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### Introduction

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## Selective desaturation of amides: a direct approach to enamides\*

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C(sp<sup>3</sup>)-H bond desaturation has been an attractive strategy in organic synthesis. Enamides are important structural fragments in pharmaceuticals and versatile synthons in organic synthesis. However, the dehydrogenation of amides usually occurs on the acyl side benefitting from enolate chemistry like the desaturation of ketones and esters. Herein, we demonstrate an Fe-assisted regioselective oxidative desaturation of amides, which provides an efficient approach to enamides and  $\beta$ -halogenated enamides.

The enamide is a vital functional group in pharmaceuticals featuring excellent biological and physiological properties (Fig. 1).1 Moreover, enamide compounds are also important and versatile synthons in organic synthesis.<sup>2</sup> Thus, the synthesis of enamides has attracted great interest from chemists for several decades.<sup>3</sup> Recently, selective C(sp<sup>3</sup>)-H bond desaturation has been widely used in organic synthesis, including oxidative desaturation,<sup>4</sup> transition-metal catalyzed desaturation,<sup>5</sup> photochemical desaturation<sup>6</sup> and electrochemical desaturation.<sup>7</sup> However, compared to the dehydrogenation reaction of carbonyl compounds,<sup>7a,b,e,g,8</sup> such as ketones,<sup>9</sup> the regioselective dehydrogenation of N-alkanoylamides on the N-alkyl side with higher C-H bond dissociation energy (BDE)<sup>10</sup> is still a tremendous challenge (Scheme 1a). Generally, the desaturation of esters11 and amides12 on the acyl side is much preferred benefitting from enolate chemistry. So far, the regioselective N- $\alpha$ , $\beta$ -desaturation of amides remains unknown (Scheme 1a).

Considering that the desaturation of amides is one of the most efficient and ideal approaches to enamides, many efforts have been made to realize the desaturation of amides. Early in the 1980s, Shono first accomplished this goal via a two-step reaction. Amides were initially oxidized to N-a-methoxyl amides13 and subsequently went through a methanol elimination process to yield the enamide product.14 Recently, trailblazing work regarding the direct desaturation of amides has



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Fig. 1 Representative drugs containing enamide fragments.

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Scheme 1 The significance and challenges for the synthesis of enamides from amides

#### Results and discussion

The azide radical, which was an electron-deficient N-centered radical, was proved to be an efficient hydrogen-abstracting species in C(sp<sup>3</sup>)-H bond functionalization<sup>18</sup> and plays versatile roles in different transformations.17-19 Hence, we attempted to use the azide radical to abstract more electron-rich N-α-C-H bonds to realize selective oxidation reaction of amides.<sup>20</sup> At the

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Table 1 Screening of reaction conditions<sup>a</sup>

$$\overset{O}{\underset{\text{act. (10 mol%)}}{\longrightarrow}} \overset{\text{cat. (10 mol%)}}{\underset{\text{Solvent, 80 °C, 12 h}}{\longrightarrow}} \overset{O}{\underset{\text{Me}}} \overset{O}{\underset{\text{act. (10 mol%)}}{\longrightarrow}} \overset{O}{\underset{\text{Me}}} \overset{O}{\underset{Me}} \overset{O}{\underset{\text{Me}}} \overset{O}{\underset{Me}} \overset{O}{\overset{O}}{\overset{O}} \overset{O}{\underset{Me}} \overset{O}{\overset{O}}{\overset{O}} \overset{O}{\overset{O}} \overset{O}{\underset{Me}} \overset{O}{\overset{O}} \overset{O}{\overset{O}} \overset{O}{\overset{O}} \overset{O}{\overset{Me}} \overset{O}{\overset{O}} \overset{O}{\overset{O}} \overset{O}{\overset{O}} \overset{O}{\overset{Me}} \overset{O}{\overset{O}} \overset{O}{\overset{O}} \overset{O}{\overset{O}} \overset{O}{\overset{O}} \overset{O}{\overset{O}} \overset{O}{\overset{$$

Entry	Cat.	[N <sub>3</sub> ]	Oxidant	Solvent	2a [%]	3a [%]
1	—	—	NIS (3.0 equiv.)	EA	0	0
2	_	$NaN_3$ (3.0 equiv.)	NIS (3.0 equiv.)	EA	54	Trace
$3^b$	_	$NaN_3$ (3.0 equiv.)	NIS (3.0 equiv.)	EA	15	0
4	_	$NaN_3$ (3.0 equiv.)	PIDA (1.8 equiv.)	EA	23	0
5 <sup>c</sup>	$FeCl_2$	$NaN_3$ (3.6 equiv.)	PIDA (1.8 equiv.)	EA	71 (64)	0
$6^d$	_	$TMSN_3$ (2.0 equiv.)	NIS (2.0 equiv.)	DCE	0	40
$7^d$	—	TMSN <sub>3</sub> (2.5 equiv.)	NIS (2.5 equiv.)	$CCl_4$	0	68 (65)

very beginning, we tried to utilize NIS and azide to synthesize the highly reactive reagent IN<sub>3</sub> in situ,<sup>19e</sup> initiating amide oxidative desaturation via a radical process. As initial attempts to realize the desaturation of amides, N-(4-methylbenzoyl) piperidine 1a was selected as the model substrate, using NIS as the oxidant and NaN<sub>3</sub> as the azide source. To our delight, after screening solvents, we found that enamide 2a was generated in ethyl acetate (EA) with moderate yield (Table 1, entry 2). NaN<sub>3</sub> was essential for this transformation (Table 1, entry 1). The iodine ion is one of the by-products in this reaction, but this conversion was inhibited when an excessive amount of NaI was used (Table 1, entry 3). To avoid the inhibiting effect of the excessive amount of by-product NaI, the oxidant NIS was replaced by PhI(OAc)<sub>2</sub> (PIDA), and the yield was reduced to 23% (Table 1, entry 4). During the screening of the amount of NaI and various catalysts (for more condition screening, see the ESI<sup>†</sup>), the yield was further raised to 64% when 30 mol% NaI and 10 mol% FeCl<sub>2</sub> was added (Table 1, entry 5). It is very interesting that the desaturated iodination product 3a was obtained in 40% vield when more soluble TMSN<sub>3</sub> was added instead of NaN<sub>3</sub> (Table 1, entry 6). 2.5 equiv. of TMSN<sub>3</sub> and NIS with CCl<sub>4</sub> as the solvent could increase the isolated yield of 3a to 65% (entry 7). Besides, no doubly dehydrogenated products were produced with a large excess of the N3 reagent and oxidant. The rotamerism was observed from many enamide and N-βhalogenated enamide products, which is confirmed by variabletemperature <sup>1</sup>H NMR experiments (see ESI, Fig. S1<sup>†</sup>).<sup>21</sup>

With the optimal conditions in hand (Table 1, entry 5), we commenced investigating the scope of this reaction. At first, the influence of the N-acyl substituent was tested. As shown, this method is compatible for broad functional groups (Table 2). Simple N-aroyl amides underwent selective desaturation to furnish corresponding enamides in good yields. Urea (2j), Ncarboxylate compound (2k), and tosyl amine (2l) were also applicable and provided the product in acceptable to good yields. It is noteworthy that N-alkanoyl amides worked well in this reaction with good yield. Benzyl amide (2m), acetamide (2n) and tert-butylamide (20) could afford the desired product in good yields. Cyclopropyl amide was also dehydrogenated

<sup>a</sup> Reaction conditions: 1a (0.4 mmol) and additives in EA (4.0 mL) under Ar, 80 °C, and 12 h. Determined by <sup>1</sup>H NMR analysis using 1,1,2,2tetrachloroethane as the internal standard. Isolated yield in parentheses. <sup>b</sup> NaI (2.0 equiv.) as the additive. <sup>c</sup> NaI (30 mol%) as the additive. <sup>d</sup> 1a (0.2 mmol) and open air reaction.



<sup>*a*</sup> Reaction conditions (Method A): reactions were conducted on a 0.4 mmol scale using 10 mol% FeCl<sub>2</sub>, 30 mol% NaI, 1.8 equiv. PIDA, 3.6 equiv. NaN<sub>3</sub>, in 4.0 mL EA, 80  $^{\circ}$ C, under an Ar atmosphere, and 12 h. Isolated yields.

successfully in good yield (2**p**). Chlorinated amide underwent this transformation in good yield with the chlorine functional group untouched (2**r**) without the detection of the  $S_N 2$  product. Especially, the ketone group (2**s**) and alkyne group (2**t**) can also be reserved under these oxidative conditions with good yields. Notably, high selective desaturation was observed in the presence of other carbonyl functional groups, for instance, ketone (2**s**) and ester (2**u**). Moreover, the desaturation of amides bearing seven- and eight-membered rings produced the corresponding enamides (2**v** and 2**w**) in moderate yields, and this method was able to apply in the synthesis of a thirteenmembered cyclic enamide (2**x**). The substituents on the piperidine showed little influence on the desaturation reaction, and substituted enamides (2**y**-2**aa**) were obtained in good yields.

We next tested the desaturation reaction of acyclic amides (Table 3). To our delight, when there were two identical substituents on amides, both *N*-alkanoyl and *N*-benzoyl acyclic amides were converted to the desired products in acceptable yields with high selectivity (**2ab–2ae**). Even in the presence of ester and ketone groups, no conjugated alkenyl product was observed in this oxidative desaturation reaction (**2af** and **2ag**). For unsymmetrical *tert*-amides, lower regioselectivity was obtained when the steric effect was similar to alkyl groups (**2ai** and **2aj**).

The  $\beta$ -halogenated enamides can be further modified to synthesize more sophisticated compounds *via* a well-developed

 Table 3
 Desaturation of acyclic amides<sup>a</sup>



<sup>*a*</sup> Reaction conditions (Method A): reactions were conducted on a 0.4 mmol scale using 10 mol% FeCl<sub>2</sub>, 30 mol% NaI, 1.8 equiv. PIDA, 3.6 equiv. NaN<sub>3</sub>, in 4.0 mL EA, 80  $^{\circ}$ C, under Ar atmosphere, and 12 h. Isolated yields.

transition metal-catalyzed cross-coupling reaction. The direct synthesis of β-halogenated enamides from amides has not been reported yet. We then tested the dehydrogenative halogenation of amides with NIS as the oxidant, TMSN<sub>3</sub> as the additive and  $CCl_4$  as the solvent (Table 4). The scope of this transformation was set out for further investigation (Table 4). The structure of the β-iodine enamide was confirmed by X-ray single crystal diffraction (3c, CCDC 2097260). Additionally, the dehydrogenative N-B-bromination of amides was achieved with 1,3dibromo-5,5-dimethylhydantoin (DBDMH) as the brominating reagent and TogniN<sub>3</sub> (ref. 18a) as the oxidant. The yields of the desired products were acceptable (Table 4). Among them, not only aroyl amide could furnish this transformation, but also alkanoyl amide could produce the desired product (3h). The N- $\beta$ -halogenated enamide can be used to synthesize more complicated enamides by utilizing the classic coupling reaction.

In order to get a better insight into the mechanism, some control experiments were designed and carried out (Scheme 2). At first, the reaction was inhibited after adding 2,2,6,6-tetramethyl-piperidine-N-oxyl (TEMPO) or 2,6-di-tert-butyl-4-methylphenol (BHT) into the reaction system (Method A), and the starting materials remained (Scheme 2a), indicating that the radical process might be part of the dehydrogenation transformation. The radical clock experiment was also carried out, but no ring opening dehydrogenation product was detected under the standard conditions (Scheme 2b). This result may not deny the free radical process because the radical with the intact cyclopropane is likely more stable than the corresponding homoallylic primary radical. Moreover, five-membered ring amide (1al) and secondary amide (1am) did not produce the dehydrogenation product but N-a-azide substituted amides were produced (4al and 4am), which are very stable compounds.17 It reveals that the carbocation intermediates may

Table 4 Dehydrogenative  $N-\beta$ -halogenation of amides<sup>*a*</sup>



 $^a$  Reaction conditions (Method B): reactions were conducted on a 0.2 mmol scale using 2.5 equiv. NIS, 2.5 equiv. TMSN<sub>3</sub> in 2.0 mL CCl<sub>4</sub>, 80 °C, under an Ar atmosphere, and 7 h. Isolated yields.  $^b$  Reaction conditions (Method C): reactions were conducted on a 0.3 mmol scale using 0.55 equiv. 1,3-dibromo-5,5-dimethylhydantoin (DBDMH), 1.1 equiv. TogniN<sub>3</sub> in 2.0 mL DCE, 80 °C, under an Ar atmosphere, and 12 h. Isolated yields.



Scheme 2 Mechanistic studies.

be key intermediates in this process (Scheme 2c). In addition, intermediate 5 was isolated under the standard conditions (Method B, Scheme 2d). Furthermore, we monitored the reaction process by *in situ* <sup>1</sup>H-NMR (see ESI, Fig. S2†). With the extension of reaction time, the intermediate 5 gradually increased and reached the peak in 4 hours, and then it was gradually converted to **3a**. This demonstrated that the *N*- $\alpha$ -azide- $\beta$ -halogenated amide is the key intermediate in the dehydrogenative halogenation reaction.

On the basis of the above experiments, a plausible mechanism was proposed (Scheme 3). The azide radical is generated *in situ* through two pathways under different conditions. Initial ligand exchange between PIDA and  $NaN_3$  would afford intermediate **A**, which undergoes thermal homolytic cleavage owing



Scheme 3 Mechanistic investigations.

to a weak I-N bond to generate an azide radical.<sup>19g,n</sup> Another pathway to generate the azide radical is the decomposition of IN<sub>3</sub>, which is produced from NIS and TMSN<sub>3</sub>.<sup>19e</sup> Then the radical intermediate **B** is produced *via* hydrogen abstraction by the azide radical.<sup>18a,19v</sup> Subsequently, intermediate **B** is converted to cationic intermediate C through a single electron oxidation process promoted by FeCl2.22 The enamide can be also generated via two pathways from intermediate B. In path a, the nucleophilic addition of intermediate C by the azide anion occurs to generate intermediate D, which produces product 2 *via* the elimination of  $HN_3$  (path a). Alternatively, enamide 2 can be generated directly from intermediate C via deprotonation (path b). Regarding the dehydrogenative N-β-halogenation of amide process, intermediate B combines with the iodine radical to obtain intermediate E,190 which will further transform into 2 by elimination. Then, enamide 2 undergoes addition quickly with IN<sub>3</sub> affording the key intermediate F. Finally, the desired product N-β-halogenated enamide 3 is formed with the concomitant elimination of the HN3 unit. The different electrophilicity of NIS and the different active azide intermediates in different solvents might account for the selective formation of the terminal product.

#### Conclusions

In summary, we described a novel, general and regioselective oxidative *N*- $\alpha$ , $\beta$ -desaturation and dehydrogenative *N*- $\beta$ -halogenation of amides. This chemistry features excellent functional group compatibility, and thus provides efficient and general access to enamides and  $\beta$ -halogenated enamides, which are biologically important scaffolds and versatile organic building blocks in pharmaceutical sciences and synthetic organic chemistry.

#### Author contributions

X. L., Z. C., S. S. and N. J. conceived and designed the experiments. X. L. and Z. C. carried out most of the experiments. X. L., Z. C., J. L., Z. Z., S. S. and N. J. analyzed the data. X. L., Z. C., S. S. and N. J. wrote the paper. N. J. directed the research.

## Conflicts of interest

There are no conflicts to declare.

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