Tetrahedron Letters,Vol.28,No.4,pp 409-412,1987
Printed in Great Britain

0040-4039/87 $3.00 + .00
Pergamon Journals Ltd.

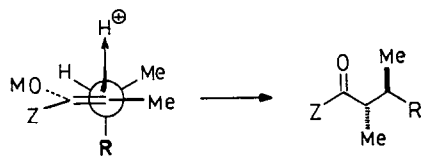
DIASTEREOSELECTIVE AUTO-PROTONATION OF ENOLATES ANTI-HOUK SELECTIVITY

Said BERRADA and Patrick METZNER*

Laboratoire de Chimie des Composés Thioorganiques (UA CNRS n° 480)
ISMRA, Université de Caen-Basse Normandie, 14032 Caen, France

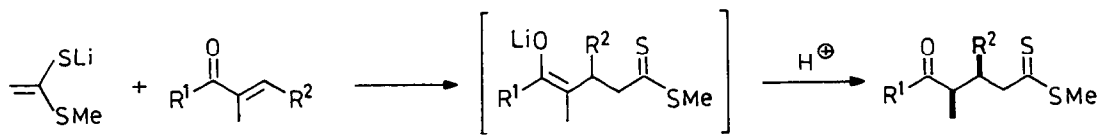
Abstract - 1,4-Addition reaction of lithiated methyl dithioacetate with α,β-disubstituted enones affords 5-oxodithioesters. The diastereoselectivity ranges from moderate to high (> 95:5) in favour of the syn isomer. This anti-Houk selectivity arises from an 'auto-protonation', involving transfer of the hydrogen α to the thiocarbonyl group towards the enolate moiety. A pseudo-cyclic transition state leading to the syn product is postulated.

The problem of stereochemical course of the electrophilic attack upon an enolate bearing a prochiral carbon adjacent to a chiral centre has not been addressed, in the acyclic series, until the past few years.[1-9] Model geometries for the transition structure of this reaction have been calculated by Houk and co-workers.[10] Some groups[2,3,5-7] have recently disclosed experimental results on the stereochemistry of the asymmetric protonation[11] of diastereotopic enolates **1**. The *anti* product **2** predominates in agreement with the Houk model.[10]



1 **2**

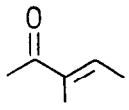
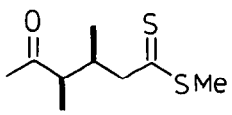
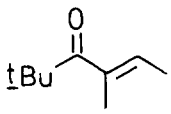
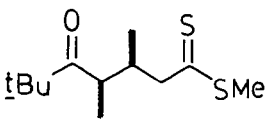
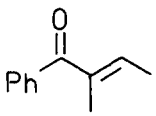
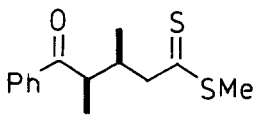
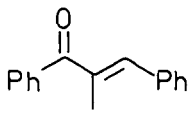
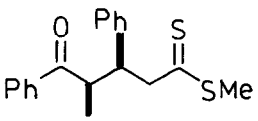
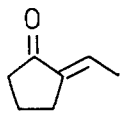
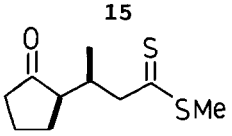
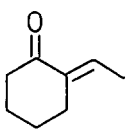
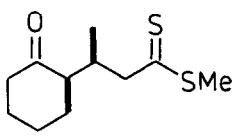
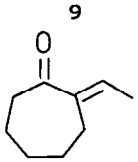
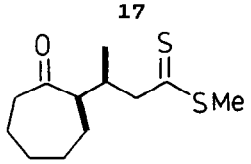
Our previous results have demonstrated that enethiolates are soft nucleophiles which undergo regioselective 1,4-addition with a variety of α-unsaturated ketones.[12-17] This prompted us to examine the addition reaction of lithium dithioacetate **3** with α,β-disubstituted enones **4-7** and the stereoselectivity of the protonation of generated enolates **11**. We now report that this reaction leads to products of *syn* stereochemistry, contrary to expectations from Houk model.



3 **4-7** **11** **12-15**

Deprotonation of methyl dithioacetate with lithium di-isopropylamide in tetrahydrofuran, followed by treatment with enones **4-7** around 0°C and quenching at -78°C with aqueous ammonium chloride gave 5-oxodithioalcanoates

Table. Protonation of 1,2-diastereotopic enolates

Entry	Enone	1,4-Additon reaction temp. °C	time	Product a)	Yield %	Diastereoisomers ratio *syn/anti*
1	 **4**	-5	20 mn	 **12**	62	76 : 24
2	 **5**	0 then 20	4 h 1 night	 **13**	64	90 : 10
3	 **6**	0	3 h 30 mn	 **14**	81	81 : 19
4	 **7**	0	4 h	 **15**	61	85 : 15
5	 **8**	-45	30 mn	 **16**	80	> 95 : 5
6	 **9**	-45	25 mn	 **17**	56 b)	> 95 : 5
7	 **10**	-25	20 mn	 **18**	80	94 : 6

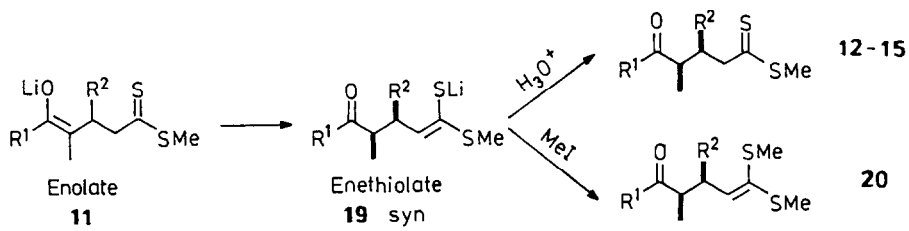
a) Major diastereoisomer. Configuration of compounds **13-18** was assigned by analogy with **12**. b) Some enone **9** was recovered (27% yield).

12-15 (table). The diastereoisomers were discerned by ^{13}C and 350 Mhz ^{1}H NMR. The *syn* configuration of the major diastereomer **12** was established by chemical correlation with the following compounds, prepared *via* reactions of known stereochemistry: (2R*,3S*) (3-methyl 2-pentyl) acetate, (3R*,4S*) 3,4-dimethyl-2-hexanone, and *trans* dihydro-4,5-dimethyl-2(3H)-furanone.

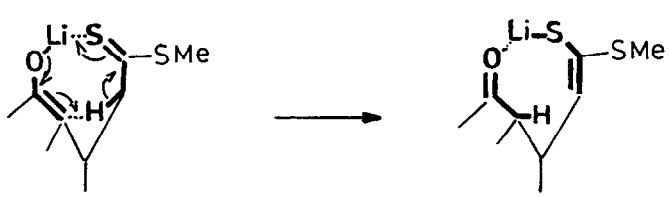
Starting from the enone **4** bearing methyl groups (entry 1), the *syn/anti* ratio is 76:24. Introduction of phenyl groups on the enone skeleton (entries 3,4) increases the percentage of *syn* isomer. The highest selectivity in this series was obtained with the *t*-butyl enone **5** (entry 2; 90:10).

These interesting selections in the acyclic series lead us to examine examples of enones generating cyclic enolates bearing a chiral side chain. Addition of lithium enethiolate **3** to 2-ethylidene cycloalcanones **8-10** yields oxodithioesters **16-18** with high *syn* selectivity (entries 5-7; ⩾94:6).

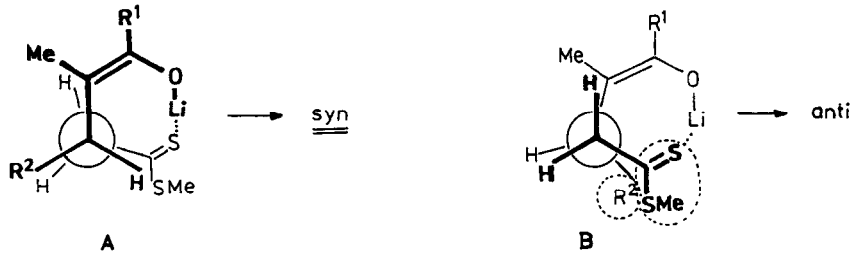
All cases studied so far afford the *syn* stereoisomer, though application of the Houk model **1** leads to an *anti* stereochemistry **2** (R = CH_2CS_2Me). To understand the difference we looked more carefully at the protonation step. From previous work,[13] we have learned that transfer of the acidic proton[18] α to the thiocarbonyl group toward the enolate moiety occurs quite easily, even under aprotic conditions. To monitor the actual species, present before addition of water, we quenched the 1,4-adduct (enolate **11** or enethiolate **19**) with iodomethane. Instead of an oxodithioester, we isolated the ketenedithioacetal **20** arising from S-alkylation[13] of enethiolate 19.



Proton transfer has thus taken place directly after the formation of enolate **11**. Stereochemistry is thus controlled at this step. An intermolecular proton delivery would probably lead to a Houk stereoproduct **2**. We prefer to put forward an intramolecular auto-protonation, involving a concerted pericyclic reaction of two 4 electrons and 4 centers moieties, depicted below.



Molecular models suggested two possible stereomodels **A** and **B** with an almost eclipsed conformation allowing good overlap between the hydrogen and π enolate orbitals. The steric interaction between R_2 and CS_2Me causes a severe destabilization of structure **B**. In contrast, model **A** appears relatively favoured and actually affords a *syn* product configuration.



Our study has brought a new solution to stereocontrol *via* 'autoprotonation' of diastereotopic enolates. It allows creation of two vicinal asymmetric centers of relative *syn* configuration by carbon-carbon bond formation in the acyclic series[19] and in cyclic systems bearing a chiral side chain. The structures obtained are present in a number of natural products. Studies aimed at exploiting the diastereoselectivity observed here and at looking closer to the protonation step mechanism are in progress.

REFERENCES

1 Evans D. A., in Morrison J. D., *'Asymmetric Synthesis', vol. 3, Stereodifferentiating Addition Reactions, part B, Academic Press, New-York*, 1984, p. 97.
2 Bernhard W., Fleming I., Waterson D., *J. Chem. Soc., Chem. Commun.*, 1984, 28-29.
3 Yamamoto Y., Maruyama K., *J. Chem. Soc., Chem. Commun.*, 1984, 904-905.
4 McGarvey G. J., Williams J. M., *J. Am. Chem. Soc.*, 1985, **107**, 1435-1437.
5 Fleming I., Lewis J. J., *J. Chem. Soc., Chem. Commun.*, 1985, 149-151.
6 Fleming I., Hill J. H. M., Parker D., Waterson D., *J. Chem. Soc., Chem. Commun.*, 1985, 318-321.
7 Kawasaki H., Tomioka K., Koga K., *Tetrahedron Lett.*, 1985, **26**, 3031-3034.
8 Fleming I., Kilburn J. D., *J. Chem. Soc., Chem. Commun.*, 1986, 305-306.
9 Kobayashi S., Mukaiyama T., *Chem. Lett.*, 1986, 221-224.
10 Paddon-Row M. N., Rondan N. G., Houk K. N., *J. Am. Chem. Soc.*, 1982, **104**, 7162-7166.
11 Duhamel L., Duhamel P., Launay J.-C., Plaquevent J.-C., *Bull. Soc. Chim. France*, 1984, II:421-430.
12 Metzner P., *J. Chem. Soc., Chem. Commun.*, 1982, 335-336.
13 Berrada S., Metzner P., Rakotonirina R., *Bull. Soc. Chim. France*, 1985, 881-890.
14 Metzner P., Rakotonirina R., *Tetrahedron*, 1985, **41**, 1289-1298.
15 Metzner P., Rakotonirina R., *Tetrahedron Lett.*, 1983, **24**, 4203-4206.
16 Berrada S., Metzner P., *Bull. Soc. Chim. France*, 1986, in the press.
17 Kpegba K., Metzner P., Rakotonirina R., *Tetrahedron Lett.*, 1986, **27**, 1505-1508.
18 Storer A. C., *Can. J. Chem.*, 1982, **61**, 1440-1448.
19 Bartlett P. A., *Tetrahedron*, 1980, **36**, 2-72.

(Received in France 26 October 1986)