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An Efficient Synthesis of Enamides from Ketones

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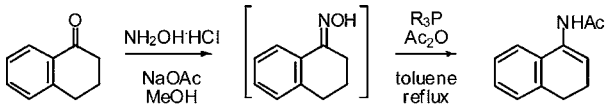
ABSTRACT



89% yield from ketone

A new synthesis of enamides from ketones is disclosed that involves a phosphine-mediated reductive acylation of oximes. The resulting enamides are isolated in good yields (up to 89%) and excellent purity, permitting a subsequent hydrogenation to access enantiopure acetamides at catalyst loadings practical for large-scale applications.

Chiral amines and their derivatives represent an important class of biologically active compounds and serve an important role as resolving agents, chiral auxiliaries, and ligands for enantioselective syntheses. Consequently, methods to synthesize amines in high enantiomeric purity are of considerable interest. In recent years, significant progress has been made to access chiral amines catalytically by the asymmetric hydrogenation of enamides, with considerable attention paid to the development of new metal−ligand complexes for this type of transformation.[1] As a result, a significant number of catalysts have become available for evaluation along these lines. Yet, despite the progress made in the area of asymmetric hydrogenation, methods to access the required enamides, especially those derived from benzylic ketones, are still limited.[2]

There are four common approaches for the preparation of enamides starting from the corresponding ketones: (1) direct condensation of amides with ketones[3] (usually acetamide), (2) reaction of N−H imines derived from ketones or nitriles with appropriate electrophiles[4] (such as acyl chlorides or anhydrides), (3) transition metal-catalyzed coupling of derivatives such as vinyl halides,[5] triflates,[2f,6a] or tosylates[6b] with amides, and (4) reductive acylation of ketoximes[2a,b] with iron metal in the presence of acyl donors (as above). This last approach is often the method of choice to prepare enamides at smaller scale. However, this method is not amenable to scale-up and adaptation in the pharmaceutical industry. Herein, we report a general method for the synthesis of enamides via ketoximes, which are easily accessible from the corresponding ketones.

In 1975, Barton et al.[7a] reported the conversion of ketoxime **1** into enamide **3** by refluxing with excess acetic anhydride and pyridine (Scheme 1). Under thermal conditions, ho-

(1) Reviews: (a) Blaser, H.-U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H.; Studer, M. *Adv. Synth. Catal.* **2003**, *345*, 103. (b) Van denBerg, M.; Haak, R. M.; Minnaard, A. J.; de Vries, A. H. M.; Vries, J. G.; Feringa, B. L. *Adv. Synth. Catal.* **2002**, *344*, 1003.

(2) (a) Burk, M. J.; Casy, G.; Johnson, N. B. *J. Org. Chem.* **1998**, *63*, 6084. (b) Zhu, G.; Casalnuovo, A. L.; Zhang, X. *J. Org. Chem.* **1998**, *63*, 8100. (c) Laso, N. M.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1996**, *37*, 1605. (d) Neugnot, B.; Cintrat, J.-C.; Rousseau, B. *Tetrahedron* **2004**, *60*, 3575. (e) Brice, J. L.; Meerdink, J. E.; Stahl, S. S. *Org. Lett.* **2004**, *6*, 1845. (f) Harrison, P.; Meek, G. *Tetrahedron Lett.* **2004**, *45*, 9277. (g) Willis, M. C.; Brace, G. N.; Holmes, I. P. *Synth* **2005**, 3229.

(3) (a) Tschaen, D. M.; Abramson, L.; Cai, D.; Desmond, R.; Dolling, U. H.; Frey, L.; Karady, S.; Shi, Y.-J.; Verhoeven, T. R. *J. Org. Chem.* **1995**, *60*, 4324. (b) Dupau, P.; Le Gendre, P.; Bruneau, C.; Dixneuf, P. H. *Synlett* **1999**, 1832.

(4) Savarin, C. G.; Boice, G. N.; Murray, J. A.; Corley, E.; DiMichele, L.; Hughes, D. *Org. Lett.* **2006**, *8*, 3903 and references cited therein.

(5) (a) Coleman, R. S.; Liu, P.-H. *Org. Lett.* **2004**, *6*, 577. (b) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667. (c) Shen, R.; Porco, J. A., Jr. *Org. Lett.* **2000**, *2*, 1333. (d) Ogawa, T.; Kiji, T.; Hayami, K.; Suzuki, H. *Chem. Lett.* **1991**, 1443.

(6) (a) Wallace, D. J.; Klauber, D. J.; Chen, C.-y.; Volante, R. P. *Org. Lett.* **2003**, *5*, 4749. (b) Klapars, A.; Campos, K. R.; Chen, C.-y.; Volante, R. P. *Org. Lett.* **2005**, *7*, 1185.

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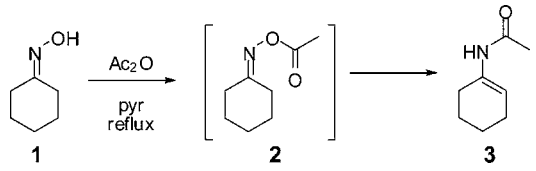
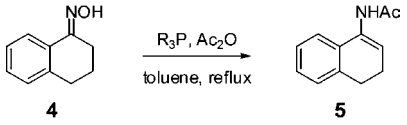
Scheme 1. Barton Protocol for Enamide Synthesis



molytic cleavage of the N−O bond of oxime acetate **2** was proposed as a plausible mechanism. We envisioned that the presence of an oxophilic reagent would enable this transformation to proceed under milder conditions. Indeed, when ketoxime **4** was treated with triphenylphosphine and acetic anhydride at stoichiometric levels in toluene at reflux, complete conversion to enamide **5** was observed.

A screening of phosphines revealed that trialkyl as well as triaryl phosphines were effective for this transformation (Table 1, entries 1−6). However, sterically hindered promot-

Table 1. Effect of Phosphine on the Rate of Enamide Formation[a]



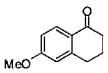
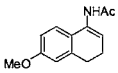
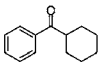
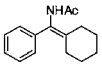
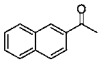
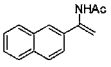
entry	phosphine	reaction time (h)	% yield[b]
1	Ph_3P	14	78
2	DPPE[c]	14	89
3	Et_3P	16	89
4	$(n\text{-}Bu)_3P$	16[d]	84
5	$(n\text{-}Oct)_3P$	14	72
6	$(Cy)_3P$	38	78
7	$(t\text{-}Bu)_3P$	38	trace
8	$(EtO)_3P$	38	trace

[a] Reaction conditions: phosphine (1.2 equiv), Ac_2O (1.2 equiv), toluene, reflux. [b] Isolated yield of enamide from ketoxime after chromatography. [c] 0.6 equiv of DPPE was used. [d] Reaction was run in *o*-xylene.

ers such as tri-*tert*-butylphosphine, and triethyl phosphite did not provide adequate conversion (Table 1, entries 7 and 8). The best results were obtained when triethylphosphine, tri-*n*-butylphosphine, or diphenylphosphinoethane (DPPE) was used (Table 1, entries 2−4). Despite its pyrophoric nature, triethylphosphine—which we utilize as a more easy-to-handle 50% solution in toluene—was our preferred reagent due to the water-soluble nature of the phosphine oxide byproduct. Optimization of the solvent revealed that toluene, *o*-xylene, and chlorobenzene were superior to 1,4-dioxane and acetonitrile. The initial reaction mixture generally consisted of both desired monoacetyl **5** and diacetyl products.[8] By simple treatment with 6 N NaOH in the presence of a catalytic amount of tetrabutylammonium hydroxide, the diacetyl species was converted into the desired product **5**.

With the optimal reaction conditions identified for substrate **4**, the scope of the reaction was investigated (Tables 2 and 3). In all cases, the oximes were prepared from the

Table 2. Enamides from Benzylic Ketones[a] via Oximes

entry	ketone	oxime[9] (% yield[b])	enamide reaction time (h)	enamide	enamide (% yield[c])
1		100	22		74
2		97	23		77
3		96	19		71
4		100	24		90
5		100	10		76
6		99	10		58
7		99	23		58
8		93	5		78

[a] Reaction conditions: (i) $NH_2OH{\cdot}HCl$ (1.2 equiv), NaOAc (1.2 equiv) solvent, reflux; (ii) Et_3P (1.2 equiv), Ac_2O (1.2 equiv), toluene, reflux. [b] Crude yield of ketoxime. [c] Unoptimized isolated yield of enamide from ketoxime after column chromatography.

corresponding ketones based on literature precedence[9] and used in the subsequent reaction without further purification.

Both benzylic and non-benzylic ketoximes may be easily converted to enamides via this method. Ketoximes derived from substituted and electron-rich α-tetralones gave good yields of enamide (Table 2, entries 1−3). Other alkylaryl ketoximes also provided reasonable yields of enamide (Table 2, entries 4−6). Even acyclic ketoximes such as a 1,1-disubstituted variant gave a moderate yield of enamide (Table 2, entry 7). Additionally, indanone-derived ketoxime gave 78% yield of enamide (Table 2, entry 8).

For the non-benzylic systems, ketoximes derived from 4-substituted cyclohexanones worked to a similar extent as

(7) (a) Boar, R. B.; McGhie, J. F.; Robinson, M.; Barton, D. H. R.; Horwell, D. C.; Stick, R. V. *Chem. Commun.* **1975**, 1237. (b) Baldwin, J. E.; Aldous, D. J.; O'Neil, I. A. *Tetrahedron Lett.* **1990**, *31*, 2051.

(8) Up to 8−10 area % of diacylated product by HPLC was observed.

(9) For standard protocol see: Bousquet, E. W.; Carothers, W. H.; McEwen, W. L. *Organic Synthesis*; Wiley and Sons: New York, 1943; Collect. Vol II, pp 313−315. For a specific procedure see: Homes, A. B.; Smith, A. L.; Williams, S. F.; Hughes, L. R.; Lidert, Z.; Swithenbank, C. *J. Org. Chem.* **1991**, *56*, 1393.

Table 3. Enamides from Non-Benzylic Ketones[a] via Oximes

entry	ketone	oxime[9] (% yield[b])	enamide reaction time (h)	enamide	enamide (% yield[c])
1		100	22		71
2		99	22		64
3		98	28		54[d,e]
4		100	22		54[d,e]

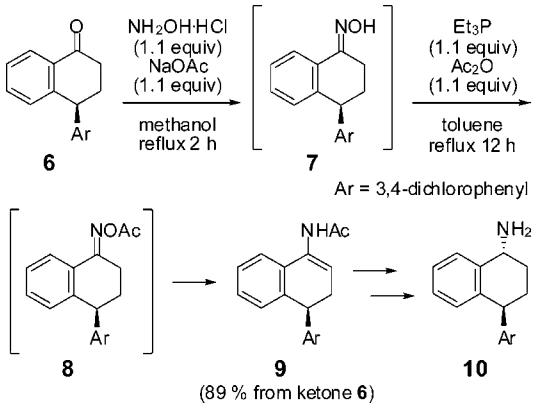
[a] Reaction conditions: (i) $NH_2OH{\cdot}HCl$ (1.2 equiv), NaOAc (1.2 equiv) solvent, reflux; (ii) Et_3P (1.2 equiv), Ac_2O (1.2 equiv), toluene, reflux. [b] Crude yield of ketoxime. [c] Unoptimized isolated yield of enamide from ketoxime after column chromatography. [d] Low yield is due to physical loss during isolation. [e] Only geometric isomer depicted was isolated.

the benzylic systems (Table 3, entries 1 and 2). Entries 3 and 4 demonstrate that further substitution can be tolerated in furnishing tetrasubstituted enamide products. In addition, entry 3 illustrates that the reaction conditions are compatible with sensitive nitrile functionality in the substrate.

In a related manner, the preparation of enamide **9** from ketone **6** has been successfully demonstrated at multikilogram scale[10] as an intermediate in a process for the manufacture of **10**, a drug candidate under development (Scheme 2). Importantly, **9** was isolated from this process by crystallization without further purification, and was suitable for large-scale hydrogenation with a practical catalyst loading.[11]

We are working toward broadening our understanding of the reaction mechanism. On the basis of LC-MS data, we believe that oxime acetate **8** is the reactive substrate for the formation of enamide **9**. Also, when pure oxime acetate[12] **8** was treated with triethylphosphine in the absence of acetic

Scheme 2. Preparation of Enamide **9** from Ketone **6**



anhydride, full conversion to enamide **9** occurred.[13] Conversely, when ketoxime **7** was treated with triethylphosphine, formation of the imine by deoxygenation of ketoxime **7** was not observed.

In summary, we have developed a new, proficient method to access enamides from ketones, especially difficult benzylic substrates. The methodology adds a valuable alternative to the currently limited number of methods for accessing enamides efficiently. It should allow for further exploitation of the plethora of catalysts and encourage use of asymmetric hydrogenation as a practical approach to access chiral amines.

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Supporting Information Available: Experimental details and physical characterization data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) The process was scaled up to manufacture over 75 kg of enamide **9** at pilot scale in 86% isolated yield from ketone **6** in 99.5 area % purity by HPLC.

(11) The enamide **9** was successfully hydrogenated at a substrate/catalyst ratio of 2000:1 at pilot scale.

(12) Oxime acetate **8** was made by combining oxime **7** with pyridine and acetic anhydride at 0 °C. The resulting slurry was quenched with ice water to yield a yellow solid, which was further treated with 10% HCl/EtOH to yield a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (m, 1H), 7.33 (m, 3H), 7.17 (m, 1H), 6.93 (m, 1H), 6.87 (m, 1H), 4.13 (m, 1H), 2.83 (m, 2H), 2.25 (s, 3H), 2.22 (m, 1H), 2.06 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 160.4, 143.6, 141.2, 132.7, 131.2, 130.7, 130.5, 130.3, 129.2, 129.1, 127.8, 127.5, 125.8, 43.9, 29.2, 22.7, 19.8.

(13) In a qualitative experiment, full conversion from **8** to **9** was observed. However, based on LC-MS, the reaction profile was inferior (81 area % purity) when compared to the standard conditions.