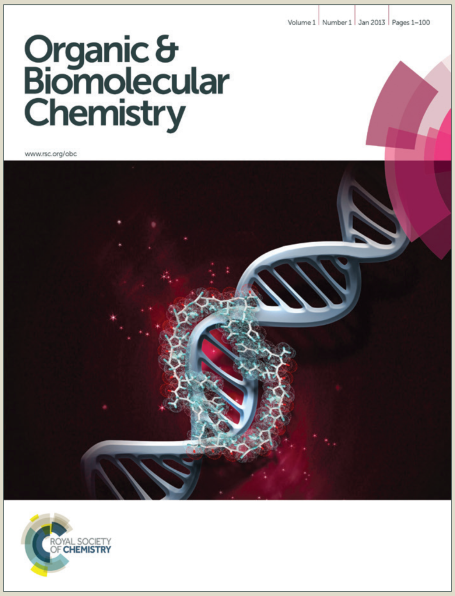
Organic & Biomolecular Chemistry

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

TBAI-Catalyzed Oxidative Synthesis of Benzamides from Acetophenones and Carbinols**

Muhammad Sharif,[b,d] Jianbin Chen,[b] Peter Langer,[b,c] Matthias Beller,[b] and Xiao-Feng Wu[a,b]*

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

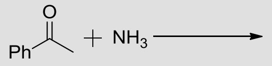
An interesting and convenient procedure for the oxidative transformation of acetophenones and carbinols to primary benzamides has been developed. By using *tetra*-n-butylammonium iodide (TBAI) as the catalyst and *tert*-butyl hydroperoxide (TBHP) as the oxidant, the desired benzamides were isolated in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

With the concept of 'green chemistry' and under the request of 'sustainable development', the developing of more efficient and greener procedure is under the current interests of modern organic synthesis.[1] Under this background, methodologies in aqueous solution and without the demand of transitional metal catalyst are matched with the requirements. In the respect of oxidation reactions which is one of 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, there many procedures have been developed.[3] For examples, 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 molecule iodine, the desired amides were produced in good yields by using water as the solvent. Our group has been interested in developing procedures for primary amides synthesis for long period and some novel procedures were achieved.[6] With our continual interesting in this topic and the attractive of 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 form styrenes,[6f] we tested the oxidation of acetophenone at the same conditions but with only trace of benzamide was detected (Table 1, entry 1). Inspired by the work from A. Wu[5] and the achievements on 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 by using di-*tert*-butyl peroxide as the oxidant while TBHP can give 62% yield under the same conditions (Table 1, entries 8 and 9).

Table 1. Oxidative synthesis benzamide from acetophenone.[a]



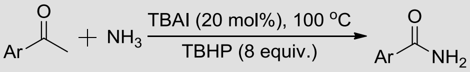
Entry	Catal.	Oxidant	Temp.	Yield[b]
1	/	TBHP (4 equiv.)	100 °C	<1%
2	TBAB (10 mol%)	TBHP (4 equiv.)	100 °C	21%
3	TBAC (10 mol%)	TBHP (4 equiv.)	100 °C	0%
4	TBAI (10 mol%)	TBHP (4 equiv.)	100 °C	40%
5	TBAI (5 mol%)	TBHP (4 equiv.)	100 °C	30%
6	TBAI (20 mol%)	TBHP (4 equiv.)	100 °C	48%
7	TBAI (20 mol%)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

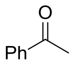
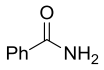
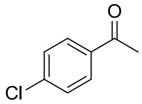
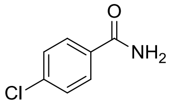
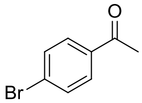
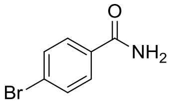
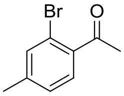
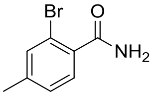
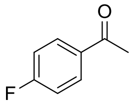
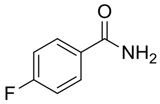
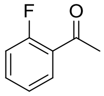
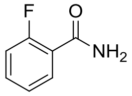
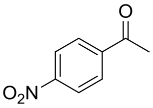
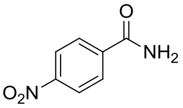
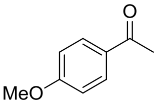
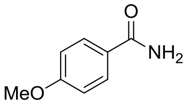
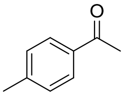
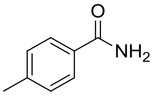
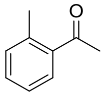
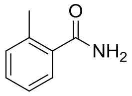
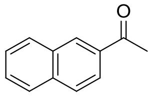
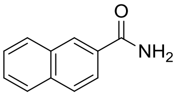
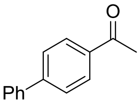
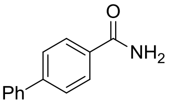
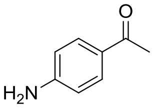
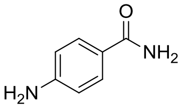
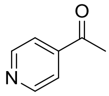
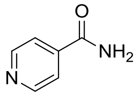
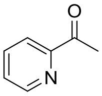
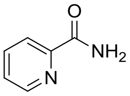
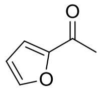
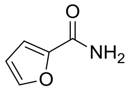
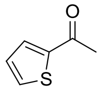
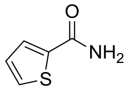
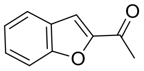
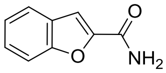
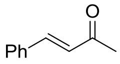
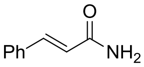
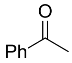
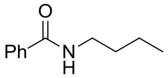
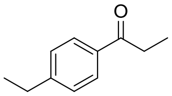
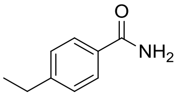
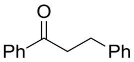
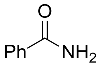
[a] Acetophenone (1 mmol), catal., oxidant, 16h. [b] Yields were determined by GC using hexadecane as internal standard. TBAB: *tetra*-n-butylammonium bromide; TBAI: *tetra*-n-butylammonium iodide; TBAC: *tetra*-n-butylammonium chloride; TBHP: *tert*-butyl hydroperoxide; DTBP: di-*tert*-butyl peroxide.

With the optimized reaction conditions in our hand, we carried out the substrates testing. Different acetophenones were tested at the first stage (Table 2). In general, moderate to good yields of the desired primary amides can be produced from electron-donating, electron-withdrawing and heterocyclic methylketones. 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). Amino group can be applied as well, which is trend to be 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 substrate as well, the corresponding aminde was produced without touch the double bond (Table 2, entry 19).To our surprise, butyl amine can be applied instead of ammonia as well which was difficult in previous report and gave 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, 22). These were all challenge substrates in iodine-mediated methodology.[5] Hence, we believe this new procedure is not just a catalytic version of the iodine-based method. Detailed mechanistic investigations are under progress.

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

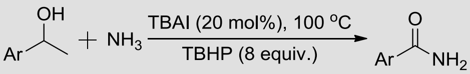


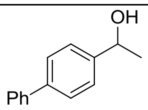
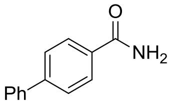
Entry	Substrate	Product	Yield[b]
1			67%
2			48%
3			39%
4			20%
5			59%
6			69%
7			51%
8			53%
9			52%
10			51%
11			60%
12			71%
13			29%
14			66%
15			78%
16			65%
17			69%
18			58%
19			20%
20			47%[c]
21			48%
22			45%

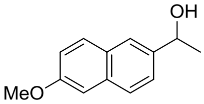
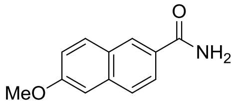
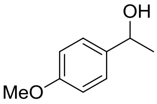
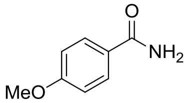
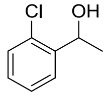
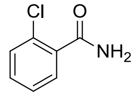
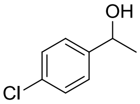
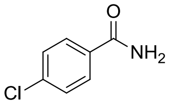
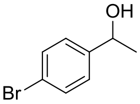
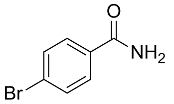
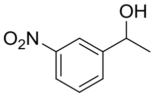
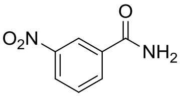
[a] Acetophenone (1 mmol), NH_3 (25% in H_2O; 1 mL), TBHP (70% in H_2O; 1.0 mL; 8 equiv.), TBAI (20 mol%), 100 °C, 16h. [b] Isolated yield. [c] 1 mmol of butyl amine was used.

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.

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

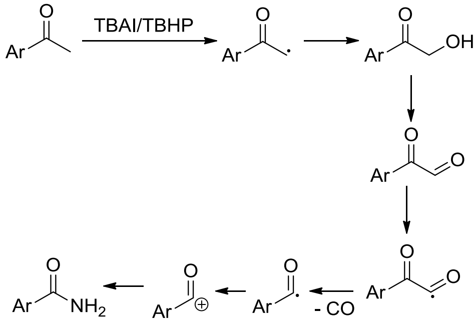


Entry	Substrate	Product	Yield[b]
1			67%

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, 16h. [b] Isolate yield.

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 thec color changing of the reaction solution. Then the radical reacted with water and subsequently been oxidized into 2-oxo-2-arylacetaldehyde which followed by decarbonylation to provide the desired acyl radical. The formed acyl radical been further oxidized and finally gave the desired benzamide derivatives after reacted with ammonia. Notably, this reaction can be inhibited by adding TEMPO in the reaction mixture. Additionally, reactions with possible intermediates, phenylglyoxal and 2-hydroxyacetophenone, were performed as well. 48% of benzamide was produced from phenylglyoxal and similar result was observed with 2-hydroxyacetophenone as well. Regarding the success on using propiophenones as substrates, propiophenones may be oxidized into the corresponding 1,2-diketones and further transformed into benzamide.[10] Concerning the release of CO, we do not have direct proves. But we fell the existing of pressure in the reaction tube after reaction when the tube cooled down.



Scheme 1. Proposed reaction mechanism.

In conclusion, an interesting procedure for the transformation of acetophenones and carbinols into the corresponding primary amides has been developed. By 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 this new procedure is not just a catalytic version of the iodine-based method. Detailed mechanistic investigations are under progress in our group.

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 with 254 nm UV light or iodine. Chemicals were purchased from Aldrich and were used without further purification otherwise noted. All compounds were characterized by ^1H NMR, ^{13}C NMR. ^1H spectra were recorded on Bruker AV 300 and AV 400 spectrometers. ^{13}C NMR spectra were recorded at 282 MHz. GC was performed on 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 pressure tube equipped with a stirring bar. Then, TBHP (70 % in H_2O; 1.0 mL; 8 equiv.), TBAI (20 mol %) were added and the final solution was kept at 100°C temperature for 16h. The mixture was cooled to room temperature and solvent was removed under vacuum. The pure products were purified by column (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 pressure tube equipped with a stirring bar. Then, TBHP (70 % in H_2O; 1.0 mL; 8 equiv.), TBAI (20 mol %) were added and the final solution was kept at 100°C temperature for 16h. The mixture was cooled to room temperature and solvent was removed under vacuum. The pure products were purified by column (Ethyl acetate:hexane=1:2).

Acknowledgements

The authors thank the state of Mecklenburg-Vorpommern, the Bundesministerium für Bildung und Forschung (BMBF) and the Deutsche Forschungsgemeinschaft for financial support. We also thank Dr. C. Fischer, S. Schareina and Dr. W. Baumann for their excellent technical and analytical support.

Notes and references

[a] Department of Chemistry, Zhejiang Sci-Tech University, Xiasha Campus, Hangzhou, Zhejiang Province, People's Republic of China, 310018
E-mail: xiao-feng.wu@catalysis.de
[b] Leibniz-Institut für Katalyse e.V. an der Universität Rostock, Albert-Einstein-Strasse 29a, 18059 Rostock, Germany

[c] Universität Rostock, Institut für Chemie, Albert-Einstein-Str. 3a, 18059 Rostock, Germany
[d] Department of Chemistry, Comsats Institute of Information Technology, 22060, Abbottabad, Pakistan

[1] a) *Metal-Catalyzed reactions in water*, Eds: P. H. Dixneuf, V. Cadierno, Wiley-VCH, **2013**; b) R. Noyori, *Chem. Commun.* **2005**, 1807-1811; c) M. -O. Simon, C. -J. Li, *Chem. Soc. Rev.* **2012**, *41*, 1415-1427; d) X. Han, M. Poliakoff, *Chem. Soc. Rev.* **2012**, *41*, 1428-1436; e) R. B. N. Baig, R. S. Varma, *Chem. Soc. Rev.* **2012**, *41*, 1559-1584.

[2] a) F. Matsuda, *Chemtech* **1977**, *7*, 306; b) C. E. Mabermann in *Encyclopedia of Chemical Technology*, Vol. 1 (Ed.: J. I. Kroschwitz), Wiley, New York, **1991**, pp. 251-266; c) D. Lipp in *Encyclopedia of Chemical Technology*, Vol. 1 (Ed.: J. I. Kroschitz), Wiley, New York, **1991**, pp. 266- 287; d) R. Opsahl in *Encyclopedia of Chemical Technology*, Vol. 2 (Ed.: J. I. Kroschwitz), Wiley, New York, **1991**, pp. 346-356.

[3] For two excellent reviews, see: a) C. L. Allen, J. M. J. Williams, *Chem. Soc. Rev.* **2011**, *40*, 3405-3415; b) R. García-Álvarez, P. Crochet, V. Cadierno, *Green Chem.* **2013**, *15*, 46-66.

[4] a) X. -F. Wu, H. Neumann, M. Beller, *Chem. Soc. Rev.* **2011**, *40*, 4986-5009; b) X. -F. Wu, H. Neumann, M. Beller, *Chem. Rev.* **2012**, *113*, 1-35; c) M. Beller, X. -F. Wu, *Transition Metal Catalyzed Carbonylation Reactions: Carbonylative Activation of C-X Bonds* Springer, **2013**.

[5] a) L. Cao, J. Ding, M. Gao, Z. Wang, J. Li, A. Wu, *Org. Lett.* **2009**, *11*, 3810-3813; b) J. Ding, L. Cao, J. Wang, W. Xue, Y. Zhu, A. Wu, *J. Chem. Res.* **2011**, 298-301; c) N. A. Angeles, F. Villavicencio, C. Guadarrama, D. Corona, E. Cuevas-Yañez, *J. Braz, Chem. Soc.* **2010**, *21*, 905-908.

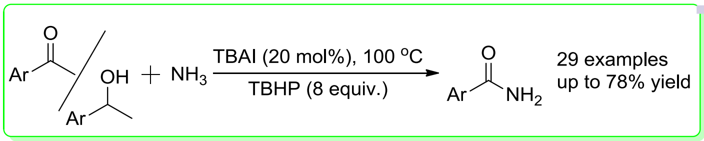
[6] a) X. -F. Wu, H. Neumann, M. Beller, *Chem. Eur. J.* **2010**, *16*, 9750-9753; b) X. -F. Wu, H. Neumann, M. Beller, *Chem. Asian J.* **2010**, *5*, 2168-2172; c) X. -F. Wu, H. Neumann, M. Beller, *Chem. Eur. J.* **2012**, *18*, 419-422; d) X. -F. Wu, C. B. Bheeter, H. Neumann, P. H. Dixneuf, M. Beller, *Chem. Commun.* **2012**, *48*, 12237-12239; e) X. -F. Wu, M. Sharif, J. -B. Feng, H. Neumann, A. Pews-Davtyan, P. Langer, M. Beller, *Green Chem.* **2013**, *15*, 1956-1961; f) M. Sharif, J. -L. Gong, P. Langer, M. Beller, X. -F. Wu, *Chem. Commun.* **2014**, *50*, 4747-4750.

[7] a) M. Uyanik, K. Ishihara, *ChemCatChem* **2012**, *4*, 177-185; b) X. -F. Wu, J. -L. Gong, X. Qi, *Org. Biomol. Chem.* **2014**, DOI: C4OB00276H.

[8] J. Wang, C. Liu, J. Yuan, A. Lei, *New J. Chem.* **2013**, *37*, 1700-1703.

[9] For selected examples on using TBAI as catalyst on oxidation reactions, see: a) X. Li, X. Xu, C. Zhou, *Chem. Commun.* **2012**, *48*, 12240-12242; b) X. Li, X. Xu, Y. Tang, *Org. Biomol. Chem.* **2013**, *11*, 1739-1742; c) X. Li, X. Xu, P. Hu, X. Xiao, C. Zhou, *J. Org. Chem.* **2013**, *78*, 7343-7348; d) Y. Gao, Q. Song, G. Cheng, X. Cui, *Org. Biomol. Chem.* **2014**, *12*, 1044-1047; e) J. Zhang, J. Jiang, Y. Li, X. Wan, *J. Org. Chem.* **2013**, *78*, 11366-11372; f) L. -T. Li, J. Huang, H. -Y. Li, L. -J. Wen, P. Wang, B. Wang, *Chem. Commun.* **2012**, *48*, 5187-5189; g) L. -T. Li, H. -Y. Li, L. -J. Xing, L. -J. Wen, P. Wang, B. Wang, *Org. Biomol. Chem.* **2012**, *10*, 9519-9522; h) H. Li, J. Xie, Q. Xue, Y. Cheng, C. Zhu, *Tetrahedron Lett.* **2012**, *53*, 6479-6482; i) K. Xu, Y. Hu, S. Zhang, Z. Zha, Z. Wang, *Chem. Eur. J.* **2012**, *18*, 9793-9797; j) G. Wang, Q. -Y. Yu, S. -Y. Chen, X. -Q. Yu, *Org. Biomol. Chem.* **2014**, *12*, 414-417; k) W. -P. Mai, G. Song, J. -W. Yuan, L. -R. Yang, G. -C. Sun, Y. -M. Xiao, P. Mao, L. -B. Qu, *RSC Adv.* **2013**, *3*, 3869-3872; l) L. Ma, X. Wang, W. Yu, B. Han, *Chem. Commun.* **2011**, *47*, 11333-11335; m) Q. Xue, J. Xie, H. Li, Y. Cheng, C. Zhu, *Chem. Commun.* **2013**, *49*, 3700-3702; n) J. Feng, S. Liang, S. -Y. Chen, J. Zhang, S. -S. Fu, X. -Q. Yu, *Adv. Synth. Catal.* **2012**, *354*, 1287-1292; o) L. Chen, E. Shi, Z. Liu, S. Chen, W. Wei, H. Li, K. Xu, X. Wan, *Chem. Eur. J.* **2011**, *17*, 4085-4089; p) J. Zhao, P. Li, C. Xia, F. Li, *Chem. Commun.* **2014**, *50*, 4751-4754.

[10] Y. -Z. Hui, Y. -H. Cai, X. -E. Chen, *Acta. Chim. Sin.* **1988**, *6*, 91-94.



An interesting and convenient procedure for the oxidative transformation of acetophenones and carbinols to primary benzamides has been developed.