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Copper-catalyzed Reaction of Anthranils with Methyl Ketones: Site-Selective C5-Dicarbonylation of Anthranils

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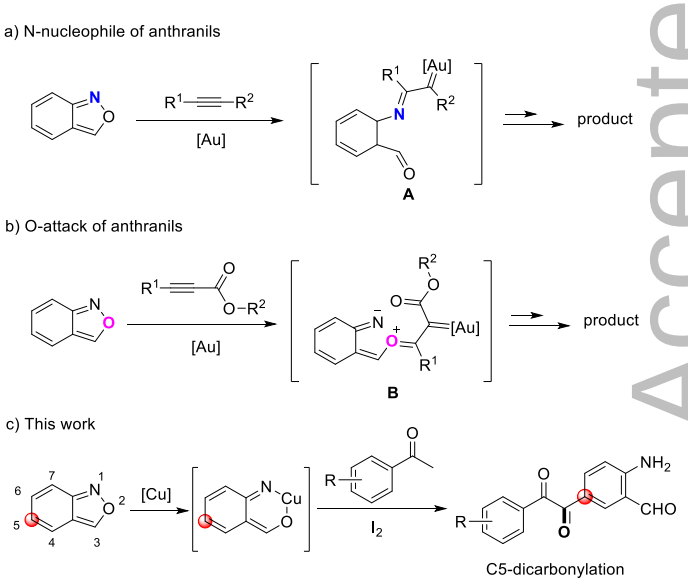
Abstract. A copper-catalyzed site-selective C5-dicarbonylation reaction of anthranils has been developed for synthesis of 1,2-dicarbonyl compounds using methyl ketone as a commercially available carbonylation reagent. This process represents the first example to implement the C5-dicarbonylation of anthranils, which involves an oxidative Csp^3–H/Csp^2–H cross-coupling reaction along with thermolytic N–O bond cleavage.

Keywords: copper-catalyzed; site-selective; Csp^3–H/Csp^2–H cross-coupling; 1,2-dicarbonyl compounds

1,2-Dicarbonyl compounds represent an indispensable class of structural motifs that are not only ubiquitous in numerous natural products[1] and pharmaceuticals,[2] but also applied as precursors in the chemical industry.[3] On account of their unique nature, developing alternative strategies for construction of 1,2-dicarbonyl compounds has received continuous attention and remains highly significant. Anthranil, a type of benzo-heterocycle compound that contains a N–O bond, has recently been used to construct various organic frameworks. The N–O bond of anthranil is labile, and it readily undergoes a ring-opening reaction. Transition metals, such as Rh(III),[4] Co(III),[5] and Cu(I),[6] can coordinate with anthranils to form *ortho*-formyl nitrene intermediates, which further transform into functional N-containing heterocycles by subsequent migration/insertion. Moreover, using anthranils as N-nucleophile has shown significant development.[7] The *in situ*-generated *α*-imino gold carbene species **A** is the key electrophilic intermediate for construction of heterocyclic skeletons (Scheme 1a).[8] These reactions lead to facile ring-opening of anthranils under transition-metal catalysis conditions and provide efficient methodologies for N1-functionalization of anthranils. Compared with using anthranils as N-nucleophile, application of the O-attack reaction has rarely been reported. Liu's group[9] developed O-attack of anthranils to propiolate, affording the gold carbene intermediate **B** via N–O bond cleavage (Scheme 1b). Using electron-deficient phosphite ligands, which increase the elctrophilicity of the gold carbene **B**, consequently controls the O-attack regioselectivity. Despite these excellent achievements, direct C5-functionalization of anthranils has not been reported yet. Based on our continuous interest in I_2–DMSO mediated reactions,[10] herein, we report a novel $Cu(OTf)_2$-catalyzed oxidative cross-coupling reaction for direct C5-dicarbonylation of anthranils by trapping *in situ*-generated phenylglyoxal derived from readily available methyl ketones (Scheme 1c). This approach successfully broadens the reaction site of anthranils, and further providing an innovative strategy for synthesis of 1,2-dicarbonyl compounds.



Scheme 1. Reactions of Anthranils

We initially used commercially available acetophenone (**1a**) and anthranil (**2**) as starting materials to investigate the dicarbonylation reaction in

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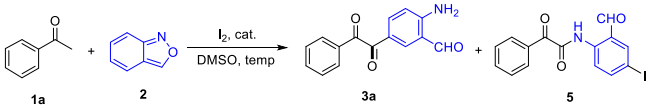
the presence of I_2 in DMSO, 1,2-dicarbonyl compound **3a** was obtained in 20% yield (Table 1, entry 1). We subsequently introduced copper salts into the reaction, which resulted in a slight increase in the yield, with the best result obtained with $Cu(OTf)_2$ (Table 1, entries 2–10). Subsequently, we investigated the effect of the temperature on the reaction from 90 to 130 °C, and 120 °C showed the best efficiency for formation of **3a** (Table 1, entries 11–14). The equivalents of $Cu(OTf)_2$ and I_2 also affected the productivity of the reaction. The optimal amount of $Cu(OTf)_2$ was 0.1 equiv, and increasing the amount of $Cu(OTf)_2$ had no effect on the yields (Table 1, entries 15–16). Using 0.8 equivalent of I_2 gave **3a** in 68% yield, decreasing the amount of I_2 was deleterious to this transformation (Table 1, entries 17). Moreover, further increasing the amount of I_2 promoted the production of side product and the chemical yield of **3a** was dropped. (Table 1, entries 18-19). Furthermore, the structure of **3a** was unambiguously determined by X-ray crystallography (see Supporting Information).

Table 1. Optimization of the Reaction Conditions.[a]

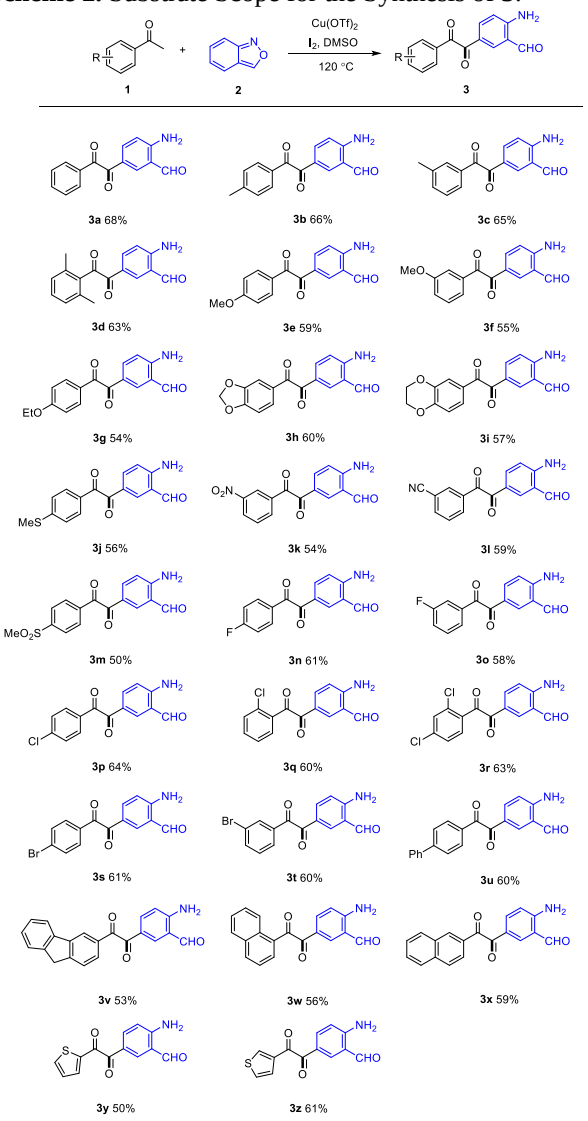


entry	catalyst (mol %)	I_2 (equiv.)	temp (°C)	**3a**[b]	**5**[b]
1	None	0.8	120	20	10
2	$Cu(OAc)_2$(10)	0.8	120	50	trace
3	$CuSO_4$(10)	0.8	120	15	trace
4	$Cu(NO_3)_2$(10)	0.8	120	5	trace
5	$CuCl_2$(10)	0.8	120	trace	trace
6	$CuBr_2$ (10)	0.8	120	25	13
7	**$Cu(OTf)_2$ (10)**	**0.8**	**120**	**68**	8
8	CuI (10)	0.8	120	46	trace
9	CuCN (10)	0.8	120	24	trace
10	CuCl (10)	0.8	120	42	trace
11	$Cu(OTf)_2$ (10)	0.8	90	trace	trace
12	$Cu(OTf)_2$ (10)	0.8	100	5	trace
13	$Cu(OTf)_2$ (10)	0.8	110	25	5
14	$Cu(OTf)_2$ (10)	0.8	130	50	20
15	$Cu(OTf)_2$ (15)	0.8	120	65	8
16	$Cu(OTf)_2$ (20)	0.8	120	67	10
17	$Cu(OTf)_2$ (10)	0.4	120	46	trace
18	$Cu(OTf)_2$ (10)	1.0	120	61	18
19	$Cu(OTf)_2$ (10)	1.2	120	59	20

[a] Reaction conditions: **1a** (0.5 mmol), **2** (0.5 mmol), and I_2 heated in 2 mL of DMSO. [b] Products were obtained in isolated yields.

Under the optimal conditions, we began to examine the substrate scope of the dicarbonylation reaction (Scheme 2). Acetophenone with electron-donating groups (Me, OMe, OEt, 3,4-OCH_2O, 3,4-$O(CH_2)_2O$, SMe, Ph) on the phenyl ring smoothly reacted with anthranil, affording the corresponding 1,2-dicarbonyl compounds in moderate yields (**3a**–**3j**, **3u**). Strong electron-withdrawing groups (NO_2, CN, SO_2Me) on the phenyl ring (**3k**–**3m**) gave products in lower efficiency than electron donating groups, while halogen groups had almost no effect on the reaction (**3n**–**3t**). Furthermore, replacing the phenyl ring with a naphthyl, fluorenyl or thienyl ring (**3v**–**3z**) gave the desired target products in 50%–61% yields. To our disappointment, the aliphatic ketones were not compatible with this transformation (see Supporting Information).

Scheme 2. Substrate Scope for the Synthesis of **3**.[a]

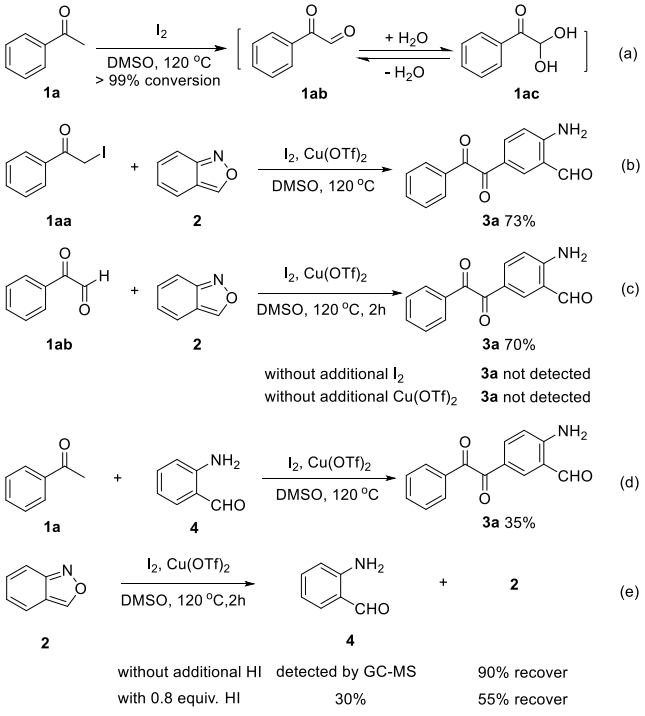


[a] Reaction conditions: **1** (0.5 mmol), **2** (0.5mmol), I_2, (0.8 equiv.) and $Cu(OTf)_2$ (10 mol%) in DMSO (2 mL) for 8 h at 120 °C.

To investigate mechanism, several control experiments were taken into consideration (Scheme 3). Acetophenone (**1a**) reacted with I_2 in DMSO affording phenylglyoxal (**1ab**) and its corresponding hydrated species (**1ac**) in quantitative yield (Scheme 3a). When acetophenone (**1a**) was replaced with α-iodo acetophenone (**1aa**), which was considered as probable precursor of α-ketoaldehyde (**1ab**), the desired 1,2-dicarbonyl compound **3a** was obtained in 73% yield (Scheme 3b). When phenylglyoxal (**1ab**) reacted with anthranil (**2**), **3a** was synthesized in 70% yield under the standard conditions (Scheme 3c). However, **1ab**

was not able to convert to the target compounds in the absence of I_2 or $Cu(OTf)_2$, indicating that I_2 and $Cu(OTf)_2$ are indispensable for subsequent conversion of this reaction. Moreover, when anthranil was replaced by 2-aminobenzaldehyde (**4**), **3a** were obtained in 35% yield (Scheme 3d). This showed that **4** might be identified as a possible intermediate that anthranil could be transferred to through a thermolytic N–O bond cleavage. HI might be the reductant for the transformation from **2** to **4**. Aminobenzaldehyde (**4**) could only be detected by GC-MS under the standard conditions, while **4** could be isolated in 30% yield with additional of HI which further verified that anthranil underwent ring-opening reaction (Scheme 3e). Besides, a radical mechanism might not exist in this process (see Supporting Information).

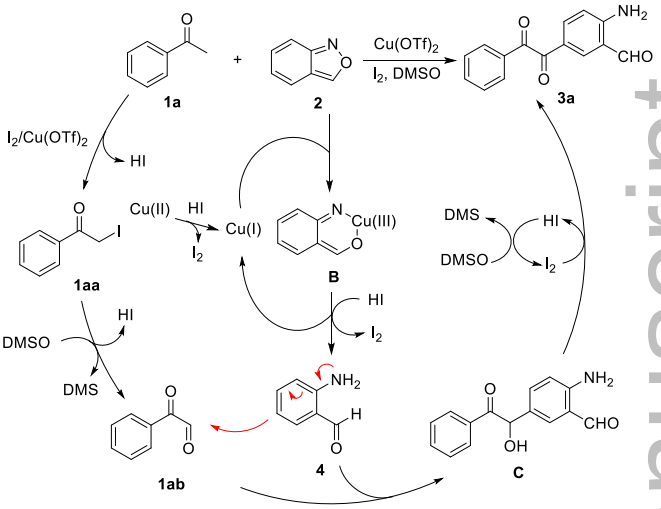
Scheme 3. Control Experiments.



Based on the control experiments and previous study, we propose a possible mechanism in Scheme 4.[11] Initially, acetophenone (**1a**) reacts with I_2 to give *α*-iodoketone (**1aa**), which transforms to **1ab** by further Kornblum oxidation with release of HI. Cu(II) can be reduced by HI to generate *in-situ* Cu(I) species. Cu(I) further inserts into the N−O bond of anthranil to obtain intermediate **B**.[12] Protonation of **B** by HI delivers the intermediate **4** and Cu(I) species is regenerated. The amino group of **4** might coordinate with Cu, thus preventing the N-attack reaction.[13] Phenylglyoxal **1ab** is subsequently trapped by **4** via a Friedel–Crafts-type reaction to give intermediate **C**. Intermediate **C** is eventually oxidized by I_2 to afford the corresponding product **3a**.

In conclusion, a high-regioselectivity copper-catalyzed dicarbonylation of anthranils via oxidative Csp^3–H/Csp^2–H cross-coupling reaction has been developed under mild conditions. This work represents the first example to realize direct C5-dicarbonylation of anthranils along with thermolytic N–O bond cleavage, providing a new method for enriching synthesis of 1,2-dicarbonyl compounds using monocarbonyl substrates as starting materials. Further studies on synthetic applications of this process are currently ongoing in our laboratory.

Scheme 4. Proposed Mechanism.



Experimental Section

A sealed tube equipped with a magnetic stirring bar was charged with acetophenone (**1a**) (60 mg, 0.5 mmol), anthranil (**2**) (59.5 mg, 0.5 mmol), iodine (101.6 mg, 0.4 mmol) and $Cu(OTf)_2$ (18.1 mg, 0.05 mmol) at room temperature, and DMSO (2 mL) was added. The resulting mixture was stirred at 120 °C for 8h. After the reaction completed, the mixture was quenched with saturation $Na_2S_2O_3$ solution (50 mL), extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 5:1) to yield the desired product **3a** as a yellow solid.

Acknowledgements

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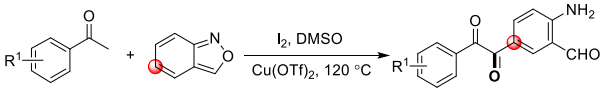

- High atom efficiency
- High regioselectivity
- The first C5-dicarbonylation of anthranils