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The syntheses of α-ketoamides *via* $^{n}Bu_4NI$-catalyzed multiple $sp^3C–H$ bond oxidation of ethylarenes and sequential coupling with dialkylformamides†

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The $^{n}Bu_4NI$-catalyzed sequential C–O and C–N bond formation *via* multiple $sp^3C–H$ bond activation of ethylarenes, using *N*,*N*-dialkylformamide as the amino source, provided α-ketoamides with moderate yields.

The α-ketoamide functional group can be found in a number of marketed and investigational drugs since it is recognized as a key functional moiety for inhibitors of hydrolytic enzymes such as serine and cysteine proteases.[1] This moiety also exists in several bioactive natural products such as in immunosuppressant drugs FK-506 and rapamycin.[2] The compounds containing the α-ketoamide scaffold such as chloropeptin I and complestatin are proved to inhibit HIV replication.[3] α-Ketoamides are also valuable precursors in organic synthesis, for example, to synthesize various heterocyclic compounds.[4] Thus, it is of great interest and important to develop efficient synthetic methods for this type of compound. Synthetically, α-ketoamides can be prepared by the oxidation of the corresponding α-hydroxyamides,[5] arylacetamides[6] or α-amino-α-cyanoketones,[7] and by the amidation of α-ketoacids.[8] Some transition metal-catalyzed reactions were also successfully used for the syntheses of α-ketoamides, *e.g.*, palladium- or copper-catalyzed double carbonylative amination of aryl halides,[9] and copper-catalyzed oxidative amidation/diketonization of terminal alkynes.[10]

Recently, the oxidative carbonylation to sp^3 C and sequential coupling has become an attractive strategy in organic synthesis, especially for the syntheses of carbonyl compounds, amides, including α-ketoamides. For example, the palladium catalyzed chelation-assisted *ortho*-acylation using methylarenes as the acylation reagents,[11] Mn(IV) promoted syntheses of amides *via* the oxidative coupling of methylarenes with urea or *N*-chloroamine,[12] copper-catalyzed oxidative coupling of aryl methyl ketones or acetaldehydes with amines, and α-oxocarboxylic acids with formamides.[13] Remarkably, a metal-free approach to α-ketoamides was recently developed by the $^{n}Bu_4NI$ or I_2-catalyzed oxidative coupling of aryl methyl ketones with dialkylformamides or amines.[14] To date, the activated methyl or methylene $sp^3C–H$ bond was centered on the benzylic C–H bond or α-C–H bond of the carbonyl group. To the best of our knowledge, the sequential dehydrogenation to the five inert $sp^3C–H$ bonds of the ethyl group and coupling were not reported. The continuing attention to the functionalization of inert $sp^3C–H$ bonds inspired us to look into the activation of multiple C–H bonds of easily available and unprefunctionalized ethylarenes. Herein, for the first time, we present the $^{n}Bu_4NI$-catalyzed sequential C–O and C–N bond formation *via* multiple $sp^3C–H$ bond activation of ethylarenes, providing an efficient approach to α-ketoamides.

In recent years, $^{n}Bu_4NI$ in combination with the oxidant TBHP, as an environmentally friendly and mild metal free catalyst, was proved to be very efficient in a series of organic reactions especially in C–H activation.[15] Thus, this $^{n}Bu_4NI$–TBHP catalytic system was tried for the multiple oxidative coupling reactions of ethylarenes with *N*,*N*-dialkylformamides. The reaction of ethylbenzene (**1a**) and *N*,*N*-dimethylformamide (DMF) (**2a**) was initially selected to study the reaction conditions (Table 1). Delightedly, in the presence of 10 mol% $^{n}Bu_4NI$ and 8 eq. TBHP, the reaction gave the product *N*,*N*-dimethyl-2-oxo-2-phenylacetamide (**3aa**) in 23% isolated yield (entry 1). Encouraged by this result, further optimization of the reaction conditions was carried out. Without $^{n}Bu_4NI$, the reaction could not proceed at all. Increasing the amount of $^{n}Bu_4NI$ to 20 mol %, and that of TBHP to 12 eq. led to the raised yield of 63% (entries 2–4). Temperature had a significant effect on the reaction. The appropriate reaction temperature was 80 °C. The yield had no significant change when elevating the reaction temperature to 100 °C, but reducing the temperature to 60 °C resulted in a depressed yield of 48% (entries 5 and 6). Apart from TBHP, other common oxidants, such as DTBP, DDQ, H_2O_2, O_2, $K_2S_2O_8$ and $PhI(OAc)_2$, were proved to be noneffec-

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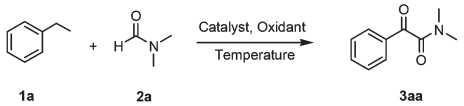
Table 1 Screening of reaction conditions[a]



1a 2a 3aa

Entry	Catalyst (mol%)	Oxidant (equiv.)	Temp. (°C)	Yield[d] (%)
1	^{n}Bu$_4$NI (10)	TBHP (8)[b]	80	23
2	^{n}Bu$_4$NI (10)	TBHP (10)	80	42
3	^{n}Bu$_4$NI (10)	TBHP (12)	80	52
4	^{n}Bu$_4$NI (20)	TBHP (12)	80	63
5	^{n}Bu$_4$NI (20)	TBHP (12)	60	48
6	^{n}Bu$_4$NI (20)	TBHP (12)	100	57
7	^{n}Bu$_4$NI (20)	DTBP (12)	80	0
8	^{n}Bu$_4$NI (20)	DDQ (4)[c]	80	0
9	^{n}Bu$_4$NI (20)	H_2O_2 (12)	80	0
10	^{n}Bu$_4$NI (20)	O_2 (1 atm)	80	0
11	^{n}Bu$_4$NI (20)	$K_2S_2O_8$ (4)[c]	80	0
12	^{n}Bu$_4$NI (20)	PhI(OAc)$_2$ (4)[c]	80	0
13	KI (20)	TBHP (12)	80	16
14	I_2 (20)	TBHP (12)	80	Trace
15	NIS (20)	TBHP (12)	80	Trace
16	CuI (20)	TBHP (12)	80	Trace

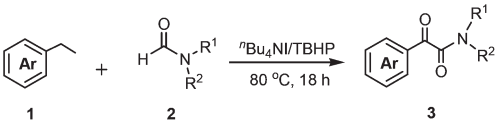
[a] Reaction conditions: **1a** (1.0 mmol), **2a** (6.0 mmol), catalyst, and oxidant under an air atmosphere for 18 h. [b] TBHP: *tert*-butyl hydroperoxide, 70% in water. [c] In DCE. [d] Isolated yield.

tive to this transformation (entries 7–12). When KI was used instead of ^{n}Bu$_4$NI, the reaction only gave a low yield of 16% (entry 13). Other iodides such as iodine, NIS and CuI showed almost no activity towards the reaction (entries 14–16).

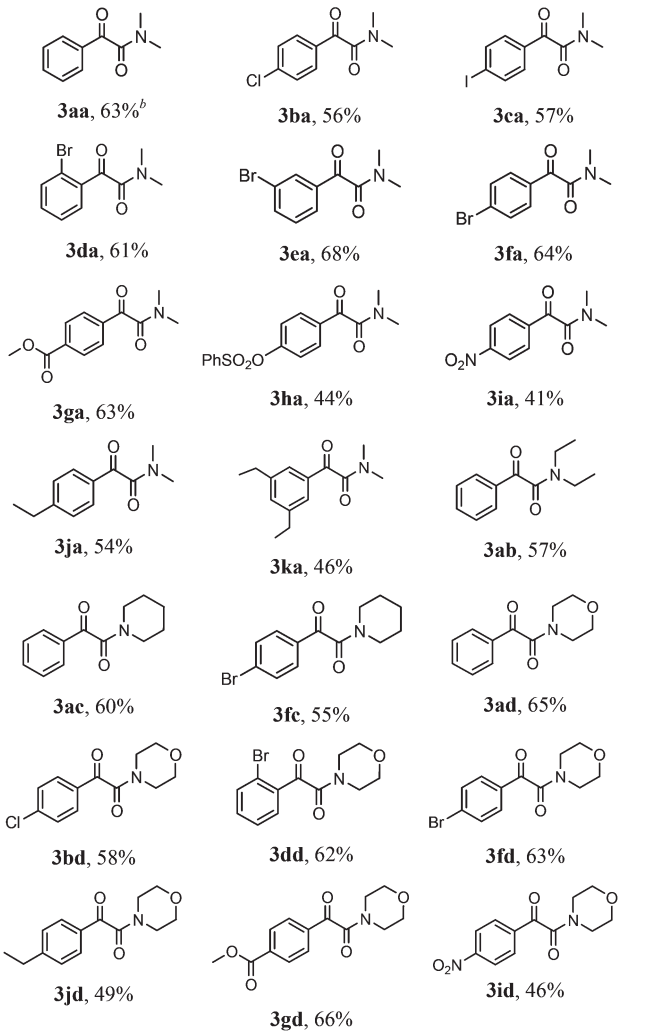
Under the optimized reaction conditions, the ^{n}Bu$_4$NI–TBHP catalyzed multiple oxidative coupling reactions of various ethylarenes with *N*,*N*-dialkylformamide were then studied (Table 2). At the beginning of our investigation, DMF was chosen as the amino source for this reaction. With most of the ethylarenes we employed, the reaction gave the corresponding products in moderate yields within a reaction time of 18 h. The reaction showed a good tolerance to the chemically active functional groups. The halogen (Cl, Br, I), ester and sulfonyloxyl group on ethylarene remained after reaction (**3ba–3ha**), and the connection position of the substituent on the benzene ring had no significant influence on the reaction (**3da–3fa**). Notably, in the case of ethylarenes with more than one ethyl group such as *p*-diethylbenzene and 1,3,5-triethylbenzene, the reaction could give monooxidation–amination products with lower yields because of the formation of some oxidation byproducts (**3ja**, **3ka**, **3jd**). The presence of NO_2 on the benzene ring led to relatively low yields because of the strong electron-withdrawing properties of the NO_2 group (**3ia**, **3id**). Next we employed a series of *N*,*N*-dialkylformamides, including cyclic and acyclic formamides (**2b–2d**), as the coupling partner; the results did not show an evident difference compared with the reaction of DMF (**3ab–3id**).

To our surprise, when *N*,*N*-diisopropylformamide was used as the amino source, instead of the general product *N*,*N*-diisopropyl-2-oxo-2-arylacetamide, *N*-isopropyl-2-oxo-2-arylacetamides were generated (Scheme 1). Though the exact mechanism is not clear, we presume that it may be related to the relatively large steric hindrance of isopropyl. It also revealed

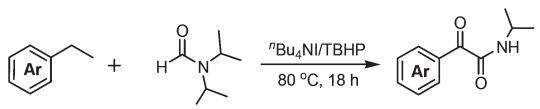
Table 2 ^{n}Bu$_4$NI-TBHP catalyzed synthesis of α-ketoamides[a]



1 2 3



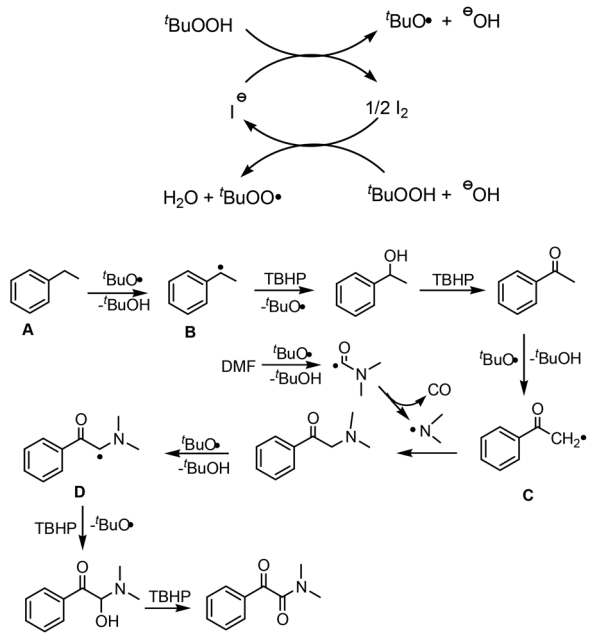
[a] Reaction conditions: **1** (1.0 mmol), **2** (6.0 mmol), ^{n}Bu$_4$NI (20 mol%), TBHP (12 eq.), under an air atmosphere at 80 °C for 18 h. [b] Isolated yield.



1 2e 3

3ae Ar = Ph (51%)
3ge Ar = *p*-MeOOCC$_6$H$_4$ (43%)

Scheme 1 Formation of *N*-isopropyl-2-oxo-2-arylacetamides.



Scheme 2 Plausible reaction mechanism.

that the cleavage of the alkyl C–N bond was possible in the $^{n}Bu_4NI$–TBHP catalytic system.

From the reaction mixture, acetophenones as the oxidation products of ethylarenes could be found. In addition, the decarbonylation of DMF has been well-documented.[16] A ^{13}C-isotope labeling experiment by Wan further proved that the cleavage of the C–N bond of DMF was possible in the $^{n}Bu_4NI$/TBHP system.[15a] Based on the above results and the related reports,[14,15] a plausible catalytic mechanism is presented as shown in Scheme 2. Firstly, TBHP decomposed to a ^{t}butoxyl radical and a hydroxyl anion under the catalysis of $^{n}Bu_4NI$. The ^{t}butoxyl radical then abstracted hydrogen from the benzylic C–H bond of ethylarene to afford the benzylic radical **B**;[15d] this was followed by the subsequent hydroxylation by TBHP to generate 1-phenylethanol, which was further oxidized by TBHP to form acetophenone. Hydrogen was subsequently ingested by the ^{t}butoxyl radical, and then a phenacyl radical **C** was formed. Meanwhile, hydrogen was abstracted from DMF by the ^{t}butoxyl radical, followed by the release of CO to form a dimethylamino radical. The dimethylamino radical was captured by the radical **C** to generate the intermediate product 2-(dimethylamino)-1-phenylethanone. According to a similar oxidation process to the previously described, this intermediate product was finally oxidized by TBHP to produce the desired product α-ketoamide.

To verify the proposed mechanism, several control experiments were carried out. When 1 mmol 2,2,6,6-tetramethyl piperidine-*N*-oxyl (TEMPO, a radical scavenger) was added to the reaction system of **1a** and **2a** under the established reaction conditions, no corresponding oxidative coupling product **3aa** was detected, which revealed that the reaction might involve a radical pathway. When acetophenone or 1-phenylethanol was used instead of ethylbenzene to react with DMF, a similar result was obtained under the same reaction conditions. But from phenylacetaldehyde, no desired product was separated. These results showed that the oxidation started from the benzylic C–H bond of ethylarene, but not from methyl. In addition, when dimethylamine was used instead of DMF, the product **3aa** was also not obtained, which implied that dimethylamine was not the reaction intermediate.

Conclusions

In summary, we developed a convenient method for the synthesis of α-ketoamides from cheap compounds, ethylarenes, in aqueous media under metal-free conditions. And also, to the best of our knowledge, it is the first example of formation of C–O and C–N bonds sequentially *via* multiple inert sp^3C–H bond activation.

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