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Boron-Catalyzed Dehydrative Friedel-Crafts Alkylation of Arenes Using *β*-Hydroxyl Ketone as MVK Precursor

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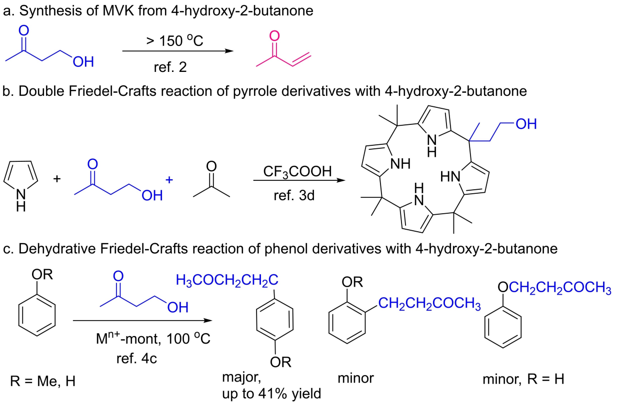
Abstract: Boron-catalyzed environmentally benign dehydrative Friedel-Crafts alkylation of indole/pyrrole and aniline derivatives with β-hydroxyl ketones has been developed for the first time. This method provides an efficient and green replacement of toxic and unstable methyl vinyl ketone (MVK) by safer and cheaper β-hydroxyl ketone. The reaction features easy operation, wide substrate scope and significantly, only water is formed as by-product.

Keywords: Boron-catalyzed; Dehydrative Friedel-Crafts alkylation; β-hydroxyl ketones; MVK

Methyl vinyl ketone (MVK) is a versatile feeding stock in organic synthesis, for example, it is widely used as Michael acceptor in Robinson annulations and Baylis-Hillman reactions, and also in the synthesis of many natural products and drug molecules,[1] such as Biperiden,[1a] Caulersin,[1b] Vinclozolin[1c] and Vitamin A acetate.[1d] However, its flammability, high toxicity, and pungent odour bring trouble with transportation and storage. On the other hand, it should be noted that MVK can easily undergo polymerization, resulting in low yield and by-products which are not easily to be purified. Thus, it is very important to find a bench-stable replacement of MVK. The utilization of 4-hydroxy-2-butanone as the precursor of MVK in an one-pot reaction should be an ideal choice. However, to develop a reaction that compatible with the dehydration of 4-hydroxy-2-butanone is quite challenging, not only due to that harsh reaction conditions are required in the conversion of 4-hydroxy-2-butanone to MVK (Scheme 1, a),[2] but also because of that the ketone moiety is an active functionality in the presence of a Lewis acid or Brønsted acid.[3] For example, in the acid catalysed/promoted reaction of pyrrole with acetone and 4-hydroxy-2-butanone, ketones are activated and double Friedel-Crafts reactions are dominant instead of the dehydration process[3d] (Scheme 1, b). To date, examples for the combination of dehydration and further transformations of in situ formed MVK are extremely limited to the Friedel-Crafts reaction of phenol derivatives,[4] and the yields and selectivities are not very good, probably due to the elevated reaction temperature (100 °C) (Scheme 1, c).[4c]

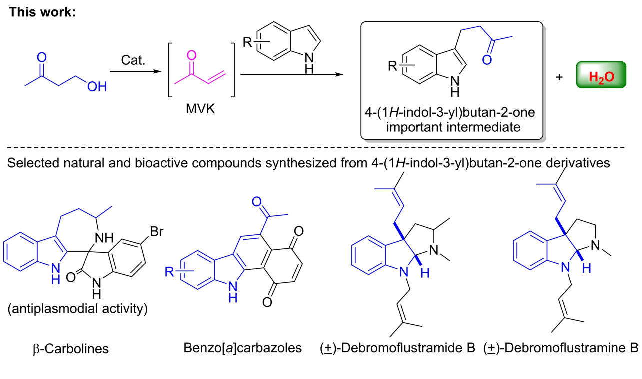
To our great surprise, the dehydrative Friedel-Crafts reaction of indoles with 4-hydroxy-2-butanone for the direct synthesis of 4-(1H-indol-3-yl)butan-2-ones, which are important intermediates to access many useful indole alkaloids,[5] such as benzo[a]



Scheme 1. Challenges in one-pot usage of 4-hydroxy-2-butanone as MVK precursor.

carbazoles,[5a] β-carbolines,[5b] (±)-debromoflustramide B,[5e] (±)-debromoflustramine B and E,[5e] has not been successfully achieved yet (Scheme 2). It is probably due to that in the presence of a Brønsted or Lewis acid catalyst, the reaction prefers to undergo double Friedel-Crafts alkylation to afford bisindole products.[6] Therefore, the development of an efficient catalytic system, which is compatible with dehydration of 4-hydroxy-2-butanone to MVK and subsequent chemoselectively MVK transformation, is highly desirable.[7]

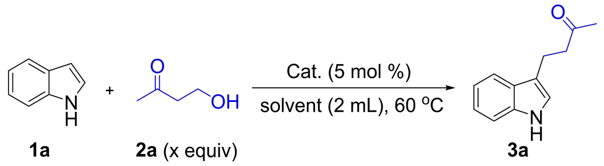
During the last decades, Lewis acids or Brønsted acids catalyzed Friedel-Crafts alkylation reaction has gained much attention because it provided an efficient method for the facile contruction of diversfied C–C and C–X (X = heteroatom) bonds.[8] Particullarly, the dehydrative Friedel-Crafts alkylation is of great interesting, not only because of the readily available starting materials were used, but also due to that only water was formed as by-product. On the other hand, electron-deficient boryl derivatives have been intensively investigated in Frustrated Lewis pair chemistry[9] and other useful transformations either as Lewis acid[10] or Brønsted acid.[11] Recently, Talor and co-workers reported arylboronic acid catalyzed dehydrative esterification and *C*-alkylation using benzylic alcohols as the electrophile. The group of Prof. Zhang reported an interesting *ortho*-functionalization of phenol with α-diazoesters using $B(C_6F_5)_3$ as a bifunctional catalyst.[12] Our group also observed that α-aryl α-dizaoesters could undergo O–H bond insertions under the bifunctional catalysis of $B(C_6F_5)_3 \cdot H_2O$ complex.[13] Moreover, we reported the first example for azide insertion of α-aryl α-dizaoesters catalysed by $B(C_6F_5)_3$.[14] To continue our reserach interesting, we envisaged that $B(C_6F_5)_3 \cdot H_2O$ may be an efficient Brønsted catalyst for dehydration of 4-hydroxy-2-butanone. Herein, we report a dehydrative Friedel-Crafts alkylation of indole and pyrrole derivatives with 4-hydroxy-2-butanone. This method has great advantages in replacement of MVK or other α, β-unsaturated ketones due to their instability and trend to polymerization. To the best of our knowledge, there is no report for the dehydrative Friedel-Crafts alkylation of indoles/pyrroles with β-hydroxyl ketones as MVK-type precursors.



Scheme 2. The first dehydrative Friedel-Crafts reaction of indoles using 4-hydroxy-2-butanone as MVK precursor.

Initially, indole **1 a** and β-hydroxy ketone **2 a** were chosen as model substrates to optimize the reaction conditions. When the reactions were performed in the presence of metal Lewis acids such as $FeCl_3$, $ZnCl_2$ and $AlCl_3$ at 60 °C in DCE, the reactions were quiet complex and **3 a** was obtained in very low yields (Table 1, entries 1–3).[15] When $BF_3 \cdot Et_2O$ was employed as Lewis acid catalyst, **3 a** was obtained in 45% yield (Table 1, entry 4). Brønsted acids CF_3COOH and TsOH showed better catalytic activity and delivered the desired product in 54% and 58% yields (Table 1, entries 5 and 6). However, PhCOOH and HCl could barely catalyze this transformation to give only trace amount of desired product (Table 1, entries 7 and 8). Interestingly, in the presence of 5 mol% $B(C_6F_5)_3 \cdot H_2O$, the desired product **3 a** was obtained in 70% yield after

Table 1. Screening of the reaction conditions.[a]

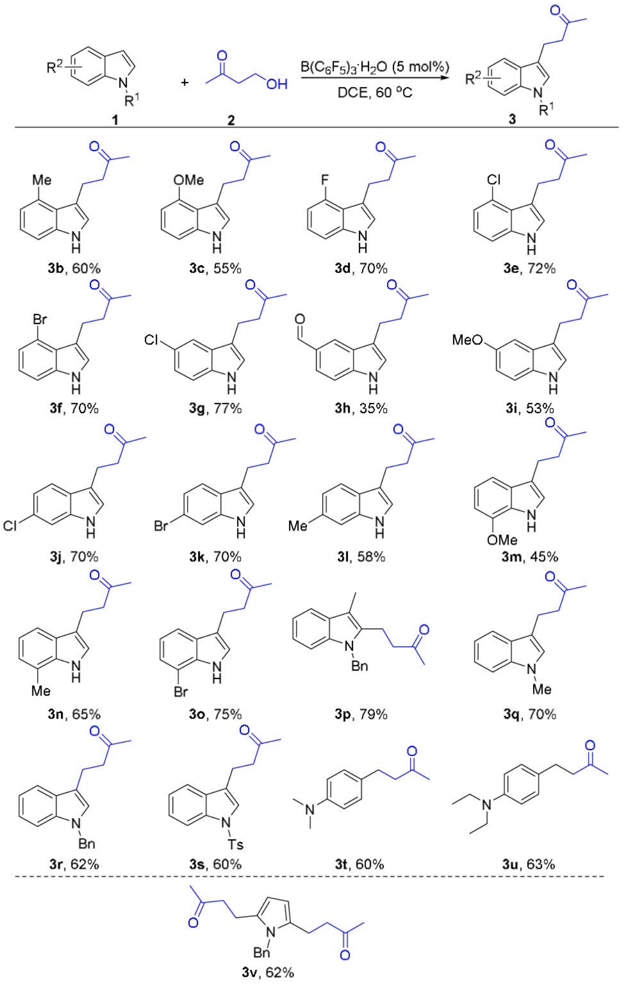


entry	cat.	sol.	x	yield (%)[b]
1	$FeCl_3$	DCE	1	20[c]
2	$ZnCl_2$	DCE	1	15[c]
3	$AlCl_3$	DCE	1	25[c]
4	$BF_3 \cdot Et_2O$	DCE	1	45[c]
5	CF_3COOH	DCE	1	54
6	TsOH	DCE	1	58
7	PhCOOH	DCE	1	trace
8	HCl	DCE	1	trace
9	$B(C_6F_5)_3 \cdot H_2O$	DCE	1	70
10	$\mathbf{B(C_6F_5)_3 \cdot H_2O}$	**DCE**	**2**	**88**
11	–[d]	DCE	2	N.R.
12	$B(C_6F_5)_3 \cdot H_2O$	DCE	2	60[e]
13	$B(C_6F_5)_3 \cdot H_2O$	Hexane	2	51
14	$B(C_6F_5)_3 \cdot H_2O$	PhCl	2	70
15	$B(C_6F_5)_3 \cdot H_2O$	Toluene	2	45
16	$B(C_6F_5)_3 \cdot H_2O$	THF	2	N.R.
17	$B(C_6F_5)_3 \cdot H_2O$	MeCN	2	N.R.
18	$B(C_6F_5)_3 \cdot H_2O$	DCE	2	75[f]
19	$B(C_6F_5)_3 \cdot H_2O$	DCE	2	68[g]

[a] Reactions were carried out on a 0.2 mmol scale under air in solvent (2 mL) at 60 °C for 24 h.
[b] Yields of isolated products.
[c] Complex mixture was formed.
[d] Without catalyst.
[e] Reaction was performed at 40 °C.
[f] 3 mol% catalyst was added.
[g] 7 mol% catalyst was added. THF = tetrahydrofuran. DCE = dichloroethane. PhCl = chlorobenzene. MeCN = acetonitrile.

24 h (Table 1, entry 9). Notably, the yield of **3 a** increased to 88% when 2 equiv. of *β*-hydroxyl ketone was added (Table 1, entry 10). In the absence of a catalyst, no reaction took place (Table1, entry 11). Conducting the reaction at 40 °C instead of 60 °C, the yield of **3 a** was decreased to 60% (Table 1, entry 12). A solvent screen showed that DCE was the most suitable solvent for this reaction (Table 1, entries 13–17). Decreasing or increasing the loadings of catalyst, the reactions furnished diminished yields of product **3 a** in both cases (Table 1, entries 18 and 19).

With the optimal reaction conditions in hand (Table 1, entry 10), we focused our attention to evaluating the substrate scope of the reaction by varying the structure of indoles (Scheme 3). For reactions of C4 substituted indoles with *β*-hydroxyl ketone **2 a** under the standard reaction conditions, products **3 b**–**3 f** were obtained in 55%-72% yields, respectively, while the electronic properties of the substitutes had no significant effect on the reaction outcomes. For indolyl substrates with C5 substituents, the reactions all went on smoothly to give corresponding products **3 g**–**3 i** in moderate yields. It had to been mentioned that for substrate bearing a 5-aldehyde group, relatively low yield of **3 h** was obtained probably due to that the activation of aldehyde with borane complex would result in unwanted side reactions. Substrates with C6 and C7 functionalities were also harmonious with this reaction, and furnished the desired products **3 j**–**3 o** in moderate yields. Specially, C3 substituted indole was also found to be a good substrate and furnished 2-substituted indole product **3 p** in 79% yield. *N*-Methyl, Bn and Ts protected indoles were also suitable for this transformation and provided the expected 3-substituted indoles **3 q**–**3 s** in 60–70% yields, respectively. For *N*,*N*-dimethylaniline and *N*,*N*-diethylaniline derivatives, the reactions also proceeded smoothly to give the *para*-functionalized products **3 t** and **3 u** in 60% and 63% yields, respectively. Notably, for pyrrole substrate, double functionalization took place and product **3 v** was obtained in 62% yield. It should be noted that when anisole was employed as substrate, no reaction take place under the standard reaction conditions, probably due to the strong interaction of oxygen atom with the boryl complex will reduce its catalytic activity.



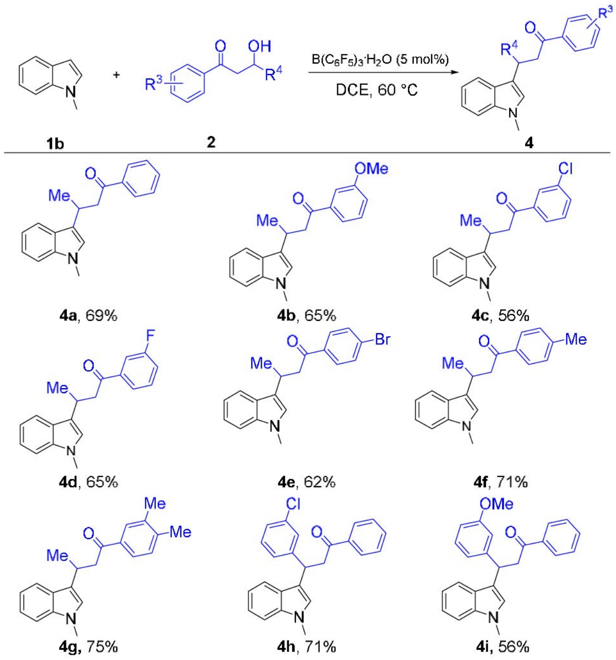
[a] All reactions were carried out on a 0.2 mmol scale under air at 60 °C in DCE (2 mL) for 24 h. [b] Isolated yields

Scheme 3. Substrate Scope of indole and electron-rich arene derivatives.[a,b]

To determine the generality of *β*-hydroxyketones, we next examined a series *β*-hydroxyketones with N-methylindole under the standard reaction conditions. The *β*-hydroxyketones were synthesized by the aldol reaction of corresponding ketones and aldehydes. As can be seen in Scheme 4, for both electron-donating and electron-withdrawing groups on the phenyl group, the reactions all proceeded smoothly to afford the desired products **4 a**–**4 i** in 56–75% yields. It is worth noting that R^4 could be phenyl groups, and corresponding products **4 h** and **4 i** were delivered in moderate to good yields.

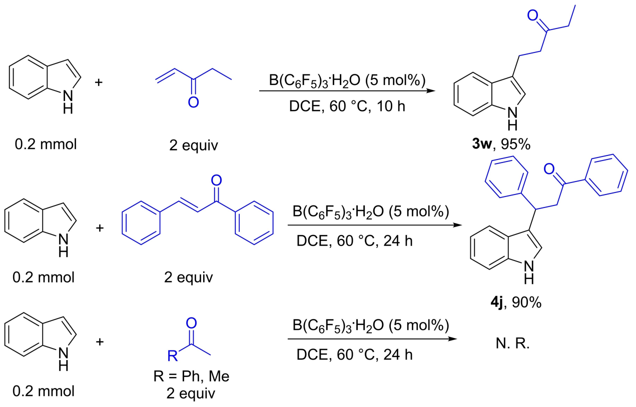
To gain a deeper understanding of the mechanism, several control experiments were conducted. As shown in Scheme 5, The reactions of indole with ethyl vinyl ketone (EVK) and chalcone in the present of $B(C_6F_5)_3 \cdot H_2O$ gave corresponding ketone products **3 w** and **4 j** in excellent yields, indicating the unsaturated ketone should be the intermediate of the reaction.[10o] While treatment of indole with acetophenone or acetone under the standard reaction conditions, no reaction took place, representing that the ketone products **3** is not active to react with indoles[6] in the presence of $B(C_6F_5)_3 \cdot H_2O$.

On the basis of the mechanistic studies, NMR experiments (SI) and previous reports,[10o,11g and j,16] we propose a putative reaction mechanism for the present dehydrative Friedel-Crafts alkylation in Scheme 6. Initially, in the presence of in the presence of B

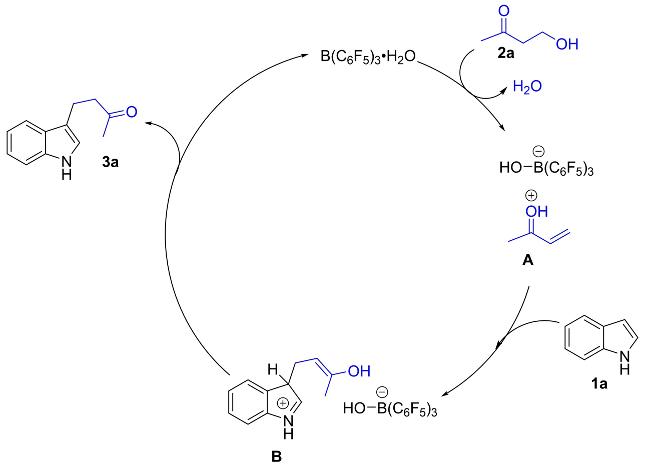


[a] All reactions were carried out on a 0.2 mmol scale under air at 60 °C in DCE (2 mL) for 24 h. [b] Isolated yields.

Scheme 4. Substrate Scope of β-hydroxyketones.[a,b]



Scheme 5. Control experiments.



Scheme 6. Plausible mechanism.

$(C_6F_5)_3 \cdot H_2O$,[16] β-hydroxyketone is activated to form intermediate **A** after elimination of one molecule of H_2O, the following Friedel-Crafts reaction of intermediate **A** with indole gives intermediate **B**, which affords the final product **3a** after tautomerization together with the regeneration of catalyst.

In summary, we have developed a novel, highly efficient catalytic system that compatible with dehydration of β-hydroxyl ketones, affording synthetically valuable 4-(1H-indol-3-yl)butan-2-one derivatives under mild conditions. Notable, boron catalyst showed special catalytic activity to facilitate the dehydration of β-hydroxyl ketones instead of activation of the ketone moiety, thus avoiding the direct use of highly toxic MVK. Moreover, aniline and pyrrole derivatives are also suitable substrates for this method. Further studies to gain more mechanistic insight and application of this methodology in organic synthesis are currently underway in our laboratory.

Experimental Section

A 10 mL reaction tube was equipped with a magnetic stir bar, followed by the addition of $B(C_6F_5)_3 \cdot H_2O$ (5.1 mg, 5 mol%) and DCE (2 mL). Subsequently 0.2 mmol of indole/pyrrole derivatives and β-hydroxyketones (2 equiv, 0.4 mmol) were added into the reaction tube. The reaction mixture was stirred at 60 °C for 24 h (monitored by TLC) then the mixture was concentrated, the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 20:1–5:1) to afford the desired products.

Acknowledgements

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