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Synthesis of Enamides via CuI-Catalyzed Reductive Acylation of Ketoximes with $NaHSO_3$

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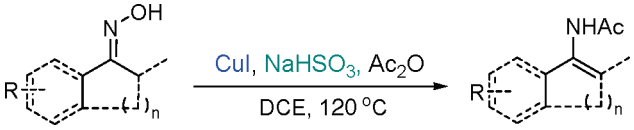
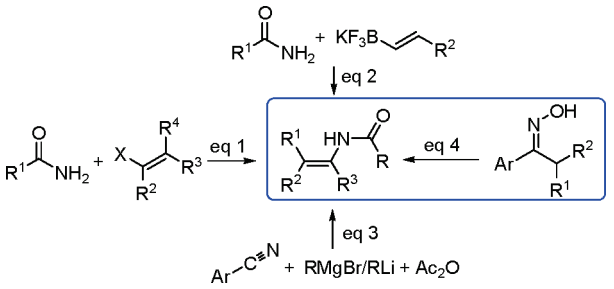


CuI-catalyzed reductive acylation of ketoximes for preparation of enamides was reported. A broad scope of enamides was obtained in high yields with $NaHSO_3$ used as the terminal reductant.

Enamides and their derivatives are versatile and powerful building blocks in organic synthesis, especially for the enantioselective hydrogenation to prepare various chiral amines[1] and for stereoselective C−C and C−N bond-formation reactions.[2] Additionally, the enamide moiety is also a key substructure in various classes of natural products and pharmaceutical lead compounds.[3] There are a number of methods for the synthesis of enamides; however, enamide formation in a practical manner is still a challenge.

SCHEME 1. Strategies for the Synthesis of Enamides



In addition to transition-metal-catalyzed cross-coupling reactions[4] (eqs 1 and 2) and addition of an organometallic reagent to a nitrile[5] (eq 3), reductive acylation of ketoximes[6] (eq 4) has proven to be the most direct approach for the synthesis of enamides (Scheme 1). Iron powder was initially used as the stoichiometric reducing reagent in this transformation.[6] However, this procedure usually involved a uncontrollable exothermic reaction and low yields.[6,7] Recently, alternative protocols for reductive acylation of ketoximes have emerged with the use of pyrophoric Et_3P[8] or $Fe(OAc)_2$[7] as the stoichiometric reducing reagents. We have previously developed the Rh/C-catalyzed hydroacylation of ketoximes for the preparation of enamides.[9] Despite these efforts, the development of a practical catalytic procedure for the synthesis of enamides under mild reaction conditions is still required. In connection with the recent investigation of Cu-catalyzed oxime transformations,[10−12] we envision that it may be possible to conduct a catalytic reductive acylation process using an inexpensive Cu catalyst and a proper reductant. In this paper, we report a practical catalytic process for the CuI-catalyzed reductive acylation of ketoximes employing $NaHSO_3$ as the economical terminal reductant. This process proceeds under mild reaction conditions and gives a broad scope of enamides in high yields.

Acetophenone oxime **1a** was chosen as a test substrate in the initial experiments to optimize the reaction conditions. A variety of formate salts such as HCO_2Na, HCO_2K, and HCO_2NH_4 were screened as the reducing reagent with CuI

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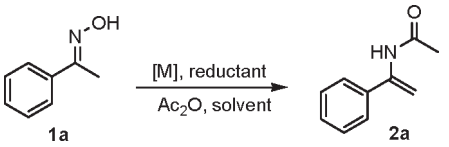
TABLE 1. Optimizing Reaction Conditions[a]



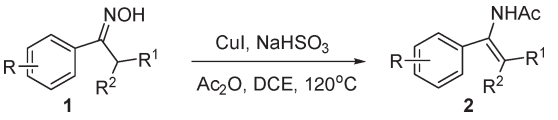
entry	catalyst	reductant	solvent	yield (%)
1	CuI	HCO_2M	toluene	0
2	CuI	$NaHSO_3$	toluene	70
3	CuI	$NaHSO_3$	DMF	36
4	CuI	$NaHSO_3$	1,4-dioxane	64
5	CuI	$NaHSO_3$	EtOH	0
6	CuI	$NaHSO_3$	DCE	83
7	CuI	Na_2SO_3	DCE	20
8	CuI	$Na_2S_2O_3$	DCE	0
9	CuI	$Na_2S_2O_4$	DCE	54
10	CuI	K_2S	DCE	8
11	CuI	Na_2NO_3	DCE	0
12	CuBr	$NaHSO_3$	DCE	35
13	CuCl	$NaHSO_3$	DCE	9
14	Cu_2O	$NaHSO_3$	DCE	5
15	$Cu(OAc)_2$	$NaHSO_3$	DCE	0
16	$Pd(PPh_3)_4$	$NaHSO_3$	DCE	0
17	Pd/C	$NaHSO_3$	DCE	5
18	$Pd(OAc)_2$	$NaHSO_3$	DCE	0

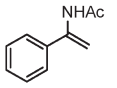
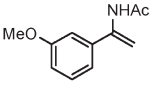
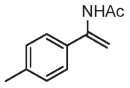
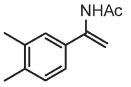
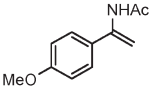
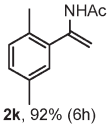
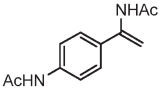
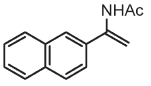
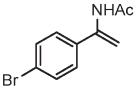
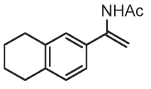
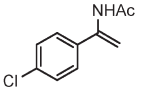
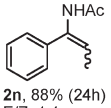
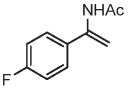
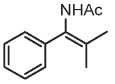
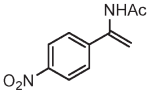
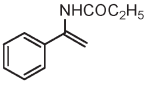
[a]Reaction conditions: **1a** (0.5 mmol), Ac_2O (1.0 mmol), reductant (1.5 mmol), and catalyst (10 mol %) in solvent (5 mL) under Ar at 120 °C for 24 h.

as the catalyst. Unfortunately, no reaction was observed after several attempts (Table 1, entry 1). To our delight, the desired enamide **2a** was obtained in 70% yield in the presence of $NaHSO_3$ in toluene with CuI used as the catalyst (Table 1, entry 2). Therefore, a variety of solvents and reducing reagents were screened for better efficiency in this transformation. DCE was found to be the most effective (Table 1, entries 2−6). Optimization of the reducing reagents revealed that Na_2SO_3, $Na_2S_2O_4$, and K_2S were inferior (Table 1, entries 7, 9, and 10), albeit $Na_2S_2O_3$ and Na_2NO_3 showed no reactivity (Table 1, entries 8 and 11). Further experiment showed that CuI was the best catalyst for this transformation; other copper or palladium precursors,[11] such as CuBr, CuCl, Cu_2O, $Cu(OAc)_2$, $Pd(PPh_3)_4$, Pd/C and $Pd(OAc)_2$, were found to be inferior (Table 1, entries 12−18).

Under the optimized conditions for this CuI-catalyzed reductive acylation process, we have explored the substrate scope (Table 2). The reductive procedure displayed good functional group tolerance and gave the acyclic enamides in good to excellent yields. Acyclic ketoximes with Cl, F, MeO, and Me, even with sensitive Br, NH_2, and NO_2 were tolerated under the reaction conditions (Table 2, entries 2−11). For the electronic effects of this transformation, we found that electron-rich ketoximes showed more reactivity and gave slightly higher yields than electron-deficient ketoximes (Table 2, entries 2−8). Interestingly, the enamide **2d** was isolated in 95% yield with 1-(4-aminophenyl)ethanone oxime **1d** as the substrate (Table 2, entry 4). The enamide **2h** was also formed in 58% yield, albeit with a strong electron-withdrawing NO_2 substitutent at the ketoxime **1h** (Table 2, entry 8). Furthermore, the tri- and tetrasubstituted acyclic enamides **2n** and **2o** were obtained in good yields in the transformation (Table 2, entries 14−15). *N*-Propyl enamide **2p** was achieved when propionic anhydride was used

TABLE 2. CuI-Catalyzed Reductive Acylation of Acyclic Ketoximes for Preparation of Enamides[a]



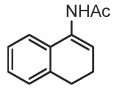
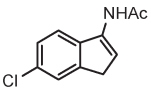
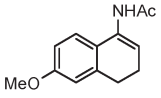
entry	enamide **2**	entry	enamide **2**
1	 **2a**, 83% (24h)	9	 **2i**, 71% (24h)
2	 **2b**, 77% (12h)	10	 **2j**, 77% (24h)
3	 **2c**, 71% (12h)	11	 **2k**, 92% (6h)
4	 **2d**, 95%[b] (12h)	12	 **2l**, 52% (48h)
5	 **2e**, 62% (30h)	13	 **2m**, 95% (12h)
6	 **2f**, 75% (36h)	14	 **2n**, 88% (24h) E/Z≈1:1
7	 **2g**, 77% (48h)	15	 **2o**, 70% (24h)
8	 **2h**, 58% (75h)	16	 **2p**, 69%[c] (24h)

[a]Reaction conditions: ketoxime **1** (0.5 mmol), Ac_2O (1.0 mmol), $NaHSO_3$ (1.5 mmol), and CuI (10 mol %) in DCE (5 mL) under Ar at 120 °C. [b]1-(4-Aminophenyl)ethanone oxime **1d** was used directly as the substrate. [c]Ac_2O was replaced by propionic anhydride (1.0 mmol).

as the substrate (Table 2, entry 16). However, only acetanilide that resulted from Beckmann rearrangement of acetophenone oxime **1a** was observed when trifluoroacetic anhydride was used.

The cyclic ketoximes were investigated as well for extending the substrate scope (Table 3). Satisfactorily, the CuI-catalyzed reductive acylation proceeded smoothly. Both α-tetralones-derived ketoximes **1q**, **1r** and indanones-derived ketoximes **1s**, **1t** exhibited good reactivity in the transformation, and the desired enamides **2q**−**2t** were obtained in good to excellent yields (Table 3, entries 1−4). It is noteworthy that ketoximes **1u**, **1v** derived from cyclohexanone or

TABLE 3. CuI-Catalyzed Reductive Acylation of Cyclic Ketoximes for Preparation of Enamides[a]

entry	enamide **2**	entry	enamide **2**
1	 **2q**, 92% (12h)	4	 **2t**, 79% (12h)
2	 **2r**, 92% (8h)	5	 **2u**, 67% (6h)
3	 **2s**, 74% (12h)	6	 **2v**, 60% (6h)

[a]Reaction conditions: ketoxime **1** (0.5 mmol), Ac_2O (1.0 mmol), $NaHSO_3$ (1.5 mmol), and CuI (10 mol %) in DCE (5 mL) under Ar at 120 °C.

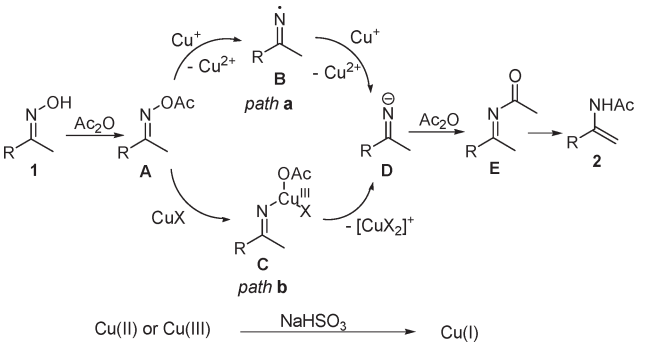
cyclopentanone also gave the desired enamides **2u** and **2v**, respectively, in good yields (Table 3, entries 5 and 6).

In addition, the CuI-catalyzed reductive acetylation of acetophenone oxime **1a** was conducted at 100 mmol scale under the standard conditions. As expected, the reaction proceeded to give enamide **2a** in 80% yield.

A plausible mechanism for the Cu-catalyzed reductive acylation of ketoximes is depicted in Scheme 2. First, acylation of ketoxime **1** gives an *O*-acetyloxime intermediate **A**. Next, reduction of the *O*-acetyloxime **A** by Cu(I) affords iminium anion intermediate **D** through a two-step electron transfer process (path **a**).[12] Acylation of iminium anion **D** followed by tautomerization of intermediate **E** produces enamide **2**. Alternatively, the cleavage of the N−O bond in *O*-acetyloxime **A** to give iminium anion **D** could be achieved by oxidative addition of A to Cu(I) followed by expulsion of $[CuX_2]^+$ (path **b**).[10,11] The Cu(II) or Cu(III) species is assumed to be reduced by $NaHSO_3$ to regenerate the active Cu(I) in the reaction.

In summary, we have developed a practical method for synthesis of enamides by CuI-catalyzed reductive acylation of ketoximes. This general procedure shows good functional group tolerance and affords a broad scope of enamides in high yields. A plausible mechanism was proposed in this paper, and the use of $NaHSO_3$ as the economical terminal

SCHEME 2. Proposed Mechanism for Cu-Catalyzed Enamides Formation



reductant makes this practical transformation attractive in both organic synthesis and industrial applications.

Experimental Section

General Procedure for CuI-Catalyzed Reductive Acylation of Ketoximes for Preparation of Enamides. A mixture of ketoxime **1** (0.5 mmol), acetic anhydride (1.0 mmol, 102.0 mg), $NaHSO_3$ (1.5 mmol, 156.2 mg), and CuI (10 mol %, 9.1 mg) was stirred in 1,2-dichloroethane (DCE, 5.0 mL) at 120 °C under Ar. After completion of the reaction (detected by TLC), the reaction mixture was cooled to room temperature, diluted with EtOAc (25 mL), and washed with NaOH (2 N, 20 mL) and brine (20 mL). The organic layers were dried over anhydrous Na_2SO_4 and evaporated in vacuo. The desired enamide **2** was obtained after purification by flash chromatography on silica gel with hexane/ethyl acetate as the eluent.

Spectroscopic Data of Enamide 2b. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 8.0 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 6.94 (bs, 1H), 5.81 (s, 1H), 5.05 (s, 1H), 2.38 (s, 3H), 2.11 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 140.3, 138.6, 135.5, 129.3, 125.9, 101.8, 24.5, 21.1.

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Supporting Information Available: Experimental procedures and spectral data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.