RSC Advances

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

COMMUNICATION

Choline chloride based eutectic solvents: Direct C-3 alkenylation/alkylation of indoles with 1,3-dicarbonyl compounds

Anita Kailas Sanap and Ganapati Subray Shankarling*

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

C-3 alkenylation/alkylation of indoles depends on the position of substituent on indole used in the reaction. C-2 substituted indole result in the formation of C-3 alkenylated indole derivatives, whereas plain indole give rise to bis(indolyl)carbonyl derivative instead of C-3 alkenylation product under the same set of reaction conditions. Deep eutectic mixtures are cost-effective, and bio-degradable.

Introduction

Indole is an important heterocyclic skeleton which represents a broad spectrum of pharmaceutical [1] and biological activities [2]. In the past decades, the modified indole structures have raised great interest in researchers. Amongst the substituted indoles, C-3 substituted indoles are of special interest as an important building block for the synthesis of therapeutic agents. They display physiological properties such as anticancer, antimigraine, antidepressant, anti-inflammatory, antiestrogen, and antagonist activity [3]. Consequently, there is progressing interest in the development of superior methods for the synthesis of C-3 substituted indoles [4]. One such strategy is the transition metal mediated intermolecular C-C bond formation between indole and α, β-unsaturated carbonyl compounds [5-10]. Organometallic couplings require one or both prefunctionalized entities such as halides or any other disposable functionality [11-12].

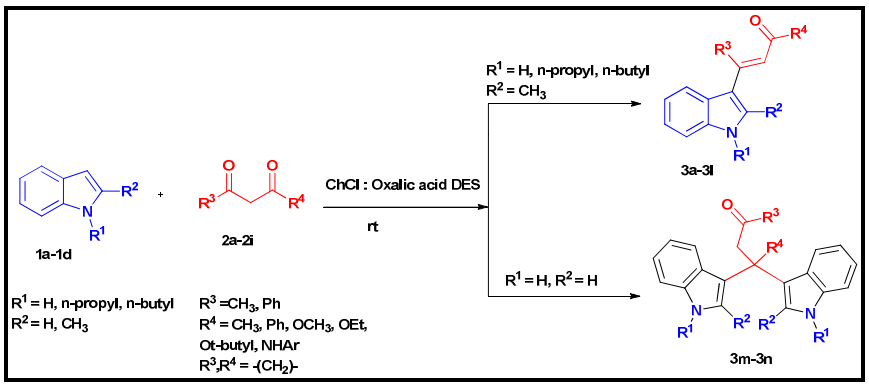
Recently, Alakananda Hajra *et al* reported the reaction of plain indole with acetylacetone in task-specific ionic liquid to give C-3 alkenylated product [12]. However, in our case, reaction of plain indole with acetylacetone and methylacetoacetate gave bis(indolyl)carbonyl derivative instead of C-3 alkenylation product. For the synthesis of C-3 substituted indoles various methods have been reported. Typically, it involves two types of reactions alkylation and alkenylation. Alkylation reactions are carried out using $FeCl_3$ [13] for coupling of alcohol with indole, SmI_3 [14] and organocatalyst (pyrrolidine + $HClO_4$) for coupling of α,β unsaturated carbonyls with indoles [4]. Alkenylation reactions are carried out using transition metal catalysts such as gold (III) [15], and $FeCl_3$ [16]. They are also reported using ionic liquids [12, 17], I_2 [18], montmorillonite K-10 [19] and various palladium catalysts [20-23]. Although these methods showed improved yields, they still hold some limitations like use of strongly acidic conditions, moisture-sensitive catalysts, expensive reagents, use of volatile organic solvents, and difficulty in recovery of reaction media or higher reaction temperatures which is not suited for practical use and incompatible with green chemistry. Even though these reactions are reported in ionic liquids like 1-butane sulfonic acid-3-methylimidazolium triflate [BSMIM]OTf [12] and *N*,*N*,*N*,*N* tetramethylguanidinium triflate (TMGTf) [17], they suffer many drawbacks over deep eutectic solvents (DES). Ionic liquids especially based on imidazole with fluorinated anions suffer from the demerits of being non-biodegradable, toxic, and commercially expensive.

Therefore, new methods need to be developed to couple indoles with carbonyl compounds directly, without activation of any coupling partner. To achieve this, we have explored the catalytic activity of DES in the conjugate addition of indoles to 1,3-dicarbonyl compounds. DES are simple ionic mixtures derived by combining quaternary ammonium salts, like choline chloride (ChCl) and hydrogen bond donors like urea, organic acids, amino acids and glycerol, or with Lewis acids like zinc chloride [24]. The hydrogen bonding interaction between hydrogen bond donor and halide ion leads to a depression in freezing point [25]. Thus, the formation of eutectic is more energetically favoured relative to the lattice energies of the pure constituents. The DES derived from choline chloride and oxalic acid is bio-degradable, non-toxic, insensitive towards moisture, recyclable and cost-effective.

In the past few years, our research group has explored applicability of DES based on choline chloride in several significant organic transformations [26-31]. We now extend their catalytic use in C-C bond formation reaction wherein acidic DES, prepared from ChCl and oxalic acid was used in the conjugate addition of indoles to α,β-unsaturated compounds (Scheme 1). However, there is no report related to the catalytic use of this mixture in C-C bond formation reaction in organic synthesis. DES can be easily prepared from inexpensive starting materials and recycled. The advantages of present methods are metal free synthesis avoiding toxic reagents and solvents with simple

*Department of Dyestuff Technology, Institute of Chemical Technology, Nathalal Parikh Marg, Matunga, Mumbai 400 019, Maharashtra, India. Fax: 91-2233611020; Tel:91-2233612708
Email:gsshankarling@gmail.com; gs.shankarling@ictmumbai.edu.in

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI:



Scheme 1 C-3 alkenylation/alkylation of indoles using ChCl: oxalic acid DES

operation, fast reaction, excellent yields and reusability of the catalyst.

In the first attempt we carried out the reaction of 2-methylindole (**1a**) with acetyl acetone (**2a**) in the presence of different DES which were prepared using literature procedure [24]. The result is shown in Table 1. Notably, the reaction could not proceed at all in the absence of the catalyst (Table 1, entry 1). Initially, we tried the reaction in individual components such as oxalic acid and ChCl instead of using DES. In oxalic acid, a trace of product formation was observed whereas in ChCl no reaction after prolonged reaction time (Table 1, entries 2, 3). Thus, it was clear that neither ChCl nor oxalic acid promotes the reaction alone. The reaction gave excellent result when a deep eutectic mixture of ChCl and oxalic acid was employed. The reaction yields 89% of **3a** at room temperature (32 ±2 ºC) in 2.5 h (Table 1, entry 4). While with the use of other DES, such as ChCl + succinic acid / tartaric acid / citric acid moderate to good yields of product was obtained in 12 h (Table 1, entries 5-8). No reactions were observed in ChCl-urea DES after prolonged reaction time (Table 1, entry 9).

Table 1: Optimization of different catalysts in C-3 alkenylation of 2-methylindole

Entry	Catalyst	Time (h)	[a]Yield of 3a (%)
1	Without catalyst	24	No reaction
2	Choline chloride	24	No reaction
3	Oxalic acid	24	Traces
4	ChCl : Oxalic acid	2.5	89
5	ChCl : Malonic acid	12	52
6	ChCl : Succinic acid	12	55
7	ChCl : Tartaric acid	12	70
8	ChCl : Citric acid	12	75
9	ChCl : Urea	12	No reaction

Reaction conditions: 2-methyl indole (1 mmol), acetyl acetone (1 mmol), DES (3 mL), rt (32 ±2 ºC), [a]Isolated yields.

In mole ratio study of reactants, 1:1 mole ratio of both the reactant was significant and gave good yield of product. In order to screen the effect of solvent, the model reaction was undertaken at rt (32 ±2 ºC) using 0.5 mL of DES in different solvents. It was observed that DES in dichloromethane (DCM) gave 61% yield of **3a** (Table 2, entry 1) and for other solvents reaction required maximum time for completion (Table 2, entries 2-7).

Table 2: C-3 alkenylation of 2-methylindole (**1a**) with acetylacetone (**2a**) in different solvents.

Entry	Solvent	Time (h)	[a]Yield of 3a (%)
1	Dichloromethane	12	61
2	Tetrahydrofuran	24	31
3	1,2-dichloroethane	24	37
4	Dioxan	24	39
5	Methanol	24	43
6	Ethanol	24	53
7	Acetonitrile	24	41

Reaction conditions: 2-methylindole (1 mmol), acetyl acetone (1 mmol), solvent (3 mL), DES (0.5 mL), rt (32 ±2 ºC), [a]Isolated yields.

Table 3: Concentration study of DES in dichloromethane for C-3 alkenylation of 2-methylindole (**1a**) with acetylacetone (**2a**)

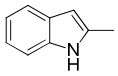
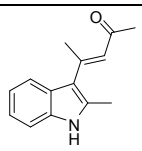
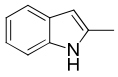
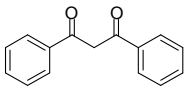
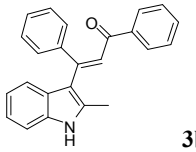
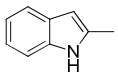
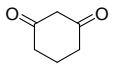
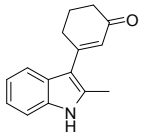
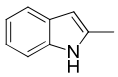
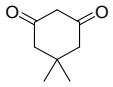
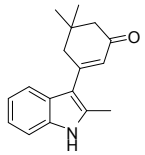
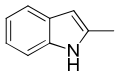
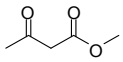
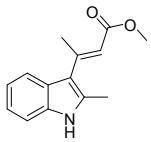
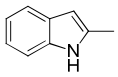
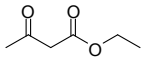
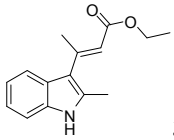
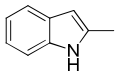
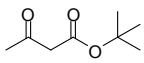
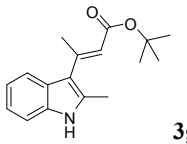
Entry	DES (mL)	DCM (mL)	DES in DCM (%)	Time (h)	[a]Yield of 3a (%)
1	4.0	0	-	2.5	89
2	3.0	0	-	2.5	88
3	2.5	0.5	83.3	2.5	61
4	2.0	1.0	65.0	2.5	61
5	1.5	1.5	50.0	2.5	53
6	1.0	2.0	33.3	2.5	40
7	0.5	2.5	16.6	2.5	32
8	0.1	2.9	3.3	2.5	11

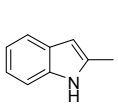
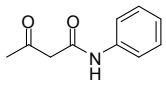
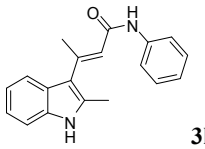
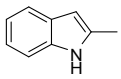
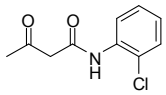
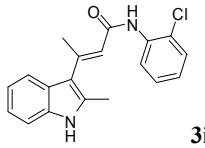
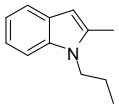
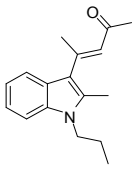
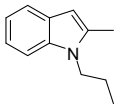
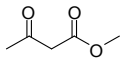
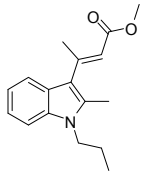
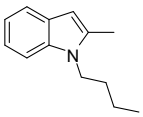
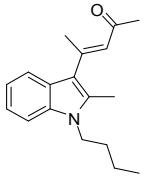
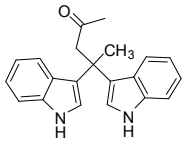
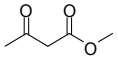
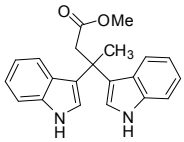
Reaction conditions: 2-methylindole (1 mmol), acetyl acetone (1 mmol), rt (32 ±2 ºC), [a]Isolated yields.

To optimize amount of catalyst, we carried out the reaction in the presence of 0.1, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0 mL of ChCl-oxalic acid DES in dichloromethane. For 1 mmol of **1a**, 3 mL of DES was sufficient and gave 88% yield of **3a** (Table 3, entry 2). No further improvements in the yield of **3a** were observed using 4 mL of DES (Table 3, entry 1). It observed that as concentration of DES decreases in dichloromethane the yield of **3a** was also extensively decreases (Table 3, entries 3-8). Hence further all the reactions were carried out in DES only (without dichloromethane).

With the optimal conditions in hand, we extended our studies to the reaction of indole with a variety of 1,3-dicarbonyl compounds to evaluate the scope of this methodology and the results were presented in Table 4. Reaction of **1a** with different 1,3-dicarbonyl compounds afford a variety of C-3 alkenylated indole derivatives **3a-l** in excellent yields with complete *E*-selectivity. The 1,3-dicarbonyl compounds involves 1,3-diketone, 1,3-ketoesters, and 1,3-ketoamide. 1,3-diketone (Table 4, entries 1-4) and 1,3-ketoesters (Table 4, entries 5-7) react very rapidly to give better to moderate yield of products. 1,3-Ketoamide reacts very sluggishly and gave lower yield of product (Table 4, entries 8,9). The reactions of *N*-substituted-2-methylindole also proceed smoothly and give good yield of products (Table 4, entries 10-12). The reaction of 2-unsubstituted indole such as **1d**, with **2a** and **2e**, results into bis(indolyl)carbonyl compounds **3m-n** (Table 4, entries 13,14) rather than the desired C-3 alkenylated product.

Table 4: C-3 alkenylation/alkylation of indoles with different with 1,3-dicarbonyl compounds in ChCl : oxalic acid DES

Entry	Indole	1,3-Dicarbonyl compound	Product	Time (h)	Yield (%)
1	 **1a**	 **2a**	 **3a**	2.5	88
2	 **1a**	 **2b**	 **3b**	3	84
3	 **1a**	 **2c**	 **3c**	2.5	83
4	 **1a**	 **2d**	 **3d**	2.5	85
5	 **1a**	 **2e**	 **3e**	2.5	74
6	 **1a**	 **2f**	 **3f**	2.5	76
7	 **1a**	 **2g**	 **3g**	2.5	77

8	 **1a**	 **2h**	 **3h**	4	73
9	 **1a**	 **2i**	 **3i**	4.5	71
10	 **1b**	 **2a**	 **3j**	3	75
11	 **1b**	 **2e**	 **3k**	3	70
12	 **1c**	 **2a**	 **3l**	3.5	76
13	 **1d**	 **2a**	 **3m**	3	61
14	 **1d**	 **2e**	 **3n**	3.5	63

Reaction conditions: Indole (1 mmol), 1,3-dicarbonyl compound (1 mmol), DES (3 mL), room temperature (32 ±2 ºC), [a]Isolated yields.

The recyclability of catalyst is an important factor affecting the economics of practical applications of DES. The model reaction of 2-methylindole (**1a**) and acetylacetone (**2a**) was selected to investigate this issue under the optimal conditions. After completion of the reaction, the reaction mass was simply filtered through a filter paper to obtain crude solid product and washed with water. Since DES is water soluble, it could be recovered by removing water under vacuum from the filtrate. The recovered DES was reused for the next run. As demonstrated in Figure 1, the DES could be recycled and reused up to four times with only a slight decrease in catalytic activity.

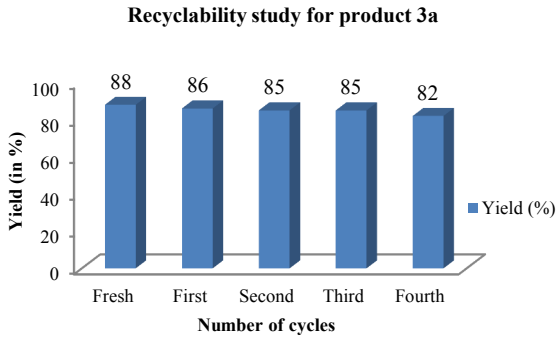


Figure 1 Studies in recycling of deep eutectic mixture (ChCl: Oxalic acid) in reaction of 2-methylindole (**1a**) with acetylacetone (**2a**)

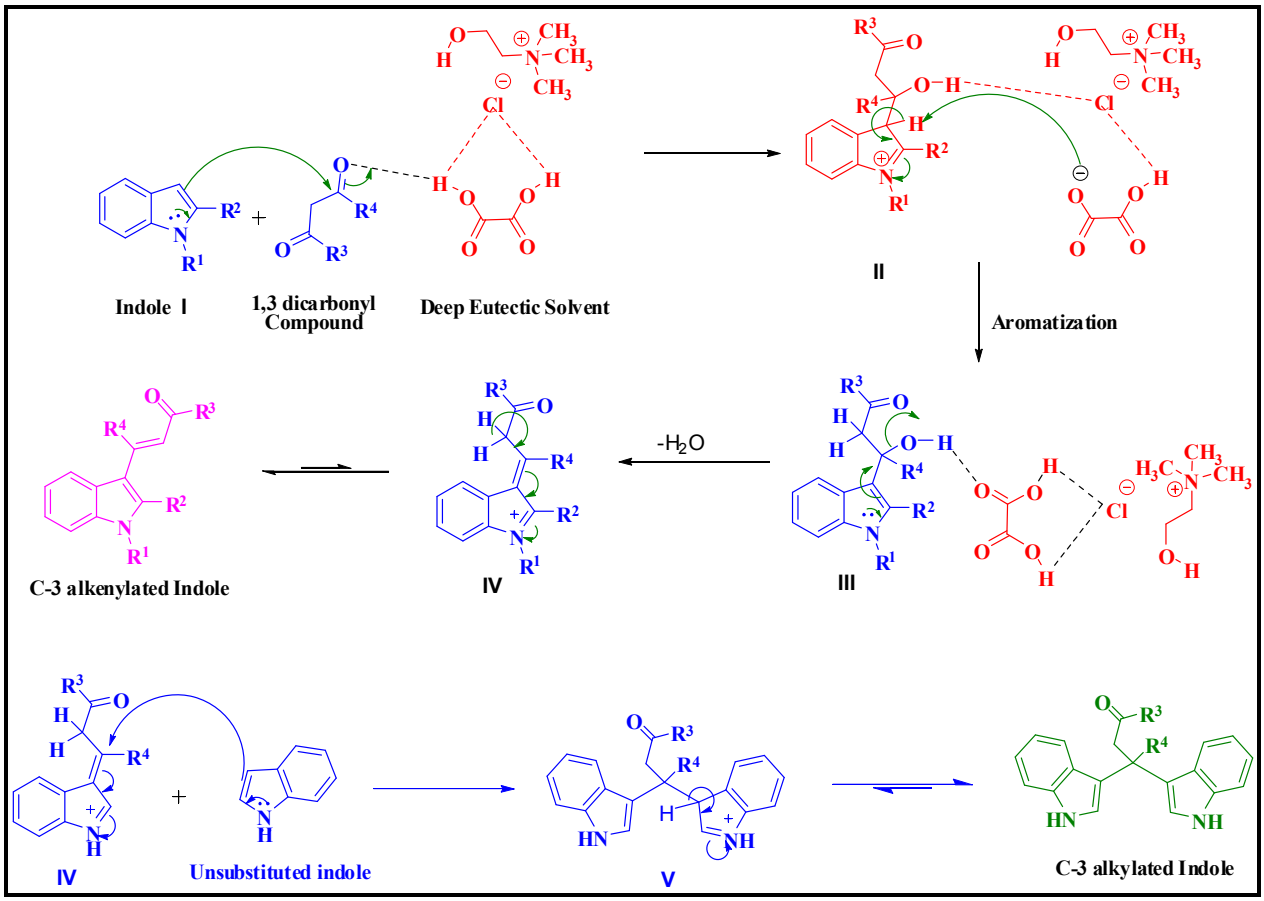


Figure 2 Plausible reaction mechanism in synthesis of C-3 alkenylated/alkylated indoles using DES as catalyst

Mechanism

In mechanism for C-3 alkenylated indoles, oxalic acid forms hydrogen bonding with ChCl. Similarly, it also forms hydrogen bond with oxygen atom of electron deficient carbonyl of 1,3-dicarbonyl compounds and increases its electrophilicity, thereby facilitating the attack of indole (Fig. 2). Finally, the hydroxyl group gets hydrogen bonded with DES and hence it facilitates a loss of water molecule to form C-3 alkenylated indole. In other case adduct IV is prone to be attacked by a plain indole at C-3 carbon atom of alkyl chain to form C-3 alkylated product.

Experimental

2-methyl indole was purchased from Aldrich Chemical Co. All the melting points reported are in degree centigrade and are uncorrected. All the IR spectra were recorded on Perkin-Elmer spectrum-100 FTIR spectrophotometer. ^{1}H NMR spectra were recorded on Varian Mercury plus 300 (300 MHz) spectrometer in $CDCl_3$/ DMSO-d6 with TMS as an internal standard, and the chemical shifts are expressed in δ unit (ppm). Mass spectra were recorded on Finnigan LCQ Advantage Max spectrometer.

Preparation of DES

The DES was prepared by combining ChCl with oxalic acid according to the procedure reported in the literature [32].

General procedure for direct C-3 alkenylation/alkylation of indoles with 1,3-dicarbonyl compounds in DES

Indole (1 mmol) was dissolved in 3 mL DES. 1,3-dicarbonyl compound (1 mmol) was added to the mixture at room temperature and stirred for appropriate time as shown in table 4. After completion of reaction, cold water was added to the reaction mixture. The precipitated solid was filtered off, and purified by column chromatography using hexane: ethyl acetate.

(*E*)-4-(2-Methyl-1*H*-indol-3-yl)pent-3-en-2-one (3a)
Brown solid, mp 120-122 °C; IR υ = 3223, 2919, 2858, 1652, 1552,1531,1424,1207,741 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.29 (s, 3H, CH_3), 2.53 (s, 3H, $COCH_3$), 2.65 (d, 3H, CH_3, J = 0.4 Hz), 6.38 (s, 1H, C3-H), 7.13-7.17 (m, 2H, C5'-H & C6'-H), 7.30 (d, 1H, C7'-H, J = 8 Hz), 7.66 (d, 1H, C4'-H, J = 8 Hz), 8.14 (bs, 1H, NH); ESI-MS: *m/z* calculated for $C_{14}H_{15}NO$ 213.28, found $[M+H]^+$ 214.2

Conclusions

In conclusion, we developed direct C-3 alkenylation/alkylation of indoles with different 1,3-dicarbonyl compounds using bio-degradable acidic deep eutectic catalyst. DES plays dual role of solvent and catalyst. The highlights of the catalyst include its bio-degradability, non-toxic nature, ease in preparation and requirement of inexpensive starting materials. The catalyst was also easily recyclable up to four times with only a slight decrease in catalytic activity. This protocol provides a practical and green alternative for C-3 alkenylation/alkylation of indoles.

Acknowledgements

A.K.S. is thankful to UGC-CAS, New Delhi for providing financial assistance and to the Institute of Chemical Technology. SAIF IIT- Bombay for spectral analysis.

Notes and references

1 A. Srivastava and S.N. Pandeya, *Int. J. Curr. Pharm. Rev. Res*., 2011, **1**, 1.
2. N.K. Kaushik, N. Kaushik, P. Attri, N. Kumar, C.H. Kim, A.K. Verma and E.H. Choi, *Molecules*, 2013,**18**, 6620.
3. S. Biswal, U. Sahoo, S. Sethy, H.K.S. Kumar M. Banerjee and J. Hooker, *Asian J. Pharm. Clin. Res*., 2012, **5**, 2.
4. D. Li, Y. Guo, Y. Ding and W. Xiao, *Chem. Commun*.,2006, 799.
5. Y. Yokoyama, T. Matsumoto and Y. Murakami, *J. Org. Chem*., 1995, **60**, 1486.
6. C. Jia, W. Lu, T. Kitamura and Y. Fujiwara, *Org. Lett*., 1999, **1**, 2097.
7. A. Maehara, H. Tsurugi, T. Satoh and M. Miura, *Org. Lett*., 2008, **10**, 1159.
8. T. Itahara, K. Kawasaki and F. Ouseto, *Synthesis*, 1984, 236.
9. L. Djakovitch and P. Rouge, *J. Mol. Catal. A: Chem*., 2007, **273**, 230.
10. L. Djakovitch and P. Rouge, *Catal. Today*, 2009, **140**, 90.
11. C.J. Li and G.W. Gribble, *Palladium in Heterocyclic Chemistry*; Pergamon: Amsterdam, 2000, 413.
12. S. Santra, A. Majee and A. Hajra, *Tetrahedron Lett*., 2011, **52**, 3825.
13. U. Jana, S. Maiti and S. Biswas, *Tetrahedron Lett*., 2007, **48**, 7160-7163.
14. X. Zou, X. Wang, C. Cheng, L. Kong and H. Mao, *Tetrahedron Lett*., 2006, **47**, 3767.
15. A. Arcadi, M. Alfonsi, G. Bianchi, G.D'Anniballe and F. Marinelli, *Adv. Synth. Catal*., 2006, **348**, 331.
16. J.S. Yadav, B.V.S. Reddy and K. Praneeth, *Tetrahedron Lett.,* 2008, **49**, 199.
17. K. Rad-Moghadam and M. Sharifi-Kiasaraie, *Tetrahedron*, 2009, **65**, 8816.
18. N. Singh and K. Singh, *Synlett*, 2012, **23**, 2116.
19. M. Chakrabarty, T. Kundu and Y. Harigaya, *J. Chem. Res*., 2004, 778.
20. S. Cacchi and G. Fabrizi, *Chem. Rev*., 2011, **111**, 215.
21. L. Djakovitch and P. Rouge, *Catal. Today*, 2009, **140**, 90.
22. C. Jia, W. Lu, T. Kitamura and Y. Fujiwara, *Org. Lett*., 1999, **1**, 2097.
23. Y. Yokoyama, T. Matsumoto and Y. Murakami, *J. Org. Chem*., 1995, **60**, 1486.
24. C. Ruß and B. König, *Green Chem*., 2012, **14**, 2969.
25. M.C. Kroon, M. Francisco, A.V.D. Bruinhorst and M.C. Kroon, *Angew. Chem. Int. Ed*., 2013, **52**, 3074.
26. A.K. Sanap and G.S. Shankarling, *Catal.Commun*., 2014, **49**, 58.
27. S.B. Phadtare, K.J. Jarag and G.S. Shankarling, *Dyes Pigmt*., 2013, **97**, 105.
28. Y.A. Sonawane, S.B. Phadtare, B.N. Borse, A.R. Jagtap and G.S. Shankarling, *Org. Lett*., 2010, **12**, 1456.
29. P.M. Pawar, K.J. Jarag and G.S. Shankarling,*Green Chem*., 2011, **13**, 2130.
30. H.R. Lobo, B.S. Singh and G.S. Shankarling, *Catal. Commun.,*2012, **27**, 179.
31. U.N. Yadav, G.S. Shankarling, *J. Mol. Liq*., 2014,**19**, 137.
32. A.P. Abbott, D. Boothby, G. Capper, D.L. Davies and R.K. Rasheed, *J. Am.Chem.Soc.*, 2004, **126**, 9142.

Scheme 1 C-3 alkenylation/alkylation of indoles using ChCl: oxalic acid DES

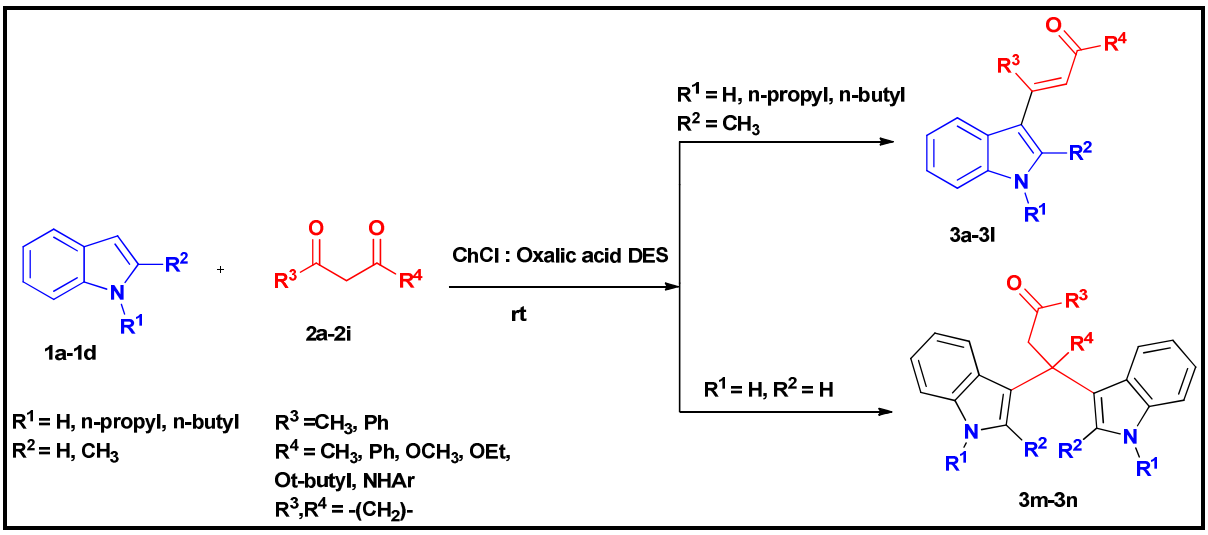


Figure 1 Studies in recycling of deep eutectic mixture (ChCl: Oxalic acid) in reaction of 2-methylindole (**1a**) with acetylacetone (**2a**).

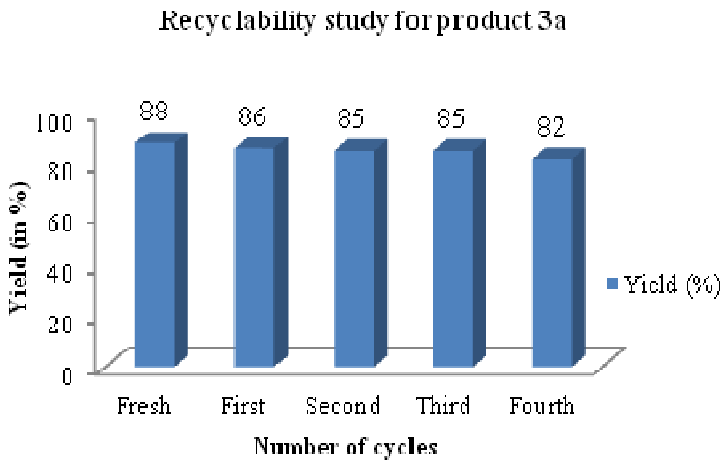


Figure 2 Plausible reaction mechanism in synthesis of C-3 alkenylated/alkylated indoles using DES as catalyst

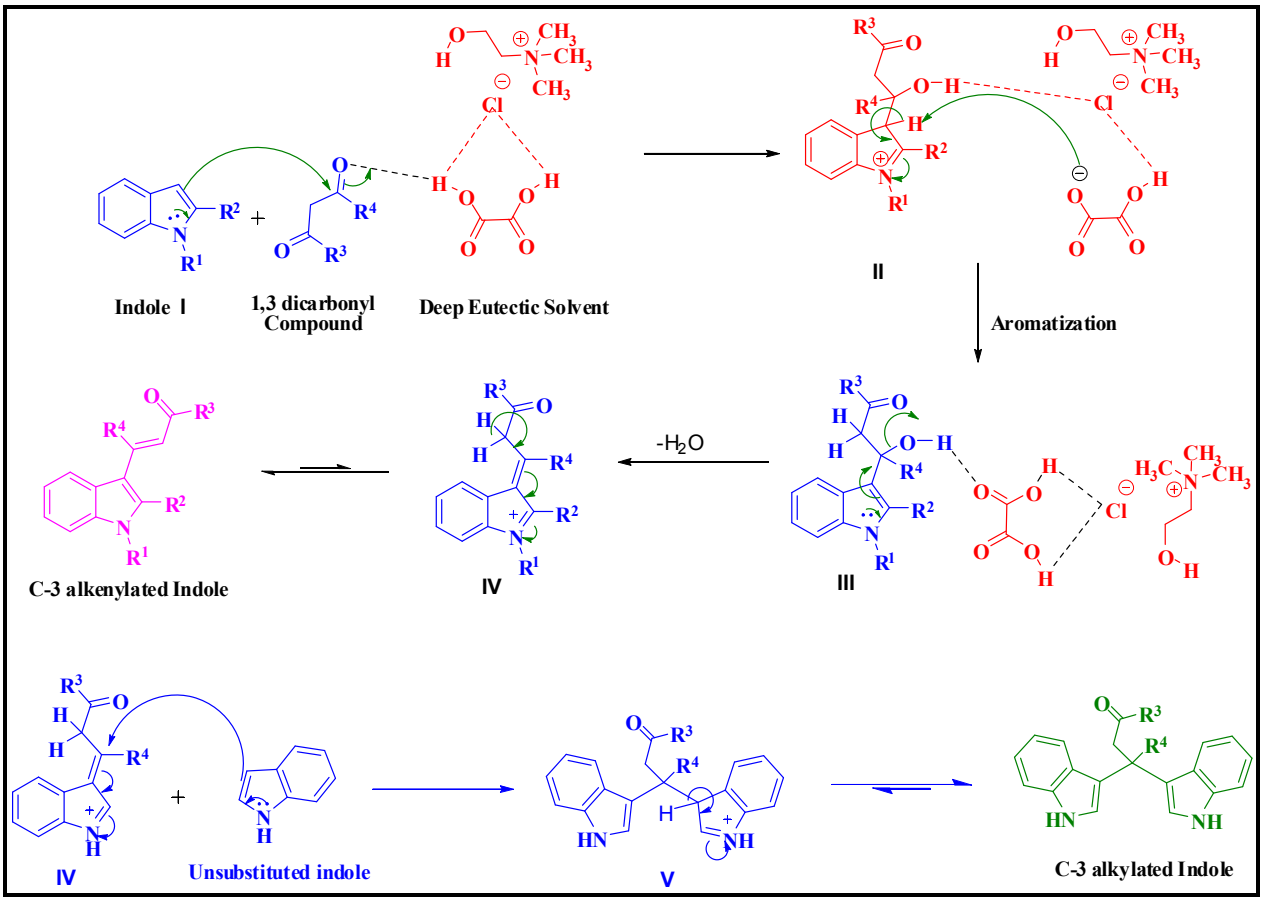


Table 1: Optimization of different catalysts in C-3 alkenylation of 2-methylindole

Entry	Catalyst	Time (h)	[a]Yield of 3a (%)
1	Without catalyst	24	No reaction
2	Choline chloride	24	No reaction
3	Oxalic acid	24	Traces
4	ChCl : Oxalic acid	2.5	89
5	ChCl : Malonic acid	12	52
6	ChCl : Succinic acid	12	55
7	ChCl : Tartaric acid	12	70
8	ChCl : Citric acid	12	75
9	ChCl : Urea	12	No reaction

Reaction conditions: 2-methyl indole (1 mmol), acetyl acetone (1 mmol), DES (3 mL), rt (32 ±2 ºC), [a]Isolated yields.

Table 2: C-3 alkenylation of 2-methylindole (**1a**) with acetylacetone (**2a**) in different solvents.

Entry	Solvent	Time (h)	[a]Yield of 3a (%)
1	Dichloromethane	12	61
2	Tetrahydrofuran	24	31
3	1,2-dichloroethane	24	37
4	Dioxan	24	39
5	Methanol	24	43
6	Ethanol	24	53
7	Acetonitrile	24	41

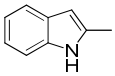
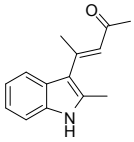
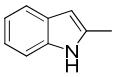
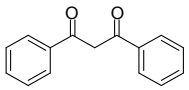
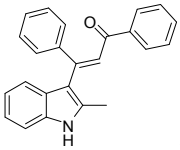
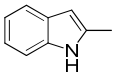
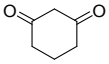
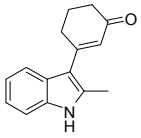
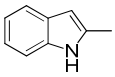
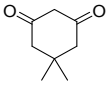
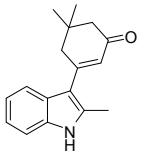
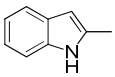
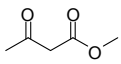
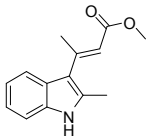
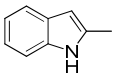
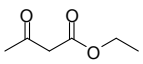
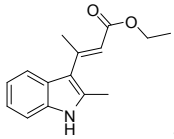
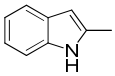
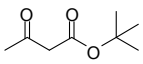
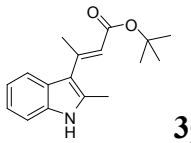
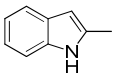
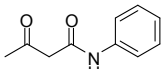
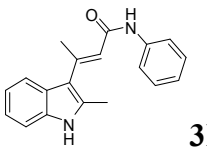
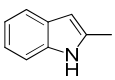
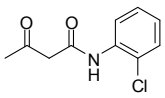
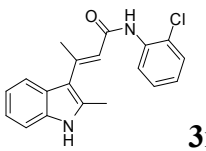
Reaction conditions: 2-methylindole (1 mmol), acetyl acetone (1mmol), solvent (3 mL), DES (0.5 mL), rt (32 ±2 ºC), [a]Isolated yields.

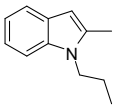
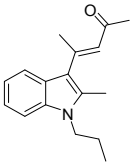
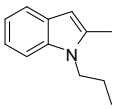
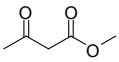
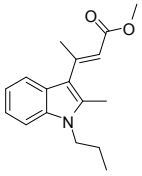
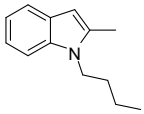
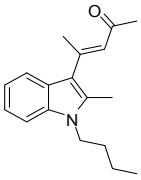
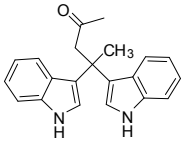
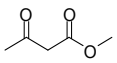
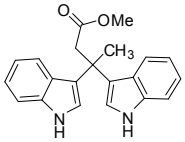
Table 3: Concentration study of DES in dichloromethane for C-3 alkenylation of 2-methylindole (**1a**) with acetylacetone (**2a**)

Entry	DES (mL)	DCM (mL)	DES in DCM (%)	Time (h)	[a]Yield of 3a (%)
1	4.0	0	-	2.5	89
2	3.0	0	-	2.5	88
3	2.5	0.5	83.3	2.5	61
4	2.0	1.0	65.0	2.5	61
5	1.5	1.5	50.0	2.5	53
6	1.0	2.0	33.3	2.5	40
7	0.5	2.5	16.6	2.5	32
8	0.1	2.9	3.3	2.5	11

Reaction conditions: 2-methylindole (1 mmol), acetyl acetone (1 mmol), rt (32 ±2 ºC), [a]Isolated yields.

Table 4: C-3 alkenylation/alkylation of indoles with different with 1,3 dicarbonyl compounds in ChCl : oxalic acid DES

Entry	Indole	1,3-Dicarbonyl compound	Product	Time (h)	Yield (%)
1	 **1a**	 **2a**	 **3a**	2.5	88
2	 **1a**	 **2b**	 **3b**	3	84
3	 **1a**	 **2c**	 **3c**	2.5	83
4	 **1a**	 **2d**	 **3d**	2.5	85
5	 **1a**	 **2e**	 **3e**	2.5	74
6	 **1a**	 **2f**	 **3f**	2.5	76
7	 **1a**	 **2g**	 **3g**	2.5	77
8	 **1a**	 **2h**	 **3h**	4	73
9	 **1a**	 **2i**	 **3i**	4.5	71

10	 **1b**	 **2a**	 **3j**	3	75
11	 **1b**	 **2e**	 **3k**	3	70
12	 **1c**	 **2a**	 **3l**	3.5	76
13	 **1d**	 **2a**	 **3m**	3	61
14	 **1d**	 **2e**	 **3n**	3.5	63

Reaction conditions: Indole (1 mmol), 1,3 dicarbonyl compound (1 mmol), DES (3 mL), room temperature (32 ±2 ºC), [a]Isolated yields.

Graphical Abstract