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Iodine-catalyzed efficient amide formation from aldehydes and amines

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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

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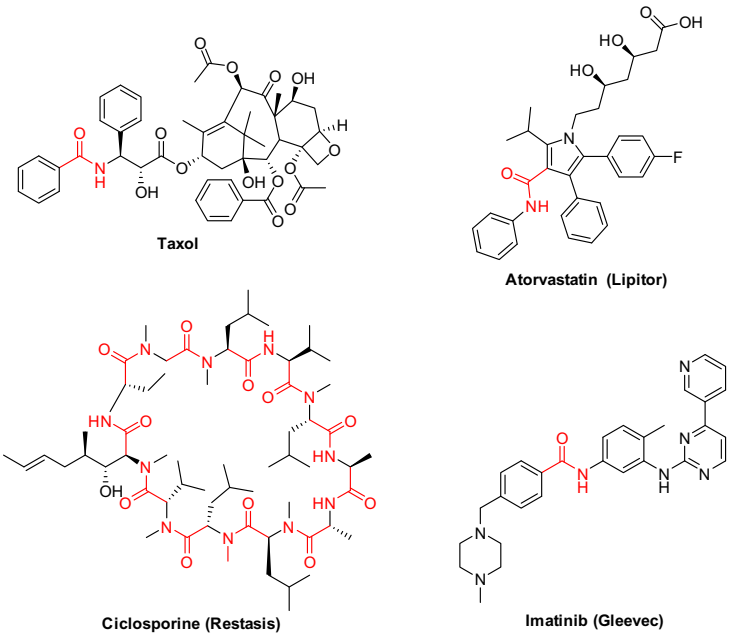
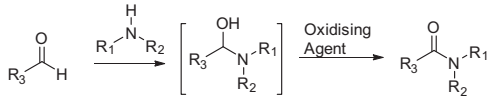
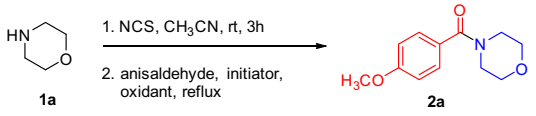


Figure 1. Some important pharmaceutical molecules containing the amide bond.



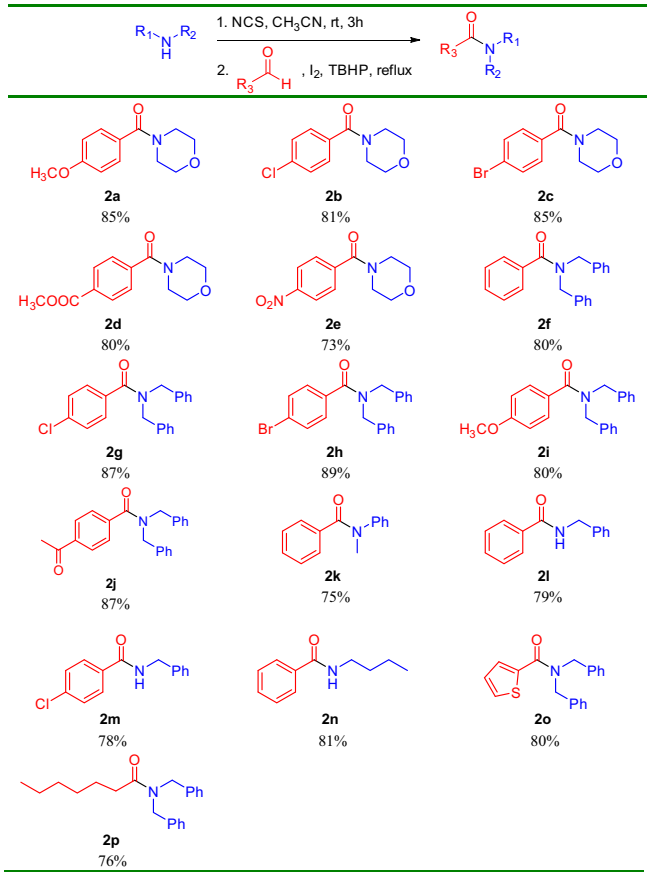
Scheme 1. The general reaction mechanism of amides from aldehydes and amines.

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.