ORGANIC
LETTERS

2009
Vol. 11, No. 17
3810−3813

Novel and Direct Transformation of Methyl Ketones or Carbinols to Primary Amides by Employing Aqueous Ammonia

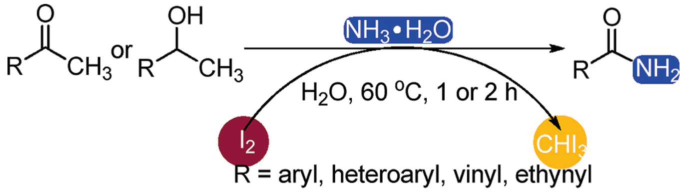
Liping Cao,[†] Jiaoyang Ding,[†] Meng Gao,[†] Zihua Wang,[†] Juan Li,[†] and Anxin Wu*,[†,‡]

*Key Laboratory of Pesticide & Chemical Biology, Ministry of Education, Central
China Normal University, Wuhan 430079, P. R. China, and Department of Chemistry,
State Key Laboratory of Applied Organic Chemistry, Lanzhou University,
Lanzhou, 730000, P. R. China*

chwuax@mail.ccnu.edu.cn

Received June 4, 2009

ABSTRACT



A novel and direct transformation of aryl, heteroaryl, vinyl, or ethynyl methyl ketones or carbinols to corresponding primary amides has been developed. An iodine-$NH_3 \cdot H_2O$ system was proven to be efficient for this reaction and afforded the expected products with good yields in aqueous media. A tandem Lieben−Haller−Bauer reaction mechanism was involved in this type of reaction and is proposed for the first time.

The field of organic functional group transformation is developing and attracting an increasing number of research groups around the world. Amide formation as a fundamental transformation in organic synthesis has attracted great attention.[1] Moreover, the primary amides occur widely in natural products, pharmaceuticals, and biomolecules, and constitute excellent intermediates and raw materials for synthetic organic chemistry.[2]

Traditionally, primary amides have been synthesized by the reactions of activated carboxylic acid derivatives, such as acids, aldehydes, acyl halides, mixed anhydrides, and esters, with amines or acyl azides and acyl hydrazides with reductants (Path I, Scheme 1).[3] Another attractive method is the hydration of nitriles to the corresponding primary amides in the presence of acids, bases, or the transition metal

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[†] Central China Normal University.

[‡] Lanzhou University.

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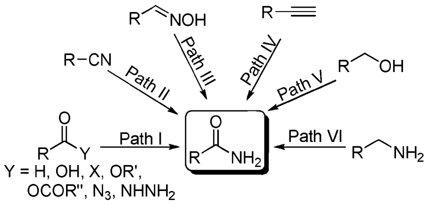
10.1021/ol901250c CCC: $40.75

Scheme 1. Preparation of Primary Amides from Various Compounds

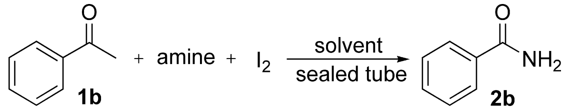


catalysts including homogeneous and heterogeneous complexes (Path II).[4] The rearrangement of aldoximes to the primary amides using transition metal catalysts has also been reported (Path III).[5] Recently, one example of oxidative primary amide synthesis has been achieved from terminal alkynes catalyzed by metalloporphyrins (Path IV).[6] Furthermore, two excellent transformations, heterogeneously ruthenium-catalyzed dehydrogenative coupling of primary alcohols with amines (Path V)[7] and oxygenation of primary amines to amides (Path VI),[8] have been reported, sequentially.

Water is essential for the survival of all known forms of life and it covers 71% of the Earth's surface. Compared to reactions in organic solvents, there are many potential advantages using water as a solvent for organic reactions: cheap, nontoxic, environmental friendly, etc. In the last two decades, a series of novel synthetic methodologies have been developed in aqueous media.[9] In the course of our continuing studies on self-sorting tandem reactions,[10] a novel transformation to access primary amides in aqueous media has been put forward. The wider application of amides and the precipitation of partially converted amides led us to explore this new protocol. In this paper, we show that a novel and direct transformation of methyl ketones or carbinols to the corresponding primary amides smoothly occurred in the presence of molecular iodine by employing aqueous ammonia. In addition to the simplicity of this procedure, the conversions are found to occur in significantly short durations. Owing to the readily available starting materials from Friedel–Crafts acylation,[11] this method could expand the scope of the formation of primary amides and simplify synthetic procedures.

Initially, we investigated the favorable condition of the transformation reaction from methyl ketones to the corresponding primary amides using acetophenone as a model substrate in the presence of molecular iodine and aqueous ammonia (25%) in various solvents (entries 1–9, Table 1).

Table 1. Optimization Studies in the Synthesis of Benzamide[a]



1b **2b**

entry	amine	T (°C)	solvent	time (h)	yield (%)[b]
1	$NH_3 \cdot H_2O$	60	MeOH	4	<5
2	$NH_3 \cdot H_2O$	60	MeCN	4	<5
3	$NH_3 \cdot H_2O$	60	THF	4	<5
4	$NH_3 \cdot H_2O$	60	CH_2Cl_2	4	<5
5	$NH_3 \cdot H_2O$	60	DME	4	<5
6	$NH_3 \cdot H_2O$	60	DMF	4	<5
7	$NH_3 \cdot H_2O$	60	EtOAc	4	<5
8	$NH_3 \cdot H_2O$	60	DMSO	4	<5
9	$\mathbf{NH_3 \cdot H_2O}$	**60**	$\mathbf{H_2O}$	**1**	**86**
10	$NH_3 \cdot H_2O$	20	H_2O	72	23
11	$NH_3 \cdot H_2O$	90	H_2O	1	85
12[c]	$NH_3 \cdot H_2O$	60	H_2O	1	28
13	$(NH_4)_2CO_3$	60	H_2O	2	NR[d]
14	$(NH_4)_2SO_4$	60	H_2O	4	NR[d]
15	NH_4Cl	60	H_2O	5	NR[d]
16	$HCOONH_4$	60	H_2O	1	NR[d]
17	CH_3COONH_4	60	H_2O	5	NR[d]

[a] Reaction conducted with 1 mmol of acetophenone, 10 mmol of amine and 3 mmol of I_2 in 25 mL solvent. [b] Isolated yields. [c] Only 1 mmol of I_2 was used. [d] No reaction.

Benzamide was obtained with 5% yields when MeOH, MeCN, THF, CH_2Cl_2, DME, DMF, EtOAc or DMSO was used as solvent. It was notable, however, that this transformation occurred smoothly in H_2O, with 86% yields.[12] Next, the effect of reaction temperature on the yield of the primary amide product **2a** was examined. A lower conversion was observed upon heating the reaction mixture to 90 °C or from performing the reaction at 20 °C when the reaction was carried out in water (entries 10–11, Table 1). Furthermore, the experimental data indicated that the reaction was not completed when the reaction time was less than 1 h at 60 °C. The number of equivalents of iodine had an influence on isolated yields of the reaction. In entry 12, the yields changed from 86 to 28% when the mole ratios between iodine and acetophenone were changed from 3:1 to 1:1. Then,

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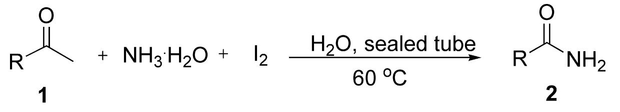
(12) The combination of ammonia and iodine in aqueous media may lead to the formation of explosive NI_3. Synthesis and properties of NI_3, see: Klapötke, T.; Tornieporth-Oetting, I. *Angew. Chem., Int. Ed.* **1990**, *29*, 677.

various amines including inorganic and organic ammonium salts were carried out upon the transformation of acetophenone to benzamide in the presence of iodine in water at 60 °C (entries 13−17, Table 1). However, most ammonium salts were completely inactive in this reaction. Ultimately, optimal conditions were identified, which provided **2a** in good yield and purity (entry 9, Table 1).

On the basis of the successful synthesis of amide **2a**, the optimized conditions were then applied to a range of other aryl methyl ketones. While the benzene rings bore electron-donating groups (e.g., −OMe, −OEt, $-OCH_2O-$) or electron-withdrawing groups (e.g., -F, -Cl, -Br, $-NO_2$), the corresponding products **2b**−**i** were obtained in good yields (81−96%, entries 2−9, Table 2). It was obvious that an electron-withdrawing substituent on the benzene ring caused a considerable increase in the yield. 6-Methoxy-2-naphthyl methyl ketone (**1j**) also gave satisfying result (79%, entry 10, Table 2). Encouraged by the results obtained with aryl methyl ketones, we turned our attention to the heteroaryl, vinyl and ethynyl methyl ketones. The presence of heteroatoms, including oxygen (**1k**) and sulfur (**1l**, **1m**, and **1n**) in the substrate, did not affect the overall efficiency, and the corresponding amides were obtained (76−80%, entries 11−14, Table 2). However, no expected products were observed when the substrate was 4-acetylpyridine (entry 15, Table 2), which was presumably coused by N-iodination of the pyridine ring which may lead to some side reactions such as nucleophilic attack at C-2 of the pyridine ring.[13] For further investigation, the reactions with unsaturated methyl ketones such as benzalacetone (**1p**) and 4-phenylbut-3-yn-2-one (**1q**) proceeded efficiently to afford the corresponding unsaturated amides in slightly lower yields (entries 16−17, Table 2). All these target molecules were characterized by NMR, MS and IR spectra.[14]

Table 2. Transformation of Various Methyl Ketones **1** to Primary Amides[a]



entry	substrates (R =)	products	time (h)	yield[b]
1	C_6H_5	**2a**	1	86
2	$4\text{-}MeOC_6H_4$	**2b**	1	83
3	$4\text{-}EtOC_6H_4$	**2c**	1	85
4	1,3-benzodioxol-5-yl	**2d**	1	81
5	$4\text{-}NO_2C_6H_4$	**2e**	1	96
6	$4\text{-}FC_6H_4$	**2f**	1	90
7	$4\text{-}ClC_6H_4$	**2g**	1	89
8	$4\text{-}BrC_6H_4$	**2h**	1	92
9	$3,4\text{-}Cl_2C_6H_3$	**2i**	1	94
10	6-MeO-2-naphthyl	**2j**	1	79
11	2-furyl	**2k**	1	78
12	2-thienyl	**2L**	1	79
13	5-Cl-2-thienyl	**2m**	1	80
14	3-thienyl	**2n**	1	76
15	4-pyridyl	**2o**	5	–[c]
16	(*E*)-$C_6H_5-CH=CH-$	**2p**	2	57
17	$C_6H_5-CH\equiv CH-$	**2q**	3	61

[a] Reactions conducted with 1 mmol of substrate, 10 mmol of $NH_3 \cdot H_2O$ (25%) and 3 mmol of I_2 in H_2O (25 mL) at 60 °C. [b] Isolated yields. [c] No amide products were observed.

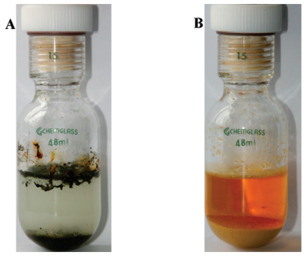
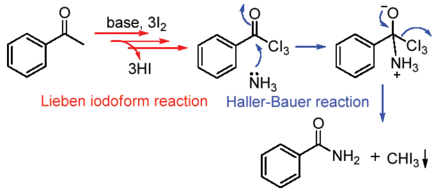


Figure 1. Initial appearance of I_2 in water (A) and after 1 h heating at 60 °C (B).

Scheme 2. Proposed Tandem Mechanism for the Transformation of Methyl Ketone to Primary Amide



Interestingly, in most of the experiments, we observed that after the completion of the reaction, the deposition of this reaction was accompanied by a distinctive color change from black to yellow, which indicated that there was a corresponding transformation of iodine to iodoform in this reaction (Figure 1). The iodoform was characterized by ^1H and ^{13}C NMR spectra.[14] On the basis of the above-described results, a possible reaction mechanism is proposed as follows using acetophenone (**1a**) as an example (Scheme 2): First, the acetophenone **1a** undergoes the formation of enolate ion under basic conditions, and three sequential α-halogenations take place to afford the α,α,α-triiodomethyl ketone.[15] This is the mechanism of the Lieben iodoform reaction. However, α,α,α-triiodomethyl ketone does not undergo rapid hydrolysis to afford the iodoform and a carboxylate in the presence of aqueous ammonia. Instead, α,α,α-triiodomethyl ketone, which is a nonenolizable ketone, is attracted by ammonia as a nucleophilic reagent, accompanied by the cleavage of

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(13) We thank the reviewers for pointing out the scope for side reactions such as nucleophilic attack at C-2 of the pyridine ring.

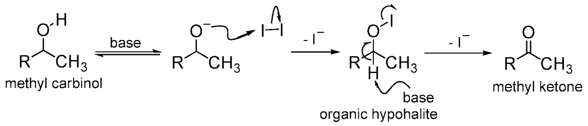
(14) See the Supporting Information.

(15) (a) Lieben, A. *Justus Liebigs Ann. Chem.* **1870**, *7*, 218. (b) Jones, M. *Organic Chemistry*, 2nd ed.; W. W. W. Norton & Company: New York, 2000; p 830.

carbon−carbon bonds leading to benzamide and iodoform. This process is a Haller−Bauer reaction.[16] Meanwhile, excess ammonia can act as a weak base to neutralize the hydrogen iodide, formed in the process of Lieben iodoform reaction. In addition, water as a solvent is indispensable to this reaction because the iodoform that is formed during the reaction is insoluble in hot water and can further promote the transformation.

It has been known that methyl carbinols can be oxidized to the corresponding methyl ketones via an organic hypohalite (Scheme 3), and subsequently, the Lieben iodoform reaction occurs. We were interested in the possibility of converting methyl carbinols into amides using these reaction conditions.

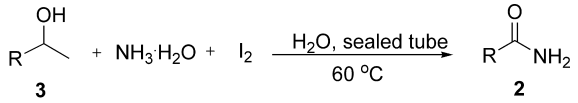
Scheme 3. Oxidation of the Methyl Carbinol to the Methyl Ketone



All treatments of 1-arylethanol **3** with 4 equiv of I_2 and 10 equiv of aqueous ammonia smoothly afforded the corresponding amides in good yields (71−94%, entries 1−5, Table 3). The results are summarized in Table 3. This conversion lent support to our tandem mechanism for the transformation of methyl ketone to primary amide via a Lieben iodoform reaction.

In summary, a novel and direct approach to primary amide compounds in the presence of iodine and aqueous ammonia has been developed in aqueous media. The reaction provides a very facile and efficient method for the preparation of primary amides. A possible tandem Lieben-Haller−Bauer reaction mechanism is proposed. To the best of our knowledge, it is the first example utilizing aqueous ammonia as a source of nitrogen in transformation of aryl, heteroaryl, vinyl or ethynyl methyl ketones or carbinols to corresponding primary amides. Further application of this methodology for the synthesis of various secondary and tertiary amides is underway in our laboratory.

Table 3. Transformation of Various 1-Arylethanol **3** to Primary Amides[a]



entry	substrates (R =)	products	time (h)	yield[b]
1	C_6H_5	**2a**	2	84
2	4-$MeOC_6H_4$	**2b**	2	81
3	4-$NO_2C_6H_4$	**2e**	2	94
4	2-furyl	**2k**	2	71
5	5-Cl-2-thienyl	**2m**	2	76

[a] Reactions conducted with 1 mmol of substrate, 10 mmol of $NH_3 \cdot H_2O$ (25%) and 4 mmol of I_2 in H_2O (25 mL) at 60 °C. [b] Isolated yields.

Acknowledgment. This work was supported by the National Natural Science Foundation of China (Grant No. 20672042 and No. 20872042).

Supporting Information Available: The general experimental methods and the characterizing data for primary amides; ^1H NMR and ^{13}C NMR spectra for compound **2** and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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