $J = 8.0$ Hz, 3H); ¹³C NMR (100 MHz, CDCl_3): δ 12.4, 13.7, 22.6, 23.1, 49.8, 60.9, 81.4, 110.3, 114.4, 119.1, 122.6, 123.3, 126.8, 128.0, 129.4, 138.1, 142.4, 153.3, 154.9, 158.1, 167.4, 168.3; EIMS (m/z): 444 (M^+); Anal. calcd for $\text{C}_{25}\text{H}_{24}\text{N}_4\text{O}_4$: C, 67.55; H, 5.44; N, 12.60; O, 14.40. Found: C, 67.52; H, 5.49; N, 12.63; O, 14.45.

2.3g Entry-5g: *6'-Amino-3'-methyl-2-oxo-1'H-spiro[indoline-3,4'-pyrano[2,3-c]pyrazole]-5'-carbonitrile*: Light red solid (86%); M.p. 287–289 °C (exp), 284–286 °C (rep);⁹ IR (KBr, ν , cm^{-1}): 3418, 3385, 3334, 3124, 2684, 2180, 1708, 1678, 1628, 1523, 1464, 1326, 1265, 1150, 1052, 945, 783, 746, 688, 627; ¹H NMR (400 MHz, CDCl_3): δ 12.22 (s, 1H), 10.73 (s, 1H), 7.13–6.92 (m, 3H), 6.91–6.67 (m, 2H), 6.51 (s, 1H), 1.83 (s, 3H); ¹³C NMR (100 MHz, CDCl_3): δ 12.5, 47.1, 58.5, 111.1, 112.5, 116.2, 122.1, 125.9, 127.8, 140.7, 162.7, 167.2, 175.1; EIMS (m/z): 293 (M^+); Anal. calcd for $\text{C}_{15}\text{H}_{11}\text{N}_5\text{O}_2$: C, 61.43; H, 3.78; N, 23.88; O, 10.91. Found: C, 61.46; H, 3.82; N, 23.85; O, 10.95.

2.3h Entry-5h: *Ethyl 6'-Amino-2-oxo-3'-phenyl-1'H-spiro[indoline-3,4'-pyrano[2,3-c]pyrazole]-5'-carboxylate*: White solid (82%); M.p. 240–242 °C (exp), 242–243 °C (rep);⁹ IR (KBr, ν , cm^{-1}): 3482, 3364, 3266, 3174, 3057, 2978, 1715, 1664, 1615, 1476, 1403, 1292, 1145, 1094, 1038, 928, 751; ¹H NMR (400 MHz, CDCl_3): δ 12.17 (s, 1H), 10.33 (s, 1H), 7.42–7.37 (m, 2H), 7.37–7.29 (m, 3H), 7.18–7.09 (m, 3H), 7.01–6.92 (m, 2H), 6.73 (d, $J = 7.6$ Hz, 1H), 3.62 (q, $J = 6.6$ Hz, 2H), 0.65 (t, $J = 7.4$ Hz, 3H); ¹³C NMR (100 MHz, CDCl_3): δ 13.7, 47.8, 60.5, 81.0, 110.7, 113.7, 124.5, 125.3, 125.8, 126.9, 127.2, 127.9, 128.3, 129.0, 130.3, 139.6, 142.1, 157.4, 161.7, 165.3, 167.2, 167.9; EIMS (m/z): 402 (M^+); Anal. calcd for $\text{C}_{22}\text{H}_{18}\text{N}_4\text{O}_4$: C, 65.66; H, 4.51; N, 13.92; O, 15.90. Found: C, 65.63; H, 4.55; N, 13.89; O, 15.94.

2.3i Entry-5i: *6'-Amino-2-oxo-3'-phenyl-1'H-spiro[indoline-3,4'-pyrano[2,3-c]pyrazole]-5'-carbonitrile*: White solid (83%); M.p. 277–279 °C (exp), 280–281 °C (rep);⁹ IR (KBr, ν , cm^{-1}): 3384, 3313, 3241, 3143, 2907, 2187, 1705, 1647, 1591, 1496, 1403, 1320, 1211, 1058, 923, 747; ¹H NMR (400 MHz, CDCl_3): δ 12.39 (s, 1H), 10.47 (s, 1H), 7.42–7.27 (m, 2H), 7.27–7.11 (m, 3H), 7.13–7.05 (m, 3H), 6.91–6.89 (m, 2H), 6.82 (d, $J = 7.6$ Hz, 1H); ¹³C NMR (100 MHz, CDCl_3): δ 48.1, 59.1, 80.9, 111.5, 114.1, 124.4, 125.3, 125.7, 126.9, 127.1, 127.8, 128.2, 129.0, 131.3, 140.2, 143.2, 160.2, 164.2, 168.2, 173.1; EIMS (m/z): 355 (M^+); Anal. calcd for $\text{C}_{20}\text{H}_{13}\text{N}_5\text{O}_2$: C, 67.60; H, 3.69; N, 19.71; O, 9.00. Found: C, 67.63; H, 3.72; N, 19.75; O, 9.03.

2.3j Entry-5j: *3,7,7-Trimethylmethyl-7,8-dihydro-1H-spiro[chromeno[2,3'-c]pyrazole-4,3-indoline]-2',5'(6H)-dione*: Yellow solid (84%); M.p. 218–220 °C (exp), 220–222 °C (rep);¹⁶ IR (KBr, ν , cm^{-1}): 3370, 3180, 2915, 1719, 1689, 1678, 1615, 1518, 1471, 1340, 1210, 1170, 1117, 1028, 928, 772, 756; ¹H NMR (400 MHz, CDCl_3): δ 12.40 (s, 1H), 10.53 (s, 1H), 7.38–7.37 (m, 1H), 7.36–7.21 (m, 2H), 7.12–7.10 (m, 1H), 2.59–2.20 (m, 2H), 2.19–2.17 (m, 2H),

1.53 (s, 3H), 0.98 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ 11.1, 27.8, 34.8, 44.6, 49.7, 51.1, 110.2, 114.4, 119.1, 122.6, 123.3, 128.0, 138.1, 142.4, 161.4, 163.6, 168.4, 200.0; EIMS (m/z): 349 (M^+); Anal. calcd for $\text{C}_{20}\text{H}_{19}\text{N}_3\text{O}_3$: C, 68.75; H, 5.48; N, 12.03; O, 13.74; Found: C, 68.71; H, 5.45; N, 12.08; O, 13.77.

2.3k Entry-5k: 5'-bromo-3,7,7-Trimethylmethyl-7,8-dihydro-1H-spiro[chromeno[2,3'-c]pyrazole-4,3-indoline]-2',5(6H)-dione: White solid (79%); M.p. 298–299 °C (exp), 301–303 °C (rep);¹⁵ IR (KBr, ν , cm^{-1}): 3314, 3231, 2913, 1719, 1652, 1629, 1614, 1589, 1471, 1342, 1276, 1125, 1036, 911, 772, 736; ^1H NMR (400 MHz, CDCl_3): δ 12.27 (s, 1H), 10.19 (s, 1H), 7.49 (s, 1H), 7.26 (d, $J = 7.4$ Hz, 1H), 7.14 (d, $J = 8.0$ Hz, 1H), 2.44–2.38 (m, 2H), 2.20–2.18 (m, 2H), 1.62 (s, 3H), 1.19 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ 10.6, 26.7, 31.4, 43.1, 48.9, 50.9, 109.4, 110.5, 111.5, 114.2, 124.2, 123.4, 126.6, 138.0, 139.7, 162.2, 199.3; EIMS (m/z): 427 (M^+); Anal. calcd for $\text{C}_{20}\text{H}_{18}\text{BrN}_3\text{O}_3$: C, 56.09; H, 4.24; Br, 18.66; N, 9.81; O, 11.21; Found: C, 56.12; H, 4.21; Br, 18.61; N, 9.85; O, 11.26.

2.3l Entry-5l: 5'-chloro-3,7,7-Trimethylmethyl-7,8-dihydro-1H-spiro[chromeno[2,3'-c]pyrazole-4,3-indoline]-2',5(6H)-dione: Cream solid (81%); M.p. 212–214 °C (exp), 215–217 °C (rep);¹⁸ IR (KBr, ν , cm^{-1}): 3209, 3112, 2910, 1709, 1689, 1656, 1612, 1510, 1469, 1339, 1208, 1164, 1115, 1028, 908, 768, 746; ^1H NMR (400 MHz, CDCl_3): δ 12.38 (s, 1H), 10.06 (s, 1H), 7.73 (s, 1H), 7.34 (d, $J = 5.6$ Hz, 1H), 6.96 (d, $J = 7.2$ Hz, 1H), 2.11 (s, 2H), 2.09 (s, 2H), 1.50 (s, 3H), 1.15 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ 10.9, 27.1, 31.6, 43.4, 49.1, 51.0, 110.3, 110.5, 114.4, 124.9, 125.9, 127.3, 138.3, 140.0, 163.7, 200.0; EIMS (m/z): 383 (M^+); Anal. calcd for $\text{C}_{20}\text{H}_{18}\text{ClN}_3\text{O}_3$: C, 62.58; H, 4.73; Cl, 9.24; N, 10.95; O, 12.50; Found: C, 62.52; H, 4.69; Cl, 9.21; N, 10.99; O, 12.53.

2.3m Entry-5m: 3-methyl-7,8-dihydro-1H-spiro[chromeno[2,3'-c]pyrazole-4,3-indoline]-2',5(6H)-dione: White solid (82%); M.p. 296–298 °C (exp), 301–302 °C (rep);¹⁵ IR (KBr, ν , cm^{-1}): 3331, 3233, 2917, 1719, 1645, 1610, 1601, 1520, 1471, 1344, 1205, 1173, 1114, 1028, 817, 771, 709; ^1H NMR (400 MHz, CDCl_3): δ 12.45 (s, 1H), 10.49 (s, 1H), 7.66 (s, 1H), 7.64–7.21 (m, 3H), 2.78–2.68 (m, 2H), 2.10–2.07 (m, 5H), 1.69–1.64 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.6, 20.1, 28.0, 36.3, 50.1, 110.2, 113.1, 114.4, 123.3, 126.7, 128.0, 138.0, 142.5, 162.1, 163.5, 167.2, 199.4; EIMS (m/z): 321 (M^+); Anal. calcd for $\text{C}_{18}\text{H}_{15}\text{N}_3\text{O}_3$: C, 67.28; H, 4.71; N, 13.08; O, 14.94; Found: C, 67.25; H, 4.74; N, 13.03; O, 14.98.

2.3n Entry-5n: 5'-bromo-3-methyl-7,8-dihydro-1H-spiro[chromeno[2,3'-c]pyrazole-4,3-indoline]-2',5(6H)-dione: Yellow solid (83%); M.p. 308–310 °C (exp); IR (KBr, ν , cm^{-1}): 3301, 3213, 2907, 1713, 1641, 1603, 1591, 1511, 1453, 1324, 1201, 1153, 1104, 1013, 809, 763, 701; ^1H NMR (400 MHz, CDCl_3): δ 12.59 (s, 1H), 10.49 (s, 1H), 7.78 (s, 1H), 7.29 (d, $J = 6.8$ Hz, 1H), 6.84 (d, $J = 8.4$ Hz, 1H), 2.63 (t, $J = 6.0$ Hz, 2H), 2.12–2.06 (m, 5H), 1.78–1.72 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.1, 21.9, 27.1, 36.0, 49.6, 110.3, 114.4,

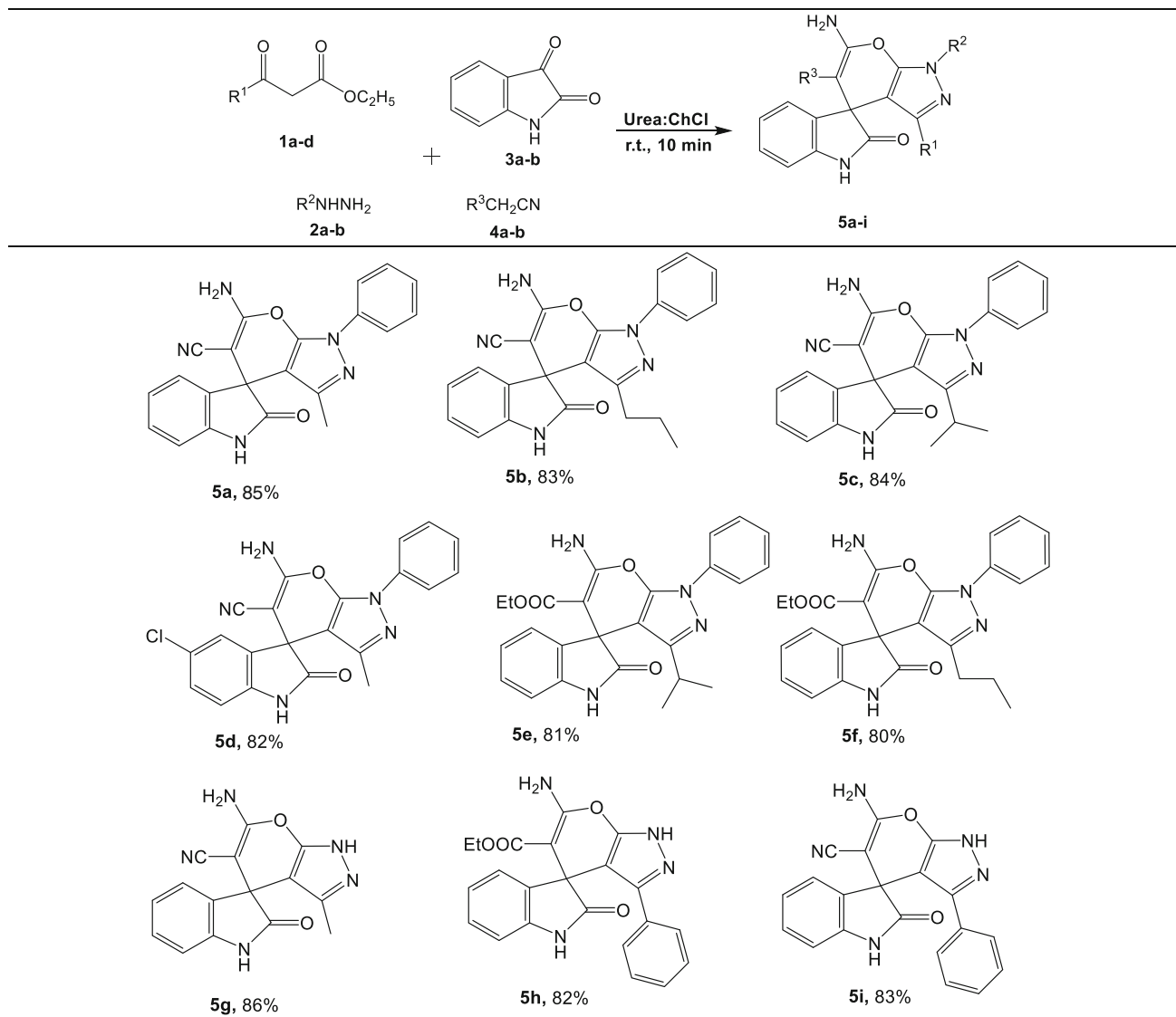
119.1, 125.9, 129.1, 129.4, 134.3, 138.2, 141.9, 161.0, 163.7, 168.1, 198.9; EIMS (m/z): 399 (M^+); Anal. calcd for $\text{C}_{18}\text{H}_{14}\text{BrN}_3\text{O}_3$: C, 54.02; H, 3.53; Br, 19.96; N, 10.50; O, 11.99; Found: C, 54.08; H, 3.53; Br, 19.91; N, 10.45; O, 11.96.

2.3o Entry-5o: 3,7,7-trimethyl-1-phenyl-7,8-dihydro-1H-spiro[chromeno[2,3'-c]pyrazole-4,3-indoline]-2',5(6H)-dione: Cream solid (81%); M.p. 243–245 °C (exp), 238–240 °C (rep);¹⁷ IR (KBr, ν , cm^{-1}): 3138, 2881, 1701, 1641, 1601, 1589, 1508, 1463, 1326, 1201, 1171, 1115, 1025, 815, 769, 709, 681, 512; ^1H NMR (400 MHz, CDCl_3): δ 10.61 (s, 1H), 7.71–7.59 (m, 3H), 7.57–7.48 (m, 2H), 7.45–7.38 (m, 4H), 2.49–2.45 (m, 2H), 2.28–2.19 (m, 2H), 1.63 (s, 3H), 1.07 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.1, 25.7, 26.8, 31.7, 40.9, 46.4, 49.3, 98.8, 107.5, 111.2, 119.7, 121.3, 122.4, 126.7, 127.9, 128.5, 132.9, 135.6, 141.2, 144.0, 143.7, 165.3, 177.4, 195.2, 195.2, 196.0; EIMS (m/z): 425 (M^+); Anal. calcd for $\text{C}_{26}\text{H}_{23}\text{N}_3\text{O}_3$: C, 73.35; H, 5.40; N, 9.82; O, 11.28; Found: C, 73.31; H, 5.44; N, 9.85; O, 11.22.

2.3p Entry-5p: 5'-bromo-3,7,7-trimethyl-1-phenyl-7,8-dihydro-1H-spiro[chromeno[2,3'-c]pyrazole-4,3-indoline]-2',5(6H)-dione: Off white solid (80%); M.p. 266–268 °C (exp), 272–274 °C (rep);¹⁵ IR (KBr, ν , cm^{-1}): 3229, 2918, 1717, 1641, 1605, 1591, 1518, 1471, 1341, 1205, 1175, 1028, 820, 771, 683, 519; ^1H NMR (400 MHz, CDCl_3): δ 10.76 (s, 1H), 7.68 (d, $J = 7.6$ Hz, 1H), 7.43 (t, $J = 7.4$ Hz, 2H), 7.29–7.12 (m, 3H), 7.09 (s, 1H), 6.93 (d, $J = 7.6$ Hz, 1H), 2.42 (s, 2H), 2.35 (s, 2H), 1.53 (s, 3H), 1.17 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.0, 25.5, 26.7, 31.7, 40.9, 46.4, 50.0, 98.1, 107.1, 110.7, 118.2, 121.0, 121.9, 126.1, 127.6, 128.1, 131.2, 134.4, 140.1, 143.2, 143.6, 165.0, 176.8, 186.1, 194.9, 195.7; EIMS (m/z): 503 (M^+); Anal. calcd for $\text{C}_{26}\text{H}_{22}\text{BrN}_3\text{O}_3$: C, 61.91; H, 4.40; Br, 15.84; N, 8.36; O, 9.52; Found: C, 61.94; H, 4.43; Br, 15.81; N, 8.31; O, 9.56.

2.3q Entry-5q: 3-methyl-1-phenyl-7,8-dihydro-1H-spiro[chromeno[2,3'-c]pyrazole-4,3-indoline]-2',5(6H)-dione: Off white solid (82%); M.p. 293–295 °C (exp), 296–298 °C (rep);¹⁵ IR (KBr, ν , cm^{-1}): 3193, 1714, 1671, 1643, 1617, 1598, 1515, 1469, 1351, 1331, 1301, 1179, 1121, 751, 681, 619; ^1H NMR (400 MHz, CDCl_3): δ 10.51 (s, 1H), 7.63–7.51 (m, 3H), 7.39–7.17 (m, 4H), 7.12–6.93 (m, 2H), 2.8–2.7 (t, $J = 6.4$ Hz, 2H), 2.81–2.78 (t, $J = 6.4$ Hz, 2H), 2.13–2.05 (m, 5H), 1.62–1.57 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 11.7, 19.8, 26.3, 35.9, 46.7, 97.6, 108.7, 112.0, 119.7, 120.6, 121.3, 126.1, 127.1, 128.7, 133.7, 139.2, 141.1, 143.0, 163.2, 175.8, 183.5, 191.6, 193.7, 194.2; EIMS (m/z): 397 (M^+); Anal. calcd for $\text{C}_{24}\text{H}_{19}\text{N}_3\text{O}_3$: C, 72.53; H, 4.82; N, 10.60; O, 12.08; Found: C, 72.50; H, 4.85; N, 10.65; O, 12.03.

2.3r Entry-5r: 5'-bromo-3-methyl-1-phenyl-7,8-dihydro-1H-spiro[chromeno[2,3'-c]pyrazole-4,3-indoline]-2',5(6H)-dione: White solid (77%); M.p. 303–305 °C (exp), 307–309 °C (rep);¹⁷ IR (KBr, ν , cm^{-1}): 3081, 2939, 1688, 1649, 1590, 1592, 1521, 1468, 1398, 1265, 1118, 748, 677, 609; ^1H NMR (400 MHz, CDCl_3): δ 10.62 (s, 1H), 7.59–7.34

Table 2. One pot synthesis of spiro[indoline-3,4'-pyrano[2,3-c]pyrazole] derivatives (**5a-i**)^a.

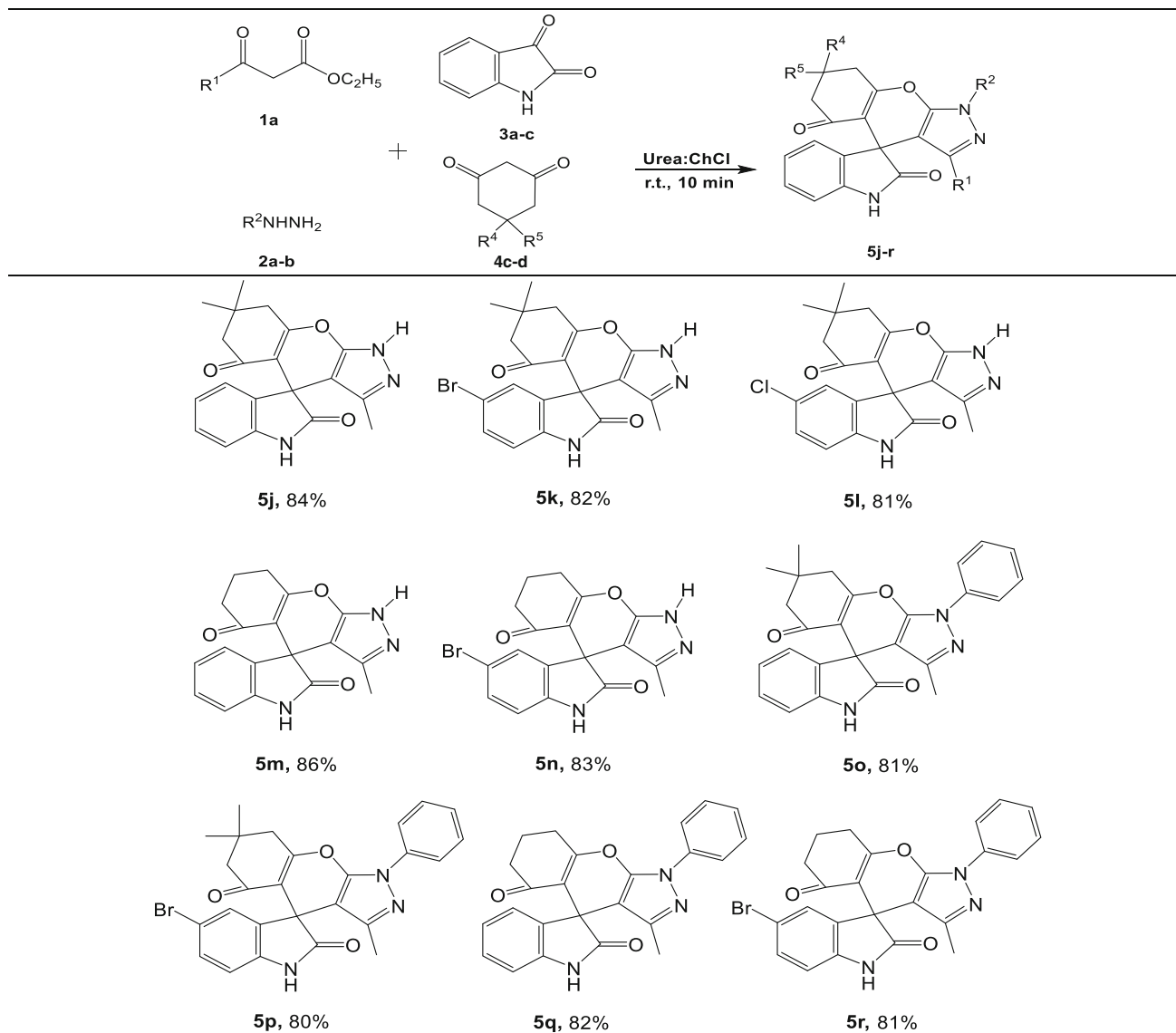
^aReaction condition: β -ketoesters (1 mmol), hydrazines (1 mmol), isatins (1 mmol) and active methylene compounds (1 mmol), 5 mL of DES (Urea:ChCl in 2:1 ratio), stirring for 10 min.

(m, 3H), 7.29–7.15 (m, 3H), 7.03–6.95 (m, 2H), 2.77–2.64 (t, $J = 6.4$ Hz, 2H), 2.22–2.17 (m, 5H), 1.73–1.67 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 11.9, 25.2, 26.7, 31.6, 46.2, 49.6, 97.1, 111.0, 111.4, 112.5, 119.7, 125.4, 125.9, 128.7, 130.3, 135.8, 136.5, 140.7, 143.9, 144.6, 165.5, 172.3, 189.9, 193.3; EIMS (m/z): 475 (M^+); Anal. calcd for C₂₄H₁₈BrN₃O₃: C, 60.52; H, 3.81; Br, 16.77, N, 8.82; O, 10.08; Found: C, 60.55; H, 3.77; Br, 16.71, N, 8.79; O, 10.12.

3. Results and Discussion

At the very onset of this work, we started the one-pot four-component reaction using ethylacetoacetate **1a**, phenyl hydrazine **2a**, isatin **3a** and malonitrile **4a** in

freshly prepared deep eutectic solvent (Figure 2) of urea:choline chloride (10 mol%, 2:1 ratio of urea:choline chloride) at room temperature. To our delight, the expected product i.e., spiro[indoline-3,4'-pyrano[2,3-c]pyrazole] derivatives **5a** was isolated with 85% yield. The overall reaction time for complete transformation took only 5 min as monitored by TLC. (entry 1, Table 1). Then, to check the optimized condition, we performed the reaction in different conditions. We increased the reaction duration from 5 min to 10 min, the yield of the isolated product increases to 90% (entry 2, Table 1). On further increasing the reaction duration up to 30 min, the yield of the product remains constant (entry 3,

Table 3. One pot *via* four component synthesis of spiro[chromeno[2,3-*c*]pyrazole-4,3'-indoline]-diones (**5j-r**).

^aReaction condition: β -ketoesters (1 mmol), hydrazines (1 mmol), isatins (1 mmol) and cyclic active methylene compounds (1 mmol), 5 mL of DES (Urea:ChCl in 2:1 ratio), stirring for 10 mins.

Table 1). Again, the effect of change in temperature was observed when the reaction temperature was enhanced to 50 °C and 60 °C, the percentage of the isolated product remains as usual of 90% (entries 4 and 5, Table 1). Also, we performed the reaction in ice-bath condition i.e., 4 °C, the isolated yield was 80% after stirring for 30 min (entry 6, Table 1). The efficiency of other DESs was also determined under optimized temperature. When the reaction was performed using various freshly prepared DESs namely malonic acid:ChCl, oxalic acid:ChCl, PTSA:ChCl, glycerin:ChCl (entries 7–11, Table 1), the reaction did not improve the yield of the product. This

indicates that the DES components participate in the reaction but not to the extent as that of urea:ChCl, which behaves as a base for abstracting protons from active methylene compounds and participate in solvating all the components and intermediates of this procedure efficiently. Lastly, when the reaction was performed under solvent-free at room temperature for 24 h, the reaction mixture did not proceed as indicated in the TLC. Thus, the optimized condition for synthesis of spirooxindole derivative starting from ethylacetoacetate **1a**, phenyl hydrazine **2a**, isatin **3a** and malonitrile **4a** required DES prepared from urea:ChCl (2:1 ratio of choline chloride: urea) as

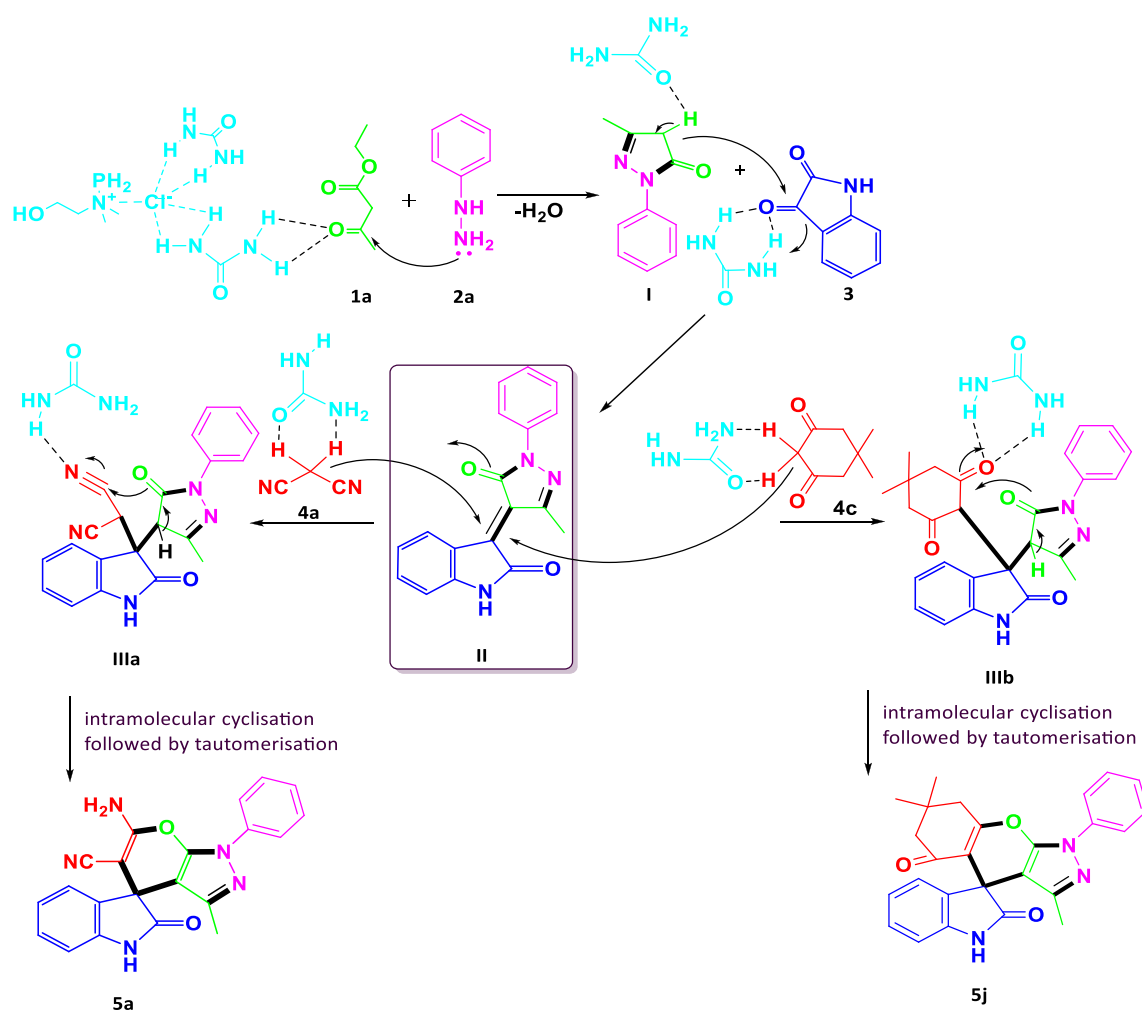
solvent and stirring the reaction mixture at room temperature for just 10 min (**5a**, 85%).

After optimization of the reaction conditions, we turned our attention to fully characterize the four component product **5a**. From ^1H NMR spectrum of **5a**, one singlet peak at $\delta = 10.7$ ppm, a multiplet peak at $\delta = 6.92\text{--}7.89$ ppm and one singlet peak at $\delta = 1.67$ ppm indicated the presence of NH proton, aromatic protons and methyl protons, respectively. From ^{13}C NMR spectrum, the presence of spirocyclic carbon was observed at 48.8 ppm, one carbonyl and one nitrile peaks were observed at 177.6 and 114.4 ppm, respectively and the peak at 13.6 ppm corresponds to lone methyl carbon.

Based on the optimized reaction conditions (entry 2, Table 1), we wish to extend the scope of this reaction using various types of substrates of each of the four components. A series of spiro[indoline-3,4'-pyrano[2,3-c]pyrazole] derivatives **5a-I**, were obtained in good yields (Table 2) and these reactions were found

to proceed very cleanly at room temperature and no side reaction products were observed. The products were tolerant of a different set of β -ketoesters **1a-d**, hydrazines **2a-b**, isatins **3a-b** and active methylene compounds **4a-b**. For instance, the treatment of β -ketoesters **1b** and **1c** bearing n-propyl and isopropyl groups with phenylhydrazine **2a**, isatin **3a** and malononitrile **4a** provided desired products **5b** and **5c** in 83% and 84% yield, respectively.

Encouraged by this success, the scope of this multi-component reaction was further investigated by changing the aliphatic active methylene compounds to cyclic active methylene compounds. Under the same reaction condition, target compounds **5j-r** (Table 3) were obtained in good yields by treating β -ketoesters **1a**, phenylhydrazines **2a-b**, isatins **3a-b** with 5,5-dimethylcyclohexane-1,3-dione **4c** and cyclohexane-1,3-dione **4d**. From the above observations, it was worthy to mention that DES function as both a promoter as well as a reaction media, which results in the



Scheme 2. Probable mechanism of spirooxindole derivatives synthesis.

successive condensation forming the desired target products **5a-r**.

The recyclability of solvent is an important factor affecting the economics of practical applications of DES. The model reaction of ethyl acetoacetate **1a**, phenylhydrazine **2a**, isatin **3a** and malononitrile **4a** was selected to investigate this issue under the optimal conditions. After completion of the reaction, the reaction mixture, including DES and products, was dissolved in water and the crude product was obtained by extraction with EtOAc. The DES was recovered from the aqueous phase by evaporation at 80 °C under vacuum and was recycled for the next reaction. As demonstrated in Figure 3, the DES could be recycled and reused up to four times with only a slight decrease in catalytic activity.

A plausible reaction mechanism for the synthesis of spiro[indoline-3,4'-pyrano[2,3-c]pyrazole] derivative **5a** and **5j** is shown in Scheme 2. The reaction begins with the activation of carbonyl group of ethylacetoacetate **1a** by the NH₂ group of DES (urea: choline chloride mixture), results in stronger H-bond formation which enhances the electrophilic character of carbonyl carbon of compound **1a**. Compound **1a** undergoes a condensation reaction with phenylhydrazine **2a** to form intermediate **I**, pyrazol-5-one derivatives. A Knoevenagel condensation between isatin **3** and intermediate **I** yield an adduct **II**. Finally, Michael addition reaction occurs between adduct **II** and malononitrile **4a**, undergoes intramolecular cyclisation followed by tautomerization to form target product **5a** and similarly with cyclic compound **4c**, the product **5j** was obtained in good yield.

4. Conclusions

In conclusion, an efficient, clean, atom-economical and green method for the preparation of spirooxindoles using DES based on choline chloride is reported. The DES was found to play as a good reaction medium. This method offers several advantages such as operational simplicity, good to excellent product yields, and avoids the use of expensive or sensitive catalyst. Further, this procedure is highly sustainable because of the employment of readily available and biodegradable deep eutectic solvent.

Supplementary Information (SI)

¹H NMR and ¹³CNMR data is available at www.ias.ac.in/chemsci.

Acknowledgements

Financial support from the CSIR [No. 02(0251)/15/EMR-II] and DST [No. EMR/2014/00033], Government of India, are gratefully appreciated.

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