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Brønsted acid ionic liquid catalyzed facile synthesis of 3-vinylindoles through direct C3 alkenylation of indoles with simple ketones

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Direct dehydrative coupling protocol for the synthesis of 3-vinylindoles by using easily available indoles and simple ketones as substrates was developed with the aid of a sulfonyl-containing Brønsted acid ionic liquid. The salient features of this protocol are high synthetic efficiency, metal- and solvent-free system, recyclable catalyst, mild conditions and easy product isolation. With the ionic liquid catalyst, a hitherto unreported straightforward method for the construction of indolo[3,2-*b*]carbazole skeleton was also developed by using 2-hydroxymethylindole and acetophenone as starting materials.

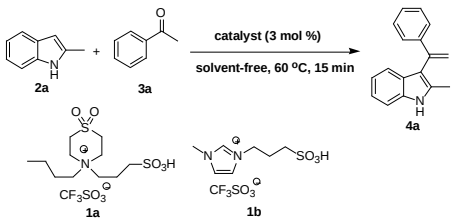
Indoles are found in many naturally occurring compounds. Because of their unique biological activities, the modification of the indole structure has aroused great interest of organic chemists.[1,2] 3-Vinylindoles are a class of unique functionalized indoles[3], which can be utilized in the synthesis of a number of biologically significant compounds,[4] such as indole alkaloids,[5] carbazoles,[6] and carbolines.[7] Some of 3-vinylindole derivatives can be used as diene equivalents for the synthesis of polyfunctional indoles.[8] 3-Vinylindoles have been reported recently to display interesting biological activities, such as anticancer agents,[9] antiviral agents,[10] and antibacterial agents.[11] Vinylindoles could be synthesized by many methods, and among which, metal-based catalyst mediated direct oxidative alkenylation of indoles has been extensively investigated recently.[12] A metal-free alkenylation protocol has also been developed by Jiao and his co-workers.[13] Acid-base catalysis has also been frequently used in the synthesis of 3-vinylindoles. For instance, hydroarylation of indole with alkyne has been established by using acid catalysts.[14] Rassu *et al* has introduced a novel 3-alkenyl-2-silyloxyindole that can be prepared from 3-alkylidene oxindoles and TBS-triflate with the aid of Et_3N.[15] Acid-catalyzed alkenylation of indoles with an aldehyde or its congeners have been employed for introducing a carbon-carbon double bond into the indole skeleton.[16] Direct alkenylation of indoles with α-oxo ketene dithioacetals has also been reported by Yu.[17] Although various methods have been reported for the synthesis of 3-vinylindoles, most of these methods often involve the use of expensive reagents or metal-based catalysts. Some of them involve the use of harsh conditions and suffer from the lack of simplicity. Therefore, the development of simple, convenient, and environmentally friendly approaches is desirable.

Direct dehydrative couplings of indoles with ketones are clean reactions to synthesize 3-alkenylated indoles as the only by-product is water. However, these reactions are strictly limited to the use of highly active ketones, such as β-diketones, β-ketoesters and phenyl benzyl ketones, as starting materials.[18] The use of inexpensive and abundantly available simple ketone as substrate in this alkenylation reaction is very attractive from the viewpoint of lowering the synthetic cost and extending the product diversity. We have recently reported a novel sulfonyl-containing Brønsted acid ionic liquid (IL) that can promote various organic reactions under solvent-free conditions (**Table 1**, **1a**).[19] Simultaneous existence of sulfonyl and sulfonic groups ensures an outstanding catalytic activity of the IL. In continuation of our research on the selective synthesis of indole derivatives,[20] we tried in this work to use the IL as a catalyst for establishing the direct dehydrative coupling of indoles and simple ketones. It was found that the protocol for the synthesis of 3-vinylindoles is indeed practicable. The established method not only opens an avenue to access 3-vinylindole derivative from cheap and easily available substrates, but also possesses many characteristic features of green organic synthesis, such as high reaction yields, recyclable catalyst and easy product separation.

Initially, a direct dehydrative coupling of 2-methylindole **2a** and acetophenone **3a** was investigated. The reaction was performed at 60 °C under solvent-free conditions. Brønsted acids, such as toluenesulfonic acid (TsOH) and trifluoromethanesulfonic acid (TfOH), are moderately active for this reaction, and after 15 minutes of reaction, the expected product **4a** was obtained in 37 % and 45 % yields, respectively (**Table 1**, entries 1 and 2). An appreciable yield decrease was observed when the reactions were performed in an organic solvent, dichloroethane (DCE). Increase of the reaction time is effective for improving the reaction yields. After 1 hour, the yield with TsOH and TfOH reached to 73 % and 84 %, respectively. We also screened many other catalysts. Lewis acids, such as $FeCl_3$ and $Sc(OTf)_3$, are less active as compared with the examined Brønsted acids (entries 3 and 4). To our great delight, Brønsted acid IL **1a** showed an excellent performance in the model reaction, and 95 % of yield could be obtained within 15 minutes (entry 5). The reaction with Forbes's IL, **1b**, only provided **4a** in 42 % yield (entry 6). Although a good yield, 72 %, was obtained after 1 hour of reaction

with **1b**, due to the fact that the polarities of **4a** and **2a** were nearly the same, which gave rise to a difficulty to the isolation of the desired product. These results demonstrated clearly that IL **1a** is indeed an efficient catalyst for the direct dehydrative coupling of **2a** and **3a**. Further investigation revealed that the reaction was also affected by temperature and catalyst amount (entries 7 and 8), and the optimal conditions are 60 ^{o}C and 3 mol % of **1a** catalyst. Because **1a** catalyst is not soluble in non-polar organic solvent, the formed product could be easily isolated by extraction with ethyl acetate. The recycled **1a** could be reused in the next run after 30 minutes of drying at 100 ^{o}C under vacuum (20 mmHg). Reuse experiments manifested that **1a** could be reused at least 5 times without significant loss of its activity in the model reaction (entry 9). If decomposition of IL **1a** occurs during the reaction, it will produce probably some acidic species, such as SO_2 and SO_3.[21] Out of this consideration, **1a** was neutralized with an aqueous solution of sodium hydroxide (1.0 N) at the end of the reaction. No precipitate was observed after adding an $AgNO_3$ (*aqu.*) into the system, indicating that sulphur oxides were not formed in our system. This manifested that IL **1a** is quite robust. In addition, under the optimal conditions, the reactions scaled up to multigram quantities provided uniform results (entry 5), indicating the practical usefulness of this method.

Table 1. Dehydrative alkenylation of **2a** with **3a**.[a]



entry	catalyst	yield (%)
1	TsOH	37 (20,[b] 73[c])
2	TfOH	45 (36,[b] 84[c])
3	$FeCl_3$	29 (19)[b]
4	$Sc(OTf)_3$	19 (15)[b]
5	**1a**	95, (91)[g]
6	**1b**	42 (73[c])
7[d]	**1a**	70
8[e]	**1a**	45
9[f]	**1a**	95

[a]: **2a**: 2.5 mmol, **3a**: 2.5 mmol, catalyst: 0.08 mmol. [b]: DCE as solvent (1.0 ml). [c]: reaction time is 1 hour. [d]: 40 ^{o}C. [e]: **1a**: 0.01 mol %. [f]: **1a** was reused in the fifth run; [g]: the reaction was performed with 10.0 mmol scale.

We probed then the scope of the reaction with respect to both the indole and the ketone components. Acetophenones with different substituents smoothly reacted with 2-methylindole, producing 2-methyl-3-(α-arylvinyl)indoles in moderate to excellent yields (**Figure 1**). Both electron-rich and electron-poor acetophenones readily participated in the reaction. Even those containing substituents in *ortho*-position of the acetyl group, such as 2-bromoacetophenone and 2-fluoroacetophenone, can be used as well, producing the desired products in high yields. Some bulky ketones, such as 1-tetralone and 2-acetonaphthone also reacted with 2-substituted indoles smoothly. Structures of the obtained product, **4n** and **4o**, have been unambiguously confirmed by the x-ray structural analysis. [22] It should be noted that preparation of these indole derivatives through conventional methods is not easy, which either involves the use of expensive reagents, such as alkynes [23] and benzoylindoles[24] or is plagued by a low yield resulting from multi-step or insufficient reaction.[25] The present system opened a cost-effective and environmentally benign method to access these compounds. Cyclobutyl phenyl ketone is also a viable reagent to alkenylate 2-methylindole without damage of the cyclobutyl group. The skeleton of **4l** has shown to be a potential antimitotic and antitumor agent.[26] The results obtained with aliphatic ketones are as competent as in the case of aryl alkyl ketone. Various ketones, such as isopropyl methyl ketone, cyclohexanone, 2-methylcyclohexanone and 2-methylcyclopentanone could be successfully applied in this reaction. Interestingly, the dehydrative coupling selectively occurred in favour of forming a densely substituted double bond when a substituent group existed in the α-position of the ketocarbonyl group. Various indoles, such as 2-phenylindole, 1-methyl-2-phenylindole, 1-ethyl-2-phenylindole, 1,2-dimethylindole, 2-methyl-6-fluoroindole and 2,5-dimethylindole could all be successfully used in this reaction. Particularly, 5-bromoindole can also be alkenylated with cyclic ketone, such as cyclohexanone. This result overcomes the difficulty of using non-C2-substituted indoles in the alkenylation reaction.[27]

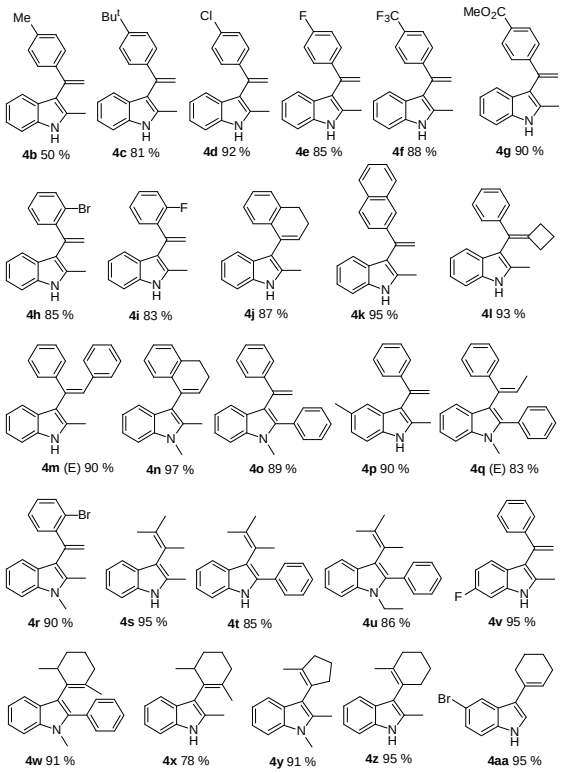


Figure 1. Substrate scope of **1a**-catalyzed C3 alkenylation of indoles with ketones.

The reaction might proceed according to the mechanism depicted in **Figure 2**. Initial event of the reaction is the formation of a carbocation intermediate (**I**). The desired product **4a** could be generated by the following H^+ elimination.[28] However, trapping of this intermediate with **2a** is also possible, which results in the formation of **5a**. Interestingly, this reaction might be reversible as 2-methylindole is a good leaving group.[27, 29] However, no **5a** was observed during the reaction. To verify this hypothesis, **5b** was synthesized and then treated with **1a** catalyst (**Scheme 1**). As we expected, **4aa** was obtained in 92 % of yield. This result led us to draw a conclusion that the reversible carbon-carbon bond formation reaction is indeed able to maximize the selectivity to **4a**.

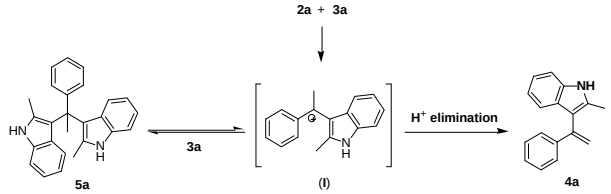
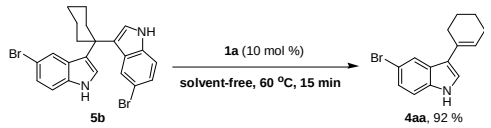
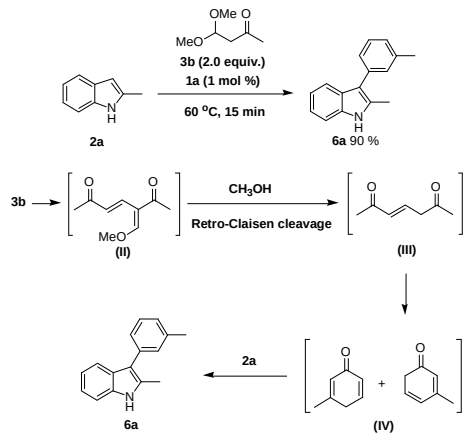


Figure 2. Proposed mechanism.



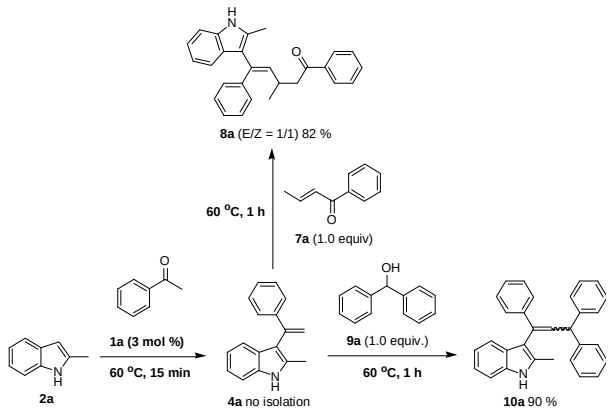
Scheme 1.Synthesis of **4aa** from **5b** catalysed by IL **1a**.

A bifunctional reagent, **3b**, was also utilized in this system, which has two active sites including the ketocarbonyl and the acetal. It was found unexpectedly that **6a** was obtained in 90 % of yield (**Scheme 2**). Remarkably, 1 mol % of **1a** is sufficient enough to promote this reaction toward completion. Previous systems for accomplishing the C3-arylation of indoles involve either the use of toxic catalysts or a time-consuming procedure.[30] This reaction might proceed through the following pathway: (i) condensation of two molecules of **3b**, which generated an intermediate (**II**);[31] (ii) formation of a 2,6-dione (**III**) through retro-Claisen cleavage; [32] (iii) intramolecular cyclization of (**III**) and (iv) C3-vinylation of **2a**. An easiness of the last step contributed probably the main power that enabled the condensation reaction to be possible.



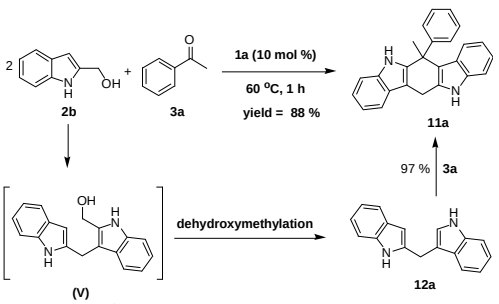
Scheme 2. C3 arylation of **2a** with **3b** catalyzed by **1a**.

1,1-Diarylethylene derivatives have been recently used as π-nucleophiles.[33] DFT calculation revealed that the electron density in the double bond of **4a** is indeed nonuniform, and a distribution in favour of CH_2 terminal is foreseeable.[22] Because the reactions of π-nucleophiles are often associated with the use of acid catalyst, we therefore envisioned that, it might be possible to establish some one-pot step-wise reactions by means of adding a suitable electrophile into the reaction system. As shown in **Scheme 3**, this idea was proved to be feasible indeed, and both **7a** and **9a** are able to act as electrophile to react with the generated **4a**.



Scheme 3. One-pot step-wise reactions.

Finally, a highly reactive indole, 2-hydroxymethylindole **2b**, was used as substrate in the title reaction in conjunction with using **3a** as an alkenylation reagent. Unexpectedly, in the presence of **1a**, a 5,6, 11,12-tetrahydro-6-methyl-6-phenylindolo[3,2-*b*]carbazole **11a** was obtained in 88 % yield (**Scheme 4**). Literature survey stated that the analogous polyheterocycles have displayed some unique biological activities.[34] Previous method to access the skeleton of this indolo[3, 2-*b*]carbazole involves the use of 2,3´-diindolylmethane as a critical precursor, which is very expensive and difficult to prepare. The reaction might proceed through the following pathway: (i) self-condensation of two molecules of 2-hydroxymethylindole that generated intermediate (**V**);[35] (ii) dehydroxymethylation of (**V**) to form 2,3´-diindolylmethane **12a**; and (iii) electrophilic alkylation of **3a** with **12a** forms the final product **11a**. Although dehydroxymethylation of indole derivatives has been rarely reported, removal of a hydroxymethyl group from an aromatic system was often used in organic synthesis. [36] Furthermore, treating 2,3´-diindolylmethane **12a** with acetophenone in the presence of **1a** produced **11a** in nearly quantitative yield, which supported properly the proposed mechanism.



Scheme 4. Synthesis of indolo[3,2-*b*]carbazole **11a**.

Conclusions

By using a sulfonyl-containing Brønsted IL as catalyst, we have successfully synthesized various 3-vinylindoles through direct dehydrative alkenylation of indoles with inexpensive and abundantly available simple ketones. Compared with the conventional methods for the synthesis of 3-vinylindoles, this method displayed many advantages including high synthetic efficiency, cost-effective reaction, recyclable catalyst and easy product isolation. Particularly, by using 2-hydroxymethylindole as substrate, a hitherto unreported straightforward method for the synthesis of indolo[3,2-*b*]carbazole derivative was established. In addition, an unexpected method for

accomplishing C3-arylation of 2-methylindole was also developed by using acetylacetaldehyde dimethyl acetal as a nonaramatic arylation reagent. All these results demonstrated clearly that the Brønsted IL is indeed an invaluable powerful catalyst for the derivatization of indoles.

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

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