

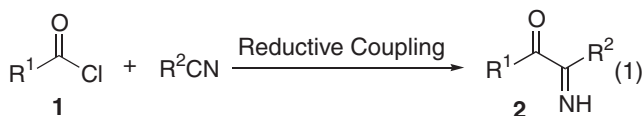
Reductive Coupling of Acid Chlorides with Nitriles Promoted by Titanium Tetraiodide. A Rapid Access to α -Imino Ketones

Makoto Shimizu,* Nobuyuki Manabe, and Hiroshi Goto
Department of Chemistry for Materials, Mie University, Tsu 514-8507

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Reductive coupling reactions of carboxylic acid chlorides and alkyl nitriles were efficiently promoted by titanium tetraiodide to give α -imino ketones in good yields.

Reductive coupling reaction of carbonyl compounds is one of the most useful methods for the construction of carbon frameworks.¹ Such reactions often use low valent metals as reducing reagents, because the reactions in most cases proceed via a single electron transfer mechanism. Whereas it has already been reported that the reductive coupling of nitriles with ketones are promoted by low valent titanium² or samarium³ to give α -hydroxy ketones, acid chlorides undergo a coupling reaction with ketones in the presence of samarium diiodide in acetonitrile to give also α -hydroxy ketones.⁴ Although nitriles were used as solvents in the latter reaction, coupling products arising from nitriles were not obtained. If nitriles work as substrates for the coupling reaction with acid chlorides, α -imino carbonyl compounds would be formed, which are useful synthetic intermediates for several organic transformations.^{5,6} We have been interested in reactions using titanium tetraiodide, which possesses good reducing ability,⁷ and have already reported selective reductions⁸ involving carbon-carbon bond formations such as the pinacol coupling reaction.⁹ We have now found that titanium tetraiodide promotes the reductive coupling reaction of carboxylic acid chlorides with alkyl nitriles to give α -imino ketones (Eq 1), and wish to describe herein such a reaction in detail.



When benzoyl chloride was treated with 1 equiv. of titanium tetraiodide in acetonitrile, α -imino ketone **2a** was formed. The amount of titanium tetraiodide and the reaction temperature were first screened, and the results are summarized in Table 1.¹

The reaction using 2.0 equiv. of titanium tetraiodide gave the α -imino ketone **2a** in 43% yield (Entry 2). However, the use of an increased amount of titanium tetraiodide did not noticeably increase the yields (Entries 3–5). Regarding the reaction temperature, the best of yield was obtained when the reaction was carried out at -40°C to room temperature. In an effort to increase the product yields, the quenching procedure was examined. Among the procedures, quenching the reaction with acetic anhydride was found to be effective, giving the coupling product in 52% yield (Entry 7).¹⁰ Under the optimum conditions, reactions with various aliphatic nitriles were carried out, and the results are summarized in Table 2.

The reaction in isobutyronitrile gave the best yield of 61% (Entry 4). Pivalonitrile, a bulky nitrile, gave a lower yield (Entry 5). Reactions in nitriles possessing heteroatoms, such as chloro-

Table 1. Comparison of reaction conditions^a

$\text{PhC}(=\text{O})\text{Cl} \xrightarrow[\text{Time}]{\text{TiI}_4 / \text{CH}_3\text{CN}} \xrightarrow{\text{Quench}} \text{PhC}(=\text{O})\text{CH}=\text{NCH}_3$				
Entry	TiI ₄ /equiv.	Time/h	Quench with	2a / % ^b
1	1.0	18.0	aq NaHCO ₃	33
2	2.0	21.0	aq NaHCO ₃	43
3	3.0	22.5	aq NaHCO ₃	44
4	4.0	23.0	aq NaHCO ₃	31
5	5.0	20.0	aq NaHCO ₃	32
6	2.0	21.5	CH ₃ COC(=O)CH ₃	36
7	2.0	22.0	(CH ₃ CO) ₂ O	52
8	2.0	22.0	TMSCl	40
9	2.0	22.0	(CF ₃ CO) ₂ O	28

^aReaction was carried out according to the typical procedure.¹¹

^bIsolated yield.

Table 2. Reductive coupling reaction of various nitriles and carboxylic acid chlorides^a

$\text{R}^1\text{C}(=\text{O})\text{Cl} \xrightarrow[\text{Time}]{\text{TiI}_4 (2.0 \text{ eq}) / \text{R}^2\text{CN}} \xrightarrow[\text{rt, 6 h}]{(\text{CH}_3\text{CO})_2\text{O} (5.0 \text{ eq})} \text{R}^1\text{C}(=\text{O})\text{CH}=\text{NR}^2$					
Entry	R ¹	R ²	t/°C	Time/h	2 / % ^b
1	Ph	CH ₃	-40-rt	21.0	52
2	Ph	C ₂ H ₅	-78-rt	22.0	54
3	Ph	C ₃ H ₇	-78-rt	23.0	25
4	Ph	(CH ₃) ₂ CH	-70-rt	21.0	61
5	Ph	(CH ₃) ₃ C	rt	20.5	20
6	Ph	ClCH ₂	-60-rt	21.0	40
7	Ph	Cl ₂ CH	-30-rt	23.0	12
8	Ph	Cl ₃ C	-40-rt	23.0	0
9	Ph	CH ₃ OCH ₂	-50-rt	21.5	42
10	2-ClC ₆ H ₄	(CH ₃) ₂ CH	-70-rt	22.0	69
11	3-ClC ₆ H ₄	(CH ₃) ₂ CH	-70-rt	22.0	66
12	4-ClC ₆ H ₄	(CH ₃) ₂ CH	-70-rt	21.5	71
13	4-CH ₃ C ₆ H ₄	(CH ₃) ₂ CH	-70-rt	22.0	55
14	4-CH ₃ OC ₆ H ₄	(CH ₃) ₂ CH	-70-rt	21.5	23
15	2-Naphthyl	(CH ₃) ₂ CH	-70-rt	22.0	43
16	<i>trans</i> -PhCH=CH	(CH ₃) ₂ CH	-70-rt	23.0	21
17	CH ₂ =CH	(CH ₃) ₂ CH	-70-rt	24.0	11
18	<i>trans</i> -C ₃ H ₇ CH=CH	(CH ₃) ₂ CH	-70-rt	24.0	35

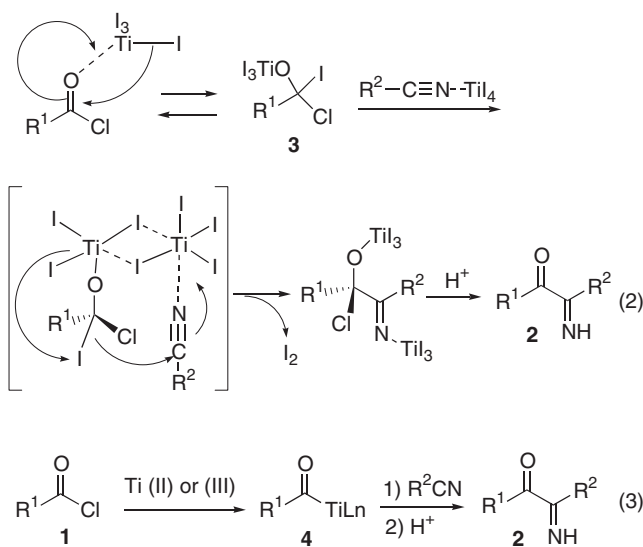
^aReaction was carried out according to the typical procedure.¹¹

^bIsolated yield.

acetonitrile and methoxyacetonitrile, also proceeded to give the coupling products in moderate yields, whereas trichloroacetonitrile did not give the desired product (Entries 6–9). When unsaturated nitriles such as acrylonitrile and crotononitrile were used,

the coupling reaction did not proceed. The reaction of aromatic acid chloride in most cases gave the good yields of the products. In particular, better yields were obtained using the aromatic acid chlorides possessing electron withdrawing groups (Entries 10–12). Although the yields were not always good, unsaturated acid chlorides gave coupling products without affecting the double bonds (Entries 16–18). However, the aliphatic acid chlorides were not good substrates for the present reaction.

Although there are several arguments on the reaction mechanism and more experiments appear to be needed, two possible pathways of the present coupling reaction are shown in Scheme 1. An initial iodination of the carbonyl group of the carboxylic acid chloride gives the iodinated intermediate **3**, which is attacked by the iodide anion from titanium tetraiodide to form an anionic species.¹² A similar attack of halide anions was observed in the reaction of α -halo ketones with metal halides.¹³ This anionic species in turn undergoes an addition reaction with nitrile to form the coupling product (Eq 2). Another involves an acyl titanium species **4** derived from the reduction of the acid chloride **1** with a low valent titanium species followed by coupling with nitrile (Eq 3). We are currently investigating the true reactive intermediate in more detail.



Scheme 1.

In conclusion, we have shown that reductive coupling reactions of carboxylic acid chlorides proceed with aliphatic nitriles to give α -imino ketones using the mild reducing ability of titanium tetraiodide. Although the product yields are moderate by the present procedure, these coupling products are not readily obtained from the reactions mediated by low valent metal reagents possessing strong reducing ability.

References and Notes

- G. M. Robertson, in "Comprehensive Organic Synthesis," ed. by B. M. Trost, Pergamon, New York (1991) Vol. 3, pp 563–612.
- a) L. Zhou and Y. Zhang, *Tetrahedron*, **56**, 2953 (2000). b) Y. Yamamoto, D. Matsumi, and K. Itoh, *Chem. Commun.*, **1998**, 875.
- a) L. Zhou, Y. Zhang, and D. Shi, *Synthesis*, **2000**, 91. b) G. A. Molander and C. N. Wolfe, *J. Org. Chem.*, **63**, 9031

- (1998).
- S. M. Ruder, *Tetrahedron Lett.*, **33**, 2621 (1992).
- a) Y. Niwa and M. Shimizu, *J. Am. Chem. Soc.*, **125**, 3720 (2003). b) Y. Niwa, K. Takayama, and M. Shimizu, *Bull. Chem. Soc. Jpn.*, **75**, 1819 (2002). c) M. Shimizu and Y. Niwa, *Tetrahedron Lett.*, **42**, 2829 (2001). d) Y. Niwa, K. Takayama, and M. Shimizu, *Tetrahedron Lett.*, **42**, 5473 (2001).
- a) M. Shimizu, K. Tsukamoto, T. Matsutani, and T. Fujisawa, *Tetrahedron*, **54**, 10265 (1998). b) M. Shimizu, K. Tsukamoto, and T. Fujisawa, *Tetrahedron Lett.*, **38**, 5193 (1997).
- a) M. Shimizu, T. Sahara, and R. Hayakawa, *Chem. Lett.*, **2001**, 792. b) R. Hayakawa, T. Sahara, and M. Shimizu, *Tetrahedron Lett.*, **41**, 7939 (2000). c) M. Shimizu, K. Shibuya, and R. Hayakawa, *Synlett*, **2000**, 1437.
- a) M. Shimizu and T. Sahara, *Chem. Lett.*, **2002**, 888. b) M. Shimizu, Y. Takeuchi, T. Sahara, *Chem. Lett.*, **2001**, 1196. c) M. Shimizu, F. Kobayashi, R. Hayakawa, *Tetrahedron*, **57**, 9591 (2001). d) R. Hayakawa, H. Makino, and M. Shimizu, *Chem. Lett.*, **2001**, 756. e) R. Hayakawa and M. Shimizu, *Org. Lett.*, **2**, 4079 (2000).
- a) M. Shimizu, H. Goto, and R. Hayakawa, *Org. Lett.*, **4**, 4097 (2002). b) R. Hayakawa and M. Shimizu, *Chem. Lett.*, **2000**, 724.
- The added acetic anhydride may remove the amine impurities derived from reduction of imino and/or nitrile species.
- A typical procedure is as follows: Isobutyronitrile (1.0 mL) was added to TiI_4 (0.5 mmol) at room temperature under an argon atmosphere, and the solution was stirred at that temperature for 10 min. To it was added a solution of benzoyl chloride (35.1 mg, 0.25 mmol) in isobutyronitrile (1.0 mL) at -70°C . After the mixture was allowed to warm to room temperature during 21 h, acetic anhydride (0.12 mL, 1.25 mmol) was added to it, and the mixture was stirred for 6 h at room temperature. Sat. aqueous NaHCO_3 and 10% aqueous NaHSO_3 were added successively. The mixture was filtered through a Celite pad and extracted with ethyl acetate (10 mL $\times$ 3). The combined organic extracts were dried over anhydrous Na_2SO_4 , and concentrated in vacuo. Purification on buffered silica gel TLC gave the adduct (26.8 mg, 61%) as a yellow powder. Mp $149\text{--}150^\circ\text{C}$; IR (CHCl_3) 3398, 3028, 1695, 1592, 1465, 1381, 1239, 1194, 1156, 1103, 898 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 1.26 (d, $J = 6.93\text{ Hz}$, 6H), 3.67 (sept, $J = 6.93\text{ Hz}$, 1H), 7.47–7.63 (m, 3H), 7.88–7.90 (m, 2H), 8.88 (br, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 18.7, 34.9, 127.7, 128.9, 133.0, 133.1, 165.3, 180.2. The buffered silica gel was prepared by suspending 93 g of silica gel (Merck 60F₂₅₄) in 230 mL of a phosphate buffer solution (pH 7.0) for 2 h and dried.
- G. W. Kabalka and Z. Wu, *Tetrahedron Lett.*, **41**, 579 (2000).
- a) C. Renner, W. Huayue, and Z. Yongmin, *J. Chem. Res., Synop.*, **1999**, 666. b) T. Tsuritani, S. Ito, H. Shinokubo, and K. Oshima, *J. Org. Chem.*, **65**, 5066 (2000). c) K. Maeda, H. Shinokubo, and K. Oshima, *J. Org. Chem.*, **63**, 4558 (1998). d) M. Z. Liu, Z. W. Guo, and Y. Z. Hui, *Youji Huaxue*, **17**, 319 (1997). e) R. Lin, L. Chen, and Y. Zhang, *Youji Huaxue*, **10**, 454 (1990). f) H. N. Borah, R. C. Boruah, and J. S. Sandhu, *Chem. Commun.*, **1991**, 154. g) S. Fukuzawa, T. Tsuruta, T. Fujinami, and S. Sakai, *J. Chem. Soc., Perkin Trans. 1*, **1987**, 1473.