Letter

Iron-Catalyzed Direct Transformation of Benzylic Amines into Carbonyl Compounds in Water

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Maki Minakawa* Takashi Sasaki

Department of Applied Chemistry, Chemical Engineering and Biochemical Engineering, Yamagata University, 4-3-16, Jonan, Yonezawa, Yamagata 992-8510, Japan minakawa@yz.yamagata-u.ac.jp



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Abstract Fe-catalyzed direct transformation of benzylic amines into carbonyl compounds was performed in H₂O. The reaction of benzylic amines with formaldehyde in the presence of FeCl₃·6H₂O in H₂O afforded the corresponding carbonyl compounds (80 °C to reflux conditions; 14 examples, up to 94% yield). O¹⁸-labeling experiments indicated that the O atom in the generated carbonyl is derived from H₂O.

Key words direct transformation, benzylic amines, carbonyl compounds, iron catalysis, formaldehyde

The direct transformation of amines into carbonyl compounds is a powerful tool for organic synthesis. However, the synthesis of carbonyl compounds from amines usually requires stoichiometric quantities or large amounts of explosive peroxides, toxic oxidizing reagents, and/or expensive late-transition metals.¹ In addition, it is widely known that the reaction of amines with formaldehyde gives aminals via imines and imine salts, as shown in Scheme 1.²



In our previous study on the N-alkylation of amines,³ we found that the reaction of benzylamine with formaldehyde produced benzaldehyde in the presence of an iron(III) catalyst in water. Here, we describe the direct transformation of benzylic amines into carbonyl compounds with formaldehyde in the presence of an iron catalyst in water under mild reaction conditions (Scheme 2).¹



In this work, the conditions were optimized for the reaction of (diphenylmethyl)amine (1a) with formaldehyde (2) (Table 1). The reaction of (diphenylmethyl)amine (1a: 0.5 mmol) with formaldehyde (2: 0.6 mmol) in the absence of any catalyst in H₂O (0.5 mL) at 80 °C for 18 hours gave benzophenone (**3a**) in <1% yield (Table 1, entry 1).⁴ The transformation reaction with FeCl₃·6H₂O as a catalyst afforded the desired product **3a** in 74% isolated yield (entry 2). The reaction in the presence of $Fe(acac)_3$ or $Fe(NO_2)_3$ gave 3a in yields of 12 and 16%, respectively (entries 3 and 4), whereas FeF₃ as catalyst produced **3a** in 54% isolated yield (entry 5). Reactions in the presence of other Fe(II) complexes resulted in lower yields of **3a** (entries 6–8). TsOH or citric acid as the catalyst afforded 3a in yields of 6 and 7%, respectively (entries 9 and 10). The reaction with other metal chlorides as catalysts resulted in lower yields of the desired product **3a** (entries 11–13). The reaction at 100 °C in the presence of FeCl₃·6H₂O generated the desired product **3a** in 94% isolated yield (entry 14). In contrast, the reaction under similar reaction conditions at 60 °C resulted in a lower yield of **3a** (entry 15). In the reaction with an excess of amine, **3a** was not detected at 80 °C (entry 16), whereas the reaction with an excess of formaldehyde gave 3a in 76% vield (entry 17).⁵ Reducing the amount of FeCl₃·6H₂O catalyst to 10 mol% (based on amine) resulted in a lower yield (entry 18). Thus, the most effective direct transformation was achieved by the treatment of (diphenylmethyl)amine (1a: 0.5 mmol) with formaldehyde (2 0.6 mmol) in the presence of FeCl₃·6H₂O catalyst (20 mol%) in H₂O at 100 °C. Moreover, when the transformation reaction was performed with aqueous HCl (0.2 M), **3a** was observed in <1% yield (entry 19).⁶ Under similar reaction conditions with 0.6 M aqueous HCl, the reaction gave **3a** in 36% yield (entry 20).⁷ Therefore, the Fe catalyst is required for the effective direct transformation of a benzylic amine with formaldehyde to form a carbonyl compound.

Table 1 Direct Transformation of (Diphenylmethyl)amine (1a) into Benzophenone (3a)^a

	$\begin{array}{c} H_2 \\ + \\ H_H \\ H \\ H \end{array}$	catalyst H ₂ O (0.5 mL) 80 °C 18 h	o J J Ja
Entry	Catalyst (mol%)	Temp (°C)	Yield ^b (%)
1	_c	80	(<1)
2	Fe(III)Cl ₃ ·6H ₂ O (20)	80	(77) 74
3	Fe(III)(acac) ₃ (20)	80	(12)
4	Fe(III)(NO ₂) ₃ ·9H ₂ O (20)	80	(16)
5	$Fe(III)F_3$ (20)	80	(60) 54
6	Fe(II)(OAc) ₂ (20)	80	(2)
7	Fe(II)Cl ₂ ·4H ₂ O (20)	80	(<1)
8	Fe(II)SO ₄ ·7H ₂ O (20)	80	(<1)
9	TsOH (20)	80	(6)
10	citric acid (20)	80	(7)
11	AlCl ₃ (20)	80	(4)
12	ZnCl ₂ (20)	80	(2)
13	CuCl (20)	80	(<1)
14	Fe(III)Cl ₃ ·6H ₂ O (20)	100	94
15	Fe(III)Cl ₃ ·6H ₂ O (20)	60	26
16 ^d	Fe(III)Cl ₃ ·6H ₂ O (20)	80	(<1)
17 ^e	Fe(III)Cl ₃ ·6H ₂ O (20)	80	76
18	Fe(III)Cl ₃ ·6H ₂ O (10)	80	(3)
19	aq HCl (0.2 M)	80	(<1)
20	aq HCl (0.6 M)	80	(36)
^a Reactio	n conditions: 1 (0.5 mmol), r	paraformaldehyde (2 : 0	.6 mmol). cata-

lyst (20 mol% based on **1**), H₂O (0.5 mL), 80 °C, 18 h. NMR yield (in parentheses) or isolated yield.

^d 1.0 mmol of **1a** was used. ^e 1.2 mmol of 2 was used. With the optimized conditions in hand, we proceeded to investigate the reaction of various benzylic amines with formaldehyde (Table 2).^{8,9} Acetophenone (**3b**) was formed in 24% yield from (1-phenylethyl)amine (1b) and 2 (entry 2). The reaction of 1-(4-methylphenyl)ethylamine (1c) with 2 generated 3c in 34% yield (entry 3). The transformations of 1,2,3,4-tetrahydronaphthalen-1-amine (1d) and [1-(1naphthyl)ethyl]amine (1e) with 2 produced the corresponding carbonyl compounds 3d and 3e in yields of 13 and 4%, respectively (entries 4 and 5).¹⁰ The reaction of benzylLetter

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(entry 6). The reaction of 4-methoxybenzylamine (1g) with 2 led to the corresponding carbonyl compound 3g in 83% yield (entry 7). The formation of aldehydes from the benzylic amines 4-methylbenzylamine (1h), 3-methylbenzylamine (1i), and 2-methylbenzylamine (1j) and 2, performed under similar conditions, gave 4-methylbenzaldehyde (**3h**), 3-methylbenzaldehyde (3i), and 2-methylbenzaldehyde (3j), respectively (entries 8-10). 4-Fluorobenzylamine (1k) was converted into 4-fluorobenzaldehyde (3k) in 51% yield (entry 11). The reaction of 4-chlorobenzylamine (11) with 2 gave 4-chlorobenzaldehvde (31) in 55% vield (entry 12).

Table 2	Direct Transformation of Benzylic Amines with Formaldehyde
To Give Carbonyl Compounds ^a	



^c No catalyst

С



 a Reaction conditions: amine 1 (0.5 mmol), paraformaldehyde (2: 0.6 mmol), FeCl_3-6H_2O (20 mol% based on 1), H_2O (0.5 mL), 80 °C, 18 h. b Isolated yield.

^c H₂O=1 4-dioxane (1:1) was used

^d Under reflux conditions.

^e H₂O-1,4-dioxane (1:0.4) was used.

Similarly, [4-(methylthio)benzyl]amine (**1m**) reacted with **2** to give benzaldehyde **3m** in 66% yield (entry 13). The reaction of (2-thienylmethyl)amine (**1n**) with **2** afforded thiophene-2-carbaldehyde (**3n**) in 52% yield (entry 12). Thus, our reaction conditions are applicable to the direct transformation of benzylic amines **1a–n** with formaldehyde (**2**) using an iron catalyst (FeCl₃·6H₂O) in water to produce



the corresponding carbonyl compounds **3a–n** in 4–94% yield (14 examples).

Unfortunately, the reaction of (2-phenylethyl)amine (**4**) with formaldehyde (**2**) under similar reaction conditions gave aldehyde **5** in <1% yield (Scheme 3).¹¹

Moreover, the treatment of *N*-(phenylmethylene)methanamine (**6**) in the presence of FeCl₃·6H₂O in refluxing H₂O for 18 hours afforded benzaldehyde (**3f**) in 61% yield (Scheme 4). The reaction without FeCl₃·6H₂O gave **3f** in <1% yield under similar reaction conditions.¹² These results therefore demonstrate that the direct formation of carbonyl compounds from benzylic amines with an Fe catalyst proceeds via intermediate imine **6** derivatives.



Scheme 4 Treatment of *N*-(phenylmethylene)methanamine (**6**) with $FeCI_3 \cdot 6H_2O$

The reaction of (diphenylmethyl)amine (**1a**) with benzaldehyde (**3f**) under similar reaction conditions gave benzophenone (**3a**) and *N*-benzylidene(diphenylmethyl)amine (**7**) in yields of 20 and 25%, respectively (Scheme 5).¹³ In this reaction, benzylamine (**1f**) was also obtained in 9% yield.



 $\label{eq:scheme 5} \begin{array}{l} \mbox{Reaction of (diphenylmethyl)amine (1a) with benzaldehyde (3f) in the presence of FeCl_3·6H_2O \end{array}$

The reaction of (diphenylmethyl)amine (**1a**) with formaldehyde (**2**) in the presence of FeCl₃·6H₂O in O¹⁸-labeled water (\geq 98 atom%) at 100 °C for 18 hours produced O¹⁸-labeled benzophenone (**3a'**) and benzophenone (**3a**) (**3a'**/**3a** = 1.3:1.0) (Scheme 6).¹⁴



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A possible reaction pathway (Scheme 7) is proposed on the basis of the above information and previously published results.^{4,15,16} The reaction of the benzylic amine **1** with formaldehyde (**2**) produces an imine intermediate.⁴ This coordinates with the Fe catalyst and an H₂O molecule to give imine intermediate **A**. The H₂O molecule coordinated to Fe could be derived from FeCl₃·6H₂O or from imine formation and it should be readily exchangeable with other H₂O molecules of the solvent. The resulting imine **A** might be converted into imine **B** through isomerization.¹⁵ Subsequently, the Fe-coordinated H₂O molecule reacts with the imine to form **C**. Finally, the release of methylamine from **C** leads to product **3** with regeneration of the Fe catalyst.



In conclusion, we have demonstrated a Fe-catalyzed direct transformation of benzylic amines into carbonyl compounds in H₂O. The benzylic amines were converted into carbonyl compounds in the presence of formaldehyde with a Fe catalyst in H₂O without stoichiometric quantities or large amounts of explosive peroxide, toxic oxidizing reagents, and/or expensive late-transition metals. The expected intermediate (internal imine), N-(phenylmethylene)methanamine, led to the corresponding carbonyl compound (benzaldehyde) in the presence of FeCl₃·6H₂O in H₂O under refluxing conditions. The reaction in the absence of Fe catalyst did not proceed under similar reaction conditions. The reaction of (diphenylmethyl)amine with benzaldehyde under similar reaction conditions afforded benzophenone, an imine intermediate [N-benzylidene(diphenyl-O¹⁸-Labeling methyl)amine], and benzylamine. experiments demonstrated that the O atom in the generated carbonyl is derived from H_2O .

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611881.

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- (5) The reaction with an excess of amine to give an aminal seems to predominate over the conventional reaction (Scheme 1). On the other hand, the reaction with an excess of formaldehyde prevented the formation of an aminal in the presence of FeCl₃·6H₂O.
- (6) 0.2 M aq HCl. The concentration was calculated for 1.0 mol equiv of HCl formed from FeCl₃·6H₂O (20 mol% based on amine).
- (7) 0.6 M aq HCl. The concentration was calculated for 3.0 mol equiv of HCl formed from FeCl₃·6H₂O (20 mol% based on amine).
- (8) Benzophenone (3a); Typical Procedure (Table 2, Entry 1) A vial was charged with (diphenylmethyl)amine (1a; 91.6 mg, 0.5 mmol), FeCl₃·6H₂O (27.0 mg, 20 mol%), and paraformaldehyde (2; 19.2 mg, 0.6 mmol) under air. H₂O (0.5 mL) was added and the mixture was stirred at 100 °C for 18 h. The aqueous phase was then extracted with EtOAc (×3) and dried (Na₂SO₄). The extract was filtered through paper and concentrated in vacuo. The residue was purified by flash column chromatogra-

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phy [silica gel, EtOAc-hexane (1:10)] to give a white solid; yield: 85.2 mg (94%); mp 47.5–49.0 °C.

¹H NMR (500 MHz, CDCl₃): δ = 7.49 (t, *J* = 6.2 Hz, 4 H), 7.58–7.61 (m, 2 H), 7.81 (d, *J* = 6.2 Hz, 4 H). ¹³C NMR (125 MHz, CDCl₃): δ = 128.4, 130.2, 132.6, 137.7, 196.9.

- (9) When amines or imine intermediates were insoluble in water, 1,4-dioxane was added.
- (10) Although amines were consumed, the desired products were obtained in low yields.
- (11) Although the reactions of (pyridin-4-ylmethyl)amine, (pyrazin-2-ylmethyl)amine, and furfurylamine with formaldehyde were also performed under similar reaction conditions, the corresponding carbonyl compounds were not obtained. In addition, 4-nitrobenzylamine with formaldehyde gave 4-nitrobenzaldehyde in 7% vield under similar reaction conditions.
- (12) Without FeCl₃·6H₂O, *N*-(phenylmethylene)methanamine (**6**) was detected in quantitative yield after the reaction.

- (13) The yields were determined by ¹H NMR analysis of the crude mixtures (based on an internal standard). After the reaction, benzaldehyde (**3f**) was also detected in 35% yield.
- (14) The products ratio (O^{18}/O^{16}) was determined by GC–MS analysis.
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