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TBAI-catalyzed oxidative synthesis of benzamides from acetophenones and carbinols†

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An interesting and convenient procedure for the oxidative transformation of acetophenones and carbinols to primary benzamides has been developed. By using tetra-*n*-butylammonium iodide (TBAI) as the catalyst and *tert*-butyl hydroperoxide (TBHP) as the oxidant, the desired benzamides were isolated in moderate to good yields in aqueous solution. Notably, not only acetophenones but also propiophenones can be applied as substrates as well. Hence, we believe that this new procedure is not just a catalytic version of the iodine-based method.

With the concept of 'green chemistry' and 'sustainable development', the development of more efficient and greener procedures is of interest in modern organic synthesis.[1] With this background, methodologies in aqueous solution without the demand for transitional metal catalysts are matched with the requirements. In respect of oxidation reactions which are among the fundamental transformations in organic chemistry, methods with high selectivity and efficiency are more desired.

Additionally, primary amides are important intermediates in organic synthesis that are used as starting materials for engineering plastics, detergents, and lubricants.[2] Based on their obvious importance, many procedures have been developed.[3] For example, primary benzamides can be synthesized by the hydration of the corresponding aromatic nitrile, by conversion of benzoic acids or acid chlorides with ammonia, by the transformation of benzaldehydes or benzaldoximes, by the oxidation of primary benzyl amines or alcohols, or by the carbonylation of aryl halides with ammonia and so on.[4] More recently, an iodine-mediated transformation of acetophenones and carbinols to primary benzamides was developed by A. Wu and co-workers.[5] In the presence of three equivalents of molecular iodine, the desired amides were produced in good yields using water as the solvent. Our group has been interested in developing procedures for primary amide synthesis for a long period and some novel procedures were developed.[6] With our continual interest in this topic and the attractive green chemistry, here, we wish to report our recent work on oxidative transformation of ketones and carbinols to the corresponding benzamides. By applying TBAI and TBHP as the catalyst system,[7] the desired amides were isolated in moderate to good yields.

With the initial results on preparation of benzamides from styrenes,[6f] we tested the oxidation of acetophenone under the same conditions but only a trace of benzamide was detected (Table 1, entry 1). Inspired by the work of A. Wu[5] and the

Table 1 Oxidative synthesis of benzamide from acetophenone[a]

Entry	Catal.	Oxidant	Temp.	Yield[b]
1	—	TBHP (4 equiv.)	100 °C	<1%
2	TBAB (10 mol%)	TBHP (4 equiv.)	100 °C	21%
3	TBAC (10 mol%)	TBHP (4 equiv.)	100 °C	0%
4	TBAI (10 mol%)	TBHP (4 equiv.)	100 °C	40%
5	TBAI (5 mol%)	TBHP (4 equiv.)	100 °C	30%
6	TBAI (20 mol%)	TBHP (4 equiv.)	100 °C	48%
7	TBAI (20 mol%)	TBHP (8 equiv.)	100 °C	80%
8	TBAI (20 mol%)	TBHP (8 equiv.)	60 °C	62%
9	TBAI (20 mol%)	DTBP (10 equiv.)	60 °C	<1%

[a] Acetophenone (1 mmol), catal., oxidant, 16 h. [b] Yields were determined by GC using hexadecane as an internal standard. TBAB: tetra-*n*-butylammonium bromide; TBAI: tetra-*n*-butylammonium iodide; TBAC: tetra-*n*-butylammonium chloride; TBHP: *tert*-butyl hydroperoxide; DTBP: di-*tert*-butyl peroxide.

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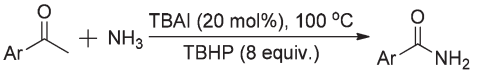
achievements in TBAI-catalyzed oxidations,[7,8] we tested some *tert*-butylammonium salts as the catalysts (Table 1, entries 2–4). To our delight, 40% of benzamide was formed in the presence of TBAI and the yield was improved to 80% with higher loading of catalyst and oxidant (Table 1, entry 7). Interestingly, the activity was totally inhibited using di-*tert*-butyl peroxide as the oxidant while TBHP can give 62% yield under the same conditions (Table 1, entries 8 and 9).

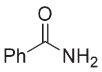
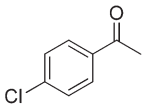
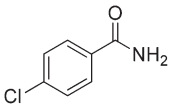
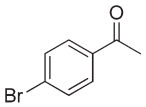
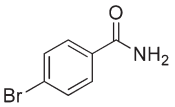
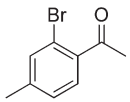
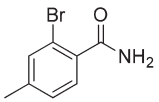
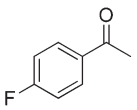
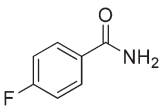
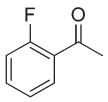
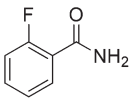
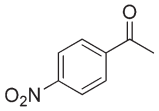
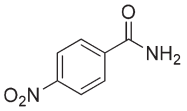
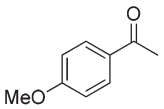
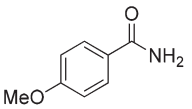
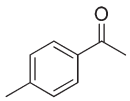
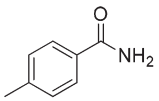
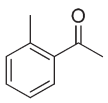
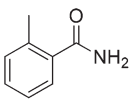
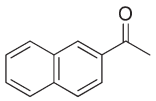
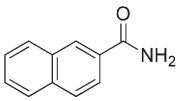
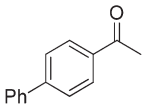
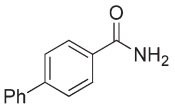
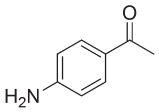
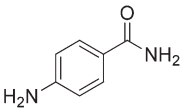
With the optimized reaction conditions in hand, we carried out the substrate testing. Different acetophenones were tested at the first stage (Table 2). In general, moderate to good yields of the desired primary amides can be obtained from electron-donating, electron-withdrawing and heterocyclic methyl-ketones. More specifically, bromo-, chloro-, fluoro-, nitro-, methyl-, methoxy-, and phenyl-substituents are tolerated under these conditions and gave the desired amides in good yields (Table 2, entries 2–12). The amino group can be applied as well, which is then oxidized, and gave the corresponding 4-aminobenzamide in 29% yield (Table 2, entry 13). Pyridine, furan, thiophene, and benzofuran as representative examples of heterocyclic compounds are all suitable substrates for this transformation; the desired heterocyclic amides were isolated in 58–78% yields (Table 2, entries 14–18). α,β-Unsaturated ketone can be applied as a substrate as well, the corresponding amide was produced without touching the double bond (Table 2, entry 19). To our surprise, butyl amine can be applied instead of ammonia as well, which was difficult in our previous study and gave a secondary amide in 47% isolated yield (Table 2, entry 20).[5b] Remarkably, not only acetophenones but also propiophenones can be applied as substrates (Table 2, entries 21 and 22). These were all challenging substrates in the iodine-mediated methodology.[5] Hence, we believe that this new procedure is not just a catalytic version of the iodine-based method. Detailed mechanistic investigations are under progress.

As carbinols can be easily transformed into the corresponding ketones under oxidative conditions, we tested carbinols as substrates for this procedure as well (Table 3). To our delight, 37–67% of the desired products were isolated without any further optimization.

A possible reaction pathway has been proposed in Scheme 1. Firstly the generated *tert*-butyloxy radical and I_2 reacted with acetophenone to give the corresponding radical species; the generation of I_2 can be proved by the color changing of the reaction solution. Then the radical reacted with water and subsequently oxidized to 2-oxo-2-arylacetaldehyde followed by decarbonylation to provide the desired acyl radical. The formed acyl radical was further oxidized to finally give the desired benzamide derivatives after reacting with ammonia. Notably, this reaction can be inhibited by adding TEMPO into the reaction mixture. Additionally, reactions with possible intermediates, phenylglyoxal and 2-hydroxyacetophenone, were performed as well. 48% of benzamide was produced from phenylglyoxal and a similar result was observed with 2-hydroxyacetophenone as well. Regarding the success on using propiophenones as substrates, propiophenones may be

Table 2 TBAI-catalyzed synthesis of benzamides from acetophenones[a]



Entry	Substrate	Product	Yield[b]
1			67%
2			48%
3			39%
4			20%
5			59%
6			69%
7			51%
8			53%
9			52%
10			51%
11			60%
12			71%
13			29%

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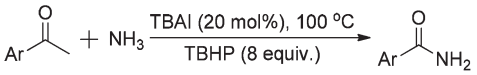

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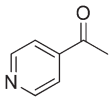
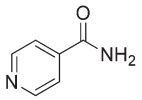
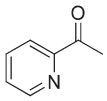
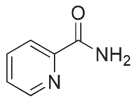
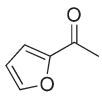
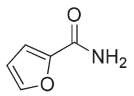
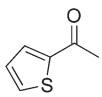
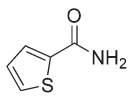
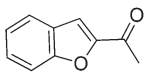
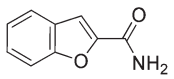
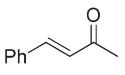
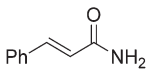
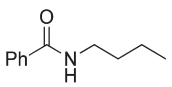
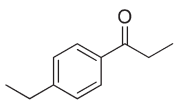
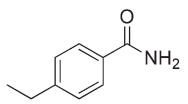
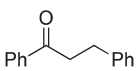
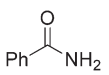
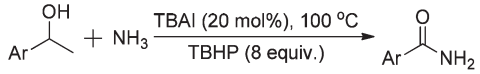
14			66%
15			78%
16			65%
17			69%
18			58%
19			20%
20			47%[c]
21			48%
22			45%

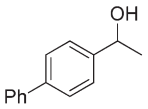
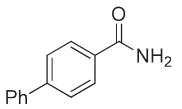
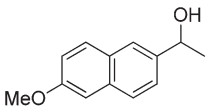
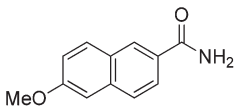
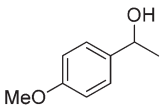
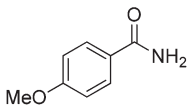
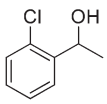
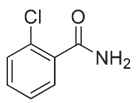
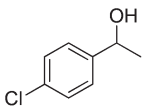
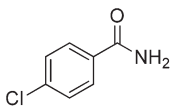
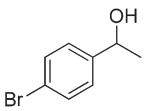
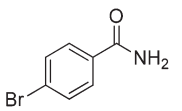
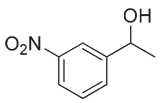
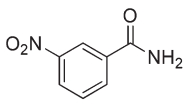
[a] Acetophenone (1 mmol), NH_3 (25% in H_2O; 1 mL), TBHP (70% in H_2O; 1.0 mL; 8 equiv.), TBAI (20 mol%), 100 °C, 16 h. [b] Isolated yield. [c] 1 mmol of butyl amine was used.

oxidized into the corresponding 1,2-diketones and further transformed into benzamide.[9] Concerning the release of CO, we do not have direct proof. But we felt the existence of pressure in the reaction tube after the reaction when the tube cooled down.

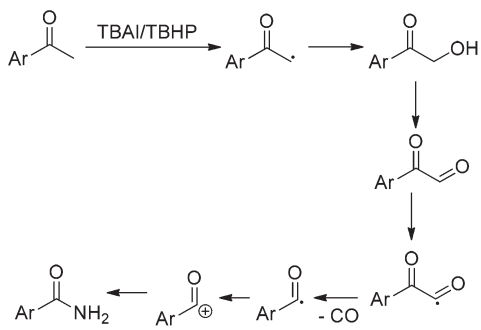
In conclusion, an interesting procedure for the transformation of acetophenones and carbinols into the corresponding primary amides has been developed. Using the combination of TBAI and TBHP, the desired amides were isolated in moderate to good yields. Notably, not only acetophenones but also propiophenones can be applied as substrates as well. Hence, we believe that this new procedure is not just a catalytic version of the iodine-based method. Detailed mechanistic investigations are under progress in our group.

Table 3 TBAI-catalyzed synthesis of benzamides from carbinols[a]



Entry	Substrate	Product	Yield[b]
1			67%
2			37%
3			53%
4			49%
5			55%
6			48%
7			49%

[a] Carbinols (1 mmol), NH_3 (25% in H_2O; 1 mL), TBHP (70% in H_2O; 1.0 mL; 8 equiv.), TBAI (20 mol%), 100 °C, 16 h. [b] Isolated yield.



Scheme 1 Proposed reaction mechanism.

Experimental section

General comments

All reactions were carried out under air. Reactions were monitored by TLC analysis (pre-coated silica gel plates with

fluorescent indicator UV254, 0.2 mm) and visualized using 254 nm UV light or iodine. Chemicals were purchased from Aldrich and were used without further purification unless otherwise noted. All compounds were characterized by ^{1}H NMR and ^{13}C NMR. ^{1}H spectra were recorded on Bruker AV 300 and AV 400 spectrometers. ^{13}C NMR spectra were recorded at 282 MHz. GC was performed on an Agilent 6890 chromatograph with a 30 m HP5 column. All yields reported refer to isolated yields. All the products are commercially available.

General procedure for the oxidative synthesis of primary amides from acetophenones

Ammonia (25% in water; 1 mL) and acetophenones (1 mmol) were added to a pressure tube equipped with a stirring bar. Then, TBHP (70% in H_2O; 1.0 mL; 8 equiv.) and TBAI (20 mol%) were added and the final solution was kept at 100 °C for 16 h. The mixture was cooled to room temperature and the solvent was removed under vacuum. The products obtained were purified by column chromatography (ethyl acetate–hexane = 1 : 2).

General procedure for the oxidative synthesis of primary amides from carbinols

Ammonia (25% in water; 1 mL) and carbinols (1 mmol) were added to a pressure tube equipped with a stirring bar. Then, TBHP (70% in H_2O; 1.0 mL; 8 equiv.) and TBAI (20 mol%) were added and the final solution was kept at 100 °C for 16 h. The mixture was cooled to room temperature and the solvent was removed under vacuum. The products obtained were purified by column chromatography (ethyl acetate–hexane = 1 : 2).

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