Efficient and practical synthesis of *N*-acetyl enamides from ketoximes by unique iron catalytic system

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Abstract: A new procedure for the iron-catalyzed synthesis of enamides from ketoximes was developed, and its mechanism was proposed. A unique reduction system, with the concerted use of KI and $Na_2S_2O_4$, was involved. The reaction exhibited a wide substrate scope and gave good yields in a short reaction time. The procedure is operationally simple and also applicable for the large-scale synthesis.

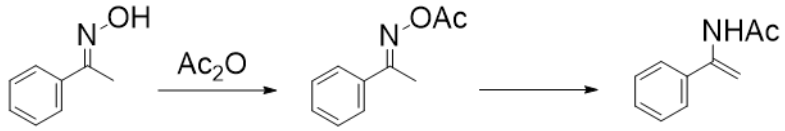
Keywords: ketoxime, enamide synthesis, iron catalyst, one-electron reduction

N-acetyl enamides are useful synthetic intermediates, which lead to biologically active compounds,[1] pharmaceutical compounds[1] and functional chiral amines.[2] A number of methods for the synthesis of *N*-acetyl enamides have been reported, which utilized nitriles,[3] amides,[4] and ketoximes[5-11] as the substrate. Among these, ketoximes are easily prepared from ketones and hydroxylamine, and the derivatives are also easily available. The acylation of the hydroxy group of the ketoxime, reductive cleavage of its N-O bond, and re-acylation via tautomerization of the imine can proceed in a one-pot reaction and is an efficient synthetic method to afford *N*-acetyl enamides (Scheme 1). The effective methods used to conduct the above reaction are listed herein. The first example was reported in 1975, using stoichiometric amounts of a chromium (II) reagent.[5] Following this, a CuI-catalyzed reaction at 120 ˚C for 24 h,[6] Ru(II)-catalyzed reactions,[7] Rh/C-catalyzed reactions with H_2,[8] phosphine-mediated system in refluxing toluene,[9] and stoichiometric amounts of Fe powder or Fe(II)-mediated reactions were proposed.[10,11] Each of these methods offered advantages with respect to the different parameters, such as temperature, reaction time, reagents, substrate scope, and yield. However, several aspects can be improved further.

In the course of our research project, we investigated the iron-catalyzed reaction and found a unique reduction pathway of Fe(III) in the catalytic cycle that should be applicable to the abovementioned reaction. Iron is cheap and abundant on the earth; however, a catalytic reaction is valuable from the environmental aspect. Herein, we report the iron-catalyzed synthesis of *N*-acetyl enamides, in which 5 mol% of the catalyst affords high to excellent yields of a wide range of products in a short reaction time.

Scheme 1.

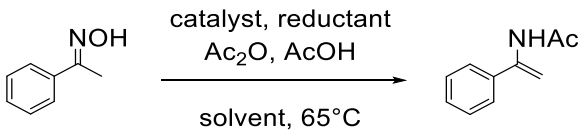
Enamide synthesis from ketoxime.



Using compound **1**, we investigated the reductant in the $Fe(OAc)_2$ catalyzed

reaction to obtain compound **2** (Table 1, see supporting information, Table S1). All the reagents and substrate were simply mixed in a solvent at 65 ˚C, and 3 equivalents of KI was used in DCE with 5 mol% of catalyst (entry 1),[7] however, compound **2** was given in 8% yield after 12 h. The reaction in the presence of $NaHSO_3$, that is often used in such reactions,[6,7] generated compound **2** in low yield (entry 2). Next, we tried adding $Na_2S_2O_4$ and found an improvement in the yield, however, substrate **1** was recovered after 12 h (entry 3). To overcome the low reactivity, we considered the reduction cycle of the iron catalyst and attempted to use of KI and $Na_2S_2O_4$ simultaneously. Gratifyingly and expectedly, the reaction rate was dramatically improved, and 90% yield was accomplished in only 1 h (entry 4). Reducing the amount of catalyst (3 mol%) lowered the reactivity, giving a lower yield (entry 5), on the other hand, a catalytic amount of KI (0.4 equivalent) worked sufficiently (entry 6). Acetic acid is an essential promoter in the reaction, although its role and mechanism are not clearly understood (entry 7).[11] Tetrabutylammonium iodide (TBAI) could be used as an iodide source, despite the low reactivity (entry 8), while the combination of KI and $NaHSO_3$ decreased the reactivity and yield (entry 9). Both THF and toluene could be used as the solvents. However, no desirable results were obtained in CH_3CN (entries 10–12). Therefore, entry 6 represents the optimum conditions for this reaction.[12]

Table 1.
Optimization of reaction conditions.[a]



1 **2**

Entry	Catalyst	Reductant	AcOH (equiv.)	Solvent	Time (h)	Yield (%)
1	$Fe(OAc)_2$ (5 mol%)	KI (3.0 equiv.)	3.0	DCE	12	8
2	$Fe(OAc)_2$ (5 mol%)	$NaHSO_3$ (2.0 equiv.)	3.0	DCE	12	5
3	$Fe(OAc)_2$ (5 mol%)	$Na_2S_2O_4$ (2.0 equiv.)	3.0	DCE	12	42
4	$Fe(OAc)_2$ (5 mol%)	KI (1.0 equiv.) $Na_2S_2O_4$ (2.0 equiv.)	3.0	DCE	1	90
5	$Fe(OAc)_2$ (3 mol%)	KI (1.0 equiv.) $Na_2S_2O_4$ (2.0 equiv.)	3.0	DCE	1.5	82
6	$Fe(OAc)_2$ (5 mol%)	KI (0.4 equiv.) $Na_2S_2O_4$ (2.0 equiv.)	3.0	DCE	1	**90**
7	$Fe(OAc)_2$ (5 mol%)	KI (0.4 equiv.) $Na_2S_2O_4$ (2.0 equiv.)	-	DCE	12	68
8	$Fe(OAc)_2$ (5 mol%)	TBAI (0.4 equiv.) $Na_2S_2O_4$ (2.0 equiv.)	3.0	DCE	3	77
9	$Fe(OAc_{)2}$ (5 mol%)	KI (0.4 equiv.) $NaHSO_3$ (2.0 equiv.)	3.0	DCE	2	75
10	$Fe(OAc)_2$ (5 mol%)	KI (0.4 equiv.) $Na_2S_2O_4$ (2.0 equiv.)	3.0	THF	24	88
11	$Fe(OAc)_2$ (5 mol%)	KI (0.4 equiv.) $Na_2S_2O_4$ (2.0 equiv.)	3.0	toluene	1	86
12	$Fe(OAc)_2$ (5 mol%)	KI (0.4 equiv.) $Na_2S_2O_4$ (2.0 equiv.)	3.0	CH_3CN	6	65

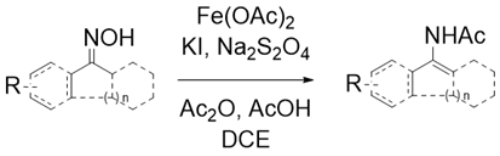
[a] Reaction conditions : **1** (0.5 mmol), Ac_2O (1.05 mmol), catalyst, reductant and AcOH in solvent (5.0 mL) under Ar at 65 °C

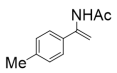
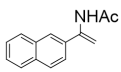
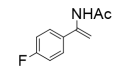
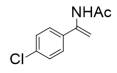
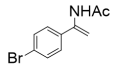
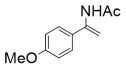
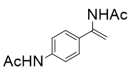
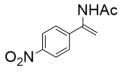
Next, we investigated the substrate scope under the optimum conditions (Table 2). Various substituents on the phenyl moiety were tested, and most of the ketoximes gave better yields of the corresponding enamides in a shorter time, as

compared with the previous reports (entries 1–8).[6,7,11] The ketoxime with naphthalene and sterically hindered ketoximes successfully afforded the desired enamides (entries 9–12). The bicyclic ketoximes and aliphatic cyclic ketoximes also gave good yields (entries 13–16). In some cases, a higher reaction temperature was necessary, because the substrate was not consumed completely at 65 ˚C. Thus, a successful transformation into the enamides from a wide range of ketoximes was accomplished using our new protocol, and we believe that this should be the improved method.

Table 2.

Syntheses of acetyl enamides.[a]



Entry	Enamide	Temp. (˚C)	Time (h)	Yield (%)	Entry	Enamide	Temp. (˚C)	Time (h)	Yield (%)
1		reflux	1.0	84	9		120[c]	30 min.	85
2		reflux	1.0	86	10		65	1.5	86
3		65	1.0	87[b]	11		reflux	1.0	76
4		65	1.0	71	12		reflux	1.0	73[d]
5		65	1.0	79	13		65	1.0	81
6		reflux	1.5	51	14		65	1.0	78
7		120[c]	40 min.	68	15		65	30 min.	73
8		65	40 min.	75	16		65	30 min.	66

[a] Reaction conditions: ketoxime (0.5 mmol), $Fe(OAc)_2$ (5 mol%), KI (0.4 equiv.), $Na_2S_2O_4$ (2.0 equiv.), Ac_2O (2.1 equiv.), AcOH (3.0 equiv.), DCE (5.0 mL) at specified temperature.

[b] $Fe(OAc)_2$ (10 mol%) and KI (1.0 equiv.) were used.

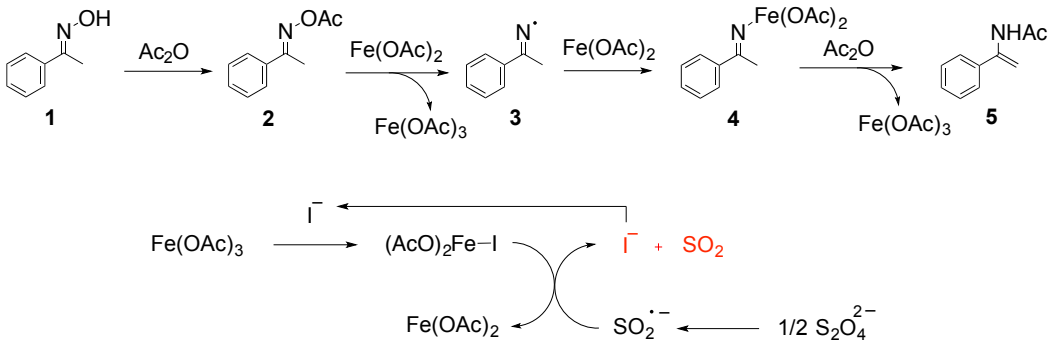
[c] The reaction was conducted in a Schlenk tube.

[d] E/Z ratio ≒ 1/2.

We used the above protocol for a large-scale experiment, and 50 mmol of compound **1** was reacted under the optimum conditions, although the temperature and reaction time were 75 ˚C and 2.5 h, respectively. A better yield (95%) of compound **2** was obtained (as compared with entry 6 in Table 1), and the operation was still simple. Therefore, we claim that our procedure is also practical.

The proposed reaction mechanism based on one-electron reduction is illustrated in Scheme 2. Fe(II) phthalocyanine (FePc) also functioned as a catalyst (Table S1), and this must exclude the other mechanism based on the oxidative addition of N-O bond to the iron catalyst.[6] The additional AcOH might promote the intermediate **4** to generate imine and $Fe(OAc)_3$. As a second role, AcOH could facilitate the electron transfer from Fe(II) to the intermediate **2** via protonation to the oxime moiety. As a third role, AcOH could promote the *in situ* generation of the Fe(III) -I bond from $Fe(OAc)_3$ and I^- by protonation of acetoxy moiety, which helped dissociation of acetoxy group. Then, Fe(II) was further generated from this bond through the homolytic cleavage supported by the SO_2-radical anion. Consequently, Fe(II) and I^- were regenerated, therefore, $Na_2S_2O_4$, which is a source of SO_2-radical anion,[13] is more effective than $NaHSO_3$ in this reaction, also, KI works as a catalyst here.

Scheme 2.
Proposed reaction mechanism.



In summary, we developed a new procedure for the iron-catalyzed synthesis of enamide from ketoxime, involving a unique reduction system with the concerted use of KI and $Na_2S_2O_4$. The reaction exhibited a wide range of substrate scope and gave good yields in a short reaction time. The procedure is operationally simple and also applicable for the large-scale synthesis. We also propose the reaction mechanism, which should provide useful information for other iron- or metal-catalyzed reactions.

Acknowledgments

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12. General procedure (entry 6): A test tube was charged with acetophenone oxime (68 mg, 0.5 mmol), KI (33 mg, 0.2 mmol), $Na_2S_2O_4$ (174 mg, 1.0 mmol), and $Fe(OAc)_2$ (4.3 mg, 0.050 mmol). To the mixture, DCE (5.0 mL), Acetic acid (90 mg, 1.5 mmol), and acetic anhydride (107 mg, 1.05 mmol) were added by syringe. The mixture was heated and stirred at 65˚C under argon for 1 hour and then cooled to room temperature. The resulting mixture was diluted with ethyl acetate and washed with sat. $NaHCO_3$ solution and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography on silica gel with hexane/ethyl acetate (3/1) as eluent to yield the desired acetyl enamide (73 mg, 0.45 mmol) in 90% yield.
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Legends

Scheme 1. Enamide synthesis from ketoxime.

Scheme 2. Proposed reaction mechanism

Table 1. Optimization of reaction conditions.

Table 2. Syntheses of acetyl enamides.