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NIS-Catalyzed Reactions: Amidation of Acetophenones and Oxidative Amination of Propiophenones

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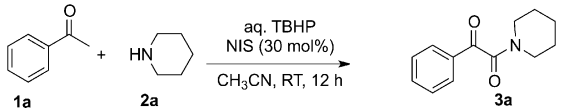
α-Ketoamides are important intermediates in organic synthesis that are present in a variety of natural products and pharmaceutically active compounds.[1] Traditionally, α-ketoamides are synthesized by the amidation of α-ketoacids[2] or cyanoketones,[3] oxidation of amides by metal oxidants, such as SeO_2, RuO_2, or CAN, and by photochemical reactions of amides.[4] Double carbonylation of aryl halides with carbon monoxide in the presence of Pd or Cu complexes is an alternate method for the synthesis of α-ketoamides.[5] Recently, Jiao and co-workers reported the synthesis of α- ketoamides by reacting phenyl acetylenes or aryl acetaldehydes by using a copper catalyst.[6,7] In addition to these reports, Ji and co-workers reported the synthesis of ketoamides by using a CuI/oxygen system with acetophenone derivatives.[8] However, the use of toxic metal oxidants, harsh reaction conditions, heavy metal impurities in drug intermediates, and the limited availability of starting materials restricts the utility of these methods. In view of the increased attention on designing environmentally benign and metal-free methods for oxidative transformations to form C–N bonds,[9] and in continuation of our research in this area, we herein present a mild and efficient conversion of acetophenones to α-ketoamides by using *N*-iodosuccinamide (NIS) as a catalyst and *tert*-butylhydroperoxide (TBHP) as a terminal oxidant at room temperature.

Optimization studies began with the reaction of acetophenone and piperidine. As can be seen from the results in Table 1, the reaction of acetophenone (**1a**) with piperidine (**2a**) in the presence of iodine and oxygen failed to give the expected product **3a** (Entry 1, Table 1). The use of a terminal oxidant, such as hydrogen peroxide, with iodine showed the formation of product ketoamide **3a** in low yield (10%; Entry 2, Table 1). The use of tetrabutylammonium iodide (TBAI) or NIS with hydrogen peroxide, or NIS with cumene hydrogen peroxide, resulted in the formation of product **3a** in 10% yield (Entries 3–5, Table 1). The reaction of **1a** with sodium iodide (10 mol%) as an iodine source and TBHP (3 equiv) as the terminal oxidant resulted in a significant improvement, forming **3a** in 75% yield (Entry 6, Table 1). Increasing the amount of sodium iodide (to 20 or 30 mol%) resulted in an enhancement of the yield of **3a** to 85 and 90%, respectively (Entries 7 and 8, Table 1).[11] Furthermore, it was noticed that changing the iodine source to NIS increased the formation of product **3a** to a 92% yield (Entry 9, Table 1). Additional screening experiments revealed that lowering the amount of NIS and TBHP was not useful in improving the yield of the product **3a** (Entries 10 and 11, Table 1). Decreasing the amount of amine or changing the solvent to toluene or THF resulted in the formation of **3a** in lower yields (Entries 12–15, Table 1). The reaction did not proceed in the absence of NIS or TBHP (Entries 16 and 17, Table 1), indicating the necessity of an iodine source as well as TBHP. It was found that the combination of *N*-bromosuccinimide (NBS) and TBHP was not useful for this reaction (Entry 18, Table 1). Therefore, we carried out fur-

Table 1. Optimization studies for the amidation of acetophenone.



1a 2a 3a

Entry	Iodine source ([mol%])	Oxidant ([equiv])	Yield [%][a]
1	I_2 (30)	oxygen	nr
2	I_2 (30)	H_2O_2	<10
3	TBAI (30)	H_2O_2	<10
4	NIS (30)	H_2O_2	<10
5	NIS (30)	CHP	15
6	NaI (10)	aq. TBHP (3)	75
7	NaI (20)	aq. TBHP (3)	85
8	NaI (30)	aq. TBHP (3)	90
9	NIS (30)	aq. TBHP (3)	92
10	NIS (30)	aq. TBHP (1)	60
11	NIS (20)	aq. TBHP (3)	75
12[b]	NIS (30)	aq. TBHP (3)	61
13[c]	NIS (30)	aq. TBHP (3)	70
14[d]	NIS (30)	aq. TBHP (3)	60
15[e]	NIS (30)	aq. TBHP (3)	62
16	–	aq. TBHP (3)	nr
17	NIS (30)	–	nr
18	NBS (30)	aq. TBHP (3)	nr

[a] Yield of isolated product. [b] One equivalent of amine was used. [c] Two equivalents of amine were used. [d] Toluene was used as the solvent. [e] THF was used as the solvent. CHP = cumene hydroperoxide, nr = no reaction.

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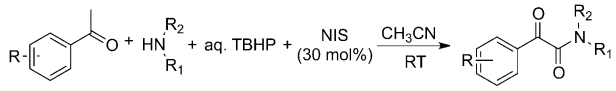
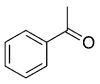
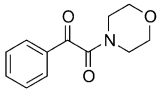
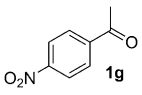
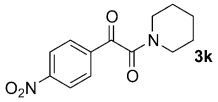
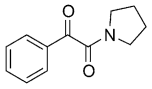
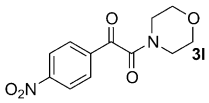
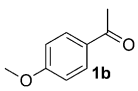
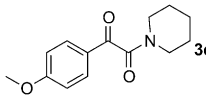
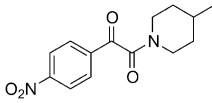
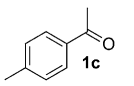
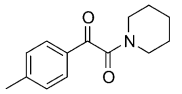
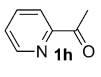
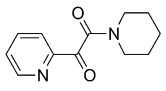
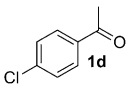
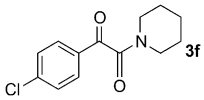
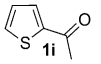
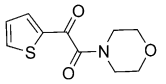
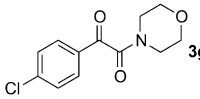
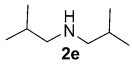
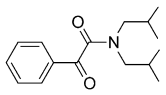
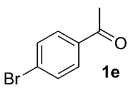
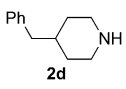
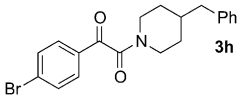
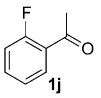
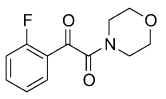
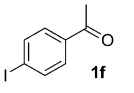
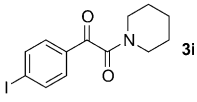
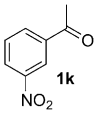
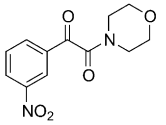
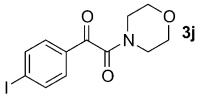
ther reactions by using acetophenone (1 mmol), amine (3 mmol), NIS (30 mol%), and TBHP (3 equiv) in acetonitrile (0.5 mL) at room temperature.

Under the optimized reaction conditions, a variety of amines were reacted with acetophenone and its derivatives to provide the corresponding ketoamides in good to excellent yields (Table 2). Acetophenones with electron-donating and electron-withdrawing groups provided the corresponding ketoamides in good yields. Acetophenone (**1a**) reacted well with morpholine (**2b**) and pyrrolidine (**2c**) to form the corresponding ketoamides **3b** and **3c** in 90 and 70% respectively (Entries 1–2, Table 2). 4-Methoxyacetophenone (**1b**) underwent a smooth reaction with **2a** under the standard reaction conditions to give the corresponding ketoamide **3d** in moderate yield (50%; Entry 3, Table 2). 4-Methylacetophenone (**1c**) reacted well with piperidine (**2a**) in the presence of NIS and TBHP to form the corresponding ketoamide **3e** in good yield (Entry 4, Table 2). 4-Chloroacetophenone (**1d**) reacted well with piperidine (**2a**) and morpholine (**2b**) in the presence of NIS and TBHP to form the corresponding ketoamides **3f** and **3g** in good yields (74 and 75%, respectively; Entries 5 and 6, Table 2). On reaction with a variety of amines, such as 4-benzylpiperidine (**2d**) and **2a** and **2b**, acetophenone derivatives containing bromo or iodo substituents at the *para* position (e.g., **1e** and **1f**) gave the corresponding products **3h**, **3i**, and **3j** in good yields (Entries 7–9, Table 2). Acetophenone derivatives that contain electron-withdrawing groups, such as a nitro group at the *para* position (**1g**), reacted satisfactorily with piperidine (**2a**), morpholine (**2b**), and 4-benzylpiperidine (**2d**) to provide the corresponding products **3k**, **3l**, and **3m** in good yields (70, 72, and 61% respectively; Entries 10–12, Table 2). Heterocyclic ketones such as 2-acetylpyridine (**1h**) and 2-acetylthiophene (**1i**) reacted well with piperidine (**2a**)

Table 2. Amidation of aromatic ketones.[a]

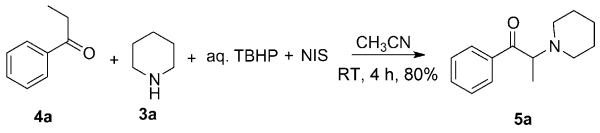


Entry	Ketone	Amine	Time [h]	Product	Yield [%][b]	Entry	Ketone	Amine	Time [h]	Product	Yield [%][b]
1			12		90	10		**2a**	10		70
2	**1a**		12		70	11	**1g**	**2b**	10		72
3		**2a**	24		50	12	**1g**	**2d**	10		61
4		**2a**	24		70	13		**2a**	10		65
5		**2a**	14		74	14		**2b**	24		60
6	**1d**	**2b**	14		75	15	**1a**		12		68
7			16		62	16			12		70
8		2a	16		65	17			12		74
9	**1f**	**2b**	16		68						

[a] Reaction conditions: acetophenone derivative (1 mmol), amine (3 mmol), aq. TBHP (70%, 3 mmol, 0.412 mL), NIS (0.3 mmol, 67.5 mg), CH_3CN (0.5 mL), RT. [b] Yield of isolated product.

and morpholine (**2b**) to form the corresponding products **3n** and **3o** in good yields (Entries 13–14, Table 2). Furthermore, the compatibility of acyclic amines for use in this reaction was established by the reaction of *N,N*-diisobutylamine (**2j**) with acetophenone (**1a**). As expected, the corresponding ketoamide **3p** was obtained in moderate yield (68%; Entry 15, Table 2). The general scope of this reaction was further explored by reacting 2-fluroacetophenone (**1j**) and 3-nitroacetophenone (**1k**) with morpholine (**2b**) to obtain the corresponding ketoamides **3q** and **3r** in good yields (Entries 16 and 17, Table 2).

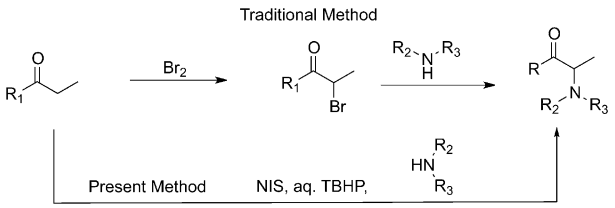
Having found suitable conditions for the satisfactory reaction of acetophenone and its derivatives with secondary amines, we focused our attention in investigating the reaction of propiophenones with secondary amines under these conditions. We thought that it would be interesting to see the outcome of this reaction because there is no possibility of the formation of an α-ketoamide in the reaction of propiophenones with secondary amines. Under the established reaction conditions, propiophenone (**4a**) underwent a cross dehydrogenative coupling (CDC) reaction at the α-position of propiophenone **4a** to furnish 2-amino-1-phenylpropan-1-one derivative **5a** in good yield (80%; Scheme 1). These de-



Scheme 1. Cross dehydrogenative coupling reaction with propiophenone.

rivatives are ubiquitous scaffolds that are present in a wide variety of therapeutic agents. Some of these compounds are used in the treatment of depression, smoking cessation, as monoamine-uptake inhibitors,[12] and as drugs for cancer.[13] They are photoinitiators[14] and precursors to β-aminoalcohols, such as pseudoephedrine analogues.[15] 2-Aminoacetophenone analogues are also important intermediates for the formation of several heterocyclic compounds[16] and are active moieties in several important drugs, such as ifenprodil, bupropion, and amfepramone, and different derivatives could be used as potential pharmacotherapies for cocaine addiction.[12c] In this context, we focused our attention on preparing different analogues of propiophenone derivatives by using this methodology.

Existing methods for the formation of amino derivatives of propiophenone involve the traditional nucleophilic displacement of an α-haloderivative of a propiophenone with an appropriate amine (Scheme 2).[12] In these methods, bromine, which is toxic, corrosive and not easy to handle, is used extensively. Often, the α-haloderivative of carbonyls are lachrymatory and will decompose on exposure to excess light. Hence, it is important to develop a user-friendly method to accomplish the synthesis of amino derivatives of propiophenone without the use of bromine (Scheme 1). In this part of the paper, we present an elegant method to



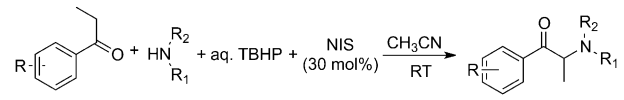
Scheme 2. Synthesis of 2-aminoacetophenones.

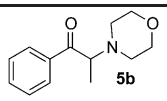
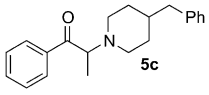
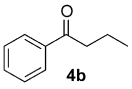
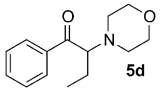
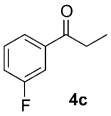
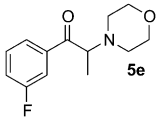
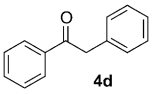
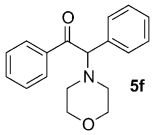
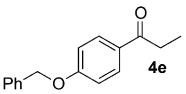
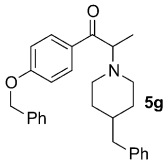
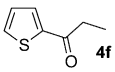
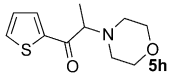
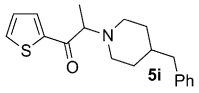
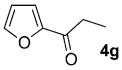
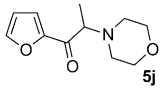
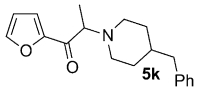
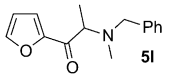
avoid the use of bromine and obtain the required compounds in moderate to good yields by using the same catalytic system as described above. To the best of our knowledge, this is the first report of the amination of propiophenone derivatives in a single step, which may find many potential applications.

The scope of the CDC reaction of various propiophenone derivatives leading to the formation of α-aminoketones is shown in Table 3. By following the standard protocol, propiophenone (**4a**) was coupled with secondary amines, such as morpholine (**2b**) and 4-benzyl piperidine (**2d**), to form the corresponding α-aminoketones in good yields (Entries 1 and 2, Table 3). Under the standard reaction conditions, butyrophenone (**4b**) reacted well with morpholine (**2b**) to form the corresponding amino derivative **5d** in good yield (Entry 3, Table 3). *m*-Fluoropropiophenone (**4c**) underwent a smooth reaction with morpholine (**2b**) to provide the aminated product **5e** in good yield (Entry 4, Table 3). A derivative of ifenprodil was synthesized by treating 4-benzyloxypropiophenone (**4e**) with 4-benzylpiperidine (**2d**) in (Entry 6, Table 3). Heterocyclic compounds, such as 1-(thiophen-2-yl)propan-1-one (**4f**) and 1-(furan-2-yl)propan-1-one (**4g**), underwent facile reactions with morpholine (**2b**), 4-benzyl piperidine (**2d**), and *N*-methylbenzylamine (**2e**) to yield compounds **5h**–**5l** (Entries 7–11, Table 3).

To understand the reaction mechanism of the amidation of acetophenone, acetophenone (**1a**) was treated with the secondary amine **2a** in the presence of NIS (30 mol%) and TBHP (3 equiv) and a radical inhibitor, such as 2,6-bis(1,1-dimethylethyl)-4-methylphenol (BHT) or 2,2,6,6-tetramethyl-piperidin-1-yl)oxyl (TEMPO). This reaction resulted in the formation of the α-ketoamide **3a** in 30% yield. This experiment suggests that the reaction probably proceeds through a radical intermediate.[17] Furthermore, acetophenone (**1a**) was reacted with stoichiometric amount of NIS and TBHP in the absence of an amine in the hope that the corresponding α-iodo compound could be obtained, but this reaction did not produce the expected iodo-intermediate. However, the reaction of 4-chlorophenacyliodide (**I**) with piperidene (**2a**, 3 equiv) in the presence of TBHP (3 equiv) and NIS (30 mol%) in CH_3CN gave the product **3f** in 70% yield (Scheme 3a). This observation is in agreement with those made by Wang et al.[17] Furthermore, the reaction of 1-(4-chlorophenyl)-2-(piperidin-1-yl)ethanone (**II**) with TBHP (3 equiv) and NIS (30 mol%) in CH_3CN furnished the product **3f** in 72% yield (Scheme 3b). These experiments suggested that the reaction might proceed through the 1-(4-

Table 3. Cross dehydrogenative coupling reactions.[a]

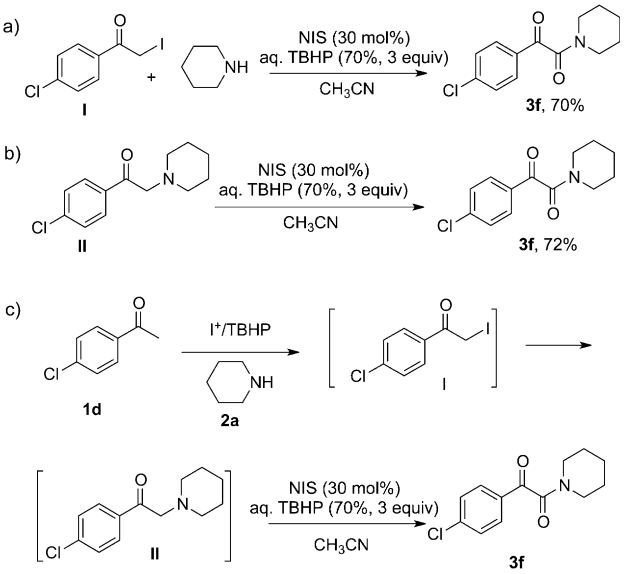


Entry	Ketone	Amine	Time [h]	Product	Yield [%][b]
1	**4a**	**2b**	4	 **5b**	74
2	**4a**	**2d**	7	 **5c**	67
3	 **4b**	**2b**	24	 **5d**	70
4	 **4c**	**2b**	5	 **5e**	63
5	 **4d**	**2b**	5	 **5f**	60
6	 **4e**	**2d**	24	 **5g**	50
7	 **4f**	**2b**	4	 **5h**	75
8	**4f**	**2d**	6	 **5i**	70
9	 **4g**	**2b**	6	 **5j**	74
10	**4g**	**2d**	5	 **5k**	76
11	**4g**	 **2f**	5	 **5l**	50

[a] Reaction conditions: propiophenone derivative (1 mmol), amine (3 mmol), aq. TBHP (70%, 3 mmol, 0.412 mL), NIS (0.3 mmol, 67.5 mg), CH_3CN (0.5 mL), RT. [b] Yield of isolated product.

chlorophenyl)-2-(piperidin-1-yl)ethanone intermediate (**II**; Scheme 3c).[19]

To further understand the reaction mechanism of the CDC reaction of propiophenone, a few control experiments were carried out. The reaction of propiophenone (**4a**) under standard reaction conditions, or in the presence of excess NIS (1 equiv) and TBHP (3 equiv), did not yield any detectable amounts of 2-iodopropiophenone, suggesting that the reaction does not proceed through an α-iodointermediate. In the presence of a radical scavenger such as TEMPO, the



Scheme 3. Tentative mechanism for the amidation of acetophenone.

reaction proceeded to give the product in good yield without the formation of any TEMPO-coupled product, indicating that this reaction does not involve the radical intermediate.[17] Further work is ongoing in our laboratory to understand the reaction mechanism and expand the scope of these reactions.

In conclusion, we have successfully demonstrated an NIS-catalyzed amidation of acetophenone derivatives by using TBHP as an oxidant. This amidation reaction is versatile and several acetophenone derivatives containing electron-withdrawing and electron-donating substituents can undergo facile amidation. It was also found that acetyl derivatives of heterocyclic compounds could be easily converted to their corresponding ketoamides. A new amination of propiophenone and its derivatives, catalyzed by NIS in the presence of TBHP, to provide their corresponding 2-aminoketone derivatives is reported. This is the first report of the amination of propiophenone derivatives in a single step that can be used to synthesize potentially important and active pharmaceutical reagents.

Experimental Section

General procedures: *1-phenyl-2-(piperidin-1-yl)ethane-1,2-dione (**3a**)*: Piperidine (255 mg, 3 mmol) was added dropwise to a stirred suspension of acetophenone (120 mg, 1 mmol) and NIS (67.5 mg, 0.3 mmol) in acetonitrile (0.5 mL), and was followed by the slower addition of TBHP (70% solution in water, 3 mmol, 0.412 mL). The reaction mixture was stirred at room temperature until the starting material was consumed (12 h, as monitored by TLC), then extracted with ethyl acetate (3×15 mL) and the combined organic layers were washed with water (2×50 mL), dried over anhydrous Na_2SO_4, and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel (EtOAc/Hexane 5:95–10:90) to provide **3a** as a pale-yellow liquid (92%, 200 mg).

1-phenyl-2-(piperidin-1-yl)propan-1-one (***5a***): Piperidine (255 mg, 3 mmol) was added dropwise to a stirred suspension of propiophenone (135 mg, 1 mmol) and NIS (67.5 mg, 0.3 mmol) in acetonitrile (0.5 mL), and was followed by the slower addition of TBHP (70% solution in water, 3 mmol, 0.412 mL). The reaction mixture was stirred at room temperature until the starting material was consumed (4 h, as monitored by TLC), the extracted with ethyl acetate (3×15 mL) and the combined organic layers were washed with water (2×50 mL), dried over anhydrous Na_2SO_4, and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel (EtOAc/Hexane 5:95–10:90) to provide **5a** as a colorless liquid (80%, 174 mg).

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Keywords: acetophenones · amination · dehydrogenation · *N*-iodosuccinimide · oxidation · propiophenones

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[19] We are thankful to anonymous referees for suggestions regarding the mechanism.

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