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FURTHER STUDIES ON THE STEREOCHEMISTRY OF METAL ENOLATE-IMINE CONDENSATION REACTIONS

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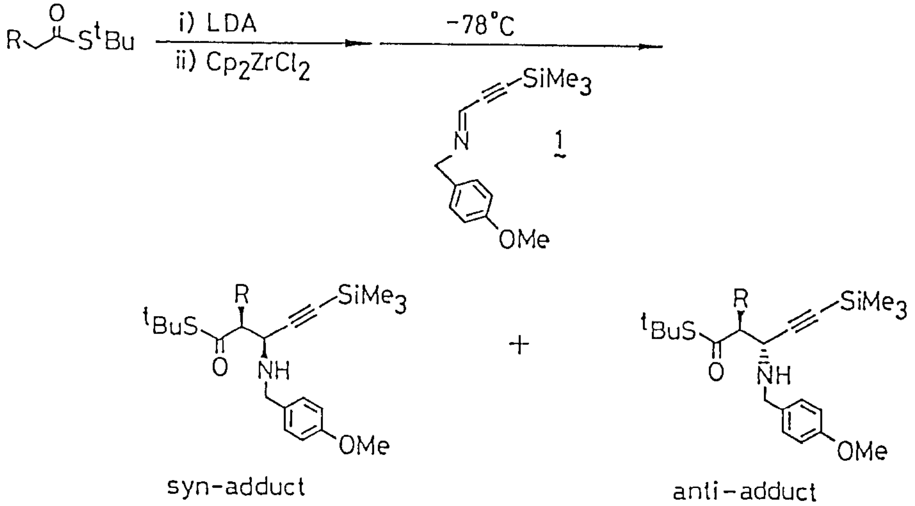
Abstract: Biscyclopentadienylchlorozirconium enolates derived from S-*tert*-butyl alkanethioates condensed with the imine 1 in a syn selective manner, while the diethylaluminum enolates derived from S-*tert*-butyl propanethioate and S-*tert*-butyl butanethioate reacted with 1 in an anti selective manner.

In recent years metal enolate-imine condensation reactions have been demonstrated to be a useful strategy for the construction of biologically significant compounds such as β-lactams, β-amino acid derivatives and amino sugars.[1] Of these reactions the boron enolate-imine condensation reaction developed in our group[1b,1d] and the tin(II) enolate-imine coupling reaction discovered by Mukaiyama[1c] seem to be particularly serviceable in terms of their generality[2] and their high stereoselectivity. The tin(II) enolate-imine condensation reaction is able to provide either syn or anti adducts in a stereoselective manner, depending on the preparative method of tin(II) enolates used,[1c] but boron enolates are useful only for the construction of anti adducts.[1b] Therefore we have searched for a methodology for the stereoselective synthesis of syn adducts for several years. In this communication we wish to report a new syn-selective metal enolate-imine condensation reaction as well as a variant of the anti-selective metal enolate-imine coupling reaction.

With a view to finding syn selectivity, the condensation reaction of a propionic acid derivative with the imine 1 derived from 3-trimethlysilyl-2-propynal and *p*-methoxybenzylamine[3] was carefully investigated under various conditions. At the outset, the zinc enolate of a propionic acid derivative was treated with the imine 1, but in all cases attempted nonselective formation of condensation products was observed in yields shown below (1. methyl propionate, syn : anti = *ca.* 1 : 1, 44%, 2. S-phenyl propanethioate, syn : anti = 1 : 1, 52%, 3. S-*tert*-butyl propanethioate, syn : anti = 1 : 1, 78%). Next,[4] we made a study of the reaction of the biscyclopentadienylchlorozirconium enolate derived from S-*tert*-butyl propanethioate with the imine 1, finding that a 4 : 1 mixture of the syn and anti adducts was produced (58% yield). Under these conditions several syn β-amino acid derivatives were obtained in a stereoselective manner, the results being summarized in Table 1. The general procedure is described for the condensation reaction of S-*tert*-butyl butanethioate with the imine

Table 1 β-Amino Acid Derivatives from S-tert-Butyl Alkanethioates

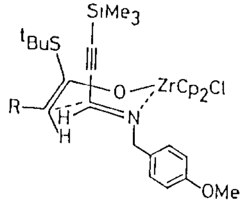


entry	R	procedure [a]	yield (%)	syn : anti [b]
1	Me	A	58	4 : 1
2	Et	A	57	5 : 1
3	i-Pr	B	43	21 : 1

a) A: The imine 1 was treated with the zirconium enolates for 60 min at -78°C, B: The imine 1 was treated with the zirconium enolate for 20 min at -78°C and for 2.5hr at 0-5°C. b) The ratio was determined after purification by silica gel column chromatography.

1 : To a solution of LDA (0.75mM) in 4 : 1 THF-hexane (2.6ml) was gradually added S-tert-butyl butanethioate (0.63mM) in THF (1ml) at -78°C and the mixture was stirred for 30 min. The lithium enolate solution was then injected via teflon tube to a solution of Cp_2ZrCl_2 (1.37mM) in THF (5ml) at -78°C. After stirring for 60 min (-78°C), the imine 1 (0.75mM) in THF (2ml) was added to the zirconium enolate in THF-hexane (-78°C). The reaction mixture was further stirred for 60 min (-78°C), and quenched with acetic acid- H_2O (0.04ml-1ml). After warming to 0-5°C, the reaction mixture was adjusted to pH 7-8 by adding saturated aqueous sodium bicarbonate, filtrated through celite, and extracted into ethyl acetate. The organic extracts were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo* to give a pale brown oil, which was purified by silica gel column chromatography (hexane-ether, 6 : 1), giving the anti adduct (9%) and the syn adduct (48%).[5]

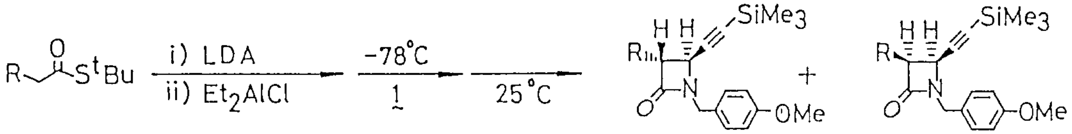
Since boron enolates derived from S-phenyl alkanethioates condense with the imine 1 in an anti selective manner,[1b] now either syn or anti products are available, depending on metal enolates used. The stereochemistry of the zirconium enolate derived from *S*-*tert*-butyl propanethioate has been already determined to be *E* (*E* : *Z* = *ca.* 9 : 1) by Evans.[6] By the same technique,[6] we have also determined the stereochemistry of the two zirconium enolates derived from *S*-*tert*-butyl butanethioate (*E* : *Z* = 18 : 1) and *S*-*tert*-butyl 3-methylbutanethioate (*E* pure). Based on these results, it seems likely that zirconium enolates react with the imine 1 preferentially *via* *pseudo*-chair transition state A , giving syn selective condensation products.[7,8]



A

In striking contrast to these results, we have found that the diethylaluminum enolate derived from *S*-*tert*-butyl propanethioate reacts with the imine 1 in an anti selective manner (78%, anti : syn = 4 : 1). This reaction is strongly characterized by the fact that the β-lactam rings 2 and 3 are simultaneously formed just by warming the reaction mixture to room temperature (25°C). The several reactions were carried out, and the results are summarized in Table 2.[9] The general procedure is described for the condensation reaction of

Table 2   β-Lactams from *S*-*tert*-Butyl Alkanethioates



2   3

entry	R	procedure [a]	yield(%)	2 : 3 [b]
1	Me	A	78	4 : 1
2	Et	B	80	3 : 1
3	*i*-Pr	A	73	1 : 7

a) A: The reaction mixture was stirred at 25°C for 4.5 hr, B: The reaction mixture was stirred at 25°C for 8 hr. b)The ratio was determined after purification by silica gel column chromatography.

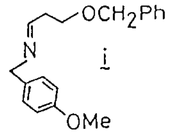
S-*tert*-butyl propanethioate with the imine 1 : To a solution of LDA (1.64mM) in 4 : 1 THF-hexane (8.2ml) was added *S*-*tert*-butyl propanethioate (1.37mM) in THF (1.5ml) at -78°C, and the reaction mixture was stirred for 30 min. To this lithium enolate solution was then added diethylaluminum chloride in hexane (2.62ml, 3.0mM)(-78°C), and the whole reaction mixture was stirred at the same temperature for 1hr followed by addition of the imine 1 (1.64mM) in THF (2.5ml). After stirring for 1 hr (-78°C),[10] the reaction mixture was gradually warmed to room temperature (25°C), and stirred for 4.5 hr. The reaction was quenched by adding saturated aqueous potassium bicarbonate, filtrated through celite, and extracted with ethyl acetate. The organic extracts were washed (brine), dried (Na_2SO_4), and concentrated *in vacuo* to give a reddish brown oil, which was purified by silica gel column chromatography (hexane-ether, 2 : 1) to afford the β-lactam 2 (63%) and 3 (15%).

It appears that the reactions (Table 2, entry 1 and 2) proceed preferentially *via* *pseudo*-boat transition state leading to the anti adducts mainly, while the reaction (Table 2, entry 3) affords the syn adduct selectively *via* the same transition state as depicted in the zirconium enolate case. However, rational explanation of these results is extremely difficult at present.

Although much more information is definitely required before a convincing mechanistic picture can be drawn for either of the metal enolate-imine condensation reactions described here, these reactions are of synthetic value.

References and Notes

1. (a) Ha, D.-C.; Hart, D.J.; Yang, T.-K. *J. Am. Chem. Soc.* 1984, *106*, 4819, Chiba, T.; Nakai, T. *Tetrahedron Lett.* 1985, *26*, 4647, Georg, G.I.; Gill, H.S. *J. Chem. Soc., Chem. Commun.* 1985, 1433, Cainelli, G.; Contento, M.; Giacomini, D.; Panunzio, M. *Tetrahedron Lett.* 1985, *26*, 937, Hatanaka, M.; Nitta, H. *ibid.* 1987, *28*, 69. (b) Iimori, T.; Shibasaki, M. *ibid.* 1985, *26*, 1523, Idem, *ibid.* 1986, *27*, 2149, Iimori, T.; Ishida, Y.; Shibasaki, M. *ibid*. 1986, *27*, 2153. (c) Mukaiyama, T.; Suzuki, H.; Yamada, T. *Chemistry Lett.* 1986, 915, Yamasaki, N.; Murakami, M.; Mukaiyama, T. *ibid.* 1986, 1013. (d) Ohtsuka, M.; Yoshida, M.; Kobayashi, S.; Ohno, M.; Umezawa, Y.; Morishima, H. *Tetrahedron Lett.* 1981, *22*, 2109. (e) For the reaction of allylic organometallic compounds with imines, see: Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Org. Chem.* 1985, *50*, 3115.
2. The both reactions are applicable to enolizable imines derived from saturated aldehydes and amines (e.g. benzylamine).
3. This imine affords very versatile condensation products.
4. The metal enolate derived from the lithium enolate and manganese(II) chloride also condensed with the imine 1, giving the β-lactams (anti, 23%; syn, 18%).
5. The stereochemistry of the both condensation products was determined by converting them to the β-lactams (*t*-BuMgCl in ether).
6. Evans, D.A.; McGee, L.R. *Tetrahedron Lett.* 1980, *21*, 3975.
7. The *Z*-enolate provided the condensation products in 20% yield (syn : anti = 1.3 : 1).



i

8. Although, in general, lithium enolates provide syn-adducts selectively, only *N*-trimethylsilyl imines and *N*-aryl imines can be utilized. See reference 1a.
9. The reaction (entry 2) should be useful for the asymmetric construction of PS-5. The diethylaluminum enolate derived from *S*-*tert*-butyl butanethioate reacted with the imine i, giving the *trans*-β-lactam (45%) exclusively.
10. The condensation reactions proceed at -78°C.

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