Use of α-Allyloxy-α-trimethylsiloxyacetate for Reductive Imino Aldol Reaction Promoted by Titanium Tetraiodide: A Rapid Access to β-Amino-α-hydroxy Esters

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Under the influence of titanium tetraiodide the reductive imino aldol reaction of α-allyloxy-α-trimethylsiloxyacetate proceeded with imines to give β-amino-α-hydroxy esters in good yields.

In conjugation with an exploration into a short approach to HIV protease inhibitors, selective preparation of β-amino-α-hydroxy carboxylic acids **1** has been needed.[1] One of the most straightforward approaches to this kind of esters involves the imino aldol reaction of α-hydroxy esters with imines, where reductive formation of glyoxylate enolates may offer the requisite enolate species.[2] We have recently found that TiI_4 is an excellent reagent for selective reduction of several substrates.[3] Recent study has also revealed that TiI_4 effects the reductive aldol reaction of *N*-tosylimine derived from ethyl glyoxylate with aldehydes to give α-amino-β-hydroxy esters stereoselectively in good yields.[4] In an analogous way to this methodology, a variety of glyoxylates were subjected to the TiI_4 mediated reductive formation of enolate. However, this approach proved fruitless, and only pinacol type homo-coupling products were obtained.[5] In an effort to generate enolate species in a chemoselective fashion, the use of acetals derived from ethyl glyoxylate was investigated. We have now found that the desired β-amino-α-hydroxy esters are obtained in good to excellent yields using reaction of α,α-dialkoxyacetates with imines promoted by TiI_4. In particular, α-allyloxy-α-trimethylsiloxyacetate (**2f**) underwent a selective imino aldol reaction to give β-amino-α-hydroxy esters, where deprotection of the alkoxy moiety was not needed for further functional group transformations.

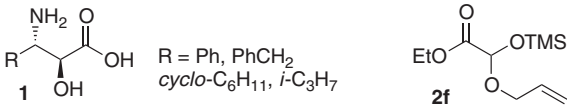
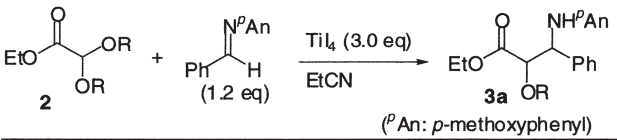


Figure 1.

In order to check the enolate formation, reduction of ethyl α,α-diethoxyacetate with TiI_4 (2.0 eq) in acetonitrile at −78 °C was carried out, and ethyl α-ethoxyacetate was obtained in quantitative yield. We next examined the reductive imino aldol reaction of α,α-dialkoxyacetates, and the results are summarized in Table 1.

As shown in Table 1, α,α-dimethoxy derivative **2a** gave the desired adduct in 11% yield, whereas better results were obtained using the diethoxy analogue **2b** (entries 1 and 5). The reactions carried out at lower reaction temperatures recorded reduced yields of the products (entries 3–5). Use of an excess amount of the acetal gave higher yields of the product (entries 6 and 7). However, the difficulty to hydrolize the ethyl ether moiety of the product called for the use of other substrates.

Table 1. Reductive aldol reaction of α,α-dialkoxyacetates **2**: Comparison of reaction conditions[a]



Entry	R	Temp./°C	Yield of **3a** / %[b]	*anti* : *syn*[c]
1	Me (**2a**)	r.t.	11	53 : 47
2	Me[d]	r.t.	26	66 : 34
3	Et (**2b**)	-78 - r.t.	18	77 : 23
4	Et	0 - r.t.	33	78 : 22
5	Et	r.t.	51	73 : 27
6	Et[e]	r.t.	67	78 : 22
7	Et[f]	r.t.	90	76 : 24

[a]Reaction was carried out according to the typical procedure.[6] [b]Isolated yield. [c]Determined by ^{1}H NMR. The assignment of the structure was made after transforming into the corresponding β-lactam.[7] [d]Methyl ester was used. [e]Acetal : imine : TiI_4 = 1.2 : 1.0 : 3.0. [f]Acetal : imine : TiI_4 = 2.0 : 1.0 : 3.0.

In an effort to find the most useful derivative for removal of the protecting group, use of four types of α,α-dialkoxyacetates **2c–f** was investigated. Among them, the use of the α-allyloxy-α-trimethylsiloxy derivative **2f** gave the adduct with a free hydroxy group. The reductive imino aldol reaction of this particular acetal **2f** was carried out with various aldimines under the optimum reaction conditions found as in the case with entry 7 in Table 1, and the results are summarized in Table 2.

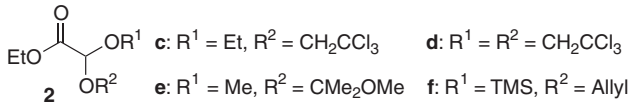
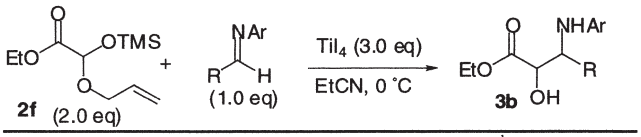


Figure 2.

The reaction of **2f** with anisyl benzalimine in the presence of TiI_4 gave the desired β-amino-α-hydroxy ester **3b**, where the amount of TiI_4 and the reaction temperature were found to be crucial (entries 1–5). The reaction carried out with 3 equivalents of TiI_4 in EtCN at 0 °C gave a satisfactory yield (entry 4). Although the diastereoselectivity was not high, the aryl benzalimines and its naphthyl analogue examined here all gave good to excellent yields of the β-amino-α-hydroxy esters (entries 6–10).

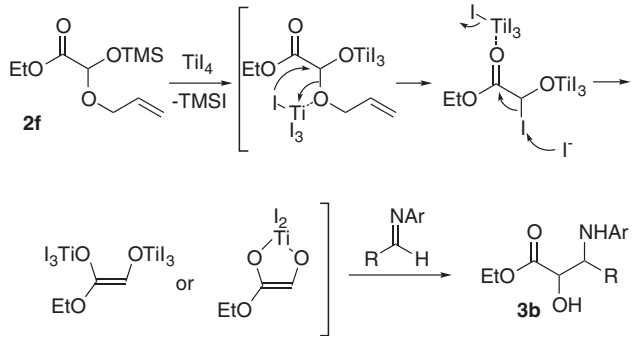
The following scheme shows a possible reaction pathway. The metal exchange reaction between TMS group and Ti(IV) gives a titanium alkoxide, which in turn is attacked by an iodide anion to form α-iodo ester. The subsequent reaction with another iodide anion effects the formation of an enolate species. The adduct is formed via a further reaction with imine.

Table 2. Reductive aldol reaction of α-allyloxy-α-trimethylsiloxyacetate **2f**[a]



Entry	R	Ar	Yield of **3b** / %[b]	*anti* : *syn*[c]
1[d]	Ph	*p*-An	14	87 : 13
2[e]	Ph	*p*-An	51	81 : 19
3[f]	Ph	*p*-An	57	56 : 44
4	Ph	*p*-An	80	64 : 36
5[g]	Ph	*p*-An	83	58 : 42
6	Ph	*o*-An	54	53 : 47
7	Ph	Ph	67	52 : 48
8	Ph	*p*-Tol	76	52 : 48
9	Ph	*p*-$EtO_2CC_6H_4$	80	45 : 55
10	1-Naphthyl	*p*-An	67	66 : 34

[a]Reaction was carried out according to the typical procedure.[6] [b]Isolated yield. [c]Determined by ^{1}H NMR (NOESY) on the corresponding oxazolidinone.[8] [d]The reaction was carried out with TiI_4 (1.0 eq) at room temp. [e]The reaction was carried out with TiI_4 (2.0 eq) at room temp. [f]The reaction was carried out at room temp. [g]The reaction was carried out at -78 – -5 °C.



Scheme 1.

In conclusion, the reductive aldol reaction of α-allyloxy-α-trimethylsiloxy ester promoted by TiI_4 afforded β-amino-α-hydroxy esters in good yields. Although the diastereoselectivity is not high, the present methodology introduces the use of a new readily removable acetal-type protecting group for reductive enolate formations.

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References and Notes

1 a) A. H. Fray, R. L. Kaye, and E. F. Kleinman, *J. Org. Chem.*, **51**, 4828 (1986). b) K. Iizuka, T. Kamijo, H. Harada, K. Akahara, T. Kubota, H. Umeyama, T. Ishida, and Y. Kiso, *J. Med. Chem.*, **33**, 2707 (1990). c) A. M. Diedrich and D. M. Ryckman, *Tetrahedron Lett.*, **34**, 6169 (1993). d) Y. Kiso, *Biopolymers*, **40**, 235 (1996). e) Y. X. Wong, D. I. Freedberg, P. T. Wingfield, S. J. Stahl, J. D. Kaufman, Y. Kiso, T. N. Bhat, J. W. Erickson, and D. A. Torchia, *J. Am. Chem. Soc.*, **118**, 12287 (1996). f) S. Kobayashi, H. Ishitani, and M. Ueno, *J. Am. Chem. Soc.*, **120**, 431 (1998). g) M. Shimizu, Y. Ikari, and A. Wakabayashi, *J. Chem. Soc., Perkin Trans. 1*, **2001**, 2519.

2 a) F. Ramirez, N. Ramanathan, and N. B. Desai, *J. Am. Chem. Soc.*, **84**, 1317 (1962). b) W. P. Newmann and A. Schwarz, *Angew. Chem., Int. Ed. Engl.*, **14**, 812 (1975). c) A. G. Davies and J. A. Hawari, *J. Organomet. Chem.*, **224**, C37 (1982). d) T. Mukaiyama, J. Kato, and M. Yamaguchi, *Chem. Lett.*, **1982**, 1291. e) A. Clerici, L. Clerici, and O. Porta, *Tetrahedron Lett.*, **36**, 5955 (1995).

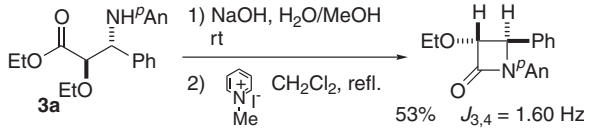
3 a) R. Hayakawa, T. Sahara, and M. Shimizu, *Tetrahedron Lett.*, **41**, 7939 (2000). b) M. Shimizu, K. Shibuya, and R. Hayakawa, *Synlett*, **2000**, 1437. c) R. Hayakawa and M. Shimizu, *Org. Lett.*, **2**, 4079 (2000). d) R. Hayakawa, H. Makino, and M. Shimizu, *Chem. Lett.*, **2001**, 756. e) M. Shimizu, T. Sahara, and R. Hayakawa, *Chem. Lett.*, **2001**, 792. f) M. Shimizu, F. Kobayashi, and R. Hayakawa, *Tetrahedron*, **57**, 9591 (2001).

4 M. Shimizu, Y. Takeuchi, and T. Sahara, *Chem. Lett.*, **2001**, 1196.

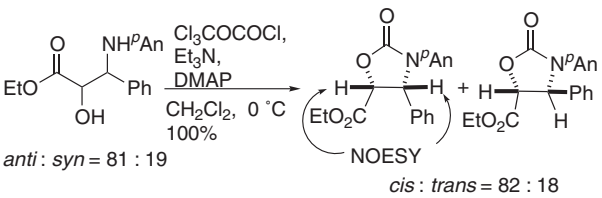
5 R. Hayakawa and M. Shimizu, *Chem. Lett.*, **2000**, 724, and references therein.

6 A typical procedure is as follows: Propionitrile (0.5 mL) was added to TiI_4 (198 mg, 0.356 mmol) at ambient temperature under an argon atmosphere. After 10 minutes stirring, to the solution of TiI_4 was added *p*-anisyl benzalimine (25.0 mg, 0.119 mmol) in propionitrile (0.5 mL) at 0 °C. After stirring for 30 min at 0 °C, a solution of ethyl 2-(2-propenyloxy)-2-trimethylsiloxyacetate **2f** (55.1 mg, 0.237 mmol) in propionitrile (0.5 mL) was added to the mixture at 0 °C, and the whole mixture was stirred for 2.5 h. The reaction was quenched with sat. aq $NaHCO_3$, 10% $NaHSO_3$, filtered through a Celite pad, and extracted with ethyl acetate (10 mL × 3). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification by flush column chromatography (hexane : ethyl acetate = 5 : 1 as an eluent) gave ethyl 2-hydroxy-3-phenyl-3-(4-methoxyphenylamino)-propionate (29.9 mg, 80%) as a colorless oil.

7 After separation of diastereomers, the adduct **3a** was hydrolyzed to the amino acid, which was cyclized using the pyridinium salt[9] to give the β-lactam. Examination of the coupling constant between H_3–H_4 indicated the stereochemistry.



8 The relative stereochemistry of the product was determined using ^{1}H NMR (NOESY) after transforming into the corresponding imidazolidinone as in the following typical example, in which the *anti*-isomer showed correlation, whereas the *syn*-analogue did a very weak correlation:



9 H. Huang, N. Iwasawa, and T. Mukaiyama. *Chem. Lett.*, **1984**, 1465.