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Friedel-Crafts alkylation of indoles in Deep Eutectic Solvent

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Application of Deep Eutectic Solvent (DES) as a solvent and a working catalyst for Friedel-Crafts alkylation of indoles with isatin as well as homocyclic carbonyl compounds has been developed. The salient features of the present protocol are practical simplicity, excellent yields, product selectivity and reusability of reaction media.

The Friedel–Crafts reactions are common and powerful methods for C-C bond formation and remain the subject of continued improvement. In the present synthesis scenario, the development of green methodologies has emerged as a distinctive field of synthetic chemistry aimed to redesign chemical processes *via* environmentally benevolent way. Medium engineering has become one of the most important ways to tackle this issue in organic reactions by using water,[1] ionic liquids[2] and DES.[3] In this context, several ionic liquids have been exploited to make the Friedel–Crafts reactions greener, but each ionic liquid contains Lewis acids (such as $ZnCl_2$,[4] $AlCl_3$,[5] and $InCl_3$[6]). The use of Lewis acid (metal halides) causes problems associated with the strong complex formed between the ketone product and the metal halide itself which provokes the use of Lewis acid catalyst.[7] Therefore, a facile and practical Lewis acid free methodology is desirable for Friedel–Crafts reactions. Taking into account the utility of DES in number of reactions,[8] we have exploited Lewis acid free DES in Friedel–Crafts reactions with indole and electron-deficient carbonyl compounds.

Indole has become a privileged structure in numerous research areas such as: pharmaceuticals, fragrances, agrochemicals, pigments, and material science.[9,10] Among several reactions of indole, the reactions involving C-3 functionalization of indole with electron-deficient carbonyl compounds especially isatins has attracted and continues to attract interest from synthetic community. However, efforts have taken in this context resulted in the formation of symmetrical 3,3-di(indolyl)indolin-2-one which have limited applications.[11] Synthesis of selective 3-substituted-3-hydroxyoxindoles is highly desirable because they are privileged scaffold in various natural products and pharmaceutical lead compound (Fig. 1).[12]

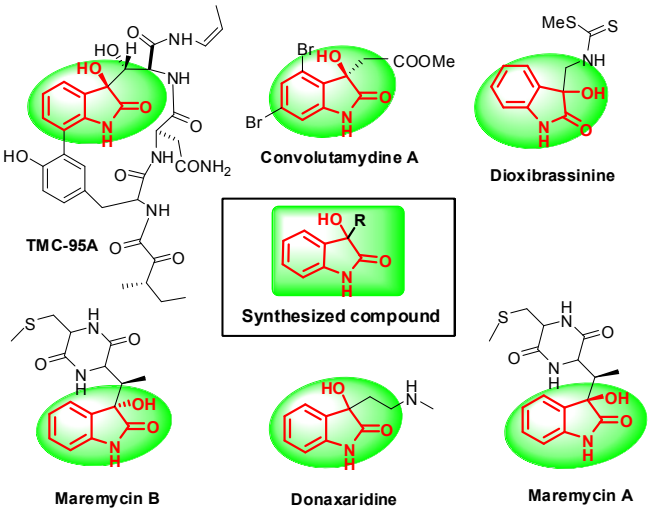


Fig. 1 Selected naturally occurring and pharmaceutical molecules with 3-substituted 3-hydroxy-oxindoles.

A protocol has been reported for selective synthesis of 3-substituted-3-hydroyoxindoles using stoichiometric amounts of β-cyclodextrin[13] but the search for more economical and environmentally benign catalytic medium is yet desirable. In continuation to our research endeavors in development of greener protocols,[14] here we wish to report application of DES in field of Friedel Crafts reaction of indoles with isatin as well as aceanthrylene-1,2-dione/acenaphthylene-1,2-dione.

To look into the prospect of new C–C bond formation, a model reaction using easily available and reasonably priced 1-methylisatin (1a) and indole (2a) was investigated in detail by varying the common solvents as

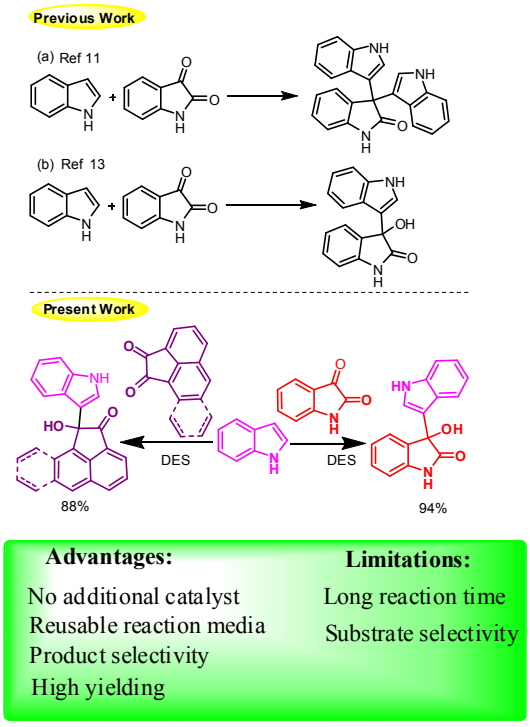


Fig. 2 Comparison of previous approaches with present approach

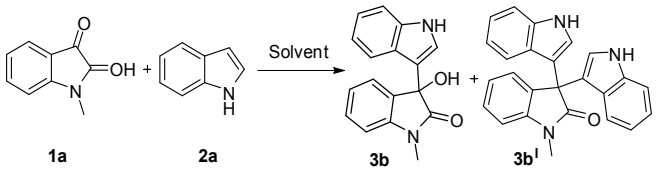
well as DESs in order to develop appropriate reaction conditions (Table 1).

When reaction was carried out in water, ethanol and acetonitrile without using catalyst at refluxed condition, desired product was not obtained indicating the necessity of catalyst. Furthermore, screening was continued by using different types of DESs, for example ChCl: CA (1:1), ChCl: Imidazole (3:7), ChCl: Urea (1:2) and ChCl: DMU (1:2) to determine their catalytic efficacies. Out of all of the trials, an exceedingly high product yield (94%) was obtained in ChCl: Urea (1:2) at room temperature (Table 1, entry 6), whereas ChCl: CA (1:1), ChCl: Imidazole (3:7) and ChCl: DMU (1:2) gave just to satisfactory yields.

These results reveal that DES is not only solvent, but also a catalyst of the reaction. Besides this, we have also studied the effect of temperature for model reaction with optimized condition. Next, to examine the versatility of the present standardized protocol, we explored the reactions of substituted isatins (benzene ring substituted isatins as well *N*-substituted isatins) with substituted indoles. To our delight, substituted isatins and indoles participated well in the reaction, diverse range of selective 3-Hydroxy-3-indolylindolin-2-ones were obtained (Scheme 1).

Moreover, with standardized conditions, substrate selectivity was studied for present protocol (Fig. 3). We performed a competitive reaction of indole (1.0 mmol) with the mixture of a number of carbonyl compounds such as acetophenone, 1-methyl isatin and benzil (1.0 mmol each).

Table 1 Optimization of reaction conditions[a]



Entry	Solvent	Temp (°C)	Time (h)	Yield (%) 3b	Yield (%) 3b[I]
1	H_2O	reflux	4	-	-
2	EtOH	reflux	4	-	-
3	CH_3CN	reflux	4	-	-
4	CA: ChCl	70	7	42	24
5	Imidazole: ChCl	70	8	64	18
6	**Urea: ChCl**	**r.t.**	**8**	**94**	**-**
7	Urea: ChCl	80	5	-	42
8	Urea: ChCl	80	5	-	92[b]
9	DMU: ChCl	75	5	68	12

[a]Reaction conditions: a mixture of 1a(1.0 mmol), 2a (1.0 mmol) and solvent (5 ml) was stirred. ChCl-choline chloride, CA–citric acid, DMU-1,3-Dimethyl urea. [b]Reaction conditions: a mixture of 1a(1.0 mmol), 2a (2.0 mmol) and solvent was stirred at 80°C

Interestingly, only the desired product 3-hydroxy-1-methyl-3-(1*H*-indol-3-yl)indolin-2-one (3b) was obtained as a sole product and the other starting carbonyl compounds were recovered intact. Hence, the present protocol seems to have a preferential substrate-selective property.

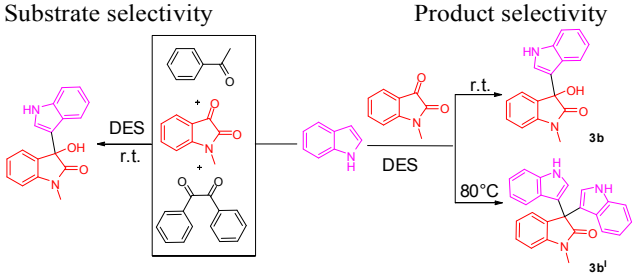
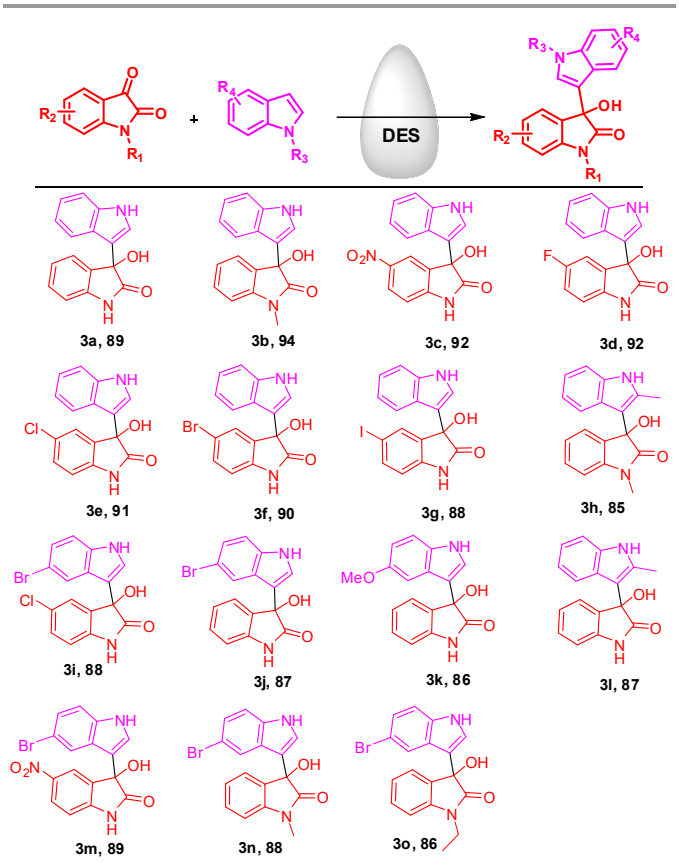


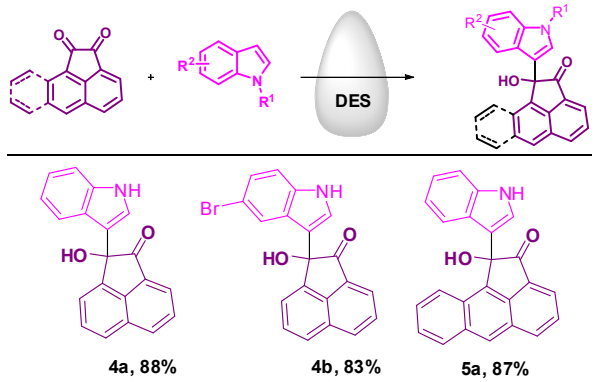
Fig. 3 Substrate selectivity and Product selectivity

Additionally, we have also studied the effect of temperature on product selectivity (Fig. 3). In this regard, when reaction (1-methyl isatin and indole, 1 mmol each) was carried out at room temperature, the desired product 3-hydroxy-1-methyl-3-(1*H*-indol-3-yl)indolin-2-one (3b, 94%) was obtained, whereas the same reaction was explored at 80°C, the selectivity was destroyed and resulted in simple ABB type pseudo multicomponent reaction i.e. the formation of 3,3-di(1*H*-indol-3-yl)-1-methylindolin-2-one (3b[I], 42%). When we performed the reaction of 1-methyl isatin and indole in 1:2 stoichiometric ratios at 80°C, the yield of product 3b[I] was increased to 92%.



Scheme 1 Synthesis of 3-Hydroxy-3-indolylindolin-2-ones. Reaction conditions: reactions were performed with isatin (1.0 mmol), indole (1.0 mmol) and DES (Urea: ChCl-1:2) at room temperature.

To examine the efficacy and scope of the present protocol for Friedel Crafts reaction, next, we explored the reaction of indole with homocyclic electron-deficient carbonyl compounds such as acenaphthylene-1, 2-dione and aceanthrylene-1, 2-dione. To our delight, the expected products were obtained in good yields (Scheme 2).



Scheme 2 Reaction of Indole with homocyclic carbonyl compounds. Reaction conditions: reactions were performed with acenaphthylene-1,2-dione/aceanthrylene-1,2-dione (1.0 mmol), indole (1.0 mmol) and DES (Urea: ChCl-1:2) at room temperature.

For model reaction, a complete study was done to assess the reusability of DES (Urea: ChCl). After completion of reaction, water was added to the reaction mixture. The DES being soluble in water comes in the water layer and product was precipitated. The solid product was separated by filtration. The DES was recovered from the filtrate by evaporating the water phase at 80°C under vacuum. For compound **3b** an alternative way was tried for recovery of DES using of 2-Methyl THF instead of water. After completion of reaction 2-Methyl THF was added to reaction mixture, product went to organic phase and DES settled down. Organic phase was separated and product was obtained by evaporating organic phase under vacuum and settled DES was used for next batch syntheses.

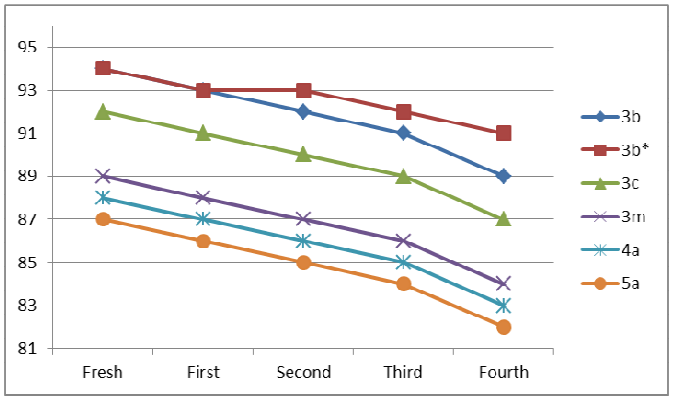


Fig. 4 Reusability data for DES (* reusability of DES using 2Me-THF during extraction)

The recovered DES was then successfully used for the next 5 batches. Furthermore, the reusability of DES was confirmed for the syntheses of compounds 3c , 3m, 4b, and 5a with five cycles and small losses in catalytic activity were observed (Fig. 4).
Beside reusability test, cross reusability test was also

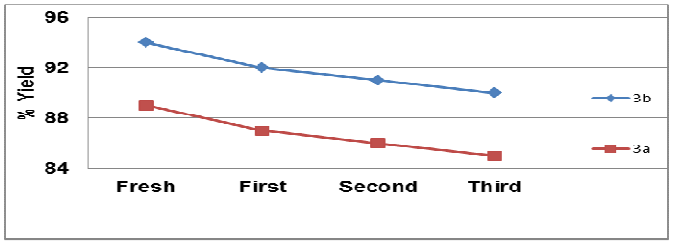


Fig. 5 Cross Reusability data for DES

performed by taking fresh DES for the synthesis of 3a, after completion of reaction DES was recovered then it was used for the first batch synthesis of 3b and vice versa. The cross reusability was carried out for 3 cycles with minute loss of catalytic activity of DES (Fig. 5). Furthermore, no substrate product contamination was observed during cross reusability experiment.

In conclusion, we have developed Lewis acid free Friedel-Crafts reaction using low-priced, non-toxic, easily available DES as a solvent and as a catalyst. The selective syntheses of 3-Hydroxy-3-indolylindolin-2-ones/2-hydroxy-2-(1H-indol-3-yl)acenaphthylen-1-(2H)-ones/1-hydroxy-1-(1H-indol-3-yl)aceanthrylen-2(1H)-ones and reusability/cross reusability of the reaction media are added advantages to this protocol, thus provides a better and practical alternative to existing methods. This research confers a step towards development of more active greener catalytic media.

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Notes and references

[†]*Electronic supplementary information (ESI) available. See DOI: 10.1039/c4gc0228 7d*
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