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A NOVEL METHOD FOR THE STEREOSELECTIVE SYNTHESIS OF β-AMINOACID DERIVATIVES VIA TIN(II) CARBOXYLIC THIOESTER ENOLATES

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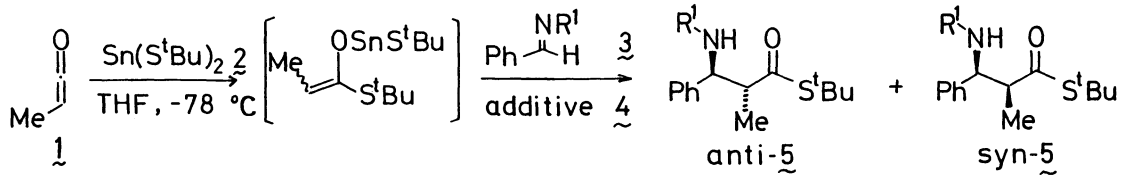
Tin(II) carboxylic thioester enolates, formed in situ from stannous 2-methyl-2-propanethiolate and ketenes, react with imines in the presence of stannous triflate to give the corresponding β-aminocarboxylic thioesters in an *anti*-selective manner. This method is successfully applied to a diastereoselective synthesis of a carbapenem antibiotic PS-5 intermediate.

In the previous communication,[1] we have demonstrated that tin(II) carboxylic thioester enolates, formed in situ from stannous thiolates and ketenes, react with aldehydes to afford the corresponding β-hydroxycarboxylic thioesters in excellent yields, and by the use of chiral diamine, the reaction proceeds enantioselectively. In addition, it has also been reported that tin(II) enolates possess enhanced reactivities toward ketones, which realize the directed aldol reaction between different two ketones.[2] In the course of our continuous investigations using the tin(II) carboxylic thioester enolates, the employment of the other electrophiles than aldehydes was studied. And it was found that the tin(II) enolates also react with imines, which are generally less electrophilic than aldehydes, to give the nitrogen analogs of aldol-type products. Now, we wish to report a stereoselective synthesis of β-aminocarboxylic thioesters by the aldol-type reaction of the tin(II) carboxylic thioester enolates with imines.

In the first place, the tin(II) carboxylic thioester enolate, formed in situ from stannous 2-methyl-2-propanethiolate and methylketene, was allowed to react with N-benzylidenebenzylamine (3a) in THF at -78 °C and the corresponding β-aminocarboxylic thioester was obtained in 41% yield with relatively low (72/28) diastereomer ratio (Table 1, Run 1). Of several imines derived from benzaldehyde, 3b and 3c showed only poor reactivities toward the enolate. However, the addition of stannous triflate effectively promoted the reactions with 3b and 3c to afford the corresponding β-aminocarboxylic thioesters in good yields. It was found that a high yield and an anti-selectivity were achieved especially in the case of N-benzylidenediphenylmethylamine (3c) (Table 1). It is supposed that the bulkiness of N-substituent, diphenylmethyl group, raises the selectivity and prevents side reactions of the imine such as oligomerization, consequently leading to the increase of the yield. In fact, unreacted N-benzylidenediphenylmethylamine was recovered even after the usual work up with H_2O, showing the stability of the

imine (3c) under the reaction conditions.

Based on these preliminary experiments, various kinds of β-amino carboxylic thioesters were obtained in good yields with high diastereoselectivities as shown in Table 2.



Scheme 1.

Table 1.

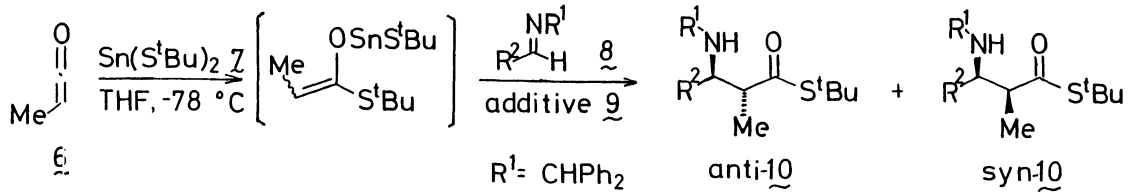
Run	Imine (R^1=)	Additive	Time/h	Yield/%	anti : syn
1	$PhCH_2$ (3a)	none	1.5	41 (5a)	72 : 28[a)b)]
2	3a	$Sn(OTf)_2$	1.5	42 (5a)	73 : 27[a)b)]
3	Ph (3b)	none	12	0	——
4	3b	$Sn(OTf)_2$	12	59 (5b)	58 : 42[c)]
5	Ph_2CH (3c)	none	12	trace (5c)	——
6	3c	$Sn(OTf)_2$	12	89 (5c)	96 : 4[a)b)]

Molar ratio of 1 : 2 : 3 : 4 = 1.2 : 1.0 : 0.75 : 0.9.

a) The ratio was determined by ^1H NMR spectroscopy.

b) After conversion to the corresponding β-lactam,[3] the stereochemistry was determined by ^1H NMR spectra. $J_{3,4}$(Hz) : anti-5a, 2.1; syn-5a, 5.3; anti-5c, 2.2; syn-5c, 6.0.

c) The stereochemistry was not determined.



Scheme 2.

Table 2.

Run	Imine (R^2=)	Additive	Method	Yield/%	anti : syn
1	Ph (8a)	$Sn(OTf)_2$	A	89 (10a)	96 : 4[a)c)]
2	PhCH=CH (8b)	$Sn(OTf)_2$	A	60 (10b)	81 : 19[a)c)]
3	(8b)	$SnBr_2$	A	55 (10b)	84 : 16[a)c)]
4	$(CH_3)_2CH$ (8c)	$Sn(OTf)_2$	B	83 (10c)	92 : 8[b)c)]
5	$Ph(CH_2)_2$ (8d)	$Sn(OTf)_2$	B	65 (10d)	92 : 8[a)c)]

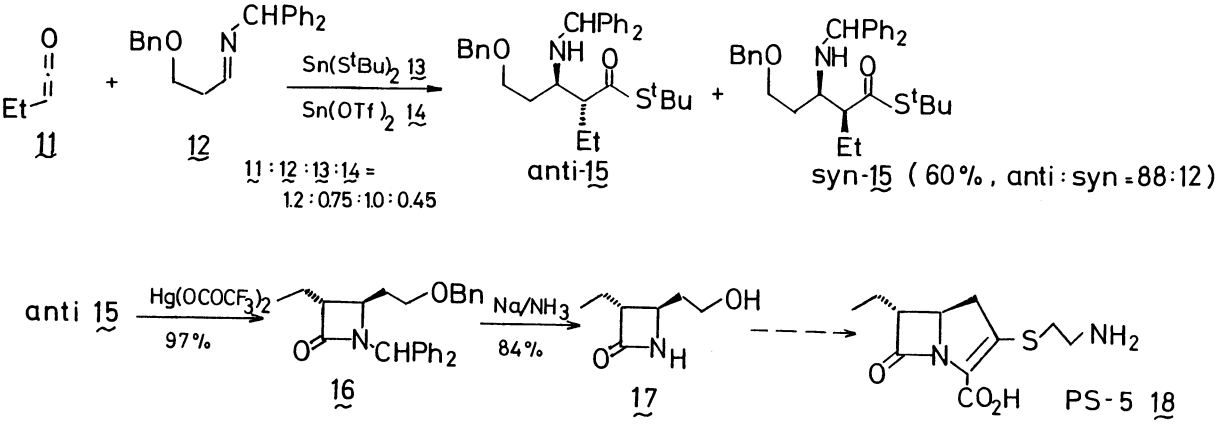
Method A : Molar ratio of 6 : 7 : 8 : 9 = 1.2 : 1.0 : 0.75 : 0.9.
Method B : Molar ratio of 6 : 7 : 8 : 9 = 1.2 : 1.0 : 0.5 : 0.33.

a) The ratio was determined by ^{1}H NMR spectroscopy.
b) Each isomer was isolated by PTLC.
c) After conversion to the corresponding β-lactam,[3] the stereochemistry was determined by ^{1}H NMR spectra. $J_{3,4}$(Hz) : anti-10a, 2.2; syn-10a, 6.0; anti-10b, 2.1; syn-10b, 5.4; anti-10c, 2.2; syn-10c, 5.4; anti-10d, 2.2; syn-10d, 5.4.

The following is a typical procedure for the preparation of *t*-butyl 3-diphenylmethylamino-2-methyl-3-phenylpropanethioate. To a THF solution (2 ml) of 1,1′-dimethylstannocene (97 mg, 0.35 mmol) was added 2-methyl-2-propanethiol (63 mg, 0.70 mmol) at room temperature under an argon atmosphere. After the mixture was stirred for 20 min, methylketene (0.42 mmol) in THF (0.84 ml), N-benzylidenediphenylmethylamine (71 mg, 0.26 mmol), and stannous triflate (131 mg, 0.32 mmol) were successively added at -78 °C. After the mixture was stirred at this temperature for 12 h, phosphate buffer was added to the reaction mixture which was subsequently extracted with chloroform. The organic layer was washed with a saturated solution of NaCl, dried with Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by preparative TLC (silica gel) to afford *t*-butyl 3-diphenylmethylamino-2-methyl-3-phenylpropanethioate (89%, anti/syn = 96/4).

The aldol-type reactions using imines as acceptors of enolates have been far less studied.[4] In particular there are only a few reports on enolizable imines[5,6] because of their own side reactions such as oligomerization and α-proton abstraction of imines. Therefore, this method provides a useful tool for the stereoselective synthesis of β-aminoacid derivatives, which are versatile precursors for the β-lactam synthesis.

Then, in order to demonstrate the potential utility of the above mentioned aldol-type reaction, we applied the present reaction to the stereoselective synthesis of a carbapenem antibiotic PS-5 intermediate. According to Scheme 3,



Scheme 3.

the tin(II) enolate, derived from ethylketene and stannous 2-methyl-2-propanethiolate, was allowed to react with the appropriately functionalized imine (12)[7] and the corresponding β-aminocarboxylic thioester (15) was obtained in an anti-selective manner as expected (60%, anti/syn = 88/12). The desired anti-product (15) which was isolated by preparative TLC, was treated with mercuric trifluoroacetate (2.0 equiv.) in acetonitrile for 12 h at room temperature to give the fully protected β-lactam (16) in 97% yield.[3] Then 16 was subsequently transformed to PS-5 key intermediate (17) by Birch reduction (Na/NH_3, 10 min) in 84% yield. The alcohol (17)[8] was identified as a single isomer by ^1H NMR.

Thus, it is noted that tin(II) carboxylic thioester enolates, formed in situ from stannous thiolates and ketenes, react with imines to give the corresponding β-aminocarboxylic thioesters and a key intermediate for the stereoselective synthesis of PS-5 is prepared in good yields with a good anti-selectivity by the use of the functionalized imine.

References

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2) R. W. Stevens, N. Iwasawa, and T. Mukaiyama, Chem. Lett., 1982, 1459.

3) Masamune et al. reported that mercuric trifluoroacetate was effective for esterification and lactonization of thioesters and recently Mukaiyama et al. used mercuric trifluoroacetate for the cyclization of β-aminothioesters and prepared various kinds of β-lactam compounds. S. Masamune, S. Kamata, and W. Schilling, J. Am. Chem. Soc., 97, 3515 (1975); T. Mukaiyama, H. Suzuki, and T. Yamada, Chem. Lett., 1986, 915.

4) D. A. Evans, S. V. Nelson, and T. R. Taber, "Stereoselective Aldol Reactions," in "Topics in Stereochemistry," ed by N. L. Allinger, E. L. Eliel, and S. H. Wilen, John Wiley & Sons, New York (1982), Vol.13, pp.59-65; T. Chiba and T. Nakai, Chem. Lett., 1985, 651; G. I. Georg, H. S. Gill, and C. Gerbardt, Tetrahedron Lett., 26, 3903 (1985); G. I. Georg and H. S. Gill, J. Chem. Soc., Chem. Commun., 1985, 1433; G. Cainelli, M. Contento, D. Giacomini, and M. Panunzio, Tetrahedron Lett., 26, 937 (1985).

5) I. Ojima and S. Inaba, Tetrahedron Lett., 21, 2081 (1980); J.-E. Dubois and G. Axiotis, ibid., 25, 2143 (1984).

6) T. Iimori and M. Shibasaki, Tetrahedron Lett., 26, 1523 (1985).

7) Iimori and Shibasaki reported that the aldol-type reaction of vinyloxyborane with the functionalized imine gave a key intermediate for the synthesis of thienamycin in one step (see Ref. 5).

8) The conversion of the alcohol (17) into optically active PS-5 (18) was already reported. D. Favara, A. Omodei-Sale, P. Consonni, and A. Depaoli, Tetrahedron Lett., 23, 3105 (1982).

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