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Acid-catalyzed acylation reaction *via* C–C bond cleavage: a facile and mechanistically defined approach to synthesize 3-acylindoles†

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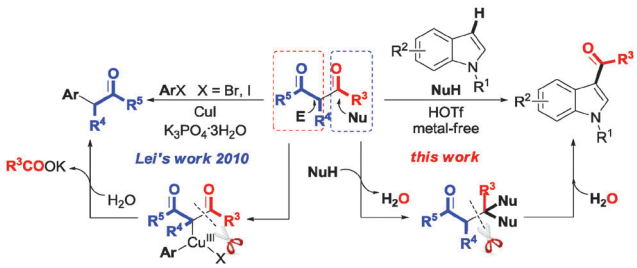
A facile acid-catalyzed acylation of indoles with 1,3-dione as an eco-friendly acylating agent was developed. This protocol combines C–C bond cleavage and heterocyclic C–H bond functionalization to form new C–C bonds. Based on the detailed mechanistic studies, a credible mechanistic pathway was proposed.

Catalytic unstrained C–C bond cleavage, similar to the emerging C–H bond functionalization,[1] has attracted much attention because of its fundamental scientific appeal and potential application in organic synthesis.[2] Among the reported catalytic systems, transition metal catalysis has found increasing applications in the C–C bond cleavage.[2–9] However, such reaction has rarely been realized by a simple and metal-free catalytic system. It is known that both C–C bond cleavage and C–H functionalization changed conventional synthetic pathways by nontraditional C–X (X = C or H) bond disconnection and reorganization of existing molecular skeletons. Therefore, the development of a novel synthetic methodology combining these two strategies for the preparation of important organic skeletons is more scientifically interesting and desirable.

Lei *et al.* reported an efficient Cu-catalyzed arylation of ketones *via* C–C cleavage of 1,3-diones (Scheme 1).[8a] In such a process, functionalized ArX acted as an electrophile to react with 1,3-diones generating Cu(III) intermediates, which underwent C–C bond cleavage to yield α-aryl ketone products and release an equivalent of R^3COOK with the assistance of external H_2O. It is worth pointing out that H_2O is not incorporated into the desired product. Furthermore, the C–C bond cleavage of 1,3-diones with alcohols or amines as partners was also intensively investigated to yield the corresponding esters or amides.[10] However, to our knowledge, the arylation of 1,3-diones with unfunctionalized heterocyclic compounds through C–C bond cleavage to obtain the corresponding carbonyl products has not been achieved. Herein, we describe an acid-catalyzed acylation reaction of indoles with 1,3-diones under mild and solvent-free conditions (Scheme 1). Based on the isolated intermediates, this method was experimentally found to involve two C–C bond formation processes and two C–C bond cleavage processes with the release of $R^5COCH_2R^4$ as a leaving group. Moreover, H_2O generated in the first C–C bond formation reaction also played an important role in the second C–C bond cleavage and its oxygen atom was finally incorporated into the 3-acylindole product. Notably, such tandem transformation could be facilely scaled up to ten grams and the HOTf catalyst was recycled when using water as the solvent. This protocol provides a practical and mild approach to synthesize 3-acylindoles, which are key structural units in many biologically active compounds and versatile feedstocks for the preparation of alkaloids and other heterocyclic intermediates.[11]



Scheme 1 C–C bond cleavage of 1,3-diones to form aryl ketones.

Initially, with the reaction of 3-methylpentane-2,4-dione (**1a**) and *N*-methylindole (**2a**) as the model reaction, the reaction conditions were optimized (Table S1 in the ESI†). Usually, Lewis acids are appropriate activators for 1,3-diones, among them $Fe(OTf)_3$ gave the highest yield (91%) of **3aa** without any solvent at 80 °C for 12 h (entries 1–9). Considering that metal triflates might release HOTf in the presence of H_2O, HOTf was then tested to catalyze such acylation. Surprisingly, **3aa** was obtained in 93% yield (entries 10 and 11). In view of the lower price of HOTf and avoiding metal contamination of the product, HOTf was employed as the optimized acid catalyst for the subsequent

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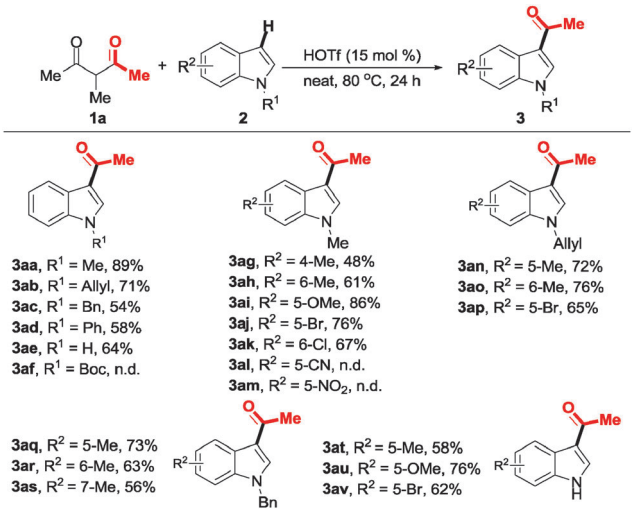
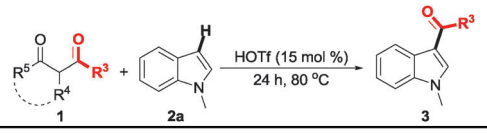


Scheme 2 HOTf-catalyzed synthesis of indolyl-3-ethanone (**3**). Conditions: **1a** (1.5 mmol), **2** (0.5 mmol), 80 °C, 15 mol% of HOTf, 24 h in air, isolated yield.

Table 1 Acid catalyzed reactions of **2a** with different 1,3-diones[a]



Entry	1,3-Diketone	Product	Yield (%)
1	**1b**, R^4 = H, R^3 = R^5 = Me	**3aa**, R^3 = Me	81, 58[b]
2	**1c**, R^4 = H, R^3 = R^5 = Et	**3ca**, R^3 = Et	75
3	**1d**, R^4 = H, R^3 = R^5 = iPr	**3da**, R^3 = iPr	74
4	**1e**, R^4 = H, R^3 = R^5 = CF_3	**3ea**, R^3 = CF_3	79
5	**1f**, R^4 = H, R^3 = R^5 = Ph	**3fa**, R^3 = Ph	38[c], 49[d]
6	**1g**, R^4 = H, R^3 = Me, R^5 = Ph	**3aa**, R^3 = Me	58[c]
7	**1h**, R^4 = H, R^3 = Me, R^5 = OEt	**3aa**, R^3 = Me	34[c], 43[d]
8	**1i**, R^4 = H, R^3 = CF_3, R^5 = Me	**3ea**, R^3 = CF_3	78
9	**1j**, $R^4 \cdots R^5$ = $-(CH_2)_3-$, R^3 = Me	**3aa**, R^3 = Me	78

[a] Conditions: **1** (1.5 mmol), **2a** (0.5 mmol), 15 mol% HOTf, in air, 24 h, 80 °C, isolated yield. [b] **2a** (20 g), 5 mol% $Fe(OTf)_3$, 36 h. [c] 0.5 mmol HOTf and 130 °C. [d] 10 mol% $Fe(OTf)_3$ with the addition of 0.5 mmol $(Tf)_2O$, 130 °C.

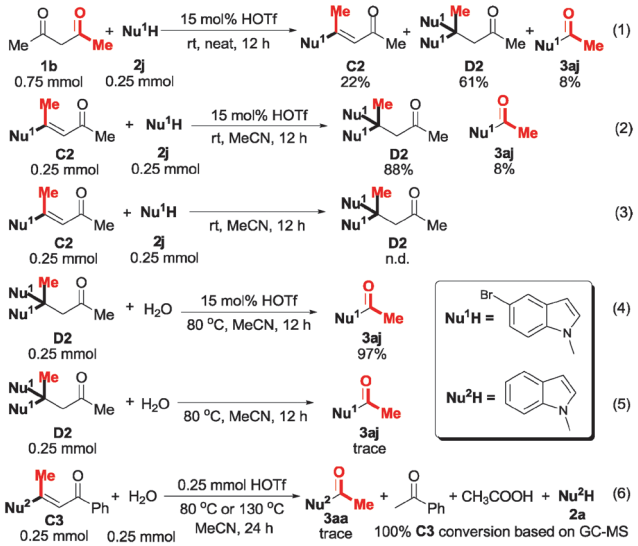
investigations unless otherwise noted. Prolonging the reaction time (24 h) could enhance the formation of the desired product in a quantitative HPLC yield (89% isolated yield, entry 12). The reaction proceeded even at room temperature to afford **3aa** with a 32% yield (entry 13). Remarkably, an interesting intermediate β,β-bisindolyl ketone (**D1**) was isolated in 49% yield (S-Eq. (1) in the ESI†). Interestingly, the HOTf catalyzed acylation even worked efficiently affording 91% yield of **3aa** (80% isolated yield) by using water as the solvent (entry 14), and the HOTf aqueous phase could be facilely separated and reused, providing 72% isolated yield of **3aa** in its second run (entry 15).

We then turned to explore the substrate scope of acylation. As shown in Scheme 2, indoles with different *N*-protecting groups reacted smoothly with **1a** to produce the corresponding indole-3-ketones (**3aa–3ae**) in moderate to good yields. The influence of substituents on the benzene ring was also examined. *N*-Methyl indoles bearing an electron-donating group (EDG) or an electron-withdrawing group (EWG) afforded 48–86% yield of the desired **3ag–3ak**. For indoles with some strong EWGs, no expected product was obtained. The *N*-allyl and *N*-benzyl indoles all worked well, providing good yields of the expected **3an–3as**. Fortunately, the reactions of *N*-unprotected indoles with **1a** also proceeded efficiently, giving **3at–3av** in good yields. It is necessary to note that these products could not be directly produced *via* classical Friedel–Crafts reaction due to the involvement of acid chloride.[12]

Subsequently, the HOTf-catalyzed C–C bond cleavage of various 1,3-diones with **2a** was also investigated. As presented in Table 1, with 15 mol% HOTf as the catalyst, **1b** and **1c** gave the desired **3aa** and **3ca** in 81% and 75% yields, respectively (entries 1 and 2). More sterically hindered **1d** also underwent such C–C bond cleavage smoothly, providing **3da** in 74% yield (entry 3). The reaction of **2a** with the 1,3-diones bearing the CF_3 group (**1e**) proceeded more efficiently, affording **3ea** in 79% yield (entry 4). Surprisingly, the reaction of **1f** with **2a** failed to give the desired **3fa** product under the above conditions, instead, the corresponding β-indolyl-α,β-unsaturated-enone was generated in 85% yield from their condensation (S-Eq. (2) in the ESI†). Increasing the HOTf amount and the reaction temperature could make this reaction happen and the desired **3fa** was isolated in 38% yield, and a higher yield (49%) could be obtained with $Fe(OTf)_3$ and $(Tf)_2O$ as the binary catalyst (entry 5).

When the 1,3-dione was changed to dissymmetric **1g**, **3aa** rather than **3fa** was obtained as the only product in moderate yield (entry 6), possibly owing to the steric effect of the phenyl group. Similarly, the reaction of **1h** also gave **3aa** instead of indolyl-3-ester as the product (entry 7). Different from **1h**, **3ea** instead of **3aa** was obtained as the sole product with a yield of 78% in the reaction of asymmetric **1i** with **2a** (entry 8). For cyclic 1,3-diones, ring-opening reaction always occurred in the presence of a Lewis acid catalyst to give the corresponding ester or amide when alcohol or amine was used as the nucleophiles.[10] However, 78% yield of **3aa** was obtained in the present acid-catalyzed reaction of **1j** with indole (entry 9). To our delight, the scaling-up (20 g) reaction of **1b** and **2a** proceeded efficiently (58% yield) utilizing $Fe(OTf)_3$ as the catalyst (entry 1). Comparatively, HOTf gave a lower (41%) yield of **3aa**.

Clarifying the mechanism of a new synthetic process is very important from the viewpoint of its scientific interest and catalytic application in designing other synthetic strategies. As reported earlier, alcohols and amines could react with 1,3-diones to form esters and amides through a retro-Claisen condensation process.[10] From the experimental investigation mentioned above, it could be proposed that the present acid-catalyzed acylation might not proceed *via* retro-Claisen condensation because two key intermediates, β-indolyl-α,β-unsaturated enone and β,β-bisindolyl ketone, were isolated during the synthesis of 3-acylindoles. To figure out this hypothesis, a control reaction between **2j** and **1b** was initially performed at room temperature. As shown in Scheme 3, 22% yield of β-indolyl-α,β-unsaturated(*E*)-enone (**C2**) was generated by the condensation of **2j** with **1b** and 61% yield of β,β-bisindolyl ketone (**D2**) was also obtained besides 8% yield of the desired **3aj** (eqn (1)). Subsequently, the isolated **C2** reacted with one

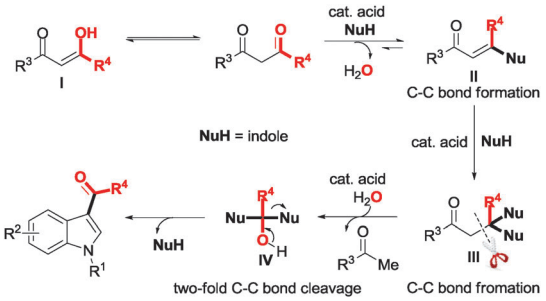


Scheme 3 Control reactions of the intermediates: reactions of eqn (1) to (6) were conducted in air. H_2O in eqn (4) and (5) was from the hydrous MeCN.

equivalent amount of **2j** to give **D2** in 88% yield (eqn (2)). As expected, such conversion could not occur in the absence of HOTf (eqn (3)). Under the optimized reaction conditions, **D2** could be quantitatively converted into the desired **3aj** (eqn (4)). However, only a trace amount of the product was detected without the acid catalyst (eqn (5)). Another possible pathway for present acylation is that water instead of a second indole adds to **C** to give the corresponding β-hydroxy ketone, which releases the desired acylindole *via* retro-aldol reaction. As displayed in eqn (6), only a trace amount of **3aa** was obtained in the reaction of **C3** with H_2O although **C3** was quantitatively converted, and a large amount of **2a**, CH_3COOH and acetophenone were detected by GC-MS (Fig. S1 in the ESI†). These results experimentally proved that **C2** and **D2** were two intermediates in the synthesis of 3-acylindole and the retro-aldol pathway accounted for only a very small proportion in this transformation.

To probe the role of these intermediates in depth and gain more kinetic information on this transformation, we tracked the concentration distribution of the substrate (**2j**), intermediates (**C2** and **D2**) and the product (**3aj**) in the reaction of **1b** and **2j** by HPLC analysis of the reaction mixture every three minutes. As shown in Fig. S2 in the ESI,† **D2** was generated with a 65% yield in three minutes based on **2j**. Subsequently, the concentration of **D2** was slowly decreased and the yield of **3aj** was increased with prolonged time, possibly suggesting that the C–C bond cleavage of **D2** to yield 3-acylindole is the rate-determining step of such a process.

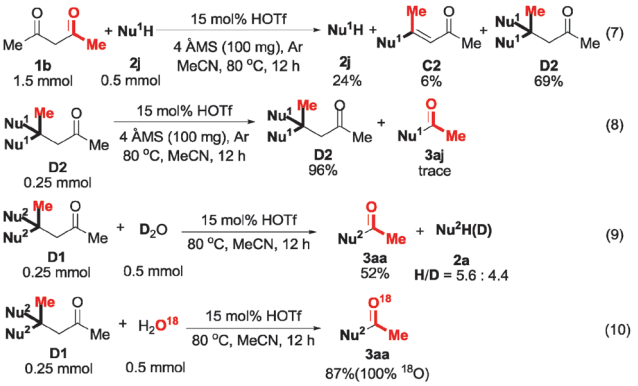
Based on the above investigations, a credible reaction pathway is proposed in Scheme 4. It is reported that Lewis acid or Bronsted acid could activate 1,3-dione through protonation or coordination to increase the electrophilicity of the carbonyl group, which is attacked by indole to give intermediate **II** with the generation of one equivalent of water. The selectivity of **II** is dependent on both the electronic and steric properties of R^3 and R^4 groups. The weaker electron donation and less steric hindrance of R^4 will generally favor the formation of **II**, which undergoes further addition with a second indole producing **III**, which undergoes C–C bond cleavage *via* β-carbon (to the carbonyl) elimination to possibly give a tertiary alcohol intermediate (**IV**) with the release of a ketone using water as the nucleophile. Finally, **IV** might undergo another β-carbon (to the hydroxyl) elimination to give the desired 3-acylindole, generating one molecule of indole to undergo further condensation with 1,3-diones to yield **II** again.



Scheme 4 A putative reaction pathway for the acid-catalyzed C–C bond formation and cleavage reactions of indoles and 1,3-diones.

To further prove the above mechanism, the control reactions of **1b** and **2j** with water were also investigated. As shown in Scheme 5, in the absence of water, **D2** and **C2** could be obtained, but no 3-acylindole was observed (eqn (7)). Moreover, the direct transformation of **D2** to **3aj** with the addition of excess 4 Å molecular sieves gave only a trace amount of **3aj** (eqn (8)). On the other hand, when D_2O was added into the similar conversion of **D1**, 52% yield of the desired **3aa** was obtained generating the same amount of *N*-methyl indole, 44% of which was deuterated through deuterium transfer from the hydroxyl group of **IV** to the C3 position of the resultant indole (eqn (9), Fig. S3 in the ESI†). Accordingly, the reaction of **D1** with $H_2{}^{18}O$ afforded 87% yield of **3aa** with the 100% ^{18}O labelled carbonyl group (eqn (10), Fig. S4 and S5 in the ESI†). These results confirmed again the involvement of water in the C–C bond cleavage of **III** to yield 3-acylindole *via* intermediate **IV**.

In conclusion, we have developed a novel and practical acid-catalyzed synthesis of 3-acylindoles from indoles and 1,3-diones through C–C bond cleavage. The present transformation works



Scheme 5 All the reactions were conducted in a glove box.

under mild conditions with good substrate tolerance and high product selectivity. Interestingly, the β-indolyl-α,β-unsaturated enone and β,β-bisindolyl ketone were isolated and found to be the key intermediates for this process based on the detailed experimental investigations. Moreover, the C–C bond cleavage was demonstrated to be the rate-determining step. Compared with the reported procedures using Friedel–Crafts reaction,[12] complex substrates[13] or noble metal catalysts,[14] this methodology provides a greener and cheaper alternative for the synthesis of 3-acylindoles from readily available substrates and will inspire more interesting designs in the application of C–C bond cleavage.

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