

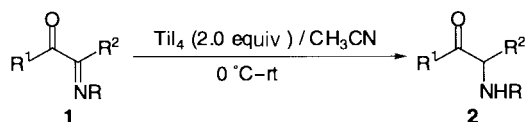
Chemoselective Reduction of α -Imino Carbonyl Compounds into α -Amino Carbonyl Compounds with Titanium Tetraiodide

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α -Imino carbonyl compounds are chemoselectively reduced with titanium tetraiodide to give α -amino carbonyl compounds in good to excellent yields

In connection with exploration into new biologically active compounds, it is highly desirable to develop ready methods for the preparation of α -amino carbonyl compounds, since many of targeted molecules in such field possess amino carbonyl and/or amino alcohol moieties.^{1,2} For the introduction of amino groups, reduction of imines is one of the most accessible methodologies,³ which involve metal borohydride reductions and hydrogenation in the presence of transition metal catalysts. However, in terms of chemoselectivity, such reductions have not been carried out readily in the presence of other functionalities. Among reduction methodologies reported the use of chlorodibutylstannane or hypervalent silanes enables the reduction of the imino groups in a chemoselective manner.⁴⁻⁷ We have recently described that TiI_4 is an excellent reagent for the pinacol coupling of aldehyde,⁸ selective reduction of 1,2-diketones to α -hydroxy ketones,⁹ that of sulfoxides to sulfides,¹⁰ and enolate formation from methoxyallene oxide.¹¹ We have now found that TiI_4 effects the reduction of α -imino carbonyl compounds **1** in a chemoselective manner to give α -amino carbonyl derivatives **2** in good yields and wish to report herein an efficient method for the preparation of α -amino carbonyl compounds.



Scheme 1.

The reduction was carried out as in the cases for 1,2-diketones described earlier. The results of investigation into the amount of TiI_4 , solvent, and *N*-substituent are summarized in Table 1.¹²

The reduction using 1.0 equiv of TiI_4 gave the α -amino ketone **4** in 88% (entry 1). The best result was obtained using 2.0 equiv of TiI_4 (entry 2). The use of more than 2.0 equiv of TiI_4 in acetonitrile afforded the reduction products in excellent yields, whereas lower yields were observed using CH_2Cl_2 or toluene as a solvent (entries 3–5). Under the optimum conditions, reduction of several *N*-substituted imines derived from benzil was carried out. When R was aryl group, the reductions proceeded in good yields, whereas in the case of the benzyl derivative, the reaction did not give the desired product (entries 6–9).

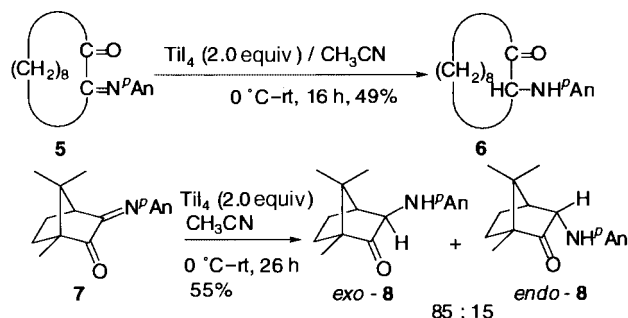
As shown below, reduction of the imines derived from cyclodecane-1,2-dione **5** and camphorquinone **7** gave the corresponding amino ketones in 49 and 55% yields, respectively,

Table 1. Reduction of α -imino ketones derived from benzil^a

Entry	R	Solvent	TiI_4 /equiv	Time/h	Yield/% ^b
1	<i>p</i> Ts	CH_3CN	1.0	22	88
2	<i>p</i> Ts	CH_3CN	2.0	22	90
3	<i>p</i> Ts	CH_3CN	3.0	22	90
4	<i>p</i> Ts	CH_2Cl_2	2.0	22	68
5	<i>p</i> Ts	Toluene	2.0	22	32
6	<i>p</i> An	CH_3CN	2.0	30	88
7	Ph	CH_3CN	2.0	22	87
8	<i>p</i> Tol	CH_3CN	2.0	20	90
9	Bn	CH_3CN	2.0	23	0

^aReaction was carried out according to the typical procedure.

^bIsolated yield.



indicating that even in the case of enolizable compounds, the present method met with moderate success.

Next, we investigated the reduction of iminocarbonyl compounds derived from phenylglyoxal and ethyl glyoxylate, and results are summarized in Table 2. Although the reduction of *N*-anisylimines did not proceed, the *N*-tosyl counterparts gave α -amino ketone and ester in good yields. These examples indicate that imines derived from aldehydes need relatively strong

Table 2. Reduction of imino carbonyl compounds^a

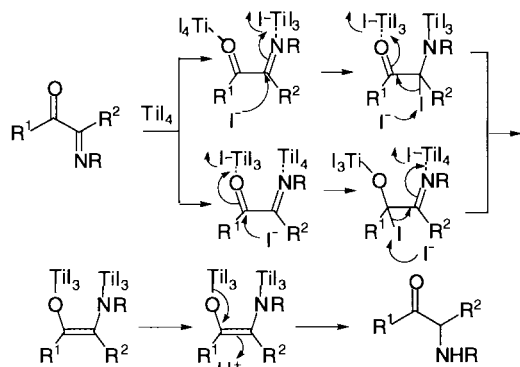
Entry	R ¹	R	TiI_4 /equiv	Time/h	Yield/% ^b
1	Ph	<i>p</i> An	2.0	15	Trace
2	Ph	<i>p</i> Ts	3.0	14	81
3	EtO	<i>p</i> Ts	2.0	21	87

^aReaction was carried out according to the typical procedure.

^bIsolated yield.

activation with an electron-withdrawing *N*-substituent.

The following scheme shows a possible reaction pathway. The present reaction appears to involve an initial attack of iodide anion at the imino or carbonyl carbon and the subsequent reaction with another iodide anion effects the formation of enolates species.¹³ The enolates thus generated are protonated to give α -amino carbonyl compounds chemoselectively. Another possible mechanism involves reduction with a low-valent titanium species. However, our previous observation that the carbonyl next to the aliphatic substituent was more readily reduced in the presence of the benzylic carbonyl which might be reduced more readily under one-electron transfer reduction conditions appears to support the above hypothesis.⁹ We are currently investigating into the true intermediate in more detail.



Scheme 2.

In conclusion, TiI_4 reduces imines in the presence of carbonyl groups in good to excellent yields. Since titanium tetraiodide is commercially available and inexpensive, and that the experimental procedure is quite simple, this method offers a convenient and practical method for α -amino carbonyl compounds.

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References and Notes

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- 12 A typical procedure (Table 1, Entry 2) is as follows: Acetonitrile (1.0 mL) was added to TiI_4 (263.3 mg, 0.474 mmol) at ambient temperature under an argon atmosphere. After stirring for 10 min, to the solution of TiI_4 was added a solution of 1,2-diphenyl-2-*p*-toluenesulfonyliminoethanone (86.1 mg, 0.237 mmol) in acetonitrile (2 mL) at 0 °C. After being stirred at 0 °C to room temperature for 21 h, the reaction was quenched with sat. aq NaHCO_3 and 10% aq NaHSO_3 . 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 by silica gel flash column chromatography (*n*-hexane : ethyl acetate = 4 : 1 as an eluent) gave 1,2-diphenyl-2-*p*-toluenesulfonylaminoethanone (78.0 mg, 90%) as a colorless oil.
- 13 The reductive formation of the titanium enolate was attested using ^1H NMR studies, and the subsequent reaction with aldehyde actually gave an aldol product.

