DOI: 10.1002/cjoc.201500190

TBHP/TEMPO-Mediated Oxidative Synthesis of Imides from Amides

Hui Yu,*[a] Yuegang Chen,[a,b] and Yonghao Zhang[a]

[a] *Department of Chemistry, Tongji University, 1239 Siping Road, Shanghai 200092, China*
[b] *Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200092, China*

A new protocol for the synthesis of imides has been developed. In the presence of copper catalyst, *N*-benzylamides were oxidized to the corresponding imides by TBHP/TEMPO system in moderate to good yields.

Keywords imides, oxidation, TBHP, CuBr, TEMPO

Introduction

As one of the most important classes of *N*-containing compounds necessary in organic and pharmaceutical chemistry, imides could be found widely in many natural products and bioactive compounds.[1] Therefore, various approaches have been developed for their preparation. Traditional methods for the synthesis of imides generally started from amides and carbonyl chlorides with stoichiometric amount of salt generated as the waste, and sometimes the preparation of corresponding carbonyl chlorides is required.[2] Aldehydes could also be utilized as the acylation reagents in place of carbonyl chlorides, but excess amounts of aldehydes or NBS had to be used in such reactions.[3] Oxidation of *N*-substituted amides provides an alternative route to imides and kinds of oxidants have been proved to be efficient.[4] Among these developed oxidants, *tert*-butyl hydroperoxide (TBHP) has attracted considerable attention as a mild oxidant and has been used successfully for the formation of carbon-carbon and carbon-heteroatom bonds in recent years.[5] In most cases, these reactions were carried out under mild conditions and only small molecules such as H_2O and *t*-BuOH were released as the main byproducts. Using TBHP as the oxidant, Taherpour has reported limited examples for the oxidative synthesis of imides from *N*-alkyl amides catalyzed by manganese(Ⅲ) acetylacetonate in ethyl acetate under microwave irradiation (90 W, 5 min);[6] Xi and her co-workers reported a novel copper-catalyzed oxidation of arene-fused cyclic amines to the corresponding cyclic imides, but this method was not suitable to acyclic amines.[7] Thus, the development of practical TBHP-mediated oxidative synthesis of imides with broad substrate scope is still desirable. Herein, as a continuation of our efforts on the oxidative functionalization of amides,[8] we report our work for the oxidative synthesis of imides from amides.

Experimental

General

Commercially available reagents were used as received without further purification unless otherwise indicated. Reactions were magnetically stirred and monitored by thin layer chromatography (TLC) using Silica Gel 60 F254 plates and were visualized by fluorescence quenching at 254 nm. For chromatographic purifications, analytically pure solvents were used and the silica gel (300－400 mesh) was used as the solid support. ^{1}H NMR and ^{13}C NMR chemical shifts (δ) were reported relative to the chemical shift of residual solvent. Reference peaks for chloroform in ^{1}H NMR and ^{13}C NMR spectra were set at δ 7.26 and 77.0, respectively.

Typical experimental procedure for the synthesis of *N*-benzoylbenzamide

To a mixture of amide (0.20 mmol), CuBr (0.04 mmol, 20 mol%), and TEMPO (0.10 mmol) in acetonitrile (1.5 mL) was added TBHP (70 wt% in H_2O, 2.0 mmol) at room temperature. The reaction vessel was capped and allowed to stir at room temperature for 8 h. Then the volatiles were removed under reduced pressure, and the crude product was purified by flash chromatography on silica gel [V(PE)∶ V(AcOEt)＝4∶1] to obtain the imide product.

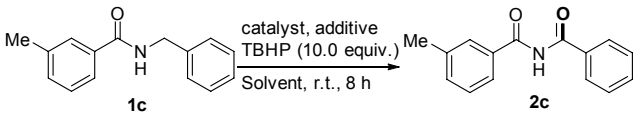
Results and Discussion

Initially, *N*-benzyl-3-methylbenzamide **1c** was cho-

* E-mail: yuhui@tongji.edu.cn; Tel.: 0086-021-65981097; Fax: 0086-021-65982287
Received March 8, 2015; accepted March 28, 2015; published online May 5, 2015.
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/cjoc.201500190 or from the author.

sen as the model substrate to optimize the reaction conditions including the catalyst, additive, solvent and temperature. As shown in Table 1, the reaction of **1c** with 10.0 equiv. of TBHP (70% solution in water) was examined in CH_3CN at room temperature and only trace of the product **2c** could be found without catalyst (Table 1, entry 1). When copper salts (20 mol %) were added to the reaction as catalysts, the yield of **2c** could be improved significantly and CuBr gave better yield than CuCl, CuI, and $CuBr_2$ (Table 1, entries 2—5). Further investigation revealed that addition of TEMPO to the reaction could increase the yield of **2c** remarkably. Different amounts of TEMPO were screened and 0.5 equiv. TEMPO gave the best result (Table 1, entries 6—9). Other commercial oxidants such as DDQ and $PhI(OAc)_2$ were also tested to promote the reaction but lower yields were obtained (Table 1, entries 10, 11). Increasing the reaction temperature to 40 ℃ resulted in a lower yield (Table 1, entry 12). The use of EtOAc or toluene as the solvent resulted in the formation of **2c** in lower yields (Table 1, entries 13, 14). When the used amount of TBHP was reduced to 5.0 equiv., the yield of **2c** decreased to 70% (Table 1, entry 15). On the basis of these results, entry 8 represents the optimal synthesis conditions.

Table 1 Optimization of the reaction conditions[a]



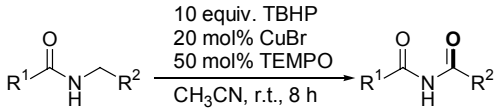
1c **2c**

Entry	Catalyst (20 mol%)	Additive (equiv.)	Solvent	Yield[b]/%
1	—	—	CH_3CN	0
2	CuCl	—	CH_3CN	54
3	CuBr	—	CH_3CN	60
4	CuI	—	CH_3CN	32
5	$CuBr_2$	—	CH_3CN	52
6	CuBr	TEMPO (0.2)	CH_3CN	68
7	CuBr	TEMPO (0.3)	CH_3CN	72
8	**CuBr**	**TEMPO (0.5)**	**CH_3CN**	**82**
9	CuBr	TEMPO (0.7)	CH_3CN	74
10	CuBr	DDQ (0.5)	CH_3CN	46
11	CuBr	$PhI(OAc)_2$ (0.5)	CH_3CN	65
12	CuBr	TEMPO (0.5)	CH_3CN	68[c]
13	CuBr	TEMPO (0.5)	EtOAc	61
14	CuBr	TEMPO (0.5)	Toluene	46
15	CuBr	TEMPO (0.5)	CH_3CN	70[d]

[a] Reaction conditions: 0.2 mmol **1c**, 2 mmol TBHP (70% solution in water), in 2.0 mL CH_3CN at room temperature for 8 h. [b] Isolated yield. [c] Reaction carried out at 40 ℃. [d] 5.0 equiv. TBHP was used.

Under the optimized reaction conditions, the effect of substrates was examined with results summarized in Table 2. *N*-Benzyl amides of various substituted benzoic acid were investigated, and the corresponding imides were obtained in good yields regardless of the electron-donating or electron-withdrawing groups and the substituted positions on the benzene ring (Table 2, entries 2—5). *N*-Benzyl-2-naphthamide also gave the desired product in 86% yield under the optimized reaction conditions (Table 2, entry 6). Heterocyclic substrates such as *N*-benzylfuran-2-carboxamide and *N*-benzylthiophene-2-carboxamide underwent smooth reactions to give the products in good yields (Table 2, entries 7, 8). Aliphatic substrates such as *N*-benzylacetamide, *N*-benzylisobutyramide and *N*-benzylpivalamide could also be converted into the corresponding products in good yields (Table 2, entries 9—11). *N*-Benzylphenylacetamide and *N*-benzyl-2-oxo-2-phenylacetamide were also suitable substrates in this reaction and the corresponding imides were obtained in 70% and 73% yields, respectively (Table 2, entries 12, 13). Carbamate such as ben-

Table 2 Oxidation of *N*-benzylamides **1** to imides **2**[a]



1 **2**

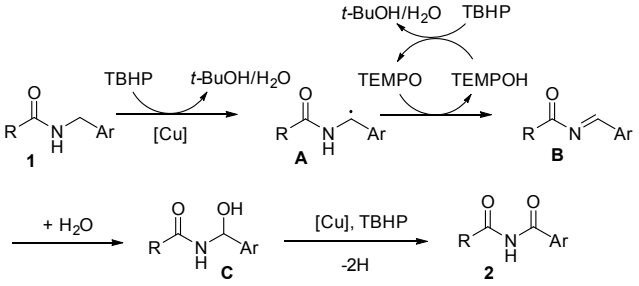
Entry	R^1	R^2	Product	Yield[b]/%
1	C_6H_5	C_6H_5	**2a**	90
2	2-MeC_6H_4	C_6H_5	**2b**	81
3	3-MeC_6H_4	C_6H_5	**2c**	82
4	4-MeC_6H_4	C_6H_5	**2d**	79
5	4-ClC_6H_4	C_6H_5	**2e**	89
6	2-Naphthyl	C_6H_5	**2f**	86
7	2-Furyl	C_6H_5	**2g**	65
8	Thiophen-2-yl	C_6H_5	**2h**	75
9	Me	C_6H_5	**2i**	83
10	*i*-Pr	C_6H_5	**2j**	95
11	*t*-Bu	C_6H_5	**2k**	69
12	Bn	C_6H_5	**2l**	70
13	C_6H_5CO	C_6H_5	**2m**	73
14	BnO	C_6H_5	**2n**	51
15	C_6H_5	4-MeC_6H_4	**2d**	65
16	C_6H_5	2-MeC_6H_4	**2o**	70
17	C_6H_5	3-MeC_6H_4	**2p**	74
18	C_6H_5	4-MeC_6H_4	**2q**	66
19	C_6H_5	4-ClC_6H_4	**2e**	trace
20	4-ClC_6H_4	4-$MeOC_6H_4$	**2r**	71
21	C_6H_5	2-Furyl	**2g**	45
22	C_6H_5	*n*-Bu	**2s**	0

[a] The reaction was carried out with **1** (0.2 mmol), CuBr (0.04 mmol), TEMPO (0.1 mmol), and TBHP (70 wt% in water, 2.0 mmol), in acetonitrile (2.0 mL) at room temperature for 8 h. [b] Isolated yields.

zyl benzylcarbamate was also tested using the optimized reaction and the product was isolated in 51% yield (Table 2, entry 14). For substrates with electron-donating group substituted at different positions on the benzyl group of *N*-benzylbenzamide, the desired products were formed in 65%—74% yields (Table 2, entries 15—18). However, for the substrate with electron-withdrawing group substituted on the benzyl group, only trace of the desired product could be found (Table 2, entry 19). For substrates with substituted group on both sides of the benzene rings, the desired product was obtained in 71% yield (Table 2, entry 20). The heterocyclic substrate *N*-(furan-2-ylmethyl)benzamide gave 45% yield of **2g**, lower than that in the case of *N*-benzylfuran-2-carboxamide (Table 2, entry 21). *N*-Butylbenzamide was also tested but no reaction occurred and all the starting materials remained untouched (Table 2, entry 22).

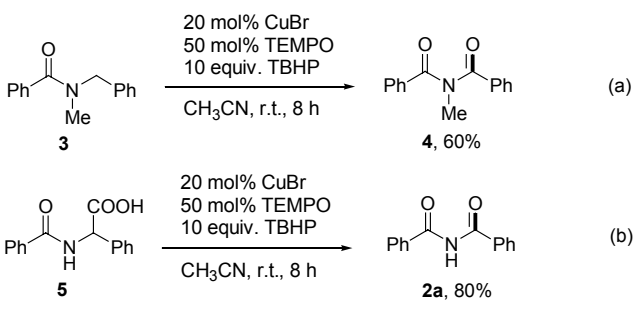
Although the detailed reaction mechanism still remains to be clarified, a reaction pathway is proposed as shown in Scheme 1. The H atom adjacent to the nitrogen atom of the amide **1** was abstracted by TBHP to give radical **A**,[8] which was oxidized by TEMPO to form acylimine **B**,[9] and TEMPO was regenerated through the oxidation of the released TEMPOH by TBHP. With the aid of copper salt, **B** was attacked by water to give the intermediate **C**. Finally, oxidative dehydrogenation of **C** afforded the product imide **2**.[10] More details for the mechanism still need further investigations.

Scheme 1 Proposed mechanism



Finally, tertiary amide *N*-benzyl-*N*-methylbenzamide **3** was also examined, and the product *N*-benzyl-*N*-methylbenzamide **4** was obtained in 60% yield (Scheme 2a). Interestingly, when *N*-benzoyl-2-phenylglycine **5** was employed to the oxidative reaction, a decarboxylative oxidation reaction occurred and the product **2a** was formed in 80% yield (Scheme 2b).

Scheme 2 Oxidation of *N*-benzyl-*N*-methylbenzamide and 2-benzamido-2-phenylacetic acid



Conclusions

In conclusion, we have developed an efficient and practical method for the synthesis of imides by simple oxidation of *N*-benzylamides. The reaction was carried out under mild conditions using TBHP as the oxidant, CuBr as the catalyst, and TEMPO as the additive.[11] The procedure was easy to handle and various imides have been synthesized under the optimized conditions.

Acknowledgement

Financial support from Tongji University (20123231) is gratefully acknowledged.

References

[1] (a) Higgins, A. M.; Jones, R. A. L. *Nature* **2000**, *404*, 476; (b) Klinge, M.; Cheng, H. M.; Zabriskie, T. M.; Vederas, J. C. *J. Chem. Soc., Chem. Commun.* **1994**, 1379; (c) Capitosti, S. M.; Hansen, T. P.; Brown, M. L. *Org. Lett.* **2003**, *5*, 2865; (d) Ross, L.; Guarino, L. A. *Virology* **1997**, *232*, 105; (e) Krohn, K.; Franke, C.; Jones, P. G.; Aust, H. J.; Draeger, S.; Shulz, B. *Liebigs Ann. Chem.* **1992**, 789; (f) Zhang, Q. T.; Tour, J. M. *J. Am. Chem. Soc*. **1997**, *119*, 5065.

[2] (a) Liu, Z. H.; Ma, Q. Q.; Liu, Y. X.; Wang, Q. M. *Org. Lett*. **2014**, *16*, 236; (b) Trost, B. M.; Hirano, K. *Angew. Chem., Int. Ed*. **2012**, *51*, 6480; (c) Tamaddon, F.; Sabeti, M. R.; Jafari, A. A.; Tirgir, F.; Keshavarz, E. *J. Mol. Catal. Chem*. **2011**, *351*, 41; (d) Li, Y. Q.; Wang, Y. L.; Wang, J. Y. *Russ. J. Org. Chem*. **2008**, *44*, 358; (e) Li, X. H.; Fang, Y. Y.; Deng, P. C.; Hu, J. C.; Li, T.; Feng, W.; Yuan, L. H. *Org. Lett.* **2011**, *13*, 4628.

[3] (a) Wang, L.; Fu, H.; Jiang, Y. Y.; Zhao, Y. F. *Chem. Eur. J*. **2008**, *14*, 10722; (b) Wang, F.; Liu, H. X.; Fu, H.; Jiang, Y. Y.; Zhao, Y. F. *Adv. Synth. Catal.* **2009**, *351*, 246; (c) Wang, J.; Liu, C.; Yuan, J. W.; Lei, A. W. *Chem. Commun.* **2014**, *50*, 4736.

[4] (a) Xu, L.; Zhang, S.; Trudell, M. L. *Chem. Commun.* **2004**, *40*, 1668; (b) Tada, N.; Ban, K.; Yoshida, M.; Hirashima, S.; Miura, T.; Itoh, A. *Tetrahedron Lett*. **2010**, *51*, 6098; (c) Jin, Z.; Xu, B.; Hammond, G. B. *Tetrahedron Lett*. **2011**, *52*, 1956; (d) Nicolaou, K. C.; Mathison, C. J. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 5992.

[5] For selected recent examples, see: (a) Zhang, J.; Shao, Y.; Wang, H.; Luo, Q.; Chen, J.; Xu, D.; Wan, X. *Org. Lett.* **2014**, *16*, 3312; (b) Yu, H.; Huang, W.; Zhang, F. *Eur. J. Org. Chem.* **2014**, 3156; (c) Yu, H.; Zhang, F.; Huang, W. *Synlett* **2014**, *25*, 843; (d) Yang, Z. J.; Liu, C. Z.; Hu, B. L.; Deng, C. L.; Zhang, X. G. *Chem. Commun.* **2014**, *50*, 14554; (e) Liu, Z.; Zhang, J.; Chen, S.; Shi, E.; Xu, Y.; Wan, X. *Angew. Chem., Int. Ed*. **2012**, *51*, 3231; (f) Ma, X.; Li, Z.; Liu, F.; Cao, S.; Rao, H. *Adv. Synth. Catal.* **2014**, *356*, 1741; (g) Burange, A. S.; Kale, S. R.; Zboril, R.; Gawande, M. B.; Jayaram, R. V. *RSC Adv.* **2014**, *4*, 6597; (h) Xie, J.; Jiang, H.; Cheng, Y.; Zhu, C. *Chem. Commun.* **2012**, *48*, 979.

[6] Taherpour, A. A.; Abramian, A.; Kardanyazd, H. *Chin. J. Org. Chem.* **2007**, *27*, 123 (in Chinese).

[7] Yan, X. Y.; Fang, K.; Liu, H. L.; Xi, C. J. *Chem. Commun.* **2013**, *49*, 10650.

[8] (a) Yu, H.; Shen, J. *Org. Lett*. **2014**, *16*, 3204; (b) Yu, H.; Shen, J. *RSC Adv.* **2015**, *5*, 9815; (c) Yu, H.; Zhang, Y. *Eur. J. Org. Chem.* **2015**, 1824.

[9] (a) Schweizer-Chaput, B.; Klussmann, M. *Eur. J. Org. Chem.* **2013**,

666; (b) Shirakawa, E.; Uchiyama, N.; Hayashi, T. *J. Org. Chem.* **2011**, *76*, 25; (c) Kumar, R. A.; Saidulu, G.; Sridhar, B.; Liu, S. T.; Reddy, K. R. *J. Org. Chem*. **2013**, *78*, 10240.

[10] (a) Yoo, W. J.; Li, C. J. *J. Am. Chem. Soc.* **2006**, *128*, 13064; (b) Ghosh, S. C.; Ngiam, J. S.; Chai, C. L.; Seayad, A. M.; Dang, T. T.; Chen, A. Q. *Adv. Synth. Catal.* **2012**, *354*, 1407; (c) Ghosh, S. C.; Ngiam, J. S. Y.; Seayad, A. M.; Dang, T. T.; Chai, C. L.; Chen, A. Q. *J. Org. Chem.* **2012**, *77*, 8007.

[11] (a) Shen, J.; Sun, J.; Qin, S.; Chu, C.; Liu, R. *Chin. J. Chem.* **2014**, *32*, 405; (b) Zhang, J.; Jiang, Z.; Zhao, D.; He, G.; Zhou, S.; Han, S. *Chin. J. Chem.* **2013**, *31*, 794; (c) Liu, D.; Zhou, H.; Gu, X.; Shen, X.; Li, P. *Chin. J. Chem.* **2014**, *32*, 117.

(Pan, B.)

