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One-Pot Synthesis of *p*-Amino-Substituted Unsymmetrical Benzils and Benzil Derivatives

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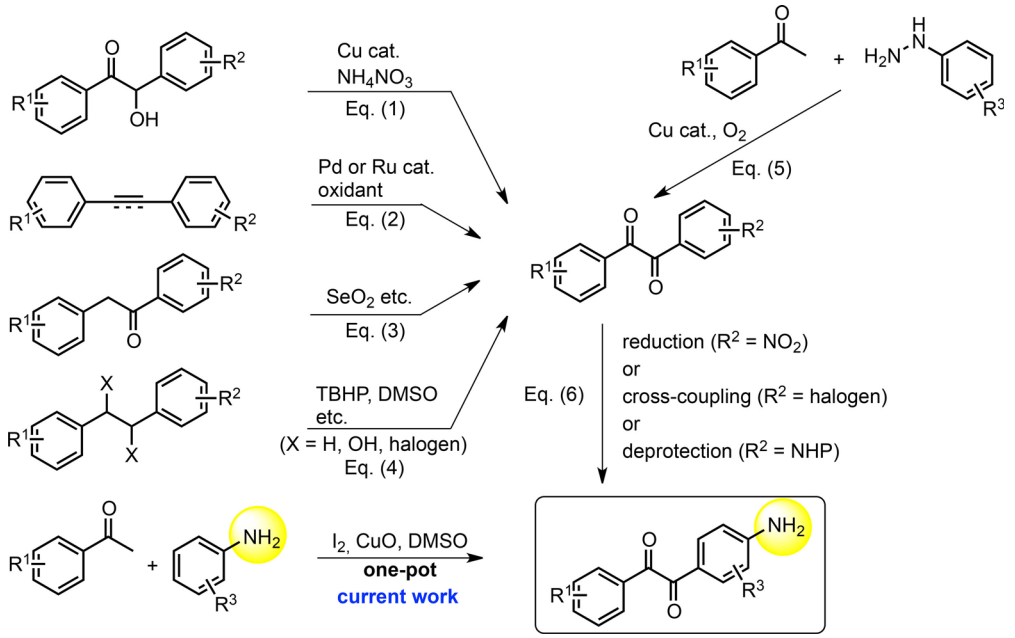
Abstract: An efficient iodine/copper(II) oxide co-promoted direct oxidative coupling of anilines and methyl aryl ketones has been developed for the synthesis of *p*-amino-substituted unsymmetrical benzils and their iodo-substituted derivatives. The chemoselectivity of the reactions can be easily controlled by adjusting the amount of iodine. This method exhibits good functional group tolerance for various substituents on the aromatic rings of the methyl aryl ketones. A possible mechanism for this reaction has been proposed based on control experiments. A couple of representative quinoxalines were synthesized from the benzil products in order to demonstrate the utility of this approach.

Keywords: benzils; methyl aryl ketones; oxidative coupling; quinoxalines; tandem reaction

1,2-Dicarbonyl derivatives are versatile structural motifs which are capable of undergoing various chemical transformations, especially for the synthesis of ligands[1] such as N-heterocyclic carbenes and diamines as well as biologically active heterocyclic compounds[2] such as imidazoles and quinoxalines. In addition, benzils and their derivatives exhibit various biological activities such as carboxylesterase inhibition in mammals.[3] Some benzils are photosensitive and can be used as photocurable coating agents.[4] As shown in Scheme 1, benzils can be conveniently synthesized by oxidation of various precursors[5] such as 2-hydroxy-1,2-diaryl-1-ethanones [Eq. (1)], 1,2-diarylalkynes or alkenes [Eq. (2)], 1,2-diaryl-1-ethanones [Eq. (3)], and 1,2-dihalogenated 1,2-diarylethanes [Eq. (4)]. Recently, Su et al. reported an efficient synthesis for benzil derivatives which uses phenylhydrazine and phenyl substituted alkenes [Eq. (5)].[6] However, straightforward synthetic methods for the synthesis of benzils with a free amine substituent are very limited. In most cases, the synthesis of amine-containing benzils occurs *via* functional group transformations of the corresponding precursors by making use of an amine precursor or a protected amine. For example, the reduction of nitro-substituted benzils,[7] the amination of halo-substituted benzils,[8] or the removal of the amino protecting group can lead to *p*-amino-substituted benzils [Eq. (6)].

There are only a few reported methods[9] that do not require amine protection for the formation of amine-containing diketones. For example, Cheng et al. developed an oxidative process[9a] which converts 1,2-diphenylalkynes to the corresponding diketones in the presence of a free amine with moderate yields. The Pd-catalyzed coupling of tetramethylammonium (pentacarbonyl)chromates with aryl iodides in a CO atmosphere[9b] to give amine-containing benzils has also been reported. However, this approach has disadvantages such as the high cost and limited availability of the substrates and catalysts. Thus the straight-forward synthesis of amino-substituted benzil derivatives is still a challenge to organic synthetic chemists and the development of an efficient approach to access these compounds is highly desirable.

Recently, several iodine-mediated oxidative couplings of acetophenone with amines have been reported.[10] A plethora of aryl α-keto amides have been conveniently synthesized by the oxidative coupling of styrene, phenylacetylene, or acetophenone with secondary amines.[11] However, only a few reports[10a,12] have explored oxidative coupling reactions with primary amines. This is probably because the formation of relative stable imine intermediate inhibits further transformation of the intermediate to α-keto amides. During our investigations of a one-pot synthetic protocol for α-keto amides from alkenes or alkynes,[13] we found that, when aniline was used, *p*-amino-substituted benzil was obtained instead of the corresponding α-keto amide. This result prompted us to further



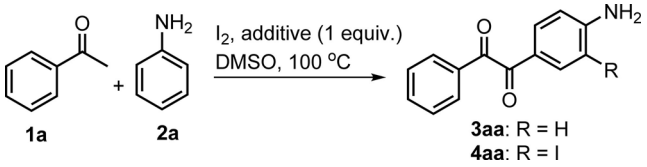
Scheme 1. Synthetic routes for *p*-amino-substituted benzils.

explore this unexpected result. In this work, a highly efficient, one-pot, oxidative coupling of methyl aryl ketones with anilines to synthesize *p*-amino-substituted benzils and their iodo derivatives is reported.[14]

During the initial studies, the reaction between acetophenone and aniline was selected as the model reaction for optimizing the reaction conditions. Acetophenone (**1a**, 1.0 equiv.) reacted with aniline (**2a**, 1.2 equiv.) and I_2 (1.2 equiv.) in DMSO at 100 °C for 12 h to give *p*-amino-substituted benzil (**3aa**) as the major product with a moderate yield (45%, Table 1, entry 1). No α-keto amide product was detected. The reaction conditions were then optimized by varying the ratio of aniline to acetophenone, the amount of iodine, and the reaction temperature and the results are shown in Table 1. Increasing the amount of I_2 to 1.6 equiv. improved the conversion yield but the iodo-product **4aa** was obtained as a side product (Table 1, entry 2). Increasing the amount of aniline to 1.6 equiv. reduced the amount of iodo-product **4aa** (Table 1, entry 4), but further increasing the amount of aniline did not improve the yield of target product **3aa**.

In order to reduce the amount of iodine, various additives were investigated and these results are also shown in Table 1. Initially CuO was chosen as the additive due to its good oxidative ability.[15] When 1 equiv. of I_2 was used, the iodo-product **4aa** was obtained as a major product (entry 5). When the amount of I_2 was decreased to 0.6 equiv., the major product **3aa** was obtained in 59% yield (entry 7). Further decreasing the amount of iodine did not lead to a better result (entry 8). Other oxidative additives were also tested. Neither TBHP (*tert*-butyl hydroper-

Table 1. Optimization of the reaction conditions.



Entry	I_2 [equiv.]	**2a** [equiv.]	Additive	Yield [%][a] **3aa**	**4aa**
1	1.2	1.2	none	56 (45)	–
2	1.6	1.2	none	40 (30)	43 (31)
3	1.6	1.4	none	54 (43)	18 (11)
4	1.6	1.6	none	66 (53)	trace
5	1	1.2	CuO	27 (18)	43 (38)
6	0.8	1.2	CuO	47 (36)	25 (16)
7	0.6	1.2	CuO	73 (59)	–
8	0.5	1.2	CuO	68 (54)	–
9[b]	0.6	1.2	CuO	56 (43)	–
10[c]	0.6	1.2	CuO	51 (37)	–
11[d]	0.6	1.2	CuO	65 (52)	–
12	0.6	1.2	TBHP	38 (24)	–
13	0.6	1.2	DTBP	45 (31)	–
14	0.6	1.2	Oxone	–	–
15	0.6	1.2	MnO_2	trace	–
16	0.6	1.2	$CuBr_2$	68 (54)	–
17	0.6	1.2	$CuCl_2$	63 (50)	–
18	0.6	1.2	$Cu(OAc)_2$	58 (44)	–
19	0.6	1.2	CuI	63 (51)	–

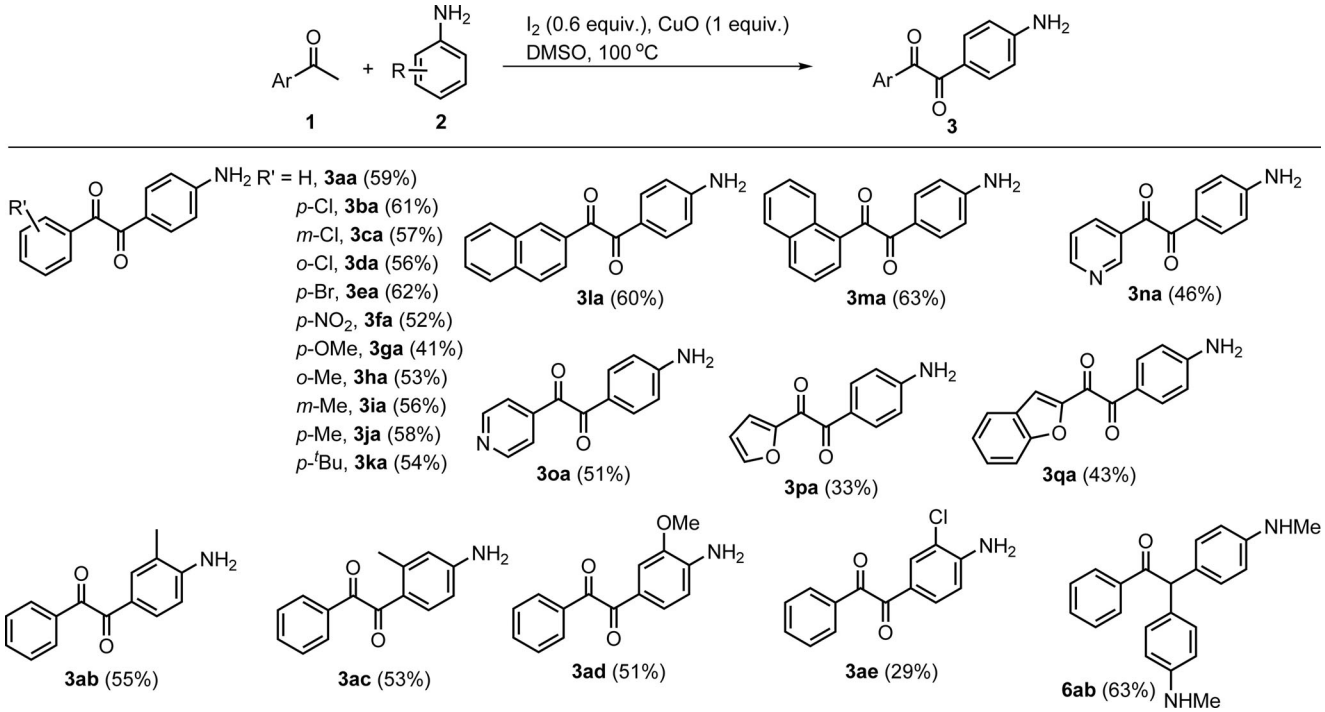
[a] The yields were determined by GC analysis. The values in parenthesis are the isolated yields.
[b] The reaction temperature was 120 °C.
[c] The reaction temperature was 140 °C.
[d] The reaction temperature was 90 °C.

oxide) nor DTBP (di-*tert*-butyl peroxide) (entries 12 and 13) gave better yields than CuO and the use of oxone resulted no desired product (entry 14). The metallic oxide MnO_2 produced only trace amounts of the desired product (entry 15). Other Cu salts were also screened and the copper halides gave results similar to those for CuO (entries 16-19). A lower amount (0.6 equiv.) of CuO was also tested and a slightly lower yield was obtained (66% *vs.* 73%).

Different reaction temperatures were also investigated (Table 1, entries 7, and 9–11) and the best results were obtained at 100 °C. Previously it had been shown that, at temperatures <70 °C, acetophenone (**1a**) is mainly converted to 2-(methylthio)-1,4-diphenyl-2-butene-1,4-dione in the presence of I_2/CuO in DMSO.[15a] This product is formed from the intermediate 2-iodo-1-phenylethanone (**1ac**) and the *in situ* generated dimethyl sulfide (DMS). Since DMS has a low boiling point (37.5 °C), a higher reaction temperature was used in these reactions in order to decrease the amount of DMS in the reaction mixture and thus suppress the formation of these side products. Based on all these results, the optimized conditions were determined to be 1.6 equiv. of aniline to acetophenone with CuO (1 equiv.) as the additive and a reaction temperature of 100 °C.

With the optimized conditions in hand, the generality and scope of the reaction were then investigated and the results are shown in Scheme 2. The reaction is applicable to a wide range of aromatic ketone substrates. Aryl methyl ketones with moderate or strong electron-withdrawing substituents (e.g., 4-Cl, 3-Cl, 2-Cl, 4-Br, and 4-NO_2) on the phenyl rings were converted into the corresponding benzil products in moderate yields (52–62%, **3ba**–**3fa**). In contrast, the aryl methyl ketone with an electron-donating group (4-OMe) gave a lower yield (41%, **3ga**). The steric effect was also investigated using substrates with substitutions at different positions of the phenyl ring (e.g., 2-Me, 3-Me, 4-Me). These all gave moderate yields (53–58%, **3ha**–**3ka**) indicating that the reaction is not significantly affected by the steric properties of the aromatic ketone. In addition, 1- and 2-acetonaphthalene were converted to the expected products in moderate yields (60–63%, **3la** and **3ma**). The optimized conditions were also applied to heteroaryl (such as pyridyl, furanyl, and benzofuryl) ketones and the corresponding products were achieved in slightly lower yields (33–51%, **3na**–**3qa**). Unfortunately, aliphatic methyl ketones including acetone, methyl ethyl ketone, and methyl isopropyl ketone failed to give any of the expected products.

Subsequently, the scope of reaction for anilines was also investigated and these results are also shown in Scheme 2. The anilines with electron-neutral groups (e.g., 2-Me, 3-Me) gave the expected products in moderate yields (55–53%, **3ab**–**3ac**). To further test if this transformation could occur at the *ortho* position to the amino group in aniline, 4-methylaniline was used under the same reaction conditions, but no cor-

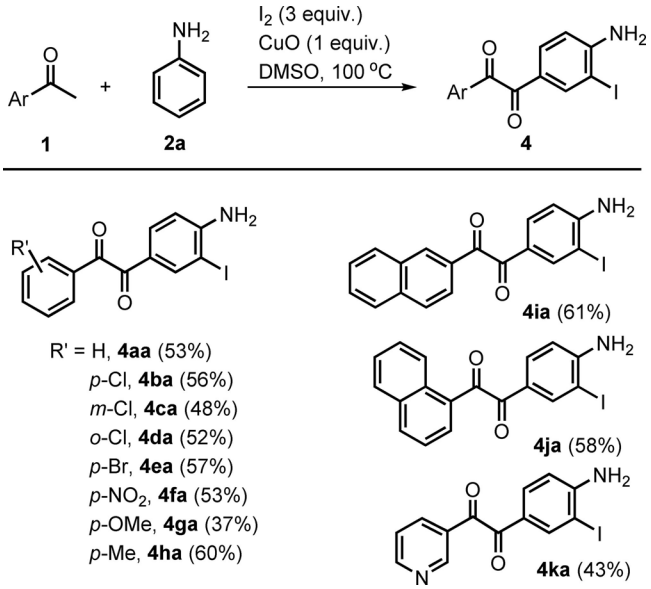


Scheme 2. Scope of methyl ketones with anilines. *Reaction conditions:* **1** (1 mmol), **2** (1.2 mmol), and I_2 (0.6 mmol) with CuO (1 mmol) in DMSO (5 mL) at 100 °C. The values in parenthesis are the isolated yields.

responding *o*-acylated product was formed, indicating that this transformation does not occur at the *ortho* position of the aniline. When an aniline bearing an electron-withdrawing group (2-NO_2) was applied to this reaction, no expected products were obtained. Therefore the electronic properties of the aniline play a key role in this reaction, and the reaction was not suitable for those anilines with electron-withdrawing substituents. *N*-Methylaniline was also investigated, but the major product was the diarylated product **6ab** instead of the expected benzil product. Acetaniline also was not suitable for this reaction.

During the above optimization of the one-pot reaction conditions, *o*-iodoaniline **4aa** was obtained as a minor product, which could serve as an important building block for heterocyclic compounds.[16] Therefore, reaction parameters were optimized for the synthesis of various iodo-derivatives. Based on the screening experiments (see the Supporting Information), increasing the amount of I_2 to 3 equiv. improved the yield of iodinated product to 53%.

The scope of the reaction for iodo-products was then investigated using these conditions (Scheme 3). Once again, the methyl ketones bearing electron-deficient groups were prone to give higher yields than the ketones with electron-rich groups (e.g., 53%, **4fa** *vs.* 37%, **4ga**). The acetonaphthalenes were also successfully converted to the expected products in moderate yields (61–58%, **4ia**–**4ja**). In addition, 3-pyridyl methyl ketone could also give the corresponding product with satisfactory yield (43%, **4ka**).



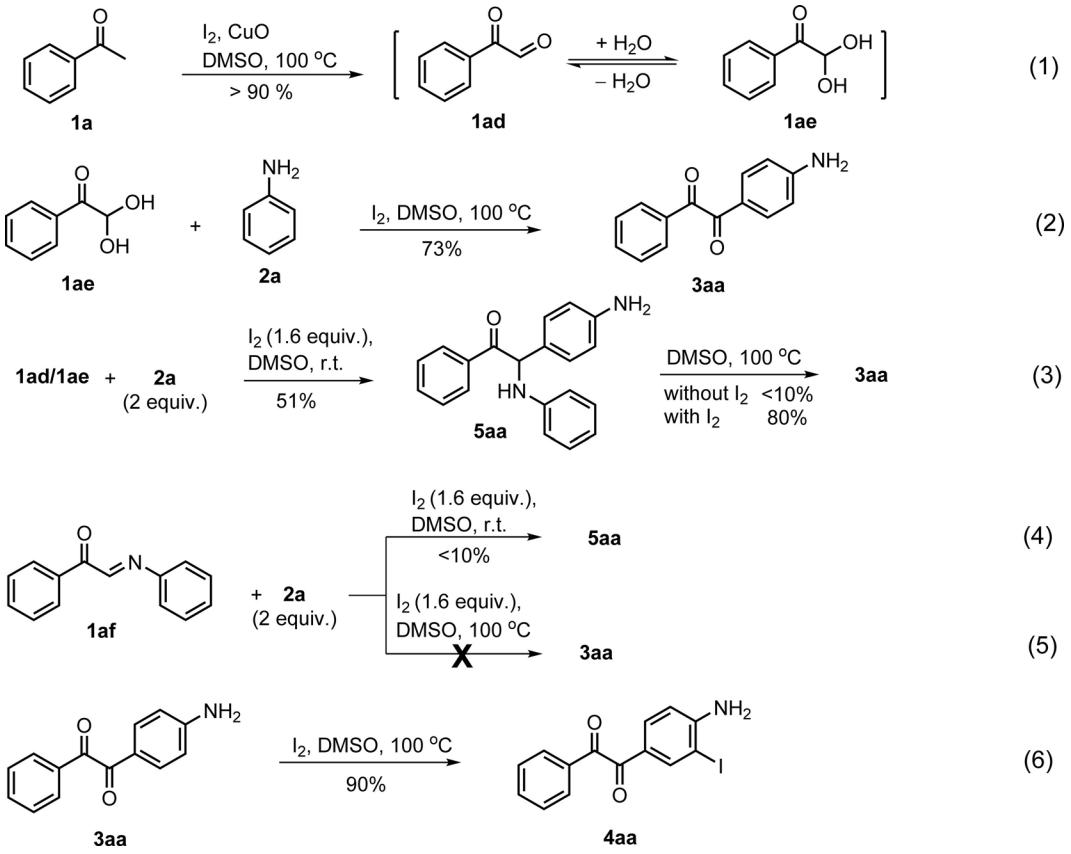
Scheme 3. Scope of iodo-products. *Reaction conditions:* **1** (1 mmol), **2a** (1.2 mmol), and I_2 (3 mmol) with CuO (1 mmol) in DMSO (5 mL) at 100 °C. The values in parenthesis are the isolated yields.

In order to gain insights into the reaction mechanism, several control experiments were conducted and the results are shown in Scheme 4. According to previously reported results,[15,17] acetophenone **1a** can easily be converted into **1ad** and **1ae** in high yields in the presence of CuO, iodine, and DMSO [Scheme 4, Eq. (1)]. When **1ad/1ae** was combined with aniline **2a**, and I_2 in DMSO at 100 °C, **3aa** was obtained in 73% yield [Eq. (2)]. This indicates that **1ad** or **1ae** might be the key intermediate for this reaction. On the other hand, at ambient temperature the reaction of aniline and a mixture of **1ad** and **1ae** (which were generated *in situ* from acetophenone **1a**) afforded **5aa** as the major product [Eq. (3)]. When I_2 was added to **5aa**, it was further converted to **3aa** with high yield in DMSO at 100 °C. In the absence of I_2, only a trace amount of **3aa** was obtained. These results imply that **3aa** might be produced through intermediate **5aa** and that iodine plays a vital role in the formation of **3aa**.

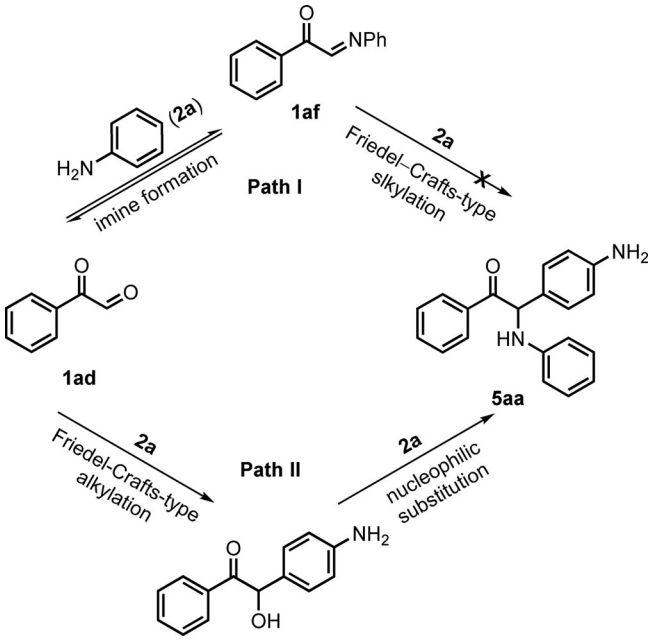
There are two possible pathways for the formation of intermediate **5aa** and they are shown in Scheme 5. Path I is *via* the formation of imine **1af** from the aldehyde and aniline followed by a Friedel–Crafts reaction with a second molecule of aniline. Path II is through a Friedel–Crafts reaction of aniline followed by a nucleophilic substitution with a second molecule of aniline. In order to clarify which pathway dominates, imine **1af** was synthesized through a known method[18] and then reacted with aniline. At room temperature, **5aa** was formed in very low yield but at an elevated temperature (100 °C) a trace amount of **3aa** was formed [Scheme 4, Eqs. (4) and (5)]. Therefore, the formation of compound **5aa** is probably mainly *via* path II. In the presence of excessive iodine, the iodo-product **4aa** was formed from **3aa** [Scheme 4, Eq. (6)].

Based on the control experiments and previous reports,[19] a plausible mechanism is proposed in Scheme 6. Initially, acetophenone **1a** is converted into intermediate **A** in the presence of I_2/CuO and DMSO by a Kornblum oxidation. As reported by Yin et al,[15] CuO and DMSO can convert *in situ* generated HI into iodine and realize a catalytic cycle for regeneration of the iodine. Then a Friedel–Crafts-type reaction between intermediate **A** and aniline affords compound **B** which could be further converted to benzil **3aa** through intermediate **5aa** in the presence of iodine. Although the conversion of **5aa** to **3aa** with imine **C** as the intermediate has been confirmed, the direct oxidation of **B** to **3aa** cannot be ruled out. When the amount of I_2 is in excess, **3aa** is further transformed into the iodo-product **4aa**.

As to the major formation of product **6ab** from *N*-methylaniline, it might involve a second Friedel–Crafts reaction of intermediate **B'** with *N*-methylaniline.[19b] The different reaction modes of aniline and *N*-methylaniline are due to the nucleophilic competition



Scheme 4. Control experiments for insights into the mechanism.

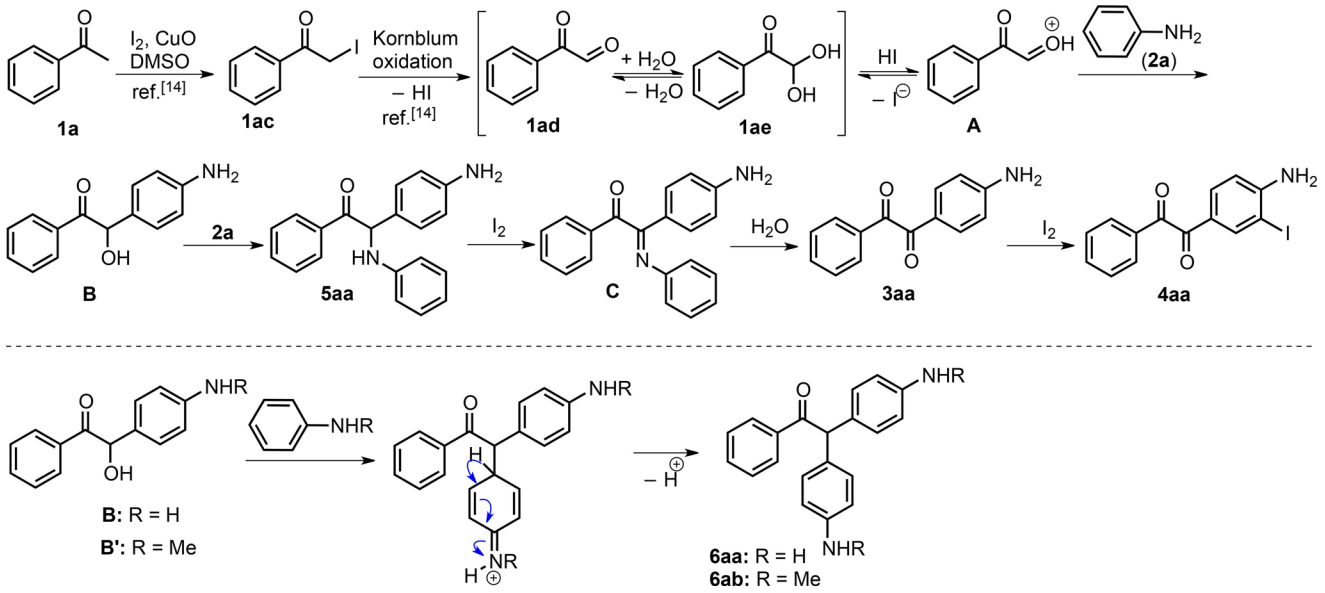


Scheme 5. Possible pathways for the formation of **5aa**.

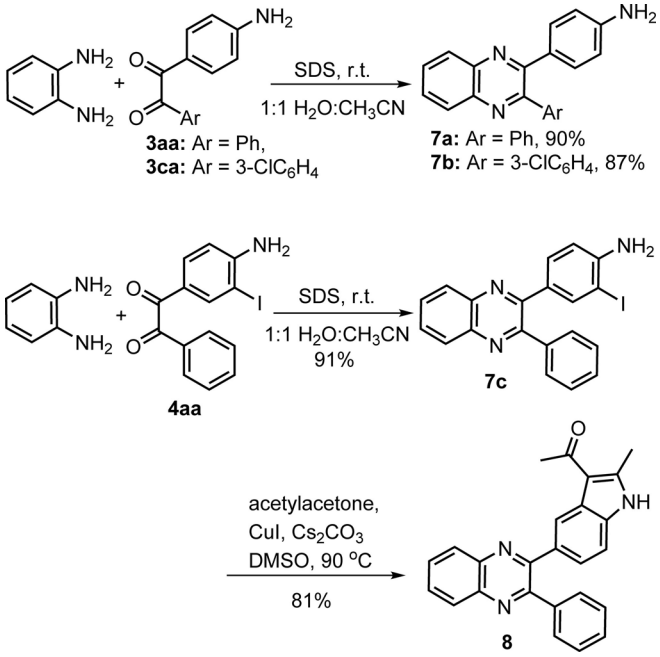
between the aromatic C-4 and the amino nitrogen. For aniline, the amine is less steric hindered, so the double alkylation product **6aa** was formed only as a by-product and in very low yield (<10%). In contrast, the *N*-methyl group is a better donating group and less nucleophilic, which renders the second Friedel–Crafts reaction more favorable.

To demonstrate the importance and applicability of this strategy, further transformations of the resulting *p*-amino-substituted benzil derivatives were performed. Quinoxalines occur widely in biologically active compounds, functional materials, and drug molecules.[20] As illustrated in Scheme 7, quinoxalines **7a** and **7b** were successfully synthesized from *p*-amino-substituted benzils **3aa** and **3ca** with high efficiencies (a 53% overall yield from the corresponding acetophenones was achieved in two steps). Further transformations of the iodo-benzil derivatives were also achieved. For example, indole-quinoxaline derivative **8** was obtained in a 39% overall yield from acetophenone in three steps. This concise and highly efficient method should be very useful for the synthesis of various *p*-amino-substituted benzils that are needed in biological and pharmaceutical screening procedures.

In conclusion, a novel method has been developed for the synthesis of *p*-amino-substituted unsymmetric benzils and their derivatives from methyl aryl ketones and anilines in the presence of I_2, CuO, and DMSO. These reactions proceed under mild conditions and are simple, efficient, and exhibit good functional



Scheme 6. Plausible reaction pathways.



Scheme 7. Synthesis of quinoxaline derivatives.

group compatibility. The method may proceed *via* a mechanism involving Kornblum oxidation, Friedel–Crafts alkylation, oxidative dehydrogenation, and hydrolysis tandem processes. However, further studies are needed to more fully elucidate the reaction mechanism. These studies along with the further development of the synthetic applications of this strategy are underway in our laboratory.

Experimental Section

Synthesis of 1-(4-Aminophenyl)-2-phenylethane-1,2-dione (3aa); Representative Procedure I

A mixture of acetophenone **1a** (120 mg, 1 mmol), CuO (80 mg, 1 mmol) and iodine (152 mg, 0.6 mmol) in anhydrous DMSO (5 mL) was stirred at 100 °C until **1a** had disappeared (monitored by thin layer chromatography). To the above reaction mixture was added dropwise aniline **2a** (112 mg, 1.2 mmol) at room temperature and the solution was then stirred at 100 °C for 12 h. The reaction was quenched with water, and then extracted with EtOAc (3× 20 mL). The combined organic layers were washed with saturated $Na_2S_2O_3$ solution, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 5:1) to afford the desired product **3aa** as a yellow solid; yield: 135 mg (59%); mp 128–129 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, J = 7.2 Hz, 2H), 7.77 (d, J = 8.6 Hz, 2H), 7.62 (t, J = 7.4 Hz, 1H), 7.48 (t, J = 7.7 Hz, 2H), 6.63 (d, J = 8.8 Hz, 2H), 4.39 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 195.5, 192.7, 152.9, 134.6, 133.5, 132.7, 129.9, 128.9, 123.3, 114.0.

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- **Free amino group**
- **No formation of α-keto amides**
- **Unsymmetrical benzils**
- **One-pot synthesis**

