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The syntheses of α-ketoamides via *n*Bu₄NI-catalyzed multiple sp³C–H bonds oxidation of ethylarenes and sequential coupling with dialkylformamides

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The *n*Bu₄NI-catalyzed sequential C−O and C−N bond formation via multiple sp³C−H bonds activation of ethylarenes, using *N,N*-dialkylformamide as the amino source, 10 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 15 bioactive natural products such as the immunosuppressant drugs FK-506 and rapamycin.[2] The compounds containing 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 20 various heterocyclic compounds.[4] Thus, it is of great interest and important to develop the efficient synthetic methods for this type of compounds. 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 25 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] copper-catalyzed oxidative amidation/diketonization of terminal alkynes.[10]

30 Recently, the oxidative carbonylation to sp³ 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 35 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 40 metal-free approach to α-ketoamides was recently developed by the *n*Bu₄NI or I₂-catalyzed oxidative coupling of aryl methyl ketones with dialkylformamides or amines.[14] Up to date, the activated methyl or methylene sp³C–H bond was centered on benzylic C–H bond or α-C–H bond of carbonyl group. To the 45 best of our knowledge, the sequential dehydrogenation to the five inert sp³C–H bonds of ethyl group and coupling was not reported. The continuing attention to the functionalization of inert sp³C–H

bonds inspired us to look into the activation of multiple C–H bonds of easily available and unprefunctionalized ethylarenes. 50 Herein, for the first time, we present the *n*Bu₄NI-catalyzed sequential C−O and C−N bond formation via multiple sp³C−H bonds activation of ethylarenes, providing an efficient approach to α-ketoamides.

In recent years, *n*Bu₄NI in combination with oxidant TBHP, 55 as an environmentally friendly and mild metal free catalyst, was proved to be very efficient in a series of organic reaction especially in C–H activation.[15] Thus, this *n*Bu₄NI-TBHP catalytic system was tried for the multiple oxidative coupling reaction of ethylarenes with *N,N*-dialkylformamides. The reaction of 60 ethylbenzene (**1a**) and *N,N*-dimethylformamide (DMF) (**2a**) was initially selected to study the reaction conditions (Table 1). Delightedly, in presence of 10 mol % *n*Bu₄NI and 8 eq TBHP, the reaction gave the product *N,N*-dimethyl-2-oxo-2-phenylacetamide (**3aa**) in 23% isolated 65 yield (entry 1). Encouraged by this result, further optimization to the reaction conditions was carried out. Without *n*Bu₄NI, the reaction could not proceed at all. Increasing the amount of *n*Bu₄NI to 20 mol %, and TBHP to 12 eq led to the raised yield of 63% (entries 2–4). Temperature had a significant effect on the 70 reaction. 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, 6). Apart from TBHP, other common oxidants, such as DTBP, DDQ, H₂O₂, O₂, 75 K₂S₂O₈ and PhI(OAc)₂ were proved to be noneffective to this transformation (entries 7–12). When KI was used instead of *n*Bu₄NI, the reaction only gave a low yield of 16% (entry 13). Other iodides such as iodine, NIS and CuI showed almost no activity to the reaction (entries 14–16).

80

Table 1 Screening of reaction conditions[a]
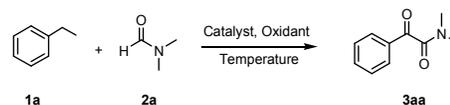
Entry	Catalyst (mol%)	Oxidant (equiv.)	Temp (°C)	Yield (%)[d]
1	$^nBu_4NI$ (10)	TBHP (8)[b]	80	23
2	$^nBu_4NI$ (10)	TBHP (10)	80	42
3	$^nBu_4NI$ (10)	TBHP (12)	80	52
4	$^nBu_4NI$ (20)	TBHP (12)	80	63
5	$^nBu_4NI$ (20)	TBHP (12)	60	48
6	$^nBu_4NI$ (20)	TBHP (12)	100	57
7	$^nBu_4NI$ (20)	DTBP (12)	80	0
8	$^nBu_4NI$ (20)	DDQ (4)[c]	80	0
9	$^nBu_4NI$ (20)	H_2O_2 (12)	80	0
10	$^nBu_4NI$ (20)	O_2 (1 atm)	80	0
11	$^nBu_4NI$ (20)	$K_2S_2O_8$ (4)[c]	80	0
12	$^nBu_4NI$ (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 air atmosphere for 18 h. [b] TBHP: *tert*-butyl hydroperoxide, 70% in water. [c] In DCE. [d] Isolated yield.

Under the optimized reaction conditions, the $^nBu_4NI$-TBHP catalyzed multiple oxidative coupling reaction of various ethylarenes with *N,N*-dialkylformamide was then studied (Table 2). At the beginning of our investigation, DMF was chosen as the amino source for this reaction. To 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 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 benzene ring led to the relatively low yields because of the strong electron-withdrawing property of 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 evident difference compared with the reaction of DMF (**3ab-3id**).

Table 2 $^nBu_4NI$-TBHP catalyzed synthesis of α-ketoamides[a]

3aa, 63%[b]   **3ba**, 56%   **3ca**, 57%
3da, 61%   **3ea**, 68%   **3fa**, 64%

3ga, 63%   **3ha**, 44%   **3ia**, 41%
3ja, 54%   **3ka**, 46%   **3ab**, 57%
3ac, 60%   **3fc**, 55%   **3ad**, 65%
3bd, 58%   **3dd**, 62%   **3fd**, 63%
3jd, 49%   **3gd**, 66%   **3id**, 46%
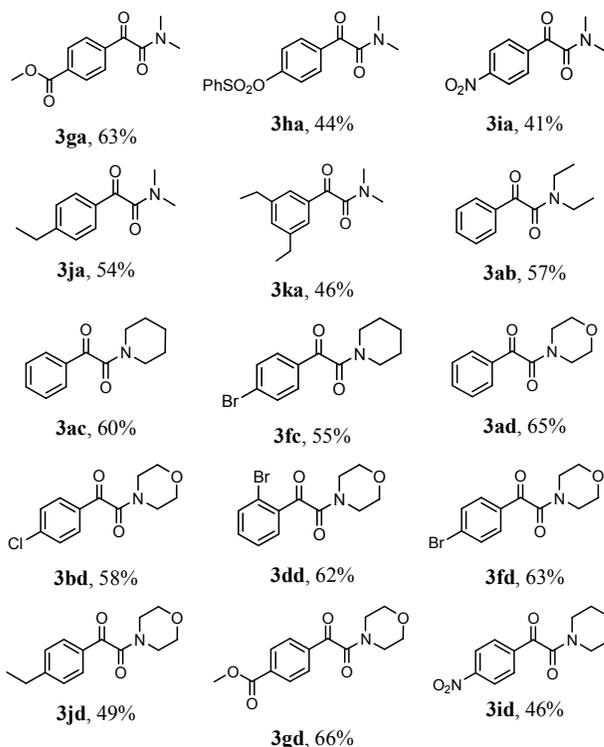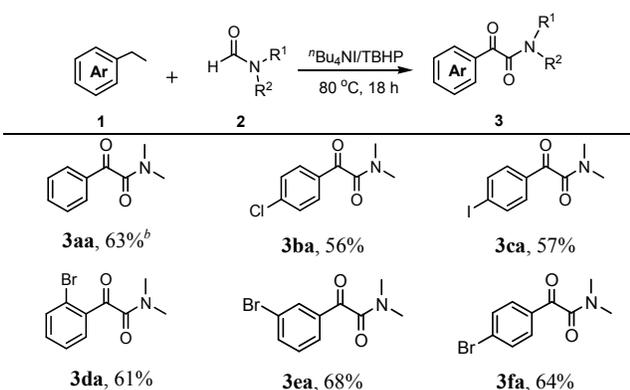
[a] Reaction conditions: **1** (1.0 mmol), **2** (6.0 mmol), $^nBu_4NI$ (20 mol%), TBHP (12 eq), under air atmosphere at 80 °C for 18 h. [b] Isolated yield.

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 that the cleavage of alkyl C–N bond was possible under the $^nBu_4NI$-TBHP catalytic system.

3ae Ar = Ph   (51%)
3ge Ar = *p*-MeOOCC$_6$H$_4$ (43%)
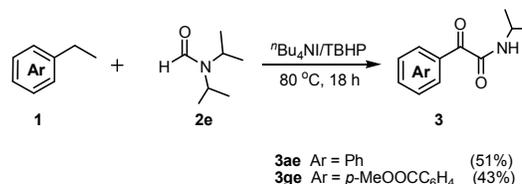
Scheme 1 Formation of *N*-isopropyl-2-oxo-2-arylacetamides.

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 C–N bond of DMF was possible under the $^nBu_4NI$/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 catalyzed by $^nBu_4NI$. The *t*butoxyl radical then abstracted hydrogen from the benzylic C–H bond of ethylarene to afford benzylic radical **B**,[15d] followed by the subsequent hydroxylation by TBHP to generate 1-phenylethanol, which was further oxidized by TBHP to form acetophenone.

Ingested hydrogen subsequently by the *t*butoxyl radical, a phenacyl radical **C** was then formed. On the other hand, DMF was abstracted hydrogen 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 the similar oxidation process to the previously described, this intermediate product was finally oxidized by TBHP to produce the desired product α-ketoamide.
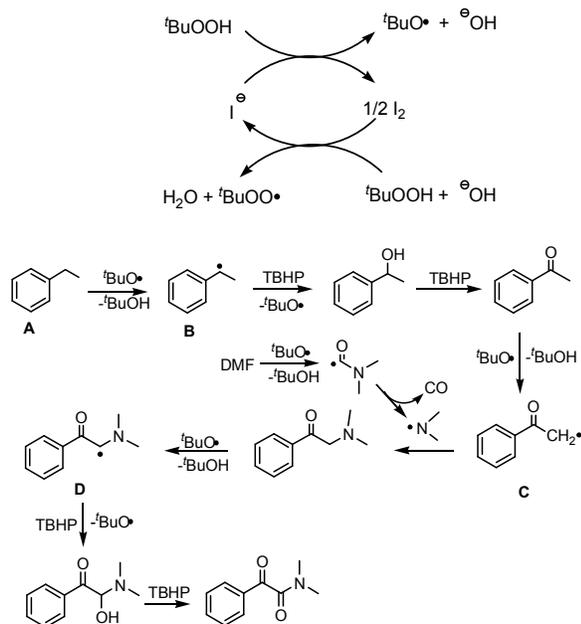
Scheme 2   Plausible reaction mechanism.

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 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 the cheap compounds ethylarenes in aqueous media and a metal-free condition. And also, to the best of our knowledge, it is the first example to form C−O and C−N bond sequentially via multiple inert sp^{3}C−H bonds activation.

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Notes and references

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