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Synthesis of α-Keto Amides by a Pyrrolidine/TEMPO-Mediated Oxidation of α-Keto Amines

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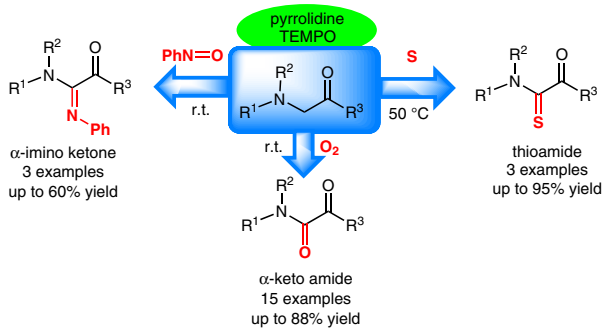

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Abstract A mild procedure has been developed for the synthesis of α-keto amides by α-oxidation of the corresponding α-keto amines mediated by pyrrolidine and TEMPO. The method can also be applied to the synthesis of α-keto thioamides and α-keto amidines.

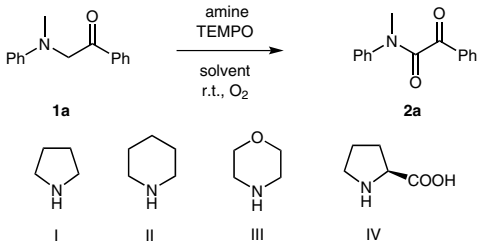
Key words oxidation, catalysis, amides, ketones, amines, thioamides

The α-keto amide is an important structural subunit that can be found in several natural products and pharmaceuticals having interesting biological activities. For example, the 19-membered cyclic peptides cyclotheonamides A and B are potent thrombin inhibitors that have been isolated from marine sponges, whereas isoquinoline-1,3,4-trione derivatives are prominent inhibitors of caspase-3, an attractive therapeutic target.[1] The α-keto amide moiety has also found use in several important transformations, such as the Pd-catalyzed intramolecular nucleophilic addition of aryl halides to give 3-hydroxyoxindoles or the stereoselective synthesis of α-silyloxy β-amino amides through a three-component coupling with [dimethyl(phenyl)silyl]lithium and a chiral butanesulfinylimine.[2] Consequently, several excellent transition-metal-catalyzed methods have been described for the preparation of α-keto amides from aryl halides,[3] α-carbonyl aldehydes,[4] terminal alkynes,[5] α-oxocarboxylic acids,[6] acetophenone,[7] or other starting materials.[8] To circumvent some of the drawbacks associated with the use of transition metals, such high cost, toxicity, and air or moisture sensitivity, recent efforts in this area have focused on developing transition-metal-free protocols. As a result, interesting alternative methods have been developed that use iodine, hypervalent iodine reagents,[9] DMSO,[10] or other oxidants.[11] However, all these metal-free protocols are impractical because they require toxic oxidants or harsh reaction conditions, they involve complex procedures for the preparation of the required starting materials, or they give a limited range of the desired products. Therefore, the development of an efficient and convenient method for the synthesis α-keto amides from readily prepared starting materials without the use of toxic reagents is a highly desirable goal. The asymmetric organocatalytic oxidation of aldehydes and ketones via an enamine intermediate to give the corresponding α-functionalized carbonyl derivatives has proven to be a highly efficient process.[12] In contrast, the corresponding enamine-mediated oxidation of aldehydes and ketones to give the corresponding α-carbonyl derivatives has received considerable less attention, the only one example being an autoxidation of an enamine derived from an α,β-unsaturated ketone to give the corresponding 1,4-dione.[13] Inspired by this observation, we became interested in the possibility of preparing α-keto amides through an enamine-mediated oxidation of readily available α-keto amines, and here we describe our preliminary results in detail. The method is also applicable to the synthesis of α-keto thioamides or α-keto amidines.[14,15]

Amino ketone **1a** was chosen as the model substrate, and selected results from our optimization study are collected in Table 1. Treatment of **1a** with pyrrolidine (5 equiv.) in CH_2Cl_2 under air resulted in the formation of α-keto amide **2a** in low yield (Table 1, entry 1); this, however, confirmed our original hypothesis. Repeating this reaction under a balloon pressure of O_2 resulted in a greatly improved conversion, and **2a** was isolated in 63% yield (entry 2). TEMPO has been used as an oxygen source for asymmetric α-oxyamination of aldehydes mediated by secondary amines.[16] When the oxidation of **1a** was performed in the presence of pyrrolidine, TEMPO (1 equiv), and O_2, there was no significant effect on the yield of **2a** (entries 3), but the reaction rate increased significantly (entries 2 and 3). The same reaction repeated under a N_2 atmosphere gave **2a** in

only 3% yield (entry 4), indicating that TEMPO is not the actual oxidant in this reaction. Decreasing the amount of TEMPO was beneficial and the optimal result, in terms of both the yield and reaction rate, was obtained by using 0.1 equivalents of the additive (entries 5–7). Decreasing the amount of pyrrolidine was, however, detrimental and resulted in a lower yield of **2a** (entries 7–10). Indeed, when the reaction was performed without any added pyrrolidine, no product was obtained, suggesting that the α-oxidation proceeds through an enamine intermediate. The effect of using other secondary amines to promote the reaction was then investigated, but none of the alternatives investigated was superior to pyrrolidine (entries 7 and 11–13). However, the effect of the solvent on the yield of **2a** was significant (entries 7, 14–19). Whereas most solvents gave lower or comparable yields to CH_2Cl_2, the use of MeCN gave α-keto amide **2a** in 83% yield, and this also defines the current best conditions for this reaction.

Table 1 Optimizing the Reaction Conditions[a]



Entry	Solvent	Amine (equiv)	TEMPO (equiv)	Yield[b] (%)
1[c]	CH_2Cl_2	I (5)	0	23
2	CH_2Cl_2	I (5)	0	63 (11)[d]
3	CH_2Cl_2	I (5)	1	66 (52)[d]
4[e]	CH_2Cl_2	I (5)	1	3
5	CH_2Cl_2	I (5)	0.7	62
6	CH_2Cl_2	I (5)	0.4	68
7	CH_2Cl_2	I (5)	0.1	69
8	CH_2Cl_2	I (3)	0.1	45
9	CH_2Cl_2	I (1)	0.1	13
10	CH_2Cl_2	–	0.1	0
11	CH_2Cl_2	II (5)	0.1	43
12	CH_2Cl_2	III (5)	0.1	12
13	CH_2Cl_2	IV (5)	0.1	NR
14	toluene	I (5)	0.1	45
15	THF	I (5)	0.1	46
16	DMSO	I (5)	0.1	66
17	1,4-dioxane	I (5)	0.1	44
18	MeCN	I (5)	0.1	83
19	pyrrolidine[f]	–	0.1	64

[a] Reaction conditions: **1a** (0.3 mmol), amine, TEMPO, stirring, O_2 (balloon pressure), solvent (1 mL), r.t., 20 h.
[b] Yields determined by GC analysis with naphthalene as an internal standard.
[c] Sealed tube under air, 20 h.
[d] Yield by GC analysis after 1.5 h.
[e] The reaction was performed under N_2 with deoxygenated solvent.
[f] Pyrrolidine (1 mL) was used as the solvent.

The scope of the pyrrolidine-mediated TEMPO-catalyzed oxidation of α-keto amines was then investigated (Scheme 1).[17,18] Various *N*-alkyl groups were well tolerated in the oxidation reaction, giving the corresponding α-keto amides **2a–c** in high yields. On changing from aryl dialkyl amines to trialkyl amines, the oxidation became significantly slower, and the reaction temperature had to be raised to 50 °C to achieve an acceptable conversion to products **2d** and **2f**. It appears that the reaction is sensitive to substituents in the benzoyl moiety, as an electron-withdrawing group resulted in a decreased yield of **2g**, whereas the presence of a *p*-bromo or *p*-methoxy substituent gave the corresponding products **2h** and **2i** in 72 and 75% yield, respectively. Substrate **1j** containing a cinnamoyl moiety gave **2j** in 43% yield, whereas the corresponding methyl ketone failed to give any of the desired oxidation product **2m**. Next, the effect of altering the substituent on the aniline moiety was investigated and it was found that electron-donating or weakly electron-withdrawing *para*-substituents were tolerated (**2k**, **2l**), whereas the *para*-nitro derivative **1n** gave only a trace of **2n**. Finally, attempts to oxidize indole derivative **1o** under the standard reaction conditions failed to give the desired product **2o**.

Encouraged by these results, we extended our investigation to include nitrosobenzene as the oxidant. As shown in Scheme 2, oxidation of **1a**, **1o**, and **1h** by using nitrosobenzene afforded amidines **2p–r** in 41, 60, and 49% yield, respectively.[15] When elemental sulfur was used as the oxidant, thioamides **2s–u** were obtained in high yields.

In conclusion, we have developed a mild procedure for the oxidation of α-keto amines to give the corresponding α-keto amides, α-thioamides, or α-keto amidines. It is believed that the reaction proceeds through an enamine intermediate that is subsequently oxidized by TEMPO or O_2.

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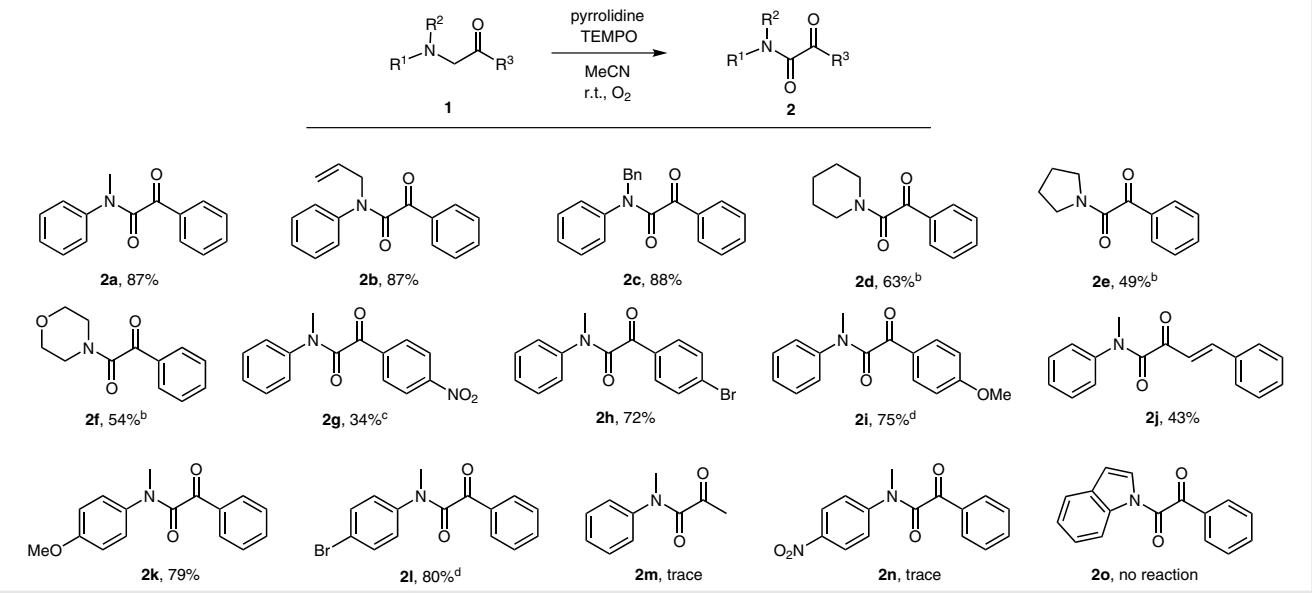
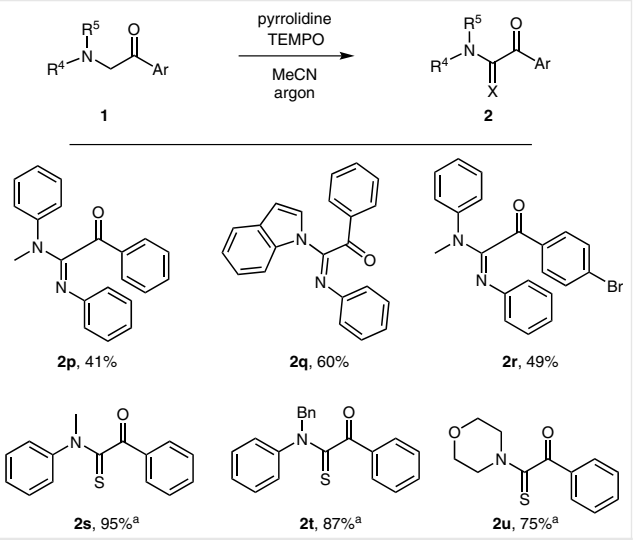
Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1562541.



Scheme 1 Oxidation of α-keto amines **1** to give α-keto amides **2**. *Reaction conditions:* **1** (0.3 mmol), pyrrolidine (1.5 mmol, 123 μL), TEMPO (0.03 mmol, 4.7 mg), MeCN (1 mL), under O_2, r.t., 20 h. [a] Stirred at 50 °C for 20 h. [b] Stirred at –25 °C for 20 h. [c] Stirred at r.t. for 72 h.



Scheme 2 Conversion of α-keto amines **1** into amidines or thioamides. *Reaction conditions:* **1** (0.3 mmol), nitrosobenzene (0.6 mmol, 64 mg), pyrrolidine (0.3 mmol, 25 μL), TEMPO (0.03 mmol, 4.7 mg), MeCN (1 mL), under argon, r.t., 20 h. [a] A mixture of **1a** (0.3 mmol), sulfur (10 equiv), pyrrolidine (1.5 mmol, 123 μL) and TEMPO (0.03 mmol, 4.7 mg) in MeCN (1 mL) was stirred under argon at 50 °C for 20 h.

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(17) ***N*-(4-Methoxyphenyl)-*N*-methyl-2-oxo-2-phenylacetamide (2k); Typical Procedure**
Pyrrolidine (123 μL, 1.5 mmol) was added to a solution of amino ketone **1k** (76.5 mg, 0.3 mmol) and TEMPO (4.7 mg, 0.03 mmol) in MeCN (1 mL) under O_2 (balloon pressure). The mixture was then stirred at r.t. for 20 h (TLC monitoring) then was concentrated. The residue was purified by column chromatography [silica gel, heptane–EtOAc (5:1)] to give a slightly yellow oil; yield: 63.4 mg (79%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88–7.77 (m, 2 H), 7.58–7.49 (m, 1 H), 7.45–7.35 (m, 2 H), 7.08–7.00 (m, 2 H), 6.74–6.63 (m, 2 H), 3.68 (s, 3 H), 3.42 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.1, 167.1, 158.9, 134.1, 133.5, 133.4, 129.2, 128.6, 128.3, 114.5, 55.2, 36.3; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{16}H_{16}NO_3$: 270.1130; found: 270.1128.

(18) **(3*E*)-*N*-Methyl-2-oxo-*N*,4-diphenylbut-3-enamide (2j)**
Slightly yellow oil; yield: 34.6 mg (43%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (d, *J* = 16.3 Hz, 1 H), 7.56–7.49 (m, 2 H), 7.47–7.37 (m, 3 H), 7.36–7.26 (m, 3 H), 7.23–7.16 (m, 2 H), 6.77 (d, *J* = 16.3 Hz, 1 H), 3.45 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.1, 167.0, 147.5, 141.7, 134.0, 131.3, 129.6, 129.0, 128.7, 128.1, 126.5, 123.4, 36.5; HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{17}H_{16}NO_2$: 266.1181; found: 266.1179.