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Greener synthesis of spirooxindole in deep eutectic solvent

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ABSTRACT

A simple and efficient synthesis of spirooxindole derivatives by one-pot, three-component reaction of isatins, malononitrile and different nucleophiles under catalyst-free condition in deep eutectic solvent is reported. A series of biological importance, spirooxindole derivatives were synthesized via a multicomponent reaction of isatin, or acenaphthoquinone, and malononitrile or cyanoacetic ester with 1,3-dicarbonyl compounds, naphtol and 4-hydroxycumarin in biodegradable choline chloride based deep eutectic solvent in good yields (50–95%). This green procedure has the advantages of higher yields, shorter reaction times, environmental friendliness, and easy work-up.

1. Introduction

Volatile organic solvents are used daily in the chemical industry, in large quantities as reaction media that contribute to the major source of environmental pollution. Substitution of hazardous volatile solvents with ones that show better environmental, health and safety properties, such as increased biodegradability is a necessity in all industry. In synthetic chemistry ecological pollution can be produced via side products or unreacted starting materials and reaction media such as solvents and catalysts. Thus development of green methodologies with high yields is pioneer and in this context, ionic liquid (IL) has attracted much attention and utilized in many organic reactions. But despite all valuable properties of ionic liquids [1–3], such as low vapor pressure, exceptional chemical and thermal stability and recyclability, they are not as green as expected [4]. At the beginning of this century a new generation of solvents named deep eutectic solvent [5] was introduced by Abbott group. DES has many advantages than IL such as simple preparation, low price, chemical inertness with water, high atom economy, passing purification problems and waste disposal encountered with common ILs while their physico-chemical properties are very close [6]. So far many organic reactions have performed in choline chloride based DES [7–10]. In all reports short reaction time and easy isolation process make DES worthy to be considered as solvent and catalyst in other valuable organic reactions.

Spirooxindoles scaffold due to their quaternary carbon center known as biological active compounds and are present in a wide variety of natural products such as phytochemicals either in alkaloids, lactones or terpenoids [11]. Since the first report of spiran preparation by Bayer in 1900 [12], there are a large number of classical and modern methods for the synthesis and structural modification of the biologically active spiro compounds [23-26]. Spiro-2-oxindole especially spiro fused to other cyclic structures (Fig. 1) is subject of tremendous interest in synthetic organic chemistry and medicinal chemistry due to its fascinating medicinal properties such as anti-HIV [13], anticancer [14], antitubercular [15], antimalarial [16], progesterone receptor modulator [17] and MDM2 inhibitor [18]. Architecture of spiro compounds due to their steric strain has been a challenge for synthetic organic chemists and recently several attempts have also been made for the formation of spirooxindoles via one pot multicomponent in literature. Although all reports have their own merits, continuing researches to find green and economical methods under catalyst free condition seem necessary.

2. Experimental section

2.1. Materials and methods

All starting materials and DES components were commercially available and purchased from Merck. Melting points were determined on Buchi 535 and were uncorrected. IR spectra were recorded on nexus 870 FTIR spectrometer (thermo Nicolet Madison WI). NMR spectra were recorded on Brucker 400 and 500 MHz spectrometer using DMSO as solvent and TMS as internal standard. All the reactions were monitored with thin layer chromatography (TLC) and UV light as detecting agent.

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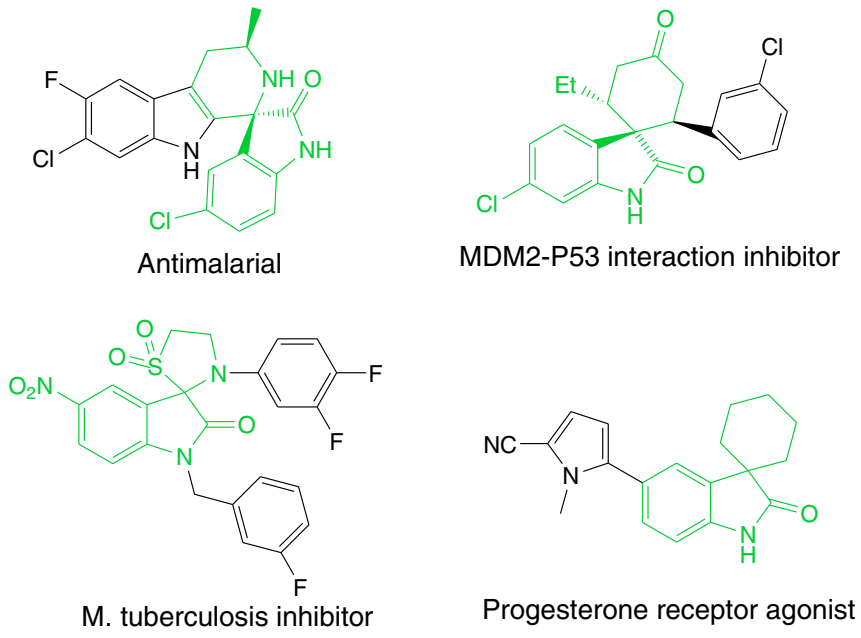


Fig. 1. Selected biologically active compounds containing spiro-2-oxindole moiety.

2.2. Deep eutectic solvent preparation

According to literature [19] 100 mmol choline chloride and the second component were mixed according to Table 1, in a round flask and were heated to obtain a clear liquid as DES called urea:ChCl (Fig. 2).

2.3. General procedure for spiro-2-oxindole preparation

In the test tube (0.5 mmol) isatin or acenaphthoquinone with 0.5 mmol active methylene and 0.5 mmol 1,3-dicarbonyl compounds/4H cumarin/α naphtol and 0.5 mL urea:ChCl were added. The reaction mixture was stirred and heated to 80 °C. The reaction completion was monitored by TLC. After reaction completion about 5 mL water was added to reaction mixture in the cases that the solid was obtained and the solid was filtered, and in the cases that a viscose liquid was obtained after water addition the ethyl acetate was added to extract the product and the organic layer was removed under vacuum. The products were recrystallized from ethanol to give pure corresponding compounds.

2.3.1. Selected data

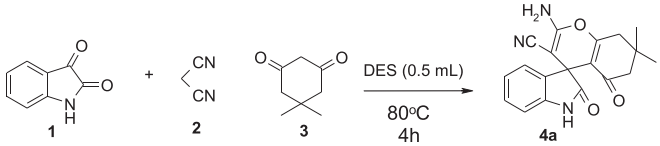
2-Amino-7,7-dimethyl-2,5-dioxo-5,6,7,8-tetrahydrospiro [chromene-4,3-indoline]-3-carbonitrile (4a): pale yellow solid, ^{1}H NMR (500 MHz, DMSO-d_6): δ H (ppm) 1.01 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 2.16 (m, 2H, $^2CH_2$), 2.57 (d, J = 15 Hz, 2H, $^4CH_2$), 6.79 (d, J = 10 Hz, 1H, ArH), 6.89 (t, J = 10 Hz, 1H, ArH), 6.98 (d, J = 5 Hz, 1H, ArH), 7.16 (t, J = 10 Hz, 1H, ArH), 7.18 (brs, 2H, NH_2), 10.36 (s, 1H, NH).

2-Amino-5-oxo-7,7-dimethyl-spiro [(4H)-5,6,7,8-tetrahydro-chromene-4,30-(30H)-indol]-(10H)-20-one-3-carbonitrile (4b): white powder, ^{1}H NMR (400 MHz, DMSO-d_6): 1.01 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 2.16 (q, J = 16 Hz, 2H, CH), 2.57 (d, J = 4Hz, 2H, CH_2), 6.81 (d, J = 8 Hz, 1H, ArH), 6.90 (t, J = 8 Hz, 1H, ArH), 7.00 (d, J = 8 Hz, 1H, ArH), 7.15 (t, J = 8 Hz, 1H, ArH), 7.24 (s, 2H, NH_2), 10.41 (s, 1H, NH).

2-Amino-2′-oxospiro[benzo[g]chromene-4,3′-indoline]-3-carbonitrile (4h): ^{1}H NMR (DMSO-d_6, 400 MHz): 5.42 (brs, 2H, NH_2), 6.58 (d, J = 8Hz, 1H, ArH), 7.02 (t, J = 8Hz, 2H, ArH), 7.11 (d, J = 8Hz, 1H, ArH), 7.31 (t, J = 8Hz, 1H, ArH), 7.47 (s, 1H, ArH), 7.61 (m, 2H, ArH), 7.70 (t, J = 8Hz, 1H, ArH), 7.92 (d, J = 8Hz, 1H, ArH), 8.30 (d, J = 8Hz, 1H, ArH), 10.71 (s, 1H, NH).

Ethyl 2-amino-2,5-dioxo-5-H-spiro [indoline-3,4-pyrano [3,2-c]-chromene]-3-carboxylate (4g): ^{1}H NMR (400 MHz, DMSO-d6): δ H (ppm) 0.84 (t, J = 8Hz, 3H, CH_3), 3.76–3.79 (m, 2H, CH_2O), 6.77 (d, J = 8Hz, 1H, ArH), 6.81 (t, J = 8Hz, 1H, ArH), 7.04 (d, J = 8Hz, 1H, ArH), 7.13 (t, J = 8Hz, 1H, ArH), 7.47 (d, J = 8Hz, 1H, ArH), 7.53

Table 1
Comparing different DESs in optimizing the reaction.



Entry	Solvent	Yield (%)[a]
1	Urea:ChCl (2:1)	95 (95, 88, 80)
2	Glycerin:ChCl (2:1)	45
3	$LaCl_3.6H_2O$:ChCl (2:1)	30
4	Malonic acid:ChCl (1:1)	35
5	PTSA:ChCl (2:1)	20
6	Tartaric acid:ChCl (0.5:1)	0

[a] NMR yields.

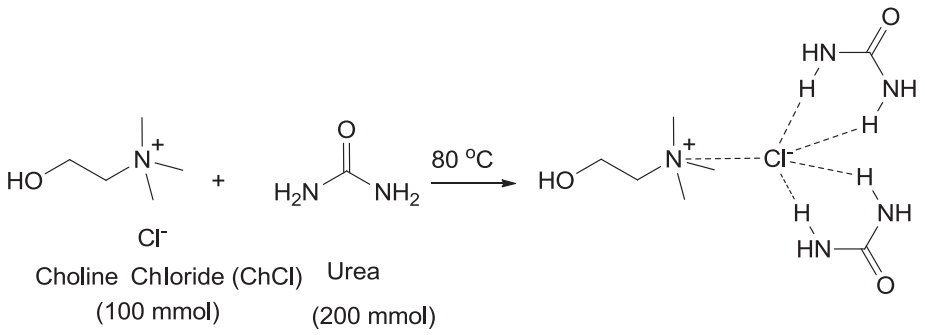


Fig. 2. Deep eutectic solvent preparation from urea and ChCl.

(t, J = 8Hz, 1H, ArH), 7.75 (t, J = 8Hz, 1H, ArH), 8.05 (d, J = 8Hz, 1H, ArH), 8.15 (br s, 2H, NH_2), 10.44 (s, 1H, NH).

Methyl 2-amino-2′-oxospiro[benzo[g]chromene-4,3′-indoline]-3-carboxylate (4i): (400 MHz, DMSO-d6): δ H (ppm) 0.78 (t, J = 8Hz, 3H, CH_3), 3.74–3.79 (m, 2H, CH_2O), 6.70 (d, J = 8Hz, 1H, ArH), 6.85 (t, J = 8Hz, 1H, ArH), 6.91 (t, J = 8Hz, 2H, ArH), 7.18 (t, J = 8Hz, 1H, ArH), 7.54 (d, J = 8Hz, 1H, ArH), 7.60 (t, J = 8Hz, 1H, ArH), 7.62 (t, J = 8Hz, 1H, ArH), 7.88 (d, J = 8Hz, 1H, ArH), 8.33 (d, J = 8Hz, 1H, ArH), 10.53 (s, 1H, NH).

Ethyl 2-amino-7, 7-dimethyl-2,5-dioxo-5, 6, 7, 8-tetrahydro-2H-spiro [acenaphthylene-1,4-chromene]-3-carboxylate (4k): (400 MHz, DMSO-d6): δ H (ppm) 0.44 (s, 3H, CH_3), 1.40 (s,3H, CH_3), 1.50 (s, 3H, CH_3), 2.55 (q, J = 16Hz, 2H, CH_2), 3.09 (t, J = 16 Hz, 2H, CH_2), 3.72–3.79 (m, 2H, CH_2), 7.71 (d, J = 8Hz, 1H, ArH), 7.97–8.01 (m, 1H, ArH), 8.17–8.27 (m, 3H, ArH), 8.40 (brs, 2H, NH_2), 8.55–8.57 (m, 1H, ArH).

3. Results and discussion

Due to our interest to develop multicomponent reaction in DESs as green and efficient media and catalyst, [20–22] herein we wished to report an efficient, simple, and green one pot, three component domino reaction of isatin (**1**) or acenaphthoquinone, and malononitrile (**2**) with active methylene compounds (**3a–e**) in urea–choline chloride based deep eutectic solvent under catalyst free condition (Fig. 3).

To optimize the reaction conditions, the three-component reaction between isatin (0.5 mmol), malononitrile (0.5 mmol) and dimedone (0.5 mmol) in urea–choline chloride was selected as the model reaction to optimize reaction condition. The results have been shown in Table 1. After carefully examining the effect of temperature of reaction, we obtained an excellent result in the absence of any catalyst for the model reaction in urea–choline chloride (0.5 mL) at 80 °C (entry 1, Table 2). Next, the reactions were repeated with different DESs under optimized temperature and only urea–choline chloride was found to be the most effective reaction media and catalyst affording 95% yield (Table 1). Other DESs were less effective and gave 60%, 38%, and 76% yields, respectively. In the cases of PTSA:ChCl and malonic acid:ChCl probably the DES components participate in the reaction but in the tartaric acid:ChCl the high viscosity plays the most important role in decreasing the yield which leads to prohibition of the sufficient reaction contacts between the starting materials.

Encouraged by the remarkable results in hands and in order to study the scope and limitations of the three-component reaction, a variety of 1,3-dicarbonyl compounds, malononitrile or cyanoacetic ester and isatin were tested using these new and green reaction media. The results summarized in Table 2 clearly demonstrate that DES is an excellent catalyst and reaction media in terms of yields and time. Gratifyingly, it was found that the one-pot reaction of isatin, and malononitrile, methyl cyanoacetate or ethyl cyanoacetate with 1,3-dicarbonyl compounds such as ethyl acetoacetate (**2b**), and dimedone (**2c**) to afford a variety of

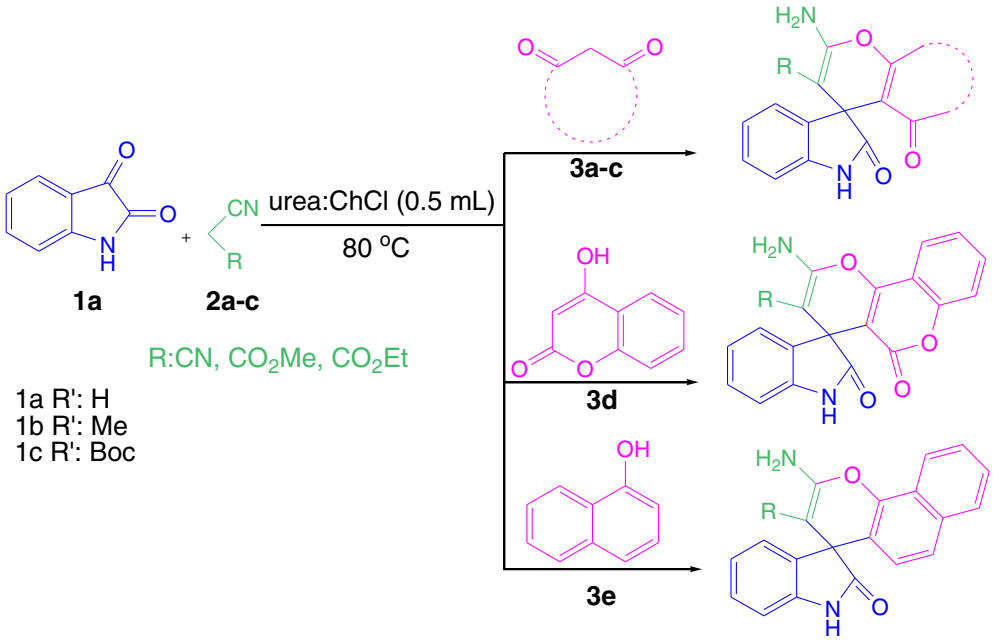
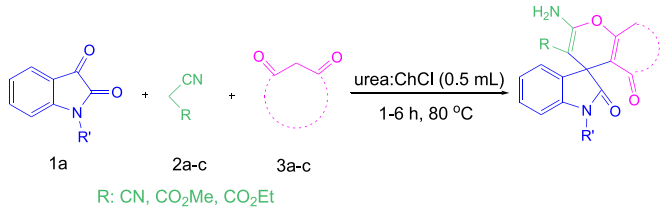


Fig. 3. One pot, green synthesis of spiro-2-oxindole in DES.

Table 2
Synthesis of spiro-2-oxindole derivatives via three choline chloride based DES.



Entry		R	3	Product	Time (h)	Yield (%)[a]	m.p	
							Found	Reported
1	Isatin	CN		**4a**	1	95	291	288–289[23]
2	Isatin	CO2Me		**4b**	2	80	282–285	255–256[24]
3	Isatin	CO_2Et		**4c**	2	72	258–264	256–257[23]
4	Isatin	CN		**4d**	1	98	>300	>300[23]
5	Isatin	CO_2Et		**4e**	3	77	262	262–263[23]
6	Isatin	CN		**4f**	4	65	294	284–286[23]
7	Isatin	CO_2Et		**4g**	4	60	248	252–253[23]
8	Isatin	CN		**4h**	2	95	>300	222[25]
9	Isatin	CO_2Et		**4i**	4	82	285–288	229[25]
10	isatin	CN		**4j**	6	50	182–189	180–183[25]
11	Acenaphthoquinone	CO_2Et		**4k**	6	55	231–241	261–263[23]
12	1-Methylindoline-2,3-dione	CN		**4l**	2	95	267–270	265–266[26]
13	1-Methylindoline-2,3-dione	CN		**4m**	2	60	275–278	277–278[26]
14	Tert-butyl 2,3-dioxoindoline-1-carboxylate	CN		**4n**	3	65	>300	>300[26]
15	Tert-butyl 2,3-dioxoindoline-1-carboxylate	CN		**4o**	3	62	>300	296–297[26]

[a] NMR yields.

spirooxindole derivatives **4a–g** in good yields (Table 2). However, the reaction with ethyl cyanoacetate and acetoacetate offered a lower yield than that with dimedone and malononitrile, which is probably due to the lower reactivity of methyl acetoacetate and ethyl cyanoacetate. On the basis of the above successful results to further expand the scope of our protocol, we investigated one-pot reactions involving, 1-hydroxynaphthalene and 2-hydroxynaphthalene or 4-hydroxy coumarin (**3d**). Under the above optimized conditions, the one-pot reactions proceeded smoothly and a variety of the desired spirooxindole products were obtained in good yields albeit with long reaction time (Table 2).

As a further application of this green protocol less reactive acenaphthoquinone **5** was tested instead of isatin in one-pot reactions, and provided moderated yields of desired products (Fig. 4).

Apart from the mild and green conditions of the process and its good results, the simplicity of product isolation and the possibility to recover and recycle DES as catalyst and reaction medium offer a significant advantage. Because DES is completely soluble in water and the spirooxindole is less soluble in water, the products can be directly separated by the addition of water and filtering after the reaction was completed. The filtrate containing products can directly recrystallize from ethanol to give analytically pure spirooxindole derivatives with highly simple workup. In the cases that viscose liquid, ethyl acetate was added to dissolve the product and participated insoluble DES and the organic layer was evaporated via vacuum, and was recrystallized from ethanol to afford pure products.

The simple reusability is one of the important properties of this DES. After the reaction was complete, water was added, and the mixture was

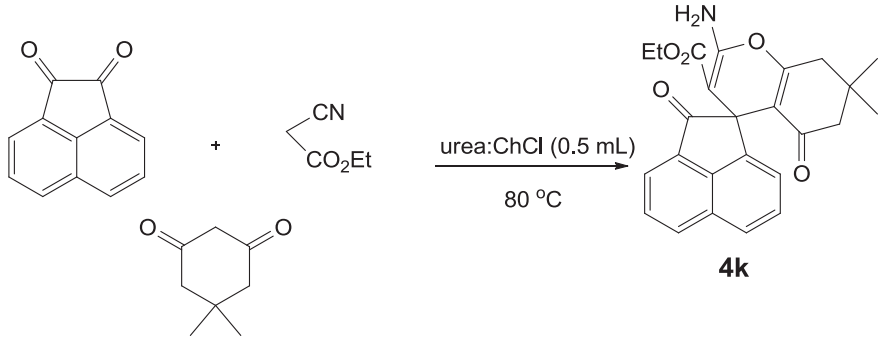


Fig. 4. One-pot, three component synthesis of spirochroman in DES.

filtered to isolate the product. The DES was recovered from the filtrate by evaporating the water phase at 80 °C under vacuum. The recycled DES was used directly with fresh substrates under identical conditions without further purification. It was shown that the DES could be used for three runs without noticeable drop in the product yield and its activity (Table 1).

Although the detailed mechanism and the role of DES in the present work have not been confirmed yet, the formation of compound **5** could be explained by the reaction sequence in Fig. 5. Weak acidic nature of choline chloride and hydrogen-bonding donors of urea in DES is the main reason for the high catalytic activity of the system. First, a Knoevenagel condensation reaction of activated isatin with hydrogen-bonding in the presence of urea with malononitrile **2** is proposed to give the Knoevenagel product (A) nucleophilic attack of 1,3-dicarbonyl compound to **A** and intramolecular cyclization to provide the spiro compound.

4. Conclusion

In summary, an efficient, simple one-pot synthesis of spiro-2-oxindole via DES based choline chloride without the use of expensive or sensitive catalyst and solvent is reported. The DES was found to play a catalyst and reaction medium. The significant advantages offered by this green protocol are the versatility of substrate, the experimentally

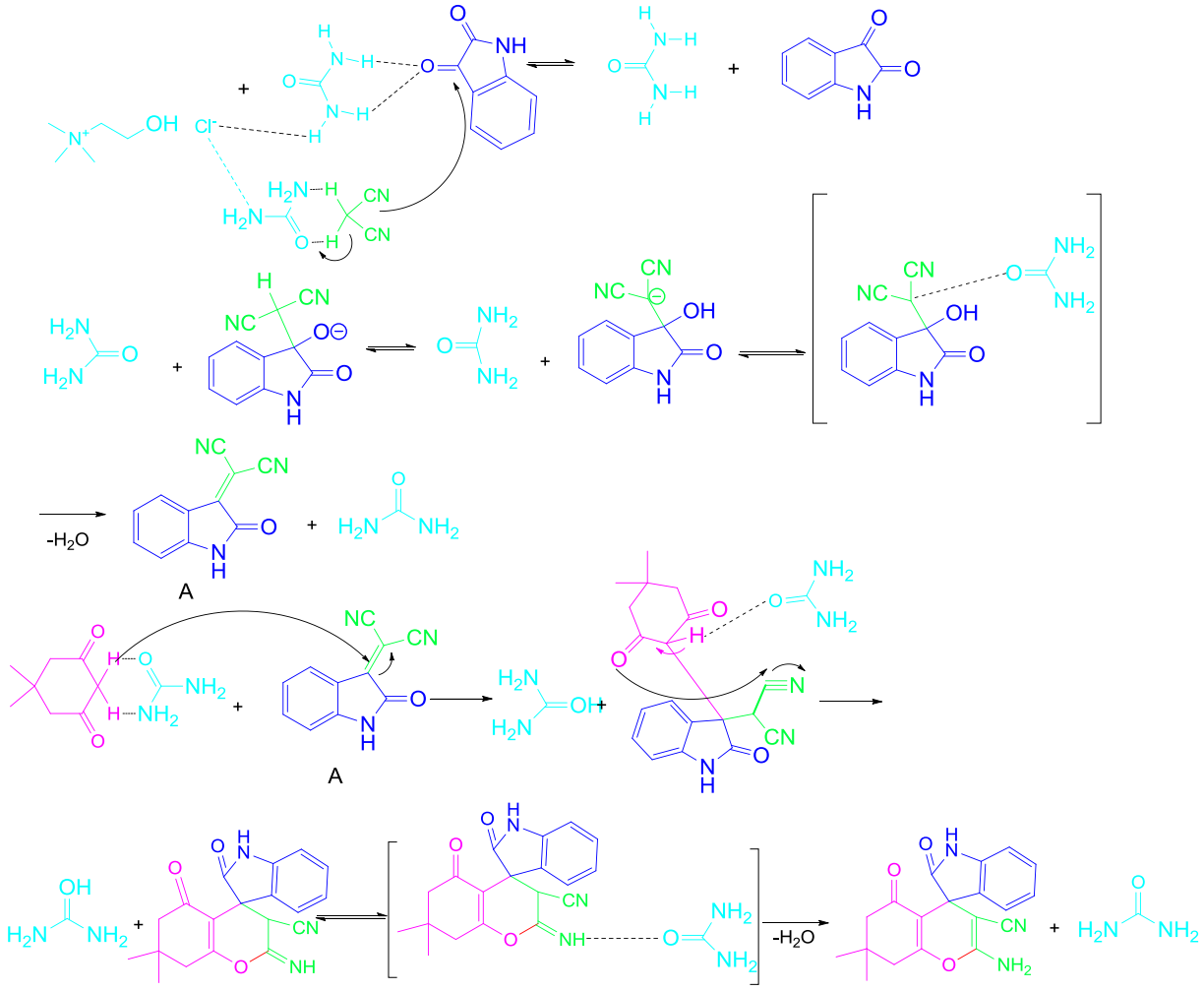


Fig. 5. Proposed mechanism for the synthesis of spiro-2-oxindole in urea:ChCl.

straightforward procedure, environmentally friendly solvent for reaction media and purification. In addition, this procedure is highly sustainable because of the employment of readily available and biodegradable deep eutectic solvent.

Acknowledgment

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