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Iodine-Mediated Oxidative Dehydrogenation of β-Acylamino Ketones for the Highly Stereoselective Synthesis of (*Z*)-β-Ketoenamides

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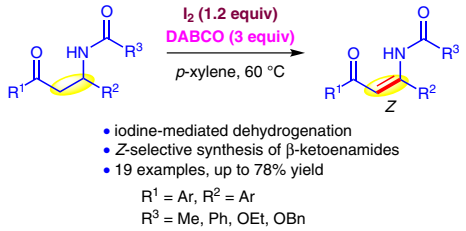

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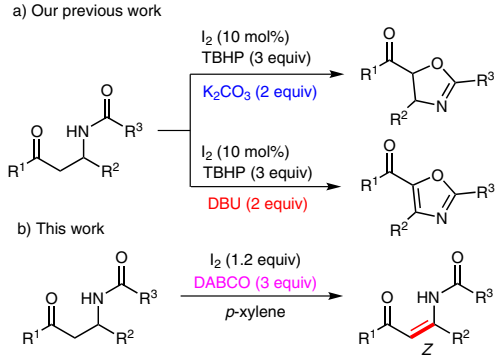
Abstract An iodine-mediated oxidative dehydrogenation of β-acylamino ketones has been developed for the synthesis of β-ketoenamides in moderate to good yields. Only *Z*-isomers are accessed due to the intramolecular H-bonding interaction in the HI-elimination step.

Key words molecular iodine, dehydrogenation, β-acylamino ketones, β-ketoenamide, *Z*-selectivity

β-Ketoenamides derivatives as versatile building blocks in organic synthesis have been used widely for the preparation of a variety of chiral 1,3-amino alcohols,[1] natural products,[2] and heterocyclic derivatives, including oxazoles,[3a] pyrimidin-2-ones,[3b] pyrimidines,[3c] pyridines,[3d,f] pyrroles,[3g] etc.[3f] In view of their importance, considerable efforts have been made for their syntheses. Conventional methods to access this class of compounds include N-acylation of β-ketoenamines,[4] condensation of 1,3-diketones with amides,[1] NaOH-catalyzed rearrangement of propargylic hydroxylamines,[3c] Brønsted acid catalyzed Meyer–Schuster rearrangement of hemiaminals,[5] three-component reaction of lithiated alkoxyallenes with nitriles and carboxylic acids,[3f,6] transition-metal-catalyzed amidation of α,β-unsaturated carbonyl compounds,[7] and rearrangement of β-tetrazolyl-*trans*-benzalacetophenones.[8] Nevertheless, these methods often required rigorous conditions, such as exclusion of moisture and air, high temperature, and utilization of strong bases or transition metals. More importantly, stereocontrol of the double bond constitutes another issue to be addressed, particularly in the synthesis of thermodynamically disfavored (*Z*)-β-ketoenamides to meet special requirements, such as total synthesis of natural products,[9a] asymmetric synthesis of chiral 4*H*-1,3-oxazines,[9b] and preparation of pyrimidines.[3c] However, the successful examples on the stereoselective synthesis of the *Z*-isomer without the use of transition-metal catalysts are rare.[10] Therefore, from an economical and an environmental point of view, it is highly desirable to develop a mild and metal-free method for the stereoselective synthesis of (*Z*)-β-ketoenamides from readily available starting materials.

Recently, molecular iodine has served as an eco-friendly reagent to achieve numerous oxidative transformations, such as aromatization,[11] carbon–carbon (C–C) bond,[12] and carbon–heteroatom bond formation.[13] During our studies on I_2-catalyzed C–O bond formation for the synthesis of oxazolines and oxazoles (Scheme 1, a),[14a] we found that when the reaction base was switched to 1,4-diazabicyclo[2.2.2]octane (DABCO), the stereoselective dehydrogenation of β-acylamino ketones, readily available compounds derived from simple ketones, nitriles, and aldehydes,[15] proceeded to provide β-ketoenamides as single *Z*-isomers mediated by molecular iodine (Scheme 1, b). These significant differences might be attributable to the distinctive properties of DABCO (e.g., pK_a value, nucleophilicity, or sterical hindrance) differing from DBU and K_2CO_3. As our continuous studies on iodine-mediated reactions,[14] we herein wish to report these unexpected results on the stereoselective oxidative dehydrogenation reaction for the synthesis of (*Z*)-β-ketoenamides.

Initially, β-acylamino ketone **1a** was chosen as the model substrate with the use of DABCO (3 equiv) as the base and molecular iodine (1.2 equiv) as the oxidant to examine the feasibility of oxidative dehydrogenation at 60 °C in toluene. To our delight, the desired product **2a** was isolated in 52% yield, and only the *Z*-isomer was obtained in this transfor-

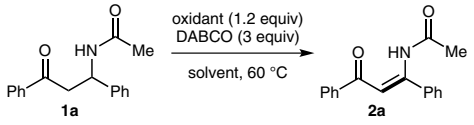


Scheme 1 Different transformations of β-acylamino ketones with the use of I_2 and bases

mation (Table 1, entry 1). A control experiment showed that no reaction occurred in the absence of iodine (Table 1, entry 2). It was observed that solvent polarity had a significant effect on the reaction efficiency (Table 1, entries 3–11). For instance, the reaction in polar solvents such as nitrile, acetate, methanol, and acetic acid gave inferior yields of (*Z*)-β-ketoenamide **2a** (Table 1, entries 3–6). When ether solvents like THF or DME were used as the solvent, oxazoline and oxazole derivatives were isolated as the major products.[16] It was observed that benzene and benzene derivatives such as chlorobenzene and *p*-xylene facilitated this transformation, and the best result (60% yield) was obtained when *p*-xylene was used as the solvent (Table 1, entries 9–11). A simple survey of commonly used oxidants indicated that molecular iodine was still the best of choice (Table 1, entries 12–14). For example, NIS decreased the yield of **2a** to 38%, while NBS and PIDA had much lower efficiency and delivered the yield of **2a** in 19% and 10%, respectively.

With the optimal reaction conditions in hand (Table 1, entry 11), we investigated the generality of the present stereoselective synthesis of (*Z*)-β-ketoamides.[17] As shown in Scheme 2, various substrates bearing electron-withdrawing or electron-donating groups on the aroyl moiety were well tolerated to give the corresponding products **2b**–**e** in moderate to good yields (51–69%). Other aromatic systems such as naphthyl, furyl, and thienyl groups were also proved to be suitable for this transformation (**2f**–**h**). Furthermore, we also varied different substituents on the aryl rings of β-acetylamino ketones. For example, when the aryl ring was replaced by the naphthyl ring, the desired product **2i** was obtained in 64% yield. It was noted that there were obvious steric and electronic effects for the substituents on the aryl moiety. For example, strong electron-withdrawing substituents (such as the nitro group) on the aryl ring resulted in better yields than that containing electron-donating groups (**2o**,**p** vs. **2j**,**k**); the substrates bearing *ortho*-substituted groups led to the lower yield of (*Z*)-β-ketoenamides due to

Table 1 Dehydrogenation of **1a**: Optimization of Reaction Conditions[a]

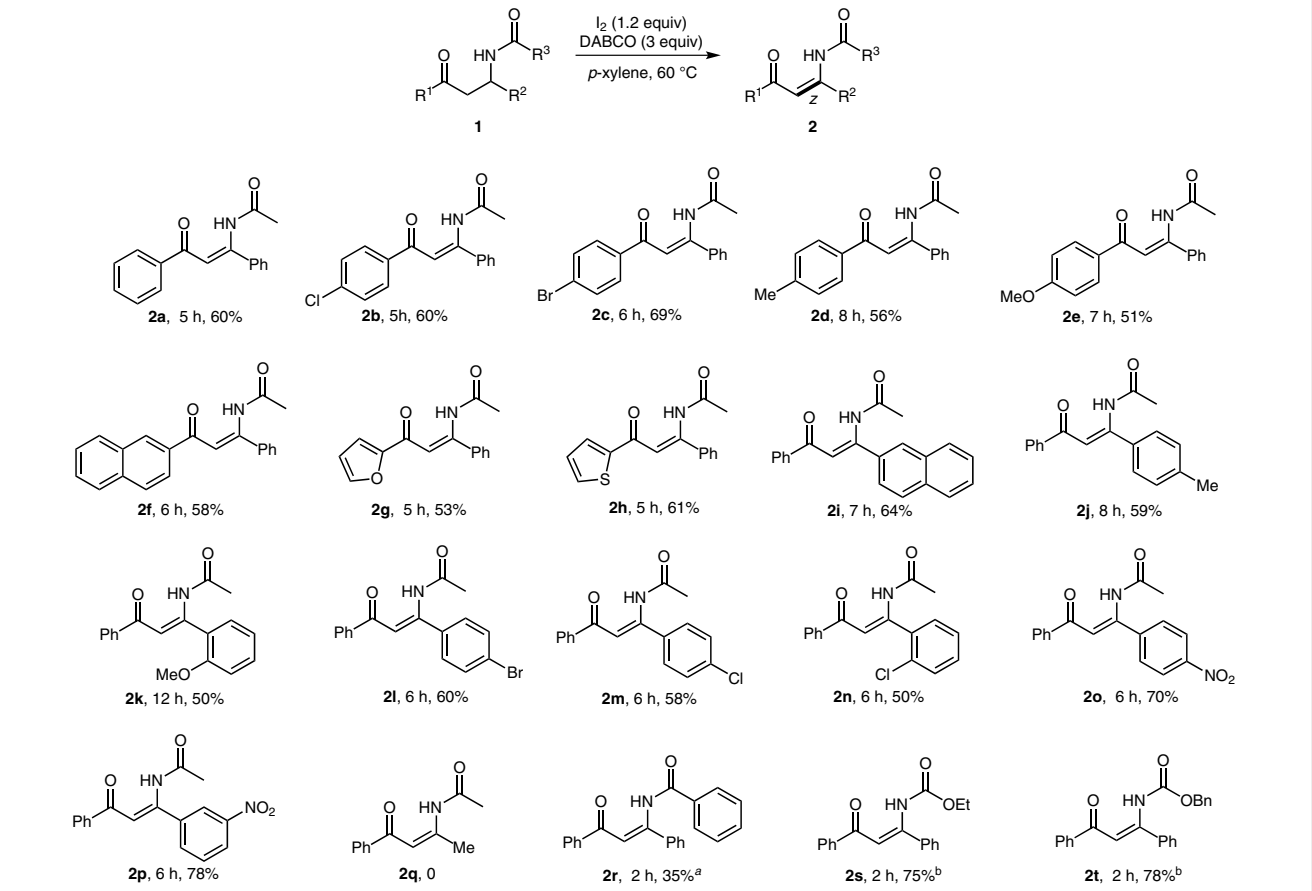


Entry	Oxidant	Solvent	Yield (%)[b]
1	I_2	toluene	52
2	–	toluene	–[c]
3	I_2	MeCN	12
4	I_2	MeOH	12
5	I_2	AcOH	–[c]
6	I_2	EtOAc	47
7	I_2	THF	48
8	I_2	DME	25
9	I_2	chlorobenzene	48
10	I_2	benzene	58
11	I_2	*p*-xylene	60
12	NIS	*p*-xylene	38
13	NBS	*p*-xylene	19
14	PIDA	*p*-xylene	10

[a] Reaction conditions: 0.2 mmol of **1a**, 0.24 mmol of oxidant, 0.6 mmol of DABCO, in 2 mL of solvent at 60 °C for 4–6 h.
[b] Isolated yield and only *Z*-isomer was observed.
[c] Not detected.

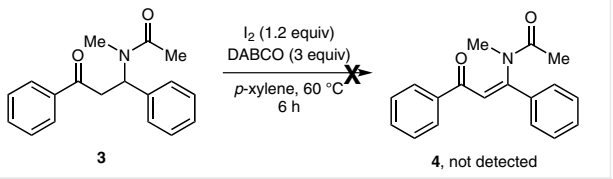
the steric hindrance (**2m** vs. **2n**). However, when the phenyl ring was replaced by a methyl group, no desired β-ketoenamide **2q** was detected. In addition, different N-protecting groups of substrates were also tested for this dehydrogenation reaction: for *N*-benzoyl substrate **1r**, the dehydrogenated product **2q** was only afforded in 35% yield, while 2,4-diphenyl-5-benzoyl oxazoline generated via C–O bond formation was isolated as the major product; two β-ketocarboxamides were also examined for this transformation and resulted in high yields of the desired products (**2s** and **2t**), which could be readily transformed to polysubstituted pyrimidines catalyzed by bases.[3c]

To understand the mechanism, a control experiment was subsequently performed. *N*-Methyl-β-acetylamino ketone **3** was prepared and tried for the present dehydrogenation reaction, while the desired product **4** was not detected (Scheme 3). This experiment indicated that the N–H bond on the amide group was essential for the success of dehydrogenation. Based on the experimental result and literature reports,[18] a plausible mechanism is proposed in Scheme 4. After the deprotonation of β-acetylamino ketone **1a** in the presence of DABCO, the nitrogen of the acetylamino group is firstly iodinated to form the N–I intermediate **B**, which leads to the intramolecular α-iodination of the carbonyl group to produce intermediate **C**. Since the intramo-



Scheme 2 Substrate scope for stereoselective dehydrogenation. Unless otherwise indicated, reactions were carried out with 0.2 mmol of **1a**, 0.24 mmol of I_2, 0.6 mmol of DABCO, in 2 mL of *p*-xylene at 60 °C; the isolated yields and reaction times are shown. [a] 2,4-Diphenyl-5-benzoyl oxazoline was isolated in 60% yield. [b] In 2 mL of THF.

lecular hydrogen bond fixes a predominant configuration of intermediate **C**,[7] elimination of HI promoted by DABCO would give the desired (*Z*)-β-ketoenamide **2a**.



Scheme 3 Control experiment for dehydrogenation

In summary, a mild and metal-free method for the dehydrogenation of β-acylamino ketones mediated by molecular iodine has been developed. In each case, only the (*Z*)-β-ketoenamide was obtained, and the high stereoselectivity of dehydrogenation was mainly attributed to the intramolecular H-bond interaction in the HI-elimination step. The ready availability of starting materials, broad substrate scope, high stereoselectivity, and mild reaction conditions make the present oxidative dehydrogenation attractive as a synthetically feasible approach for the preparation of (*Z*)-β-ketoenamides.

Acknowledgment

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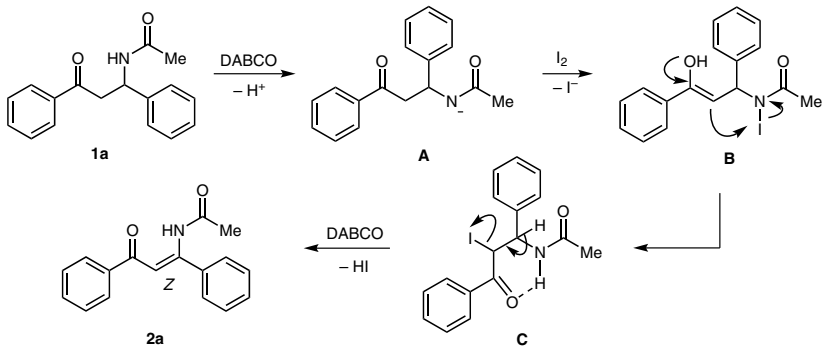
Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561582.



Scheme 4 Proposed mechanism for stereoslective dehydrogenation

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(16) For the corresponding structures of oxazoline and oxazole derivatives, see ref. 13a. For the screening of bases and results of catalytic reaction studies, see Supporting Information.

(17) **General Procedure for Iodine-Mediated Oxidative Dehydrogenation**

A 10 mL oven-dried reaction vessel was charged with **1a** (53 mg, 0.2 mmol), DABCO (67 mg, 0.6 mmol), and iodine (61 mg, 0.24 mmol) in *p*-xylene (2.0 mL). The resulting solution was stirred at 60 °C for 5 h. After the reaction was complete, sat. $Na_2S_2O_3$ aq solution (10 mL) was added to quench the reaction, and the mixture was extracted by EtOAc (3 × 10 mL). The organic layer was separated and dried over anhydrous Na_2SO_4. After the removal of the solvent in vacuo, the residue was purified by flash column chromatography with PE–EtOAc (9:1) to give **2a**.

(*Z*)-*N*-(3-Oxo-1,3-diphenylprop-1-en-1-yl)acetamide (2a)
Yield 27 mg (60%); reaction time 5 h; white solid; mp 60–62 °C; R_f = 0.35 (PE–EtOAc = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.27 (s, 1 H), 7.98–7.95 (m, 2 H), 7.57 (tt, 1 H, *J* = 4.8, 0.8 Hz), 7.50–7.46 (m, 4 H), 7.45–7.40 (m, 3 H), 6.33 (s, 1 H), 2.25 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.7, 168.9, 156.3, 138.6, 136.2, 132.7, 129.8, 128.7, 128.1, 127.8, 127.4, 104.8, 25.1. ESI-HRMS: *m/z* calcd for $C_{17}H_{16}NO_2$ $[M + H]^+$: 266.1176; found: 266.1179.

(18) **(*Z*)-Ethyl (3-Oxo-1,3-diphenylprop-1-en-1-yl)carbamate (2s)**
Yield 44 mg (75%); reaction time 2 h; yellow oil; R_f = 0.51 (PE–EtOAc = 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.95 (s, 1 H), 7.97 (d, 2 H, *J* = 7.2 Hz), 7.57–7.41 (m, 8 H), 6.28 (s, 1 H), 4.13 (q, 2 H, *J* = 7.2 Hz), 1.26 (t, 3 H, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.2, 157.0, 152.9, 138.7, 136.0, 132.5, 129.8, 128.6, 128.0, 127.8, 127.5, 103.5, 61.9, 14.2. ESI-HRMS: *m/z* calcd for $C_{18}H_{17}NO_3Na$ $[M + Na]^+$: 318.1101; found: 318.1104.

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