Tetrahedron Letters xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Iodine-catalyzed efficient amide formation from aldehydes and amines

Peng Wang [a,*], Jiaxuan Xia [b], Yueqing Gu [a,*]

[a] Department of Biomedical Engineering, School of Engineering, China Pharmaceutical University, 210009 Nanjing, China
[b] School of Pharmacy, China Pharmaceutical University, 210009 Nanjing, China

ARTICLE INFO

Article history:
Received 26 September 2015
Revised 3 November 2015
Accepted 9 November 2015
Available online xxxx

Keywords:
Amide
Iodine
Catalyst
Aldehyde
Amine

ABSTRACT

An efficient iodine-catalyzed radical oxidative amidation of aldehydes with amines has been developed. This methodology was employed to prepare amides in good to excellent yields with the advantages of wide functional group tolerance and operational simplicity.

Introduction

The amide bond is one of the most important functional groups in modern chemistry, with application in a number of natural products, pharmaceuticals, and polymer syntheses (Fig. 1).[1–3] In the past decades, various kinds of approaches have been reported for amide synthesis, including the condensation between carboxylic acid derivatives with amines, which is the most commonly used method in the formation of amides. However, many drawbacks, such as low atom economy, high waste pollution, and poor functional group tolerance etc. restrict its application range.[4] Recently, some alternative methods have been figured out to address these problems, for example rearrangement of aldoximes and ketoximes, coupling of nitriles with alcohols or amines, palladium-catalyzed aminocarbonylation, and N-arylation or N-alkenylation of amides.[5–16] Oxidative amidation is one example of the versatile methods.

Oxidative amidation of aldehydes into amides has been known since the early 1980s. As shown in Scheme 1, the general reaction mechanism of this transformation is initiated by the coupling of aldehyde with amine to form the hemiaminal intermediate, which was subsequently oxidized to the amide product.[17,18] To date, increasing attention is being devoted to this transformation. Several reaction systems including palladium, copper, lanthanide, and iron catalysts have been reported.[19–22] In spite of this transformation with good atom-economic and cheap starting materials superior to other methods mentioned above, the application of metal catalysts raises a whole new set of issues. Hence, with a good capacity for electron transfer processes, inexpensive and environmentally friendly iodine has recently been reported to serve as an alternative catalyst for transition metals in many reactions.[23,24]

In fact, iodine catalysis has been widely applied in the direct oxidation functionalization of carbonyl compounds. Recently, many C–N bond formation reactions of carbonyl compounds have been reported under iodine-catalyzed oxidation conditions.[25–28] Wang and co-workers[29] reported the iodine-catalyzed synthesis of *N*,*N*-dimethyl aryl amides from benzylic alcohols and dimethylformamide, via a radical pathway. Although it is a fundamentally different approach to amide synthesis, the scope of amide was limited to *N*,*N*-dimethyl aromatic amides. Therefore, the development of alternative methods to amide bond formation utilizing iodine as catalyst remains an area of active research. During the last few years, our group has been involved in the development of oxidation-related reactions employing various oxidation systems.[30] Herein, we developed an efficient iodine-catalyzed oxidative amidation of aldehydes into amides, utilizing TBHP as an oxidant.

Results and discussion

In a pilot experiment, morpholine **1a** (1 mmol) reacted with *N*-chlorosuccinimide (NCS, 1.1 mmol) in acetonitrile at room temperature. Then the corresponding *N*-chloromorpholine was

* Corresponding authors.

http://dx.doi.org/10.1016/j.tetlet.2015.11.027
0040-4039/

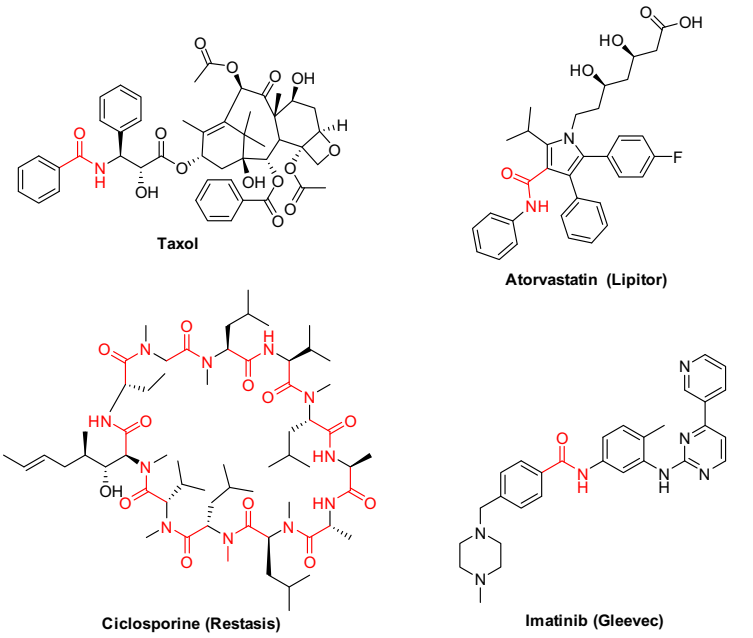
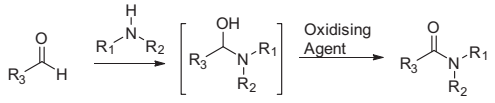
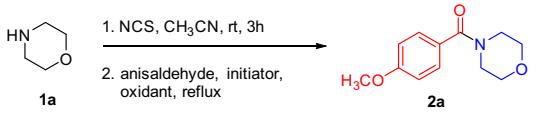


Figure 1. Some important pharmaceutical molecules containing the amide bond.



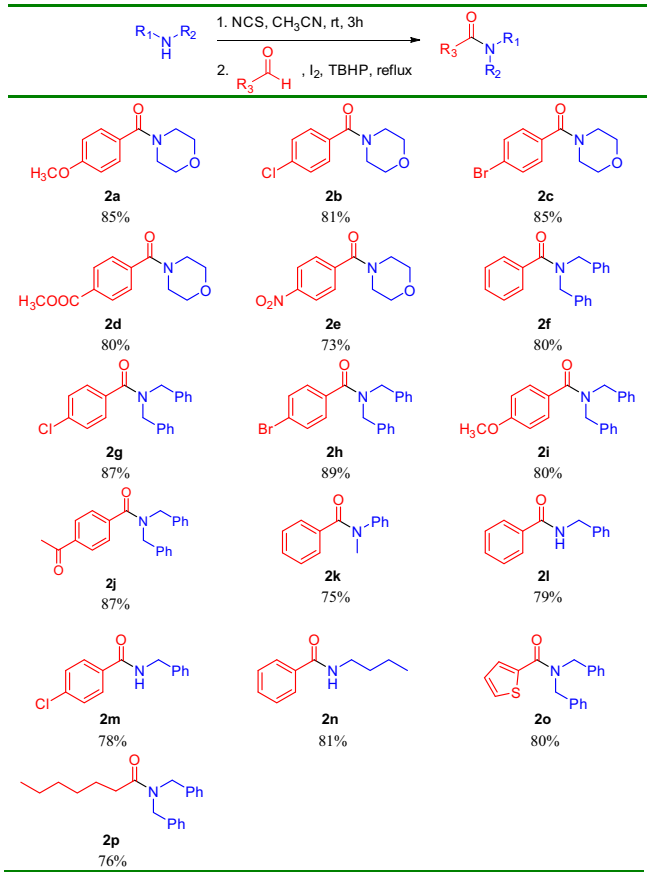
Scheme 1. The general reaction mechanism of amides from aldehydes and amines.

Table 1
Optimization study for the synthesis of amide **2a** from anisaldehyde and morpholine[a]

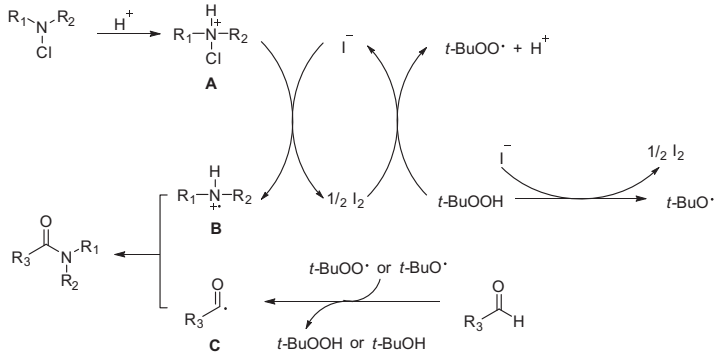


Entry	Initiator	Oxidant	Time (h)	Yield[b] (%)
1	I_2	TBPB	3	45
2	I_2	TBHP	3	85
3	I_2	TBHP	12	83
4	I_2	H_2O_2	12	0
5	I_2	CAN	12	0
6	I_2	Oxone	12	0
7[c]	I_2	TBHP	3	70
8[d]	I_2	TBHP	3	35
9[e]	I_2	TBHP	12	60
10[f]	I_2	TBHP	3	86
11	I_2	—	12	0
12	—	—	12	0
13	—	TBHP	12	0
14	TBAI	TBHP	12	38
15	KI	TBHP	12	20

[a] Reaction conditions: morpholine **1a** (1 mmol) and *N*-chlorosuccinimide (NCS) (1.1 mmol) in 5 mL acetonitrile at room temperature for 3 h. To this reaction mixture were added anisaldehyde (2 mmol), catalyst (20 mol %), and oxidant (5 mmol) under reflux.
[b] Isolated yield by column chromatography.
[c] I_2 (10 mol %).
[d] TBHP (1 mmol).
[e] At room temperature.
[f] Under nitrogen.



Scheme 2. Substrate scope for the synthesis of amides.



Scheme 3. Proposed reaction pathway.

quantitatively formed after 3 h. This reaction mixture solution, containing *N*-chloromine generated in situ, was directly treated, without any purification, with anisaldehyde (2 mmol), iodine (20 mol %), and *tert*-butyl peroxybenzoate (TBPB 5 mmol) under reflux for 3 h, generating the amide **2a** in only 45% yield (Table 1, entry 1). By switching the oxidant from TBPB to *tert*-butyl hydroperoxide (TBHP), the product amide **2a** was obtained with a significant improvement of yield to 85% (Table 1, entry 2). Increasing the reaction time, even in reflux for 12 h, had a slight influence in improving the yield (Table 1, entry 3). Other oxidants such as H_2O_2, CAN, and oxone gave no product (Table 1, entries 4–6). With respect to the amount of iodine in the procedure, it was found that 20 mol % were optimal. The decrease in the amount to 10 mol % was detrimental (Table 1, entry 7). Likewise, the decrease in the amount of TBHP from 5 equiv to 1 equiv led to a collapse of the yield from 85% to 35% (Table 1, entry 8). When the reaction was performed at room temperature with a considerable lengthening of the reaction time, the amide was achieved with a substantial yield reduction (Table 1, entry 9). No obvious yield increase was observed under nitrogen (Table 1, entry 10). Moreover, no product formation was observed when performing the reaction without the oxidant (TBHP) or iodine (Table 1, entries 11–13). Other initiators were also investigated. In comparison with iodine, TBAI or KI resulted in lower yields of the product **2a** (Table 1, entries 14 and 15). Therefore, the optimal reaction conditions were iodine (20 mol %) as the catalyst, with TBHP (5 equiv) as oxidant and CH_3CN as solvent.

With the optimal conditions in hand, we next investigated the scope of this reaction, as illustrated in Scheme 2. The aldehyde bearing electron-donating substituent gave the desired product in excellent yield (**2a**). It is worth noting that aldehydes containing functional groups such as *p*-Cl, *p*-Br, and *p*-$COOCH_3$ were all tolerated (**2b**–**2d**). Besides, the electron-withdrawing substituted aldehydes were also efficiently transformed into the desired products in good yields (**2e**).

Next, we conducted the reaction with a series of *N*,*N*-dialkylamines showing excellent tolerance (**2f**–**2k**). These results indicated that acyclic as well as cyclic amines were shown to be effective in this reaction. Similarly, both electro-donating groups, such as OMe, and withdrawing groups, such as acetyl, were well tolerated providing the desired amides in satisfied yields. Furthermore, primary amines gave the corresponding *N*-mono-substituted amides in good yields (**2l**–**2n**).

To extend the application of this reaction, thiophene-2-carbaldehyde was subjected to the optimized reaction conditions, giving the desired heteroaryl amides (**2o**) in favorable yields. When the aromatic aldehyde was replaced by aliphatic aldehyde, the corresponding amide was obtained in acceptable yield (**2p**).

According to these results and previous publications,[17,27] a plausible reaction mechanism is described in Scheme 3. The first step is the formation of *tert*-butylperoxyl radical and iodide anion from the reaction between TBHP with iodine. Then the intermediate **A** from *N*-chloroamine is transformed into an amino radical **B** on the basis of the redox reaction of iodide. Moreover, the *tert*-butoxyl radical is generated from TBHP in the presence of iodide anion. Then the *tert*-butylperoxyl and/or *tert*-butoxyl radicals grab hydrogen from the aldehyde to generate acyl radical **C**, which subsequently could combine with the amino radial **B** to form amides.

Conclusions

In conclusion, we have developed an efficient approach to the synthesis of functionalized amides from aldehydes and amines. Unlike the previous study that uses metal catalysts, the protocol described herein uses a catalytic amount of iodine as catalyst together with TBHP as an oxidant. This methodology can be applied in preparing a wide range of amides directly from aromatic and aliphatic aldehydes and variously substituted amines. Further applications of this chemistry to synthesis of functionalized amides are under current investigation.

Acknowledgements

We are grateful for the financial support from the NSFC (National Nature Science Foundation of China, No. 81501529) and Fundamental Research Funds for the Central Universities (ZJ15011).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.11.027.

References and notes

1. Humphrey, J. M.; Chamberlin, A. R. *Chem. Rev.* **1997**, *97*, 2243.
2. Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337.
3. Yu, C.; Mosbach, K. *J. Org. Chem.* **1997**, *62*, 4057.
4. Valeur, E.; Bradley, M. *Chem. Soc. Rev.* **2009**, *38*, 606.
5. Martinelli, J. R.; Clark, T. P.; Watson, D. A.; Munday, R. H.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 8460.
6. Dang, T. T.; Zhu, Y. H.; Ghosh, S. C.; Chen, A. Q.; Chai, C. L. L.; Seayad, A. M. *Chem. Commun.* **1805**, *2012*, 48.
7. Wu, X. F.; Neumann, H.; Beller, M. *Chem.-Eur. J.* **2010**, *16*, 9750.
8. Zhang, F. L.; Zhu, X.; Chiba, S. *Org. Lett.* **2015**, *17*, 3138.
9. Gaspa, S.; Porcheddu, A.; De Luca, L. *Org. Biomol. Chem.* **2013**, *11*, 3803.
10. Mahajan, S.; Sharma, B.; Kapoor, K. K. *Tetrahedron Lett.* **1915**, *2015*, 56.
11. Qiu, J.; Zhang, R. H. *Org. Biomol. Chem.* **2013**, *11*, 6008.
12. Martinez-Asencio, A.; Yus, M.; Ramon, D. J. *Tetrahedron* **2012**, *68*, 3948.
13. Garcia-Alvarez, R.; Diaz-Alvarez, A. E.; Borge, J.; Crochet, P.; Cadierno, V. *Organometallics* **2012**, *31*, 6482.

14. Crochet, P.; Cadierno, V. *Chem. Commun.* **2015**, *51*, 2495.
15. Allen, C. L.; Lawrence, R.; Emmett, L.; Williams, J. M. J. *Adv. Synth. Catal.* **2011**, *353*, 3262.
16. Kaur, S.; Kumar, M.; Bhalla, V. *Chem. Commun.* **2015**, *51*, 4085.
17. Cadoni, R.; Porcheddu, A.; Giacomelli, G.; De Luca, L. *Org. Lett.* **2012**, *14*, 5014.
18. Allen, C. L.; Williams, J. M. J. *Chem. Soc. Rev.* **2011**, *40*, 3405.
19. Suto, Y.; Yamagiwa, N.; Torisawa, Y. *Tetrahedron Lett.* **2008**, *49*, 5732.
20. Ghosh, S. C.; Ngiam, J. S. Y.; Seayad, A. M.; Tuan, D. T.; Chai, C. L. L.; Chen, A. Q. *J. Org. Chem.* **2012**, *77*, 8007.
21. Ghosh, S. C.; Ngiam, J. S. Y.; Chai, C. L. L.; Seayad, A. M.; Dang, T. T.; Chen, A. Q. *Adv. Synth. Catal.* **2012**, *354*, 1407.
22. Yao, H. Y.; Yamamoto, K. *Chem.-Asian J.* **2012**, *7*, 1542.
23. Wu, X. F.; Gong, J. L.; Qi, X. X. *Org. Biomol. Chem.* **2014**, *12*, 5807.
24. Richardson, R. D.; Wirth, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 4402.
25. Zhang, X. B.; Wang, L. *Green Chem.* **2012**, *14*, 2141.
26. Xie, J.; Jiang, H. L.; Cheng, Y. X.; Zhu, C. J. *Chem. Commun.* **2012**, *48*, 979.
27. Tang, S.; Liu, K.; Long, Y.; Gao, X. L.; Gao, M.; Lei, A. W. *Org. Lett.* **2015**, *17*, 2404.
28. Achar, T. K.; Mal, P. *J. Org. Chem.* **2015**, *80*, 666.
29. Xu, K.; Hu, Y. B.; Zhang, S.; Zha, Z. G.; Wang, Z. Y. *Chem.-Eur. J.* **2012**, *18*, 9793.
30. Wang, P.; Cai, J.; Yang, J. B.; Sun, C. L.; Li, L. S.; Hu, H. Y.; Ji, M. *Tetrahedron Lett.* **2013**, *54*, 533.

Please cite this article in press as: Wang, P.; et al. *Tetrahedron Lett.* (2015), http://dx.doi.org/10.1016/j.tetlet.2015.11.027