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# Intramolecular Cooperative C–C Bond Cleavage Reaction of 1,3-Dicarbonyl Compounds with 2-Iodoanilines To Give *o*-(N-Acylamino)aryl Ketones and Multisubstituted Indoles

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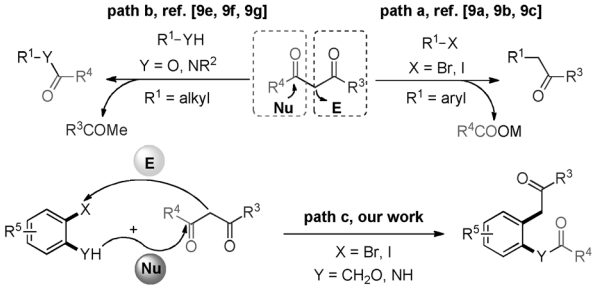
**Abstract:** A copper-catalyzed C–C bond cleavage reaction of 1,3-dicarbonyl compounds with 2-iodoanilines was developed. In this process, the *ortho* effect played an important role in the reactivity and a new reaction pathway that involved a (2-aminophenyl)-bis-(1,3-dicarbonyl) copper species was clearly observed by a time-course HRMS analysis of the reaction mixture. Unlike the previous reports, both the nucleophilic and electrophilic parts of the 1,3-dicarbonyl compound were coupled with 2-iodoaniline by C–C bond cleavage to form *o*-(N-acylamino)aryl ketones, which could be efficiently converted into multisubstituted indoles.

## Introduction

In recent years, the development of more efficient and rapid C–C bond cleavage methods has attracted much attention because of its fundamental scientific appeal and potential application in organic synthesis.[1] To date, various effective C–C bond cleavage strategies have been developed, such as the use of directing chelating groups,[2] oxidative cleavage,[3] and the cleavage of functional substrates bearing carbonyl,[4] ester,[5] carboxyl,[6] cyano,[7] or hydroxyl[8] groups. In particular, 1,3-dicarbonyl compounds have been widely used as versatile substrates to construct acyl or ketone compounds by C–C bond cleavage.[9] The groups of Guo and Koning independently revealed that α-arylacetic acid esters could be directly obtained by copper-catalyzed coupling of aryl halides and ethyl acetoacetate and spontaneous deacylation of the coupling product.[9a, b] Lei and co-workers reported an efficient copper-catalyzed arylation of ketones by C–C bond cleavage of 1,3-diones.[9c] As reported in these methods, a functionalized ArX species acted as an electrophile and reacted with 1,3-dicarbonyl compounds to generate a proposed $Cu^{III}$ intermediate, which underwent C–C bond cleavage to yield α-aryl ketones or α-arylacetic acid esters with simultaneous release of one equivalent of $R^4COOM$ (Scheme 1, path a). In other cases, nucleophilic alcohols or amines could also react with a 1,3-dicarbonyl compound in the presence of a metallic (e.g., Fe, In) Lewis acid catalyst to yield the corresponding esters or amides and one equivalent of the ketone moiety $R_3COMe$[9f–h] (Scheme 1, path b).




**Scheme 1.** Metal-catalyzed C–C single-bond cleavage.

Very recently, we developed an acid-catalyzed acylation reaction of the indole C3–H position with 1,3-diones by C–C bond cleavage to synthesize 3-acylindoles.[9i] Unfortunately, in all the cases mentioned above, only acyl or ketone moieties could be incorporated into the target products after C–C bond cleavage. From the viewpoint of atom economy and synthetic efficiency, developing an efficient C–C bond cleavage approach that uses both the reactivity attributes of 1,3-dicarbonyl compounds to construct the target products is of great interest. To achieve this goal, we speculated that bifunctional substrates containing both electrophilic and nucleophilic groups might be a reasonable choice to react with 1,3-dicarbonyl compounds (Scheme 1, path c).

Indoles are a ubiquitous heterocyclic motif in pharmaceutical agents and natural products.[10] Therefore, the development of methods to construct these compounds in an efficient manner is of continuing interest to organic chemists. So far, many kinds of substrate have been used for indole synthesis;[11] *ortho*-haloanilines are one of the most-common substrates and they react with alkynes or alkenyl halides by Pd-catalyzed

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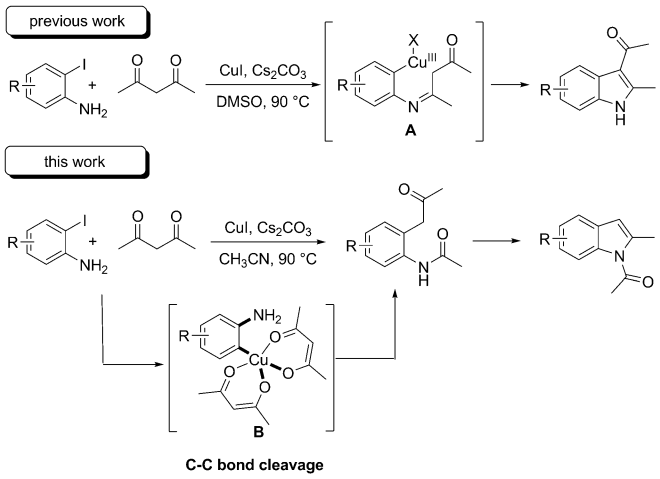
domino C–C and C–N bond-forming reactions to yield the desired substituted indoles.[12a,b] In addition, the Cu-catalyzed reaction of 2-iodoaniline with 1,3-diketones in the highly polar solvent dimethyl sulfoxide (DMSO) could specifically produce 2,3-disubstituted indoles[12c–e] (Scheme 2). In this process, an intermolecular condensation between the nucleophilic amine and the more-electron-deficient carbonyl group is proposed to take place first to give imine intermediate **A**, followed by intramolecular C–C cross-coupling to form the indole. Inspired by this work, we speculated that if we adjust the conditions so that C–C cross-coupling between the C–I bond and the methylene group of the 1,3-dione takes place first, followed by internal nucleophilic attack of the amino group to one carbonyl group, after which C–C bond cleavage would occur. By this pathway, we would obtain *o*-(N-acylamino)aryl ketone products. In this process, the amino group and C–I bond of *ortho*-iodoaniline acted as nucleophilic and electrophilic groups, respectively. Its key is to control the selectivity of the C–C bond-forming reaction in preference to production of the imine intermediate. To our delight, we could tune the reaction solvent and successfully realize this new reaction pathway to yield *o*-(N-acylamino)aryl ketones, which are valuable synthetic intermediates in organic synthesis,[13] for example, in this work, they can be readily converted to multisubstituted indoles by an $FeCl_3$-catalyzed reaction. From this perspective, the present method also provides a facile alternative for indole synthesis.



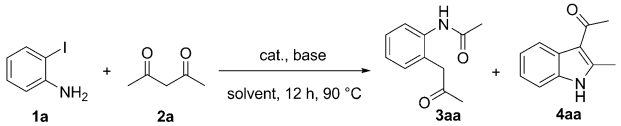

**Scheme 2.** Previous synthesis of indoles from 2-iodoanilines and 1,3-diketones, and our work.

## Results and Discussion

### Optimizing the reaction conditions

First, we studied the reaction between 2-iodoaniline (**1a**) and acetylacetone (**2a**). Based on initial speculation that the solvent polarity will affect the reaction selectivity, a series of solvents were examined (Table 1, entries 1–5). Use of non-polar solvents hexane and dioxane led to no reaction or only trace amounts of the desired product, *o*-(N-acylamino)phenyl propan-2-one (**3aa**) (Table 1, entries 1 and 2). Interestingly, with the polar solvent acetonitrile, the reaction showed excellent selectivity for **3aa** (34% yield) with no concomitant formation of 2,3-disubstituted indole **4aa** (Table 1, entry 3). With the more-polar solvent DMF, **3aa** was obtained in 53% yield, but **4aa** was also generated in 42% yield (Table 1, entry 4). In DMSO **4aa** was obtained as the major product in 59% yield (Table 1, entry 5). All these results indicate that the solvent can change the reactivity and final-product selectivity of this transformation, probably due to solvent–catalyst interactions.[14] A control experiment confirmed that no reaction took place without the copper catalyst (Table 1, entry 6). After examining several bases, $Cs_2CO_3$ was found to be the most efficient for this reaction (Table 1, entries 3, 7–10). Compared to CuI (Table 1, entry 9), $Cu_2O$, CuBr, and CuOAc also efficiently catalyzed this reaction (Table 1, entries 11–13). However, $FeCl_2$, $Co(OAc)_2$, and $NiI_2$ failed to efficiently catalyze the transformation (Table 1, entries 14–16). The optimal ratio of **2a**/**1a** was 5:1 (Table 1, entries 17 and 18). Increasing the amount of base resulted in a decreased product yield (Table 1, entry 19). Conducting the reaction at higher or lower temperatures led to a slight decrease in the product yield (Table 1, entries 20 and 21).

**Table 1.** Optimization of the reaction conditions.[a]




| Entry[a] | Catalyst | Base | Solvent | Yield [%][b] 3aa | 4aa |
|---|---|---|---|---|---|
| 1 | CuI | $K_3PO_4 \cdot 3H_2O$ | hexane | n.d.[c] | n.d. |
| 2 | CuI | $K_3PO_4 \cdot 3H_2O$ | dioxane | trace | n.d. |
| 3 | CuI | $K_3PO_4 \cdot 3H_2O$ | $CH_3CN$ | 34 | n.d. |
| 4 | CuI | $K_3PO_4 \cdot 3H_2O$ | DMF | 53 | 42 |
| 5 | CuI | $K_3PO_4 \cdot 3H_2O$ | DMSO | 33 | 59 |
| 6 | – | $K_3PO_4 \cdot 3H_2O$ | $CH_3CN$ | n.d. | n.d. |
| 7 | CuI | $K_2CO_3$ | $CH_3CN$ | 66 | 26 |
| 8 | CuI | $Na_2CO_3$ | $CH_3CN$ | n.d. | n.d. |
| 9 | CuI | $Cs_2CO_3$ | $CH_3CN$ | 75 | 16 |
| 10 | CuI | KO*t*Bu | $CH_3CN$ | 37 | trace |
| 11 | $Cu_2O$ | $Cs_2CO_3$ | $CH_3CN$ | 71 | 18 |
| 12 | CuBr | $Cs_2CO_3$ | $CH_3CN$ | 74 | 20 |
| 13 | CuOAc | $Cs_2CO_3$ | $CH_3CN$ | 75 | 21 |
| 14 | $FeCl_2$ | $Cs_2CO_3$ | $CH_3CN$ | trace | n.d. |
| 15 | $Co(OAc)_2$ | $Cs_2CO_3$ | $CH_3CN$ | 17 | 12 |
| 16 | $NiI_2$ | $Cs_2CO_3$ | $CH_3CN$ | 8 | n.d. |
| 17 | CuI | $Cs_2CO_3$ | $CH_3CN$ | 81 (66)[d] | 15 |
| 18 | CuI | $Cs_2CO_3$ | $CH_3CN$ | 27[e] | 15 |
| 19 | CuI | $Cs_2CO_3$ | $CH_3CN$ | 63[f] | 14 |
| 20 | CuI | $Cs_2CO_3$ | $CH_3CN$ | 76[g] | 18 |
| 21 | CuI | $Cs_2CO_3$ | $CH_3CN$ | 74[h] | 11 |

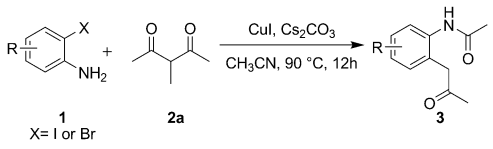
[a] Reaction conditions: **1a** (0.5 mmol, 1 equiv), **2a** (1.5 mmol, 3 equiv), base (1.5 mmol, 3 equiv), metal catalyst (10.0 mol%), solvent (2 mL), 90 °C, 12 h. [b] Determined by HPLC analysis with acetanilide as an internal standard. [c] Not detected. [d] **2a** (5 equiv) was used, isolated yield in parentheses. [e] **2a** (1 equiv) was used. [f] $Cs_2CO_3$ (5 equiv), **2a** (5 equiv) were used. [g] 110 °C, **2a** (5 equiv) was used. [h] 70 °C, **2a** (5 equiv) was used.

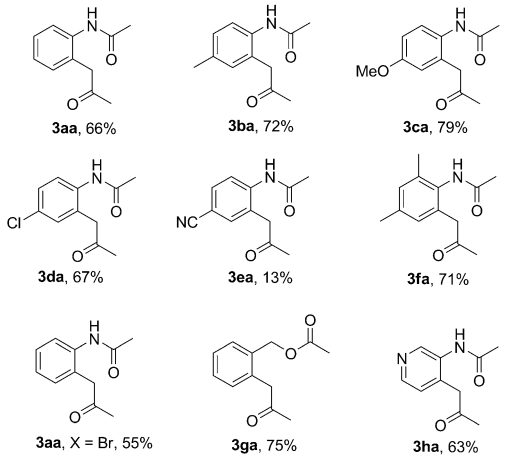
### C–C Bond cleavage

With the optimized conditions in hand, we investigated the substrate scope for this C–C bond-activation reaction. First, a wide array of 2-iodoanilines **1** were treated with **2a** and moderate-to-excellent yields of **3** were obtained (Table 2). 2-Iodoanilines with electron-donating substituents, such as methyl and methoxy groups, *para* to the amino group reacted smoothly with **2a** to provide **3ba** and **3ca** in 72 and 79% yield, respectively. 2-Iodo-4-chloroaniline gave **3da** in 67% yield, which offered the possibility for further functionalization. 2-Iodo-4,6-dimethylaniline with methyl groups at both the *ortho*- and *para* positions of the amino group afforded **3fa** in 71% yield. However, the presence of a strong electron-withdrawing group decreased the efficiency dramatically (e.g., **3ea**). This poor efficiency may due to decreased nucleophilicity of the amino group. Therefore, the process may be favored by substrates with electron-donating substituents. To our delight, 2-bromoaniline also reacted smoothly with **2a** under the same conditions, although a relatively lower yield of **3aa** (55%) was obtained compared with the reaction of **1a**. (2-Iodophenyl)methanol, with a hydroxyl nucleophile and C–I electrophile, also worked efficiently and gave the expected product 2-(2-oxopropyl)benzyl acetate (**3ga**) in 75% yield. Moreover, this method could apply to heteroaromatic 2-iodoanilines; for example, reaction of 4-iodopyridin-3-amine provided *N*-(4-(2-oxopropyl)-pyridin-3-yl)acetamide (**3ha**) in 63% yield.

The reactions of **1a** with different 1,3-dicarbonyl compounds **2** were also investigated (Table 3). Diketone **2a** and heptane-3,5-dione (**2b**) gave the desired 3-acylindoles **3aa** and **3ab** in 66 and 83% yield, respectively (Table 3, entries 1 and 2). Hindered substrate 2,6-dimethylheptane-3,5-dione (**2c**) also underwent smooth C–C bond cleavage to provide **3ac** in 68% yield (Table 3, entry 3). However, the more-hindered substrate 2,2,6,6-tetramethylheptane-3,5-dione (**2d**) afforded only a trace of product **3ad** (Table 3, entry 4). 1,3-Diphenylpropane-1,3-dione (**2e**) also successfully reacted with **1a** to give **3ae** in moderate yield (Table 3, entry 5). To our delight, the C–C bond cleavage reaction of 3-methylpentane-2,4-dione (**2f**), substituted at the methylene position, proceeded smoothly with an enhanced reaction temperature and prolonged reaction time to give **3af** in 54% yield (Table 3, entry 6). Using asymmetric 1,3-diketone substrates **2i** and **2j**, **3ai** and **3aj** were obtained selectively in good yields (Table 3, entries 7 and 8). *Tert*-butyl-3-oxobutanoate (**2k**) also reacted with **1a** to produce **3ak** in 31% yield (Table 3, entry 9). For cyclic 1,3-diketone **2l**, acetylation product **3al** was obtained in 68% yield without observation of any ring-opening product (Table 3, entry 12).

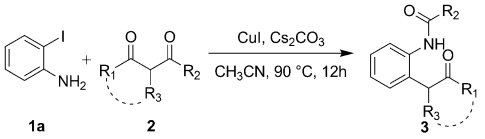
**Table 2.** Cu-catalyzed reactions of **1** with **2a**.[a]




[a] Reaction conditions: **1** (0.5 mmol), **2a** (2.5 mmol), CuI (10.0 mol%), $Cs_2CO_3$ (1.5 mmol), $CH_3CN$ (2 mL), 90 °C, 12 h; isolated yields shown.

**Table 3.** Copper-catalyzed reactions of **1a** with 1,3-dicarbonyl compounds **2**.[a]



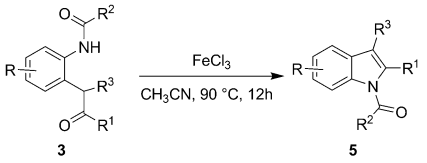

| Entry | 2 | Product | Yield [%][b] |
|---|---|---|---|
| 1 | **2a**: $R^3$ = H, $R^1$ = $R^2$ = Me | **3aa** | 66 |
| 2 | **2b**: $R^3$ = H, $R^1$ = $R^2$ = Et | **3ab** | 83 |
| 3 | **2c**: $R^3$ = H, $R^1$ = $R^2$ = *i*Pr | **3ac** | 68 |
| 4 | **2d**: $R^3$ = H, $R^1$ = $R^2$ = *t*Bu | **3ad** | trace |
| 5 | **2e**: $R^3$ = H, $R^1$ = $R^2$ = Ph | **3ae** | 43 |
| 6 | **2f**: $R^1$ = $R^2$ = $R^3$ = Me | **3af** | 31 (54)[c] |
| 7 | **2i**: $R^3$ = H, $R^1$ = Ph, $R^2$ = Me | **3ai** | 71 |
| 8 | **2j**: $R^3$ = H, $R^1$ = *t*Bu, $R^2$ = Me | **3aj** | 82 |
| 9 | **2k**: $R^3$ = H, $R^1$ = O*t*Bu, $R^2$ = Me | **3ak** | 31 |
| 10 | **2l**: $R^3$–$R^1$ = –$(CH_2)_3$–, $R^2$ = Me | **3al** | 68 |

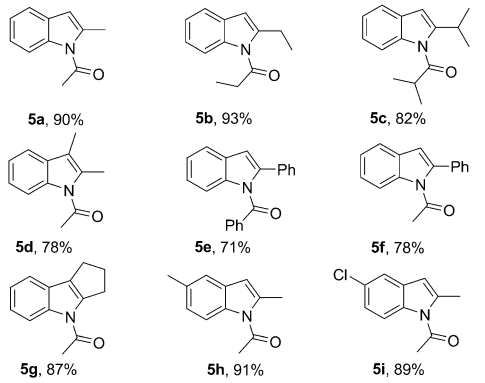
[a] Reaction conditions: **1a** (0.5 mmol), **2** (2.5 mmol), CuI (10 mol%), $Cs_2CO_3$ (1.5 mmol), $CH_3CN$ (2 mL), 90 °C, 12 h. [b] Isolated yield. [c] Yield obtained at 110 °C after 36 h.

### Intramolecular cyclization

Subsequently, in the presence of a Lewis acid catalyst ($FeCl_3$), the *o*-(N-acylamino)aryl ketones **3** underwent efficient cyclization to produce multisubstituted indoles **5** (Table 4).[13] For example, **3aa**, **3ab**, and more-hindered substrate **3ac** afforded the corresponding 1,2-disubstituted indoles **5a**, **5b**, and **5c**, respectively, in 82–93% yield. *o*-(N-acylamino)aryl ketone **3af**, with a methyl substituent at the methylene position, also cyclized smoothly to form 1,2,3-trisubstituted indole **5d** in 78% yield. *o*-(N-Acylamino)aryl ketones **3ae** and **3ai** containing an acetophenone group underwent cyclization to generate 2-phenylindoles **5e** and **5f** in good yields. To our delight, cyclic *N*-(2-(2-oxocyclopentyl)phenyl)acetamide (**3al**) also cyclized successfully to produce fused polycyclic 1-(2,3-dihydrocyclopen-

**Table 4.** Fe-catalyzed synthesis of 1,2-disubstituted indoles **5** from **3**.[a]



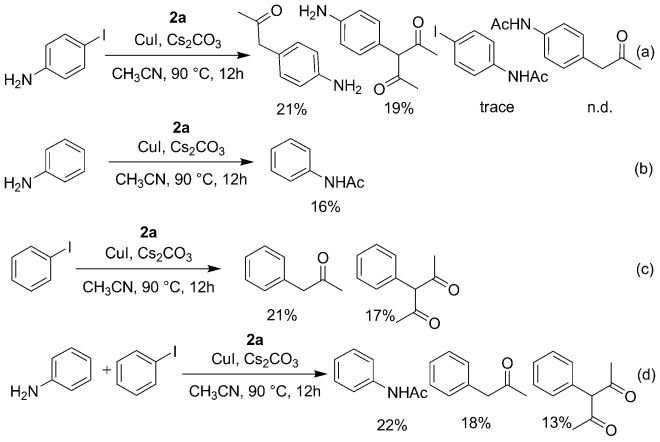

[a] Reaction conditions: **3** (0.25 mmol), $FeCl_3$ (10 mol%), $CH_3CN$ (1 mL), 90 °C, 12 h; isolated yields shown.

taindol-4(1*H*)-yl)ethanone (**5g**) in 87% yield. Moreover, *o*-(N-acylamino)aryl ketones with methyl- and chlorine substituents on the phenyl subunit (**3ba** and **3da**) provided the corresponding cyclized products **5h** and **5i** in 91 and 89% yield, respectively. This reaction provides a practical application for this cascade reaction.

### Mechanistic study

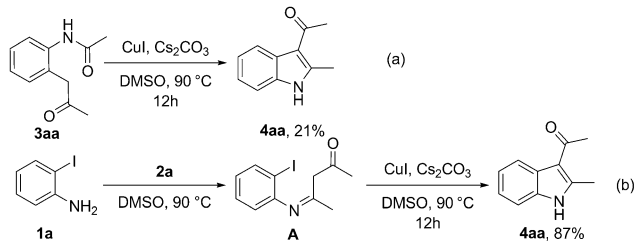
A set of control reactions were conducted to gain some insight into the reaction mechanism. Unlike **1a**, the reaction of 4-iodoaniline with **2a** produced 1-(4-aminophenyl)propan-2-one and 3-(4-aminophenyl)pentane-2,4-dione in 21 and 19% yield, respectively, along with a trace amount of *N*-(4-iodophenyl)acetamide, but no *N*-(4-(2-oxopropyl)phenyl)acetamide was detected (Scheme 3a). Furthermore, when aniline reacted with **2a**, only 16% yield of *N*-phenylacetamide was obtained (Scheme 3b). After the reaction of iodobenzene with **2a**, 1-phenylpropan-2-one and 3-phenylpentane-2,4-dione were obtained in 21 and 17% yield, respectively (Scheme 3c). Moreover, when a mixture of aniline and iodobenzene reacted with **2a**, *N*-phenylacetamide (22%), 1-phenylpropan-2-one (18%), and 3-phenylpentane-2,4-dione (13%) were obtained (Scheme 3d). Clearly, the internal *ortho* effect between the C–I bond and the amino group plays a decisive role in the reaction activity and selectivity, therefore with 4-iodoaniline as the substrate only intermolecular acylation of amine group or alkylation of C–I bond occurred while no *N*-(4-(2-oxopropyl)phenyl)acetamide was obtained. Moreover, the reactivity of all these control substrates was much lower than that of **1a**.

In early reports, the reactions of **1a** and 1,3-diketones in DMSO mainly afford 2,3-disubstituted indoles as the major




**Scheme 3.** Control reactions of **2a** with 4-iodoaniline, iodobenzene, and aniline. Ac = acetyl.

products. For this reaction in acetonitrile a completely different product, namely an *o*-(N-acylamino)aryl ketone, was isolated as the major product, along with a small quantity of an indole byproduct. We envisioned that a different reaction pathway leads to the different reaction outcome. One possible route for the indole byproduct formation is further annulation of the *o*-(N-acylamino)aryl ketone **3** through intramolecular condensation. *o*-(N-Acylamino)aryl ketone **3aa** could be transformed, albeit in low yield (21%), into 2,3-substituted indole **4aa** in the presence of CuI and base in DMSO at 90 °C (Scheme 4a). Other-




**Scheme 4.** Control reactions for the synthesis of **4aa**.

wise, imine **A** could also be generated in situ by condensation of **1a** and **2a**, then provide indole **4aa** in excellent yield (87%) under the same conditions (Scheme 4b). We conclude that in DMSO the condensation of the amino group of **1a** with 1,3-diketone **2a** occurs first, followed by intramolecular C–C cross-coupling of **A** to afford 2,3-disubstituted indole **4aa**. On the contrary, for our procedure in acetonitrile[15] C–I bond activation may be the first step, followed by intramolecular attack of the amino group to one carbonyl group, which results in the formation of *o*-(*N*-acylamino)aryl ketones **3**.

In-situ HRMS (ESI) analysis of the reaction mixture was performed at different time points. At $t = 0$, the peak corresponding to **1a** (*m/z* 219.9627) was detected (Figure 1). With prolonged reaction time, a peak at *m/z* 376.06 appeared and increased gradually for the first 3 h, then decreased until it had almost disappeared by 16 h. In the meantime, the peak corre-

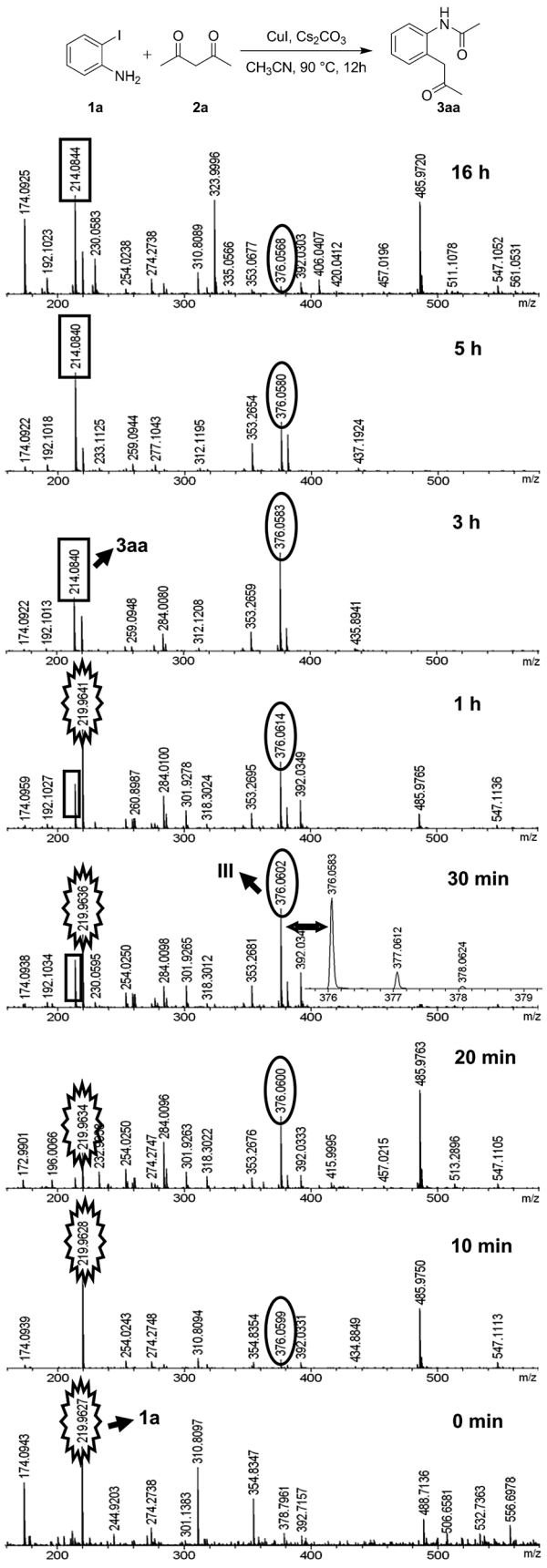
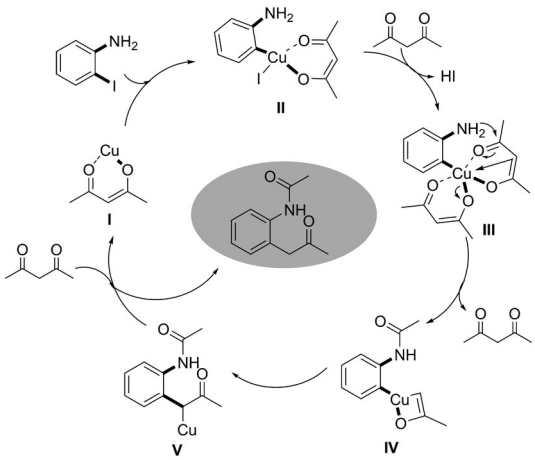



**Figure 1.** Observed HRMS data for intermediate **III** and product **3aa** at different time points.

sponding to **1a** decreased while that of **3aa** (*m/z* 214.08) rose gradually. Therefore, we speculated that **III** (*m/z* 376.06 $[\mathbf{III}+Na]^+$; Scheme 5, Figure 2) might be an intermediate in this C–C bond cleavage transformation, which further supported C–I bond activation as the first step of this reaction.




**Scheme 5.** Plausible mechanistic pathway for the reaction of **1** and **2**.

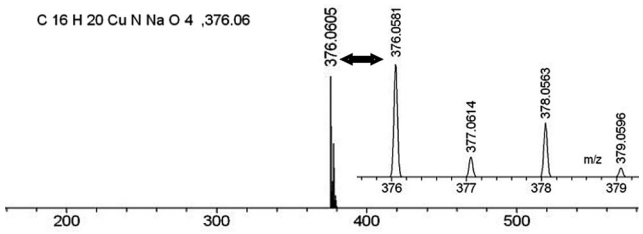



**Figure 2.** Calculated HRMS spectrum for intermediate **III**.

Based on the results of the above-mentioned control reactions and HRMS investigation, a proposed mechanism for this C–C bond cleavage reaction is shown in Scheme 5. First, with the assistance of base, copper reacts with **2a** to produce copper(I) complex **I**, which undergoes further oxidative addition with **1a** to give copper(III) intermediate **II**. Intermediate **III** is the generated by ligand exchange between iodine and a second molecule of **2a**. Subsequently, intramolecular nucleophilic attack of the amino group onto one carbonyl group of intermediate **III** is accompanied by C–C bond cleavage to give intermediate **IV**. Intermediate **IV** undergoes reductive elimination to furnish intermediate **V**. The subsequent reaction of **2a** and **V** regenerates the copper(I) intermediate **I** for the next catalytic cycle.

## Conclusion

We have developed an efficient method to synthesize (N-acylamino)aryl ketones by copper-catalyzed C–C bond cleavage between 2-iodoanilines and 1,3-dicarbonyl compounds. In this process, both the nucleophilic and electrophilic parts of the 1,3-dicarbonyl compounds were coupled with 2-iodoanilines to

form *o*-(N-acylamino)aryl ketones, which could be efficiently converted into multisubstituted indoles by an $FeCl_3$-catalyzed reaction. The reaction solvent played a decisive role in selection of the reaction pathway. Furthermore, an *ortho* effect between the C–I and amine functionalities showed significant influence on the coupling with the entire 1,3-dicarbonyl compound and improved the reactivity of the transformation. This simple and practical method complements the classical method for the construction of *o*-(N-acylamino)aryl ketones and indoles, and has a practical value to synthetic chemists designing new transformations by C–C bond cleavage.

## Experimental Section

### Reaction of 1a and 1,3-dicarbonyl compounds 2

Compound **1a** (0.5 mmol), 1,3-dicarbonyl compound **2** (2.5 mmol), CuI (0.05 mmol), $Cs_2CO_3$ (1.5 mmol), and $CH_3CN$ (2 mL) were added to a Schlenk tube, which was then capped. The mixture was stirred for 12 h at 90 °C. After cooling to room temperature, the resultant reaction mixture was purified by flash column chromatography on silica gel.

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**Keywords:** C–C bond cleavage · copper · domino reactions · *ortho* effect · reaction mechanisms

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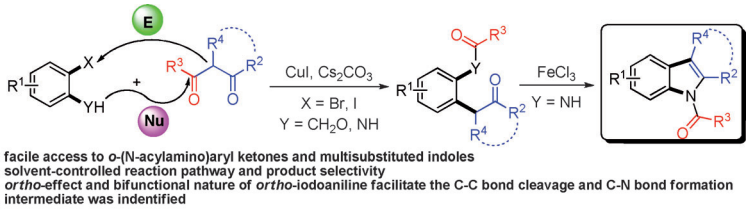


**Break it up!** An intramolecular cooperative C–C bond cleavage reaction between 2-iodoanilines and 1,3-dicarbonyl compounds was developed to provide efficient access to *o*-(N-acylamino)aryl ketones, which could further be converted to multisubstituted indoles (see scheme).

**Synthetic Methods**

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■■ – ■■

**Intramolecular Cooperative C–C Bond Cleavage Reaction of 1,3-Dicarbonyl Compounds with 2-Iodoanilines To Give *o*-(N-Acylamino)aryl Ketones and Multisubstituted Indoles**