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THE DIASTEREOSELECTIVE ADDITION OF TIN(II) ENOLATES DERIVED FROM CARBOXYLIC THIOESTERS TO α-IMINOESTER

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The diastereoselective addition of the Sn(II) enolates derived from carboxylic thioesters to α-iminoester is described. The Sn(II) enolates of t-butylthiol esters react smoothly with α-iminoester to afford the corresponding β-aminoacid derivatives in good yield with high diastereoselectivity.

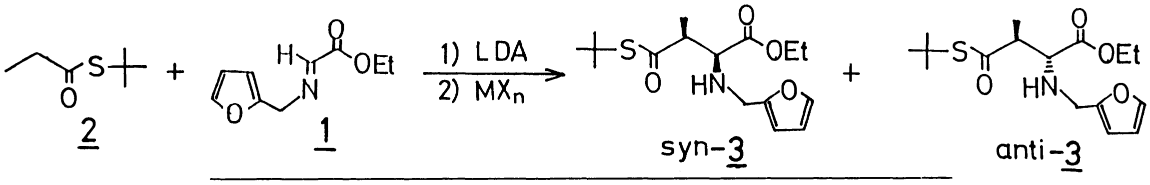
Imines are one of the most promising classes of compounds for the synthesis of nitrogen containing molecules, such as amino sugars, amino acids, and β-lactams. Recently, much effort1) has been made to employ imino compounds for the preparation of these valuable natural products. However, because of the low reactivity of imines compared to the corresponding carbonyl compounds, and also of various types of side reactions,2) such as oligomerization or abstraction of the α-proton, there still remain several problems in employing imino compounds for carbon-carbon bond forming reactions.

We have already reported various stereoselective aldol-type reactions by the use of Sn(II) enolates3) and, in these reactions, it was shown that the Sn(II) atom has considerable affinity toward the nitrogen atom. Therefore Sn(II) is expected to efficiently activate the imino group and, in addition, high stereoselectivity can be anticipated in the addition reaction of Sn(II) enolates to imines based on the characteristic properties of Sn(II) species.

In this communication, we wish to report a highly diastereoselective addition of the Sn(II) enolate derived from carboxylic thioesters to α-iminoester <u>1</u> which is prepared easily from ethyl glyoxylate and furfurylamine.4) This iminoester is highly reactive due to the electron withdrawing effect of the ethoxycarbonyl group. Moreover, it can be purified by vacuum distillation without polymerization, and stored in a refrigerator for more than a week.

First, we examined the effect of metals in the addition of various metal enolates to the α-iminoester <u>1</u>. As shown in Table 1, in cases of lithium and magnesium enolates, no adduct was obtained, probably because the α-iminoester was decomposed by the strongly basic enolates. Titanium and aluminum enolates gave the adducts in low yields. However, it is noted that, in case of titanium enolate, the preferential formation of anti-isomer is observed. Contrary to these results, Sn(II) enolates afforded the syn-isomer5) of β-aminoacid derivative <u>3</u> in good yield and with high stereoselectivity, as expected. Especially, in the case of stannous chloride, the best yield and very high syn-stereoselectivity were achieved.

Table 1. The effect of metals[a)]



Entry	MX$_n$	Yield/%	syn : anti[b)]
1	(Li)	0	——
2	$MgCl_2$	0	——
3	$ZnCl_2$	0	——
4	$Ti(O^iPr)_2Cl_2$	30	29 : 71
5	Et_2AlCl	25	50 : 50
6	$SnCl_2$	72	95 : 5
7	$SnBr_2$	53	93 : 7
8	$Sn(OTf)_2$	60	80 : 20

a) The reaction was carried out in Et_2O at -78 °C.
b) Determined by HPLC analysis (LiChrosorb SI60, AcOEt-hexane).

In the next stage, the effect of the solvents on this reaction was examined (Table 2).

Table 2. The effect of solvents

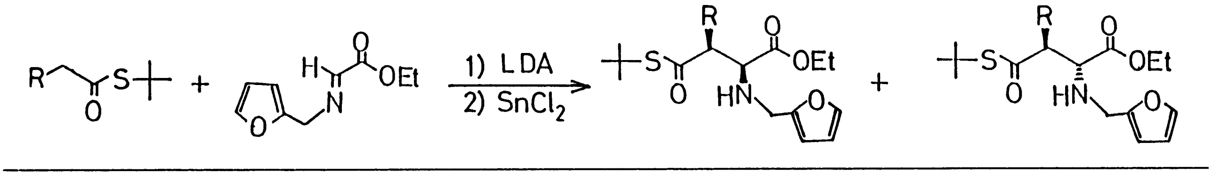
Entry	Solvent	Yield/%	syn : anti[b)]
1	Et_2O	72	95 : 5
2	THF	65	86 : 14
3	DME	60	91 : 9
4	CH_2Cl_2	65	82 : 18
5	Toluene	60	71 : 29
6	Et_2O[a)]	82	95 : 5

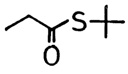
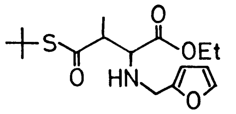
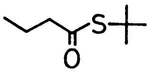
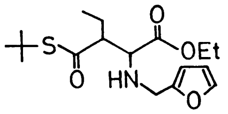
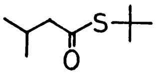
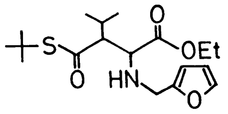
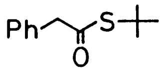
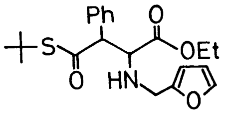
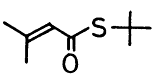
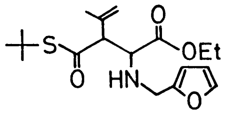
a) Two equivalents of Sn(II) enolate were employed to α-iminoester.
b) Determined by HPLC analysis (LiChrosorb SI60, AcOEt-hexane).

In every case, the syn adduct was obtained in good yield, and particularly when ether was used as solvent the best results were obtained in both yield and diastereoselectivity. Furthermore, when two equivalents of Sn(II) enolate were employed, the yield of the β-aminoacid derivative 3 improved to 82%.

Then, the addition reactions of several thioester enolates were tried under the best reaction conditions. In all cases, the β-aminoacid derivatives were obtained in good yield and with high diasteroselectivity (Table 3).

Table 3. Various thioester enolates[a)]



Entry	Thioester	Product[b)]	Yield/%	Diastereomer ratio[c)]
1			82	95 : 5
2			61	95 : 5
3			60	95 : 5
4			68	93 : 7
5			60	——

a) The reaction was carried out in Et_2O at -78 °C.

b) All the products gave satisfactory ^1H-NMR and IR spectra.

c) Diastereomer ratio was determined by HPLC analysis.

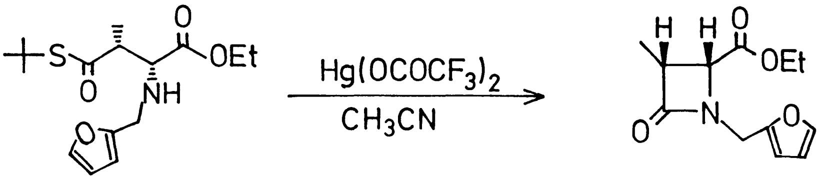
A typical procedure is described for the reaction of t-butyl propanethioate (2) with ethyl N-furfuryliminoacetate (1); under an argon atmosphere, to the solution of lithium diisopropylamide (0.68 mmol) in 2 ml of dry ether was added t-butyl propanethioate (2) (100 mg, 0.68 mmol) in 1.5 ml of dry ether at -78 °C over five minutes. After the mixture was stirred for 30 minutes, stannous chloride (156 mg, 0.82 mmol) was added as a powder and the mixture was vigorously stirred for another 30 minutes. To this mixture, ethyl N-furfuryliminoacetate (1) (62 mg, 0.34 mmol) was added and the reaction mixture was stirred for 3 h at -78 °C. The reaction was quenched by adding pH 7 phosphate buffer and the mixture was filtered through Celite pad and the product was extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4. After evaporation of the solvents, the crude product was purified by silica gel TLC (AcOEt-hexane) to afford ethyl 3-(t-butylthio)carbonyl-2-furfurylaminobutylate (3) (92 mg, 82% yield, syn:anti=95:5).

Thus, it is noted that the Sn(II) enolates of t-butylthioesters react smoothly with α-iminoester to give the corresponding β-aminothioesters in good yield with high diastereoselectivity.

Further applications of the present reaction are now under way.

References

1) For example, T. Iimori and M. Shibasaki, Tetrahedron Lett., 26, 1523 (1985); Y. Yamamoto, W. Ito, and K. Maruyama, J. Chem. Soc., Chem. Commun., 1985, 1131; T. Chiba, M. Nagatsuma, and T. Nakai, Chem. Lett., 1984, 1927.
2) J. -C. Fiaud and H. B. Kagan, Tetrahedron Lett., 1971, 1019.
3) T. Mukaiyama, N. Iwasawa, R. W. Stevens, and T. Haga, Tetrahedron, 40, 1381 (1984); and the references cited therein.
4) G. H. Hakimelahi and G. Just, Synth. Commun., 10, 429 (1980).
5) The relative stereochemistry was determined as follows: On treatment of the β-aminoacid derivative 3 with mercuric trifluoroacetate (see Ref. 6), the corresponding β-lactam was obtained in good yield. The examination of NMR spectrum indicates that the β-lactam thus obtained has cis configuration (J=6.0 Hz) and accordingly, it is concluded that the β-aminoacid derivative 3 has 2,3-syn stereorelationship.



6) Masamune reported that mercuric trifluoroacetate is effective for esterification and lactonization reactions of thioesters; S. Masamune, S. Kamata, and W. Schilling, J. Am. Chem. Soc., 97, 3515 (1975).

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