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A Facile and Practical Synthesis of *N*-Acetyl Enamides

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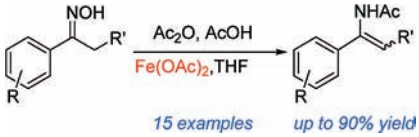
Received October 22, 2009



A facile and practical method for the synthesis of *N*-acetyl α-arylenamides has been developed from corresponding ketoximes as the starting materials with ferrous acetate as the reducing reagent. This methodology offers mild reaction conditions, simple purification procedures, and high yields for a variety of *N*-acetyl enamides.

Chiral amines and their derivatives have played numerous roles in synthetic organic chemistry such as resolving reagents, ligands, or catalysts for asymmetric transformations. These structures can be commonly found in biologically active natural products, agrochemicals, and drugs. As a result, the synthesis of chiral amines has been of particular interest for decades. While various methods are available, catalytic asymmetric hydrogenation of *N*-acetyl enamides has recently emerged as one of the most efficient and atom-economical methods.[1] Despite the development of many efficient hydrogenation transformations, syntheses of chiral amines via hydrogenation of *N*-acetyl enamides have rarely been reported on large scales. One major reason for this may be attributed to the lack of efficient methods for practical synthesis of *N*-acetyl enamides. Herein we report a facile and efficient method for the synthesis of *N*-acetyl enamides from the corresponding ketoxime starting materials with ferrous acetate as the reducing reagent. The new method provides mild reaction conditions, simple isolation procedures, and high yields for a variety of *N*-acetyl enamides.

Several methods are available for the preparation of *N*-acyl enamides: (1) direct condensation of amides with ketones;[2] (2) addition of an organometallic reagent to a nitrile followed by a quench of the resulting imine with an electrophile;[3] (3) transition metal-catalyzed coupling of vinyl derivatives such as vinyl halides,[4] triflates,[5] or tosylates[6] with amides; (4) Heck arylation of vinylacetamide;[7] and (5) reductive acylation of ketoximes.[8] Although the direct condensation of amides with ketones is attractive, this method is successful only in a few cases and is not general. Addition of an organometallic reagent to a nitrile often provides a complex reaction mixture and a low yield. A modified procedure[3a] with methyllithium as the reagent in the presence of lithium bromide offers higher yields. However, this reaction requires cryogenic conditions. Transition metal-catalyzed coupling of vinyl derivatives with amides and Heck arylation of vinylacetamide are usually not cost-effective. The most common method at a small scale is reductive acylation of ketoximes with $Fe/Ac_2O/AcOH$ as reagents.[8a−d] However, this heterogeneous reaction is not amenable to scale-up. Singh and co-workers[8f] reported a homogeneous method albeit with the use of pyrophoric phosphine as the reducing reagent. An attractive alternative[8g] was recently reported utilizing hydrogen as the reducing source in the presence of a Rh/C catalyst, although its compatibility with various sensitive functionalities is a concern. Despite these efforts, the development of a facile and practical synthesis of *N*-acetyl enamides with a broad substrate scope remains a challenge.

We believe the reduction of ketoximes[9] with an iron species remains among the most versatile and economical methods for the synthesis of *N*-acetyl enamides with various functionalities. During preliminary experiments with 1-(4-bromophenyl)ethanone oxime (**1a**) as the substrate, we found that the traditional method ($Fe/Ac_2O/AcOH$) was

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(9) Ketoximes were prepared from corresponding ketones and hydroxylamine hydrochloride in quantitative yields, see refs 8a−g. For a specific procedure, see: Holmes, A. B.; Smith, A. L.; Williams, S. F.; Hughes, L. R.; Lidert, Z.; Swithenbank, C. *J. Org. Chem.* **1991**, *56*, 1393.

Published on Web 11/18/2009 DOI: 10.1021/jo902259u

SCHEME 1

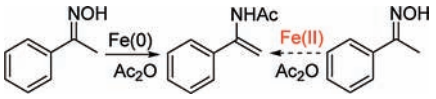
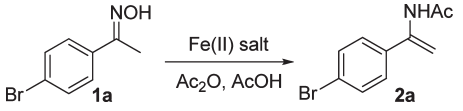


TABLE 1. Fe(II) Salt Screening and Reaction Optimization[a]



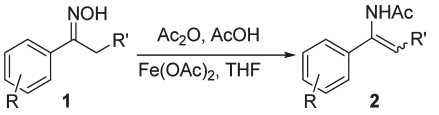
entry[b]	Fe(II) salt	solvent	T (°C)	yield (%)[c]
1	$FeSO_4 \cdot 7H_2O$	toluene	100	0
2	$FeCO_3$	toluene	100	7
3	$Fe(C_2O_4) \cdot 2H_2O$	toluene	100	0
4	$FeCl_2$	toluene	100	0
5	$Fe(OAc)_2$	toluene	100	74
6	$Fe(OAc)_2$	toluene	70	70[d]
7	$Fe(OAc)_2$	THF	65	89
8	$Fe(OAc)_2$	EtOAc	70	83
9	$Fe(OAc)_2$	DMF	70	88
10	$Fe(OAc)_2$	MeCN	70	70
11	$Fe(OAc)_2$	THF	65	54[d,e]
12	$Fe(OAc)_2$	THF	65	90[f]

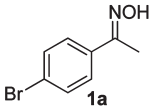
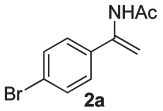
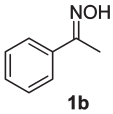
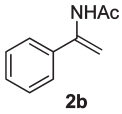
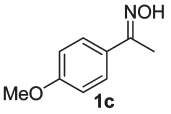
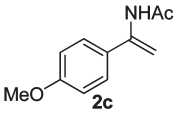
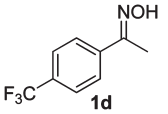
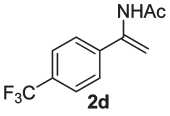
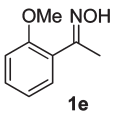
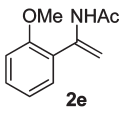
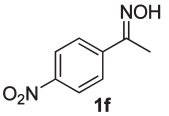
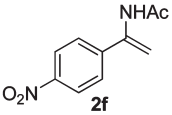
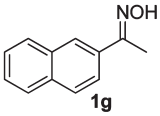
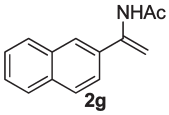
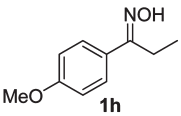
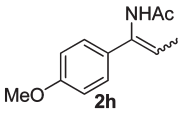
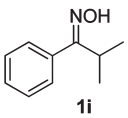
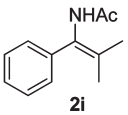
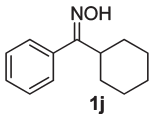
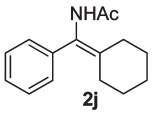
[a]Reaction conditions unless otherwise noted: **1a** (4 mmol, 1 equiv, 0.2 M), Fe(II) salt (8 mmol, 2 equiv), Ac_2O (12 mmol, 3 equiv), AcOH (12 mmol, 3 equiv), solvent (20 mL), 15 h. [b]All reactions were conducted under nitrogen with degassed solvent. [c]Assayed yield by HPLC. [d]The reduction was incomplete. Acetylated oxime intermediate was still observed after 15 h. [e]No AcOH was added. [f]2 equiv of Ac_2O was used.

not suitable for scale-up. Using a magnetic stirrer at a gram scale, the reaction was heated to ~70 °C whereupon a rapid exotherm to 90 °C was observed. This uncontrollable exotherm resulted in inconsistent yields for the reaction. At a larger scale, with a mechanical stirrer, the initiation of the reaction was much slower. The reaction proceeded slowly at ~90 °C and needed to be heated for longer periods, which resulted in the formation of various impurities. These inconsistent results with iron metal led us to believe that this method is unsuitable for large scales. It has been demonstrated previously[10,11] that Fe(II) salts could also be employed for reductive cleavage of N−O bonds. We thus envisioned Fe(II) salts could also be suitable for reductive acylation of oximes (Scheme 1). Moreover, the reduction with an Fe(II) salt could avoid the inconsistent initiation period observed in the reaction with iron metal and provide a milder and more consistent reaction profile. 1-(4-Bromophenyl)ethanone oxime (**1a**) was thus chosen as the substrate for screening different commercially available Fe(II) salts (Table 1).

The reactions (entries 1−5, Table 1) were conducted in toluene at 100 °C under nitrogen for 15 h with a ferrous salt (2 equiv), AcOH (3 equiv), and Ac_2O (3 equiv) as the reagents. While $FeSO_4 \cdot 7H_2O$, $FeCO_3$, $Fe(C_2O_4) \cdot 2H_2O$, and $FeCl_2$ provided disappointing results (< 7% yield, entries 1−4), reaction with $Fe(OAc)_2$ as the reagent led to the formation of the desired enamide **2a** in 74% assay yield (entry 5). More importantly, no sudden increase of reaction temperature was observed during reaction, indicating smooth reduction without an observable initiation period. The reaction also proceeded smoothly at a lower

TABLE 2. Synthesis of Acyclic α-Arylenamides[a]



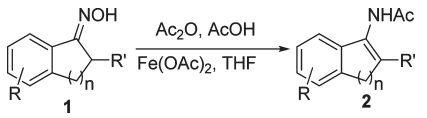
entry	ketoxime **1**	enamide **2**	yield (%)[b]
1			90
2			78
3			82
4			87
5			77
6			45
7			77
8			80[c]
9			66
10			67

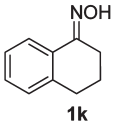
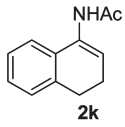
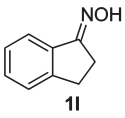
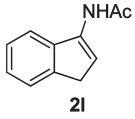
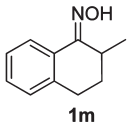
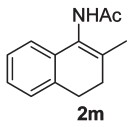
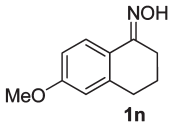
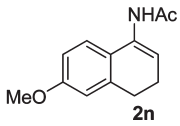
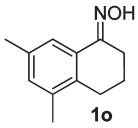
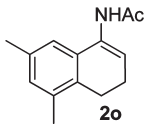
[a]Reaction conditions: oxime **1** (4 mmol, 1 equiv), $Fe(OAc)_2$ (8 mmol, 2 equiv), AcOH (12 mmol, 3 equiv), Ac_2O (8 mmol, 2 equiv), THF (20 mL), at 65−67 °C for 7−15 h under nitrogen. [b]Unoptimized isolated yields. [c]E/Z ratio ≈ 1/1.5.

(10) (a) Smith, L. I.; Opie, J. W. *Organic Synthesis*; Wiley: New York, 1955; Collect. Vol. III, p 56. (b) Kurasawa, Y.; Okamoto, Y.; Takada, A. *Heterocycles* **1984**, *22*, 1391.

(11) Reduction of oximes to imines with Ti(III) or Cr(II) salts was also reported, see: (a) Boar, R. B.; McGhie, J. F.; Robinson, M.; Barton, D. H. R.; Horwell, D. C.; Stick, R. V. *J. Chem. Soc., Perkin I* **1975**, 1237. (b) Barton, D. H. R.; Bowles, T.; Husinec, S.; Forbes, J. E.; Llobera, A.; Porter, A. E. A.; Zard, S. Z. *Tetrahedron Lett.* **1988**, *29*, 3343.

TABLE 3. Synthesis of Cyclic α-Arylenamides[a]



entry	ketoxime **1**	enamide **2**	yield (%)
1	 **1k**	 **2k**	80
2	 **1l**	 **2l**	50
3	 **1m**	 **2m**	55
4	 **1n**	 **2n**	82
5	 **1o**	 **2o**	74

[a]The reaction conditions were similar to those shown in Table 2. Yields were not optimized.

temperature (70 °C). A solvent screening (entries 6−10, Table 1) showed both THF and DMF provided improved yields over EtOAc, MeCN, and toluene. Further studies showed 2 equiv of acetic anhydride are sufficient for this transformation and the addition of acetic acid is beneficial for the reactivity. Under the optimized conditions (entry 12, Table 1), enamide **2a** is formed in 90% assay yield.

The new method was used for the synthesis of an array of acyclic *N*-acetyl α-arylenamides with different functionalities. As shown in Table 2, high yields (77−90%) were achieved on various oxime substrates (entries 1−5) regardless of the electronic effect and substitution pattern on the aromatic ring. The reaction conditions are also compatible with a sensitive nitro group, providing the desired enamide product in moderate yield (45%, entry 6). The 2-naphthyl enamide product was isolated in 77% yield (entry 7). Preparations of several trisubstituted and tetrasubstituted enamides were also successful (entries 8−10). It is noteworthy that the yields shown in Table 2 are comparable or higher than those of the previously reported methods.[8a,f,g]

Cyclic enamides were also formed in high yields as shown in Table 3. Good yields were observed on α-tetralone-derived ketoxime substrates (entries 1 and 3−5). A tetrasubstituted enamide was also obtained in 55% unoptimized yield. A moderate yield (50%) was achieved on an indanone-derived ketoxime (entry 2).

To test the scalability of this method for the synthesis of *N*-acetyl enamides, reductive acetylation of oxime **1a** was demonstrated at a 20 g scale under similar conditions described in Table 2 in a reactor equipped with a mechanical stirrer. The reaction went to completion after stirring at 65 °C for 12 h. Water and ethyl acetate were then added to dissolve the iron salts. The ethyl acetate layer was separated and the solution was solvent-switched to heptane and ethyl acetate to provide the desired product *N*-(1-(4-bromophenyl)vinyl)acetamide in 81% isolated yield from crystallization. In contrast to the Fe/Ac_2O/AcOH method where a filtration to remove excess iron powder is generally required, this method eliminates a tedious filtration operation and offers a simpler procedure for scale-up activities.

In conclusion, we have developed an efficient and practical method for the synthesis of *N*-acetyl α-arylenamides by using ferrous acetate as the reducing reagent. Compared to the traditional method with iron metal as the reducing reagent, the new method provides milder reaction conditions, simpler purification procedures, and higher yields for a variety of *N*-acetyl α-arylenamides. The mild reaction profile is amenable for scale-up activities, which would facilitate the industrial application of asymmetric hydrogenation of *N*-acetyl α-arylenamides for chiral amine syntheses.

Experimental Section

***N*-(1-(4′-Bromophenyl)vinyl)acetamide (2a).** To a 500 mL reactor equipped with a mechanical stirrer was charged 1-(4′-bromophenyl)ethanone oxime **1a** (20.00 g, 93.4 mmol) and THF (125 mL).[12] To the solution was further charged acetic anhydride (17.7 mL, 187 mmol, 2 equiv) and acetic acid (16.1 mL, 280 mmol, 3 equiv). The resulting mixture was purged with nitrogen for 20 min before iron(II) acetate (32.5 g, 187 mmol) was added. The mixture was then heated and stirred at 65 °C under nitrogen for 12 h and then cooled to room temperature (assay yield of **2a**: ~90%). Water (125 mL) was added to the reaction mixture followed by 10% $NaHCO_3$ solution (~50 mL) to adjust the pH to approximately 5.0. The mixture was then extracted with EtOAc (2 × 125 mL). The combined organic layers were washed sequentially with 10% $NaHCO_3$ solution (100 mL) and brine (100 mL). The mixture was distilled at reduced pressure and solvent-switched to EtOAc−heptane. Crystallization from EtOAc−heptane yielded the desired product **2a** (18.1 g, 81%) as a white crystalline solid. **2a**:[8a] mp 112−113 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.38 (s, 1H), 7.57 (d, J = 8.3 Hz, 2H), 7.28 (d, J = 8.3 Hz, 2H), 5.56 (s, 1H), 5.03 (s, 1H), 2.00 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.0, 140.6, 137.1, 131.1, 128.3, 121.3, 102.9, 23.6.

Supporting Information Available: General experimental methods and procedures, spectroscopic data, and ^{1}H NMR or ^{13}C NMR spectra of all *N*-acetyl enamide products. This material is available free of charge via the Internet at http://pubs.acs.org.

(12) A higher concentration (~0.75 M) was employed for a better volume efficiency.