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nBu$_4$NI-catalyzed direct synthesis of α-ketoamides from aryl methyl ketones with dialkylformamides in water using TBHP as oxidant†

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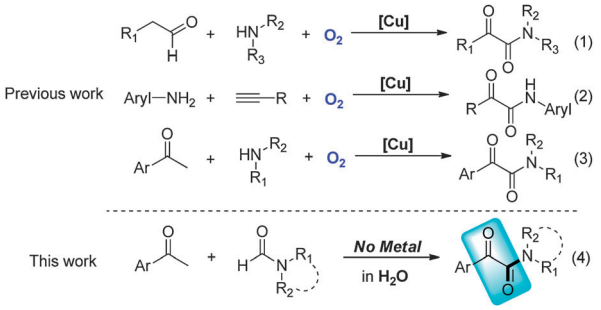
A novel and easy practical direct synthesis of α-ketoamides has been developed without metals in water. This procedure was catalyzed by nBu$_4$NI using TBHP as oxidant from simple substrates, aryl methyl ketones and dialkylformamides.

α-Ketoamides are key units of many natural products, biological compounds and pharmaceuticals. They have been widely developed to design inhibitors of peptidases,[1] histone deacetylases[2] and human cytosolic phospholipase A_2,[3] also have been used to inhibit several classes of proteases, such as serine proteases, cysteine proteases, and HIV proteases.[4] Because of their important biological properties in the field of medicinal chemistry, a lot of synthetic routes have been developed.[5] Among these methods, condensation of *a*-keto acids or *a*-keto acyl halides with amines,[5a] reactions of acid chlorides with carbamoylstannanes or carbamoylsilanes,[5c,d] oxidative amidation of 2,2-dibromo-1-aryl moieties,[6] oxidation of α-hydroxyamides and α-aminoamides,[7] palladium-catalyzed double carbonylation of diaryliodonium salts or aryl halides,[8] oxidation of ynamides[9] and oxidative amidation of arylglyoxals with secondary amines mediated by SeO_2[10] have been widely used. Nevertheless, many of these developments suffer from complicated starting materials, harsh conditions and metal salts. Recently, copper catalysis was used in the efficient direct synthesis of α-ketoamides using O_2 as oxidant was reported by Jiao[11a,b] and Ji[11c] (eqn (1)–(3) in Scheme 1). Although, environmentally friendly molecular oxygen as oxidant greatly improved the efficient methodologies for the synthesis of α-ketoamides, catalytic metal and expensive substrates (terminal alkynes) were still needed. There is still room for the development of other novel, simple and highly efficient methods for the direct synthesis of α-ketoamides. Recently, the radical catalytic system "nBu$_4$NI-TBHP" has received a lot of considerable attention especially in C–H activation chemistry due to its mild, high efficiency and environmentally friendly characteristics.[12]

Herein, we present a nBu$_4$NI-catalyzed radical oxidative coupling of readily available aryl methyl ketones with dialkylformamides using TBHP as oxidant to access α-ketoamides in water. This method offers a new, green and metal-free approach to α-ketoamides with H_2O and CO or CO_2 as the main byproducts.



Scheme 1 Representative synthesis of α-ketoamides from simple methods.

Initially, we chose *p*-chloroacetophenone (**1a**) and DMF (**2a**) as model substrates to optimize the reaction conditions. Some screening results are summarized in Table 1. As shown in Table 1, among those catalysts tested, nBu$_4$NI was found to be the most effective catalyst (entry 6). On the contrary, the reaction did not work under the same conditions using nBu$_4$NBr as catalyst (entry 1). When KI was used as catalyst instead of nBu$_4$NI, the reaction also proceeded to obtain **3aa** in 60% yield (entry 11). Metallic catalyst containing an iodide anion, copper (I) iodide, was also examined here, but 30% catalyst loading only showed very low activation (entry 12). However, CuI show high activation in Ji's work[11c] (eqn (3) in Scheme 1). Iodine was not effective for this transformation under the same conditions (entry 13). The reaction in the absence of nBu$_4$NI or TBHP was unsuccessful (entries 8 and 9). Therefore, we considered that nBu$_4$NI and TBHP were both important in this transformation.[12b–d] Then, other oxidants such as H_2O_2, DTBP and BPO were also examined, and none showed activation under the standard conditions (entries 2–4). 80% isolated yield was also obtained under neat conditions (entry 10), nevertheless, temperature influenced the reaction activation remarkably (entry 7).

To evaluate the scope of this transformation, the novel radical oxidative amidation protocol was extended to different aryl methyl ketones and dialkylformamides under the optimized conditions (Table 2). The results indicated both electron-rich

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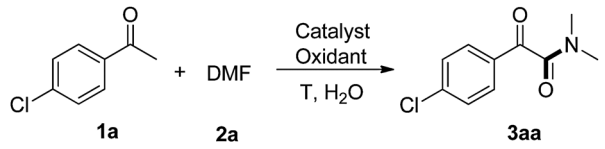
Table 1 Optimization of reaction conditions[a]



1a **2a** **3aa**

Entry	Catalyst (mol%)	Oxidant (equiv.)	T (°C)	Yield[b] (%)
1	nBu$_4$NBr (20)	TBHP (5)	100	Trace
2	nBu$_4$NI (20)	H_2O_2 (5)	100	0
3	nBu$_4$NI (20)	DTBP (5)	100	0
4	nBu$_4$NI (20)	BPO (5)	100	0
5[c]	nBu$_4$NI (30)	BPO (10)	100	0
6	nBu$_4$NI (20)	TBHP (5)	100	84 (74)[e]
7	nBu$_4$NI (20)	TBHP (5)	80	61
8	nBu$_4$NI (20)	TBHP (0)	100	0
9	nBu$_4$NI (0)	TBHP (5)	100	Trace
10[d]	nBu$_4$NI (20)	TBHP (5)	100	80
11	KI (20)	TBHP (5)	100	60
12	CuI (30)	TBHP (10)	100	30
13	I_2 (30)	TBHP (5)	100	Trace

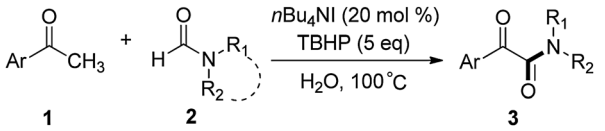
[a] Reaction conditions: **1a** (1.0 mmol), **2a** (2.5 mmol), H_2O (2 mL), under air atmosphere, 16 h, TBHP: *tert*-butyl hydroperoxide 70% in water, DTBP: di-*tert*-butyl peroxide 98%, H_2O_2 30% in water. [b] Isolated yield. [c] DCE instead of H_2O. [d] Under neat conditions. [e] 10 mol% catalyst was used.

and electron-deficient aryl methyl ketones could be successfully transformed into the corresponding products in moderate to good yields. Generally, ketones bearing electron-withdrawing substituents proceeded more efficiently than those bearing electron-donating substituents. For example, when 4-fluoroacetophenone (**3c**) was coupled with DMF, product **3ca** was obtained in 90% yield, however, 4-methylacetophenone (**3d**) gave a decreased yield (64%). Likewise, only 57% product yield was obtained when 2,4-dimethylacetophenone (**3e**) coupled with DMF though 10 eq of TBHP was used. A lot of functional groups such as Cl (**3a**), F (**3c**), F_3C (**3j**), NO_2 (**3f**) and OTs (**3k**) were tolerated under the optimized conditions. Besides, substituents on the different positions of the aryl methyl ketones did not affect the reaction efficiency remarkably. Heteroaryl methyl ketones including furan and pyridine could be also transformed into desired products (**3ha**, 75%; **3ia**, 80%) under the optimized conditions. Furthermore, different dialkylformamides including *N,N*-diethylformamide (**2b**), piperidine-1-carbaldehyde (**2c**), morpholine-4-carbaldehyde (**2d**), 4-methylpiperazine-1-carbaldehyde (**2e**) were put into the current conditions and the corresponding products were obtained in moderate to high yields (**3bb–3be**, 58–82%). But when DMAc instead of DMF coulped with *p*-chloroacetophenone under the optimized conditions, no desired product was observed (**3aa**, 0%).

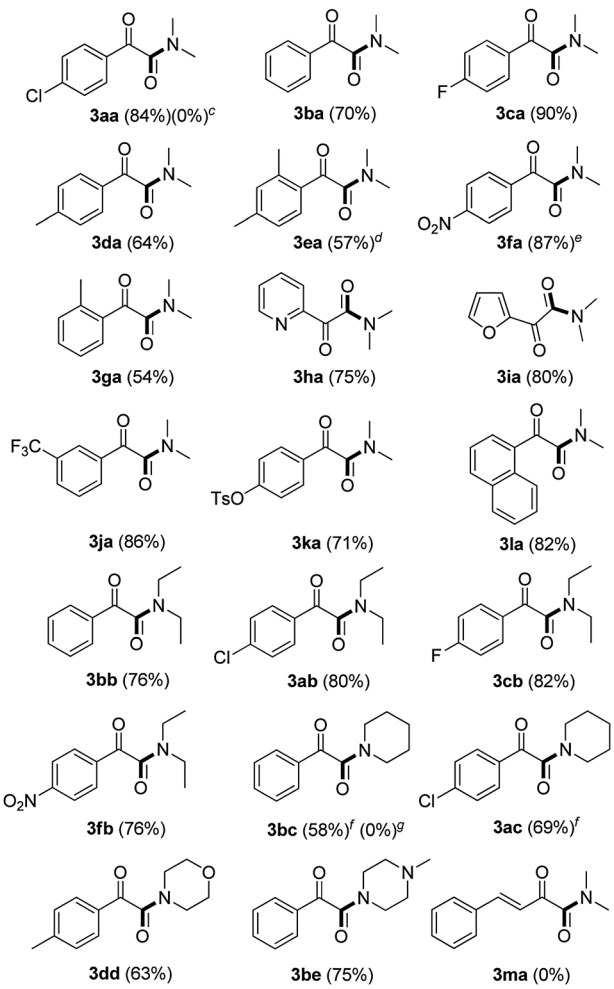
Furthermore, no desired product was observed when piperidine was used instead of piperidine-1-carbaldehyde (**2c**) in our catalyst system (**3bc**, 0%). This indicates that the formyl group plays an important role in this transformation under the current conditions. As for **3ma**, no product produced may be due to the double bond in **1m** that could be oxidized under the optimized conditions.

Due to oxidative properties of the catalyst system, we tried to extend the synthetic utility of this method. Interestingly, when 1-arylethanols were subjected to this reaction directly,

Table 2 nBu$_4$NI-catalyzed synthesis of α-ketoamides from aryl methyl ketones with dialkylformamides[a,b]



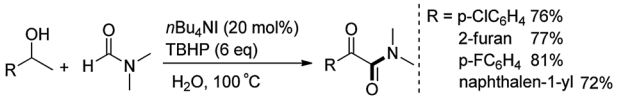
1 **2** **3**



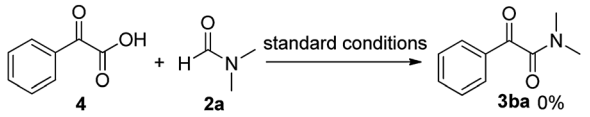
[a] Reaction conditions: aryl methyl ketone (1 mmol), dialkylformamide (2.5 mmol), nBu$_4$NI (20 mol%), TBHP (5 mmol), H_2O (2 mL), 100 °C, 16–24 h. [b] Isolated yield. [c] DMAc instead of DMF. [d] TBHP (10 mmol). [e] 85 °C. [f] Under neat conditions. [g] Piperidine instead of piperidine-1-carbaldehyde.

it showed similar results with aryl methyl ketones under current conditions (Scheme 2). As shown in Scheme 2, 1-arylethanols were also compatible with the catalyst system to access α-ketoamides in satisfactory yields.

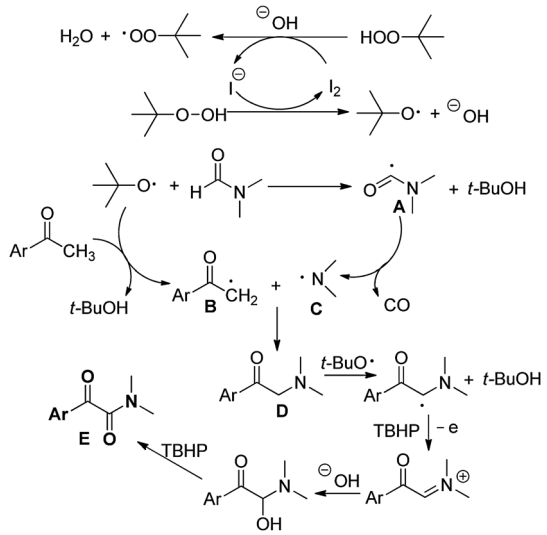
At first, we considered the aryl methyl ketones may be demethylated under the oxidative conditions. So the reaction of 2-oxo-2-phenylacetic acid (**4**) coupled with DMF under the



Scheme 2 nBu$_4$NI-catalyzed synthesis of α-ketoamides from 1-arylethanols with DMF.



Scheme 3 Evidence that **4** is not an intermediate of this nBu$_4$NI-catalyzed radical oxidative transformation.



Scheme 4 Proposed preliminary mechanisms.

standard conditions was investigated. However, the product **3ba** was not obtained. This result indicates that **4** is not intermediate of this nBu$_4$NI-catalyzed radical oxidative transformation (Scheme 3). On the basis of the above results and Wan's studies on the "nBu$_4$NI-TBHP" system,[12b–d] a plausible mechanism for the radical oxidative coupling is illustrated in Scheme 4. At the beginning, the *tert*-butoxyl radical forms catalytically with the assistance of the iodide anion. This radical traps H from the aryl methyl ketone and DMF respectively to form radicals **A** and **B**. Then, aminyl radical **C**[12b] produced from **A** coupled with radical **B** to generate intermediate **D**. Finally, **D** is oxidized by TBHP to form the desired product **E** (Scheme 4).

In conclusion, we have developed a novel protocol for direct synthesis of α-ketoamides which are important structural units in lots of biological compounds or drugs. This transformation catalyzed by nBu$_4$NI in water is free of metal, environmentally friendly and both substrates were cheap and easily available. Further investigation on the reaction are ongoing in our laboratory.

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