COMMUNICATION

OBC
www.rsc.org/obc

Diastereoselective reductive imino-aldol reaction of α-imino esters promoted by titanium tetraiodide: synthesis of α,β-diamino esters

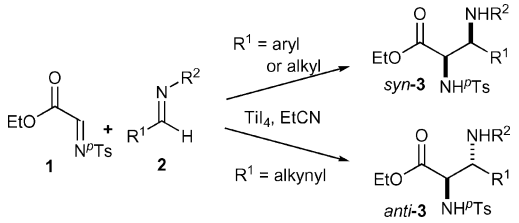
Makoto Shimizu,* Koji Inayoshi and Tetsuya Sahara

Department of Chemistry for Materials, Mie University, Tsu, Mie, 514-8507, Japan.
E-mail: mshimizu@chem.mie-u.ac.jp; Fax: +81 59 231 9413

Received 18th April 2005, Accepted 6th May 2005
First published as an Advance Article on the web 18th May 2005

Under the influence of titanium tetraiodide reductive imino-aldol reaction of the *N*-tosylimine derived from ethyl glyoxylate proceeded with aldimines to give α,β-diamino esters in good yields in a highly diastereoselective manner.

Our previous investigations have revealed that titanium tetraiodide is a good reagent for efficient C–C bond forming reactions[1] involving reductive formation of enolate species[1d,e] from α-imino- and α-allyloxy-α-trimethyksiloxy acetates. Although aldol type reactions proceeded well, there has been much room for the improvement of diastereoselectivity. Much attention has been focused recently on the stereoselective preparation of 1,2-diamines due to the increasing importance of such compounds for the synthesis of many biologically important natural products as well as drugs for therapeutic purposes.[2] They also serve as chiral auxiliaries and/or ligands for metals in catalytic asymmetric synthesis, and several approaches to their preparation have been developed.[3] During explorations into the utility of titanium tetraiodide for the reductive formation of enolates, we found that reaction of the enolate of α-aminoacetate generated from α-iminoacetates[4] with aldimines proceeded to give α,β-diamino esters in good yields. This paper describes a stereoselective reductive imino-aldol reaction of α-iminoacetate (Scheme 1).

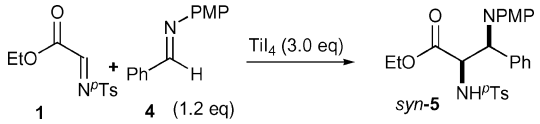


Scheme 1

Firstly, the reaction of α-imino ester **1** with *p*-anisylbenzalimine **4** was examined under various reaction conditions, and Table 1 summarizes the results. As shown, the reaction in toluene did not proceed, whereas a small amount of the adduct **5** was obtained in dichloromethane (entries 1 & 2). Better yields were obtained when the reaction was carried out in propionitrile or acetonitrile. In particular, the use of acetonitrile as solvent appeared to be superior in terms of the diastereoselectivity (entries 9 & 10). The use of an excess of the α-iminoacetate **1** gave the best result (entry 10). Under the optimum conditions, a variety of imines were subjected to the present reductive imino aldol reaction, and Table 2 summarizes the results.

As shown in Table 2, among the substituents at the imino nitrogen atom, 2-methoxyphenyl and phenyl groups effected the addition reaction efficiently, while the 4-dimethylaminophenyl derivative decreased the yield of the desired adduct (entries 1–4). The use of the 4-toluenesulfonyl derivative gave no reaction presumably due to the lack of the site of the imino nitrogen where TiI_4 could chelate (entry 6). Regarding the diastereoselectivity, the imines derived from benzaldehyde and cyclohexanecarboxaldehyde gave *syn*-adducts **3** as major isomers (entries 1–7).

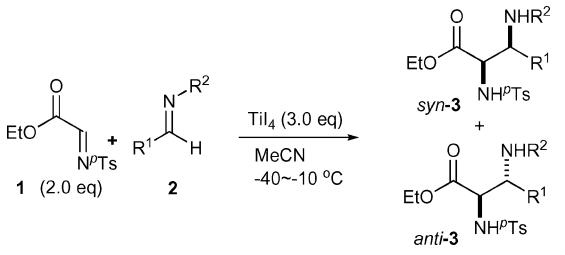
Table 1 Reaction of α-imino ester **1** with *p*-anisylbenzalimine **4** under various conditions[a]



Entry	Solvent	Temp. (°C)	Time (h)	**5** (%)[b]	*syn* : *anti*[b,c]
1	$PhCH_3$	−78 to −10	3.5	0	—
2	CH_2Cl_2	−78 to −10	3.5	12	58 : 42
3	EtCN	−78 to −30	2.5	56	80 : 20
4	EtCN	−78 to −20	3.0	61	86 : 14
5	EtCN	−78 to −10	4.0	61	84 : 16
6	EtCN	−78 to 0	5.0	56	78 : 22
7	EtCN	−78 to rt	22.5	58	51 : 49
8	EtCN	−40 to −10	3.0	51	81 : 19
9	MeCN	−40 to −10	3.0	66	94 : 6
10[d]	MeCN	−40 to −10	3.0	77	94 : 6

[a] The reaction was carried out according to the typical experimental procedure.† [b] Isolated yield. [c] Determined by ^1H NMR and/or HPLC. [d] **1** (2.0 eq) and **4** (1.0 eq.) were used.

Table 2 Reaction of α-imino ester **1** with various imines **2**[a]



Entry	R^1	R^2	Time (h)	**3** (%)[b]	*syn* : *anti*[b]
1	Ph	2-$MeOC_6H_4$	2.5	80	89 : 11
2	Ph	2,4-$(MeO)_2C_6H_3$	2.5	52	89 : 11
3	Ph	Ph	2.5	85	93 : 7
4	Ph	4-$Me_2NC_6H_4$	3.0	17	>99 : 1
5	Ph	2-$MeSC_6H_4$	3.0	57	92 : 8
6	Ph	4-Ts	3.0	0	—
7	*cyclo*-Hex	4-$MeOC_6H_4$	3.0	50	94 : 6
8[d]	PhC≡C	4-$MeOC_6H_4$	2.0	55	7 : 93
9[d]	TMSC≡C	4-$MeOC_6H_4$	2.0	44	1 : >99

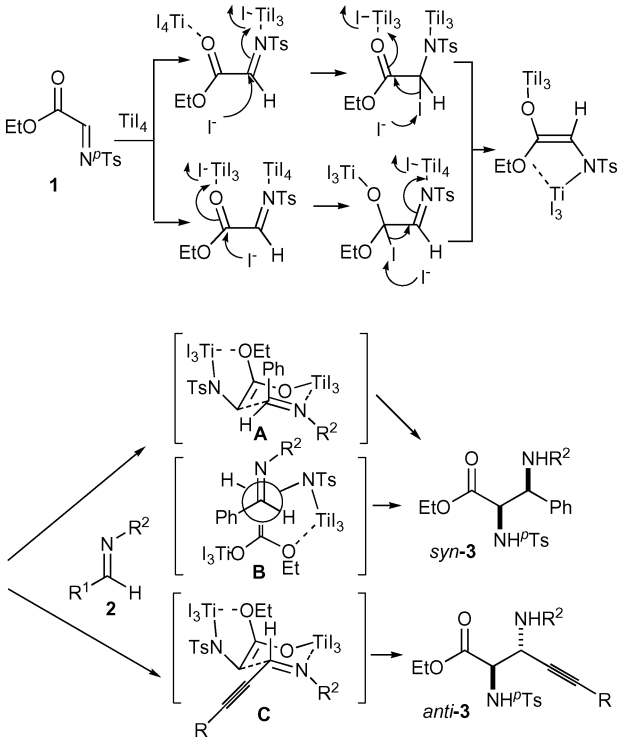
[a] The reaction was carried out according to the typical experimental procedure.† [b] Isolated yield. [c] Determined by ^1H NMR and/or HPLC. [d] The reaction was carried out at −40 °C.

Those possessing triple bonds recorded reversal of the diastereoselectivity, affording *anti*-adducts **3** predominantly (entries 8 & 9).‡

Although arguments on the stereochemical outcome need more experimental support, 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

DOI:10.1039/b505335h

to effect the formation of the enolate species.[5] The enolate thus generated reacts with the imines derived from benzaldehyde and cyclohexanecarboxaldehyde *via* a six membered cyclic transition state **A** or an acyclic counterpart **B** which appears to be favored due to the absence of a 1,3-diaxial interaction as in the case with **A** to give the *syn*-α,β-diamino ester **3** stereoselectively. Regarding the formation of *anti*-adducts in the cases with sterically less demanding acetylene derivatives, an involvement of addition to the *Z*-imine which would form *via in situ* isomerization of the corresponding *E*-isomer may account for the reversal of the diastereoselectivity (Scheme 2).



Scheme 2

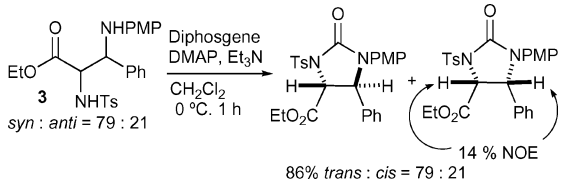
In conclusion, the reductive imino aldol reaction of the *N*-tosyl imine derived from ethyl glyoxylate promoted by TiI_4 afforded α,β-diamino esters selectively in good yields, where good to high diastereoselectivities were observed. Since titanium tetraiodide is commercially available and inexpensive, this procedure offers a convenient method for the reductive formation of α-amino ester enolate that is a useful synthon for the introduction of an aminoacetate moiety.

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, of the Japanese Government, and a grant from the Chugai Pharmaceutical Co. is also gratefully acknowledged.

Notes and references

† A typical procedure is as follows: acetonitrile (1.0 mL) was added to TiI_4 (395 mg, 0.711 mmol) at ambient temperature under an argon atmosphere. After 10 minutes stirring, to the solution of TiI_4 was added *N*-benzylideneaniline (43.0 mg, 0.237 mmol) in acetonitrile (1.0 mL) at −40 °C. After stirring for 30 min at −40 °C, ethyl 4-toluenesulfonyliminoacetate (121.0 mg, 0.474 mmol) was added at −40 °C, and the mixture was stirred at −40 °C to −10 °C for 3.0 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 on silica gel TLC (*n*-hexane : ethyl acetate = 9 : 4 as an eluent) gave ethyl 3-phenylamino-3-phenyl-2-(4-toluenesulfonylamino)propionate (87.9 mg, 85%, *syn* : *anti* = 93 : 7) as a colorless oil.

‡ The relative stereochemistry of the product was determined using ^{1}H NMR (NOE) after transforming into the corresponding imidazolidinone as in the following typical example, in which the *cis*-imidazolidinone derived from the *anti*-isomer **3** showed an NOE, whereas the *trans*-analogue did not:



1 (*a*) M. Shimizu and T. Toyoda, *Org. Biomol. Chem.*, 2004, **2**, 2891; (*b*) M. Shimizu and H. Goto, *Lett. Org. Chem.*, 2004, **1**, 346; (*c*) M. Shimizu, H. Goto and R. Hayakawa, *Org. Lett.*, 2002, **4**, 4097; (*d*) M. Shimizu and T. Sahara, *Chem. Lett.*, 2002, 888; (*e*) M. Shimizu, Y. Takeuchi and T. Sahara, *Chem. Lett.*, 2001, 1196; (*f*) M. Shimizu, T. Sahara and R. Hayakawa, *Chem. Lett.*, 2001, 792; (*g*) R. Hayakawa, H. Makino and M. Shimizu, *Chem. Lett.*, 2001, 756; (*h*) M. Shimizu, F. Kobayashi and R. Hayakawa, *Tetrahedron*, 2001, **57**, 9591; (*i*) R. Hayakawa and M. Shimizu, *Org. Lett.*, 2000, **2**, 4079; (*j*) R. Hayakawa, T. Sahara and M. Shimizu, *Tetrahedron Lett.*, 2000, **41**, 7939; (*k*) M. Shimizu, K. Shibuya and R. Hayakawa, *Synlett*, 2000, 1437; (*l*) R. Hayakawa and M. Shimizu, *Chem. Lett.*, 2000, 724.

2 D. Lucet, T. Le Gall and C. Mioskowski, *Angew. Chem., Int. Ed.*, 1998, **37**, 2580.

3 (*a*) K. R. Knudsen, T. Risgaard, N. Nishiwaki, K. V. Gothelf and K. A. Jorgensen, *J. Am. Chem. Soc.*, 2001, **123**, 5843; (*b*) M. Periasamy, G. Srinivas, G. V. Karunakar and P. Bharathi, *Tetrahedron Lett.*, 1999, **40**, 7577; (*c*) H. Adams, J. C. Anderson, S. Peace and A. M. K. Pennell, *J. Org. Chem.*, 1998, **63**, 9932; (*d*) A. Viso, R. Fernández de la Pradilla, C. Guerrero-Strachan, M. Alonso, M. Martínez-Ripoll and I. André, *J. Org. Chem.*, 1997, **62**, 2316; (*e*) C. Alvarez-Ibarra, A. G. Csák, B. Colmenero and M. L. Quiroga, *J. Org. Chem.*, 1997, **62**, 2478; (*f*) N. Taniguchi and M. Uemura, *Synlett*, 1997, 51; (*g*) D. Enders and R. Schiffers, *Synthesis*, 1996, 53; (*h*) N. Kise, K. Kashiwagi, M. Watanabe and J. Yoshida, *J. Org. Chem.*, 1996, **61**, 428; (*i*) M. Shimizu, M. Kamei and T. Fujisawa, *Tetrahedron Lett.*, 1995, **36**, 8607; (*j*) M. Shimizu, T. Iida and T. Fujisawa, *Chem. Lett.*, 1995, 609; (*k*) M. Meguro, N. Asao and Y. Yamamoto, *Tetrahedron Lett.*, 1994, **35**, 7395; (*l*) T. Shono, N. Kise, H. Oike, M. Yoshimoto and E. Okazaki, *Tetrahedron Lett.*, 1992, **33**, 5559; (*m*) M. T. Reetz, R. Jaeger, R. Drewlies and M. Hübel, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 103; (*n*) D. Tanner, C. Birgersson and H. K. Dhaliwal, *Tetrahedron Lett.*, 1990, **31**, 1903; (*o*) C. Betschart, B. Schmidt and D. Seebach, *Helv. Chim. Acta*, 1988, **71**, 1999; (*p*) P. Mangeney, T. Tejero, A. Alexakis, F. Grosjean and J. Normant, *Synthesis*, 1988, 255; (*q*) A. Chong, K. Oshima and K. B. Sharpless, *J. Am. Chem. Soc.*, 1977, **99**, 3420.

4 A. E. Taggi, A. M. Hafez and T. Lectka, *Acc. Chem. Res.*, 2003, **36**, 10.

5 (*a*) C. Rener, W. Huayue and Z. Yongmin, *J. Chem. Res. (S)*, 1999, 666; (*b*) T. Tsuritani, S. Ito, H. Shinokubo and K. Oshima, *J. Org. Chem.*, 2000, **65**, 5066; (*c*) K. Maeda, H. Shinokubo and K. Oshima, *J. Org. Chem.*, 1998, **63**, 4558; (*d*) M. Z. Liu, Z. W. Guo and Y. Z. Hui, *Youji Huaxue*, 1997, **17**, 319; (*e*) R. Lin, L. Chen and Y. Zhang, *Youji Huaxue*, 1990, **10**, 454; (*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.