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Configuration-dependent Stereochemistry in 2,4-Dichloro-3-pentanone—Its Enol Trimethylsilyl Ether Interconversion

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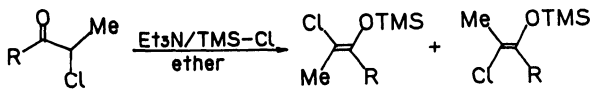
Et_3N-promoted enol trimethylsilylation of meso- and dl-2,4-dichloro-3-pentanone in ether respectively shows 97% Z- and 86% E-selectivity, while Z- and E-products respectively give dl (70% de) and meso (24% de) ketones stereoselectively upon protonation.

Stereochemistry of kinetic deprotonation of ketones may be explained by two types of steric interactions of groups on C_α with a carbonyl substituent and with an approaching base.[1,2] Here we report a novel example of kinetic deprotonation in which the reaction stereochemistry is mainly controlled by configuration of the carbonyl substituent. Figure 1 shows the reaction of meso-2,4-dichloro-3-pentanone (**1a**) with 2.2 equiv. Et_3N in the presence of 2.0. equiv chlorotrimethylsilane (TMS-Cl) in ether at 25 °C.[3] The reaction gave preferentially an enol silyl ether **2a** of Z-configuration practically in quantitative yield based on the consumed ketone.[4] The Z-content in the product slightly decreased as the reaction progressed. This arises from concomitant occurrence of isomerization of meso-**1a** to



1a (R=CHMeCl)	Z-2	E-2
meso	97%	3%
dl	14%	86%
1b (R=Me)	49%	51%

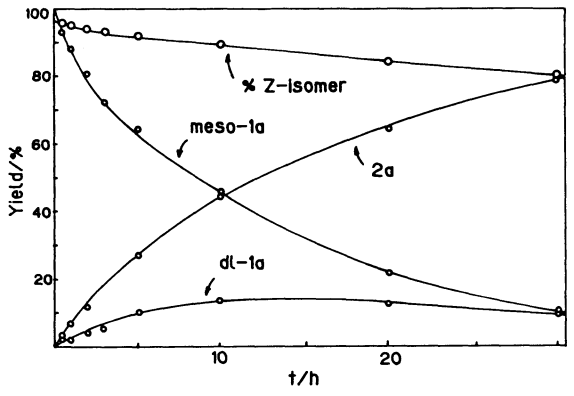


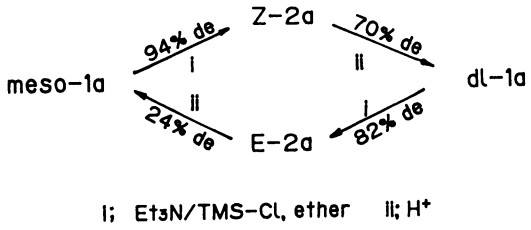
Fig. 1. Enol silylation of meso-**1a**.

dl-**1a** during the enol silylation; since the enol silylation proceeded more rapidly than the isomerization, unreacted ketone did not reach equilibrium (meso/dl=30/70 at 25 °C) even after 80% completion of the silylation. Both E- and Z-**2a** did not undergo isomerization under the reaction conditions.[5] Extrapolation of Z/E ratios to the zero conversion gives a ratio of 97/3 indicating the enol silylation of meso-**1a** to be highly stereoselective in preference for the formation of Z-isomer

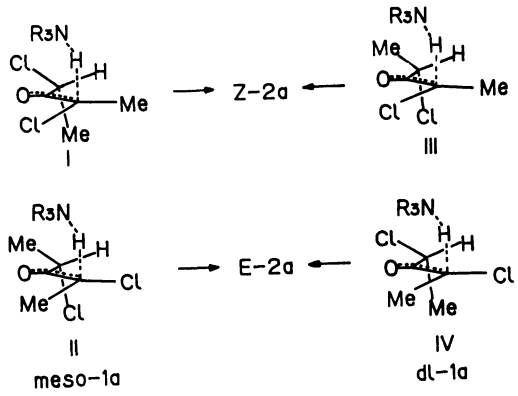
with 94% de. In contrast, a similar analysis for the reaction of dl-**1a** under the same conditions revealed that dl-**1a** predominantly yielded E-**2a** with an extrapolated value of 82% de. These results are interestingly compared with the fact that the enol silylation of 3-chloro-2-butanone (**1b**) under the same reaction conditions gave a 1:1 mixture of E- and Z-isomers as for 2-chloro-3-trimethylsiloxy-2-butene.

A large diastereoselectivity (DSS), which is a stereochemical split between the reactions of the two diastereomeric ketones [DSS=%Z (from meso-**1a**)-%Z (from dl-**1a**)], strongly suggests the deprotonation of **1a** to be a kinetically controlled process, although Et_3N-promoted deprotonation of ketones is generally classified as a thermodynamic process.[6] meso- and dl-**1a** are equally subject to the steric interactions of C_α-groups (Me and Cl) with a carbonyl group R and with Et_3N if R acts as a steric bulk. Clearly the configuration of R plays a major role in controlling the reaction stereochemistry.

Ketonization of **2a** to **1a** was also diastereoselective. Interestingly, Z-**2a** and E-**2a** respectively gave upon treatment with concd. HCl in THF at 25 °C a 85/15 and a 38/62 mixtures of dl- and meso-**1a** showing a reversed diastereoselectivity as compared to the forward reaction. Both ketones did not isomerize significantly to each other under acidic hydrolysis conditions. Thus, the combined results show a peculiar stereochemical cycle in ketone-enolate interconversion (Scheme 1) formally against microscopic reversibility.



Scheme 1.



Scheme 2.

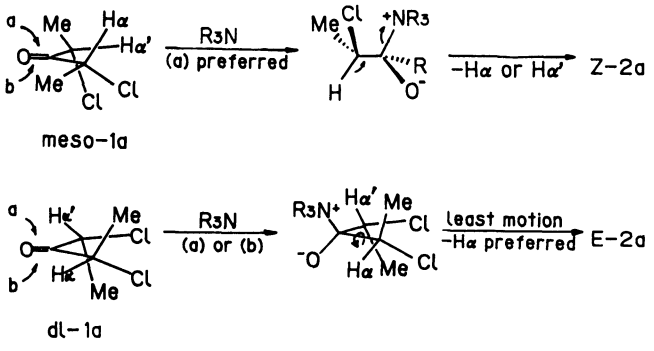
Stereochemistry of the enol silylation of **1a** markedly changes with solvent and base, as shown in Table 1. Polar solvents reduced both stereo- and diastereoselectivities. For example, in DMF the enol silylation occurred much more rapidly but showed lower stereoselectivity than in ether. At -60 °C, both meso- and dl-**1a** exhibited small Z-selectivity without a significant DSS. It should be noted that this does not arise from a rapid isomerization between meso- and dl-**1a**; in fact, the enol silylation proceeded much more rapidly than the isomerization in DMF. Replacement of Et_3N with DABCO or n-Bu_3N did not cause a significant change in the stereochemistry but with DBU resulted in a marked decrease in the stereosectivity. Deprotonation with a strong base LDA did not show a significant diastereoselectivity. Both meso- and dl-**1a** gave exclusively E-**2a** when the ketone was added to a solution of LDA in the presence of TMS-Cl at -78 °C, although the stereoselectivity significantly decreased under thermodynamic conditions.[7,8]

Table 1. Stereochemistry in Enol Trimethylsilylation of 2,4-Dichloro-3-pentanone (**1a**)[a]

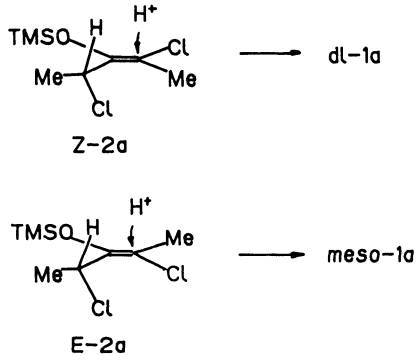
Base	Reaction conditions Solvent	Temp/°C	% Z-**2a**[b] from meso-**1a** ($t_{1/2}$)[c]	dl-**1a** ($t_{1/2}$)[c]	DSS/%
Et_3N	ether	25	97 (14h)	14 (17h)	83
Et_3N	C_6H_6	25	97 (5h)	16 (11h)	81
Et_3N	CH_2Cl_2	25	87 (3h)	38 (4h)	45
Et_3N	DMF	25	52 (3m)	41 (3m)	11
Et_3N	DMF	-60	57	60	3
Et_3N	DMF/C_6H_6 (1:9)	25	88 (2h)	22 (2h)	66
DABCO	C_6H_6	25	94	16	78
$n\text{-}Bu_3N$	C_6H_6	25	92[d] (v.slow)	15[d] (v.slow)	77
DBU	C_6H_6	25	46[e] (<1m)	9[e] (<1m)	37
LDA[f]	THF	-78	4[e]	10[e]	6
LDA[g]	THF/HMPA (2:1)	-78	20[e]	37[e]	17
LDA[g]	THF	-78	10[e]	23[e]	13

a) All reactions were carried out by taking **1a**, 2.2 equiv. base, and 2.0 equiv. TMS-Cl in a given solvent (ca. 0.25 M for **1a**). b) Determined by extrapolation to the zero conversion except otherwise noted. c) Time at which 50% of **1a** was converted to **2a**. d) Determined after 5% conversion. e) Determined after completion of the reaction. f) **1a** was added to a solution of LDA and TMS-Cl. g) TMS-Cl was added to an enolate solution prepared from 1.0 equiv. LDA.

Precise origin of the large diastereoselectivity for the Et_3N-promoted enol silylation of **1a** is not clear yet. One explanation is to assume enolate-like transition states I for meso-**1a** and IV for dl-**1a** in which C_α'-groups take such a conformation that it provides the least hindered space for a coming base, as shown in Scheme 2. Steric difference between I and II and that between IV and III are presumably more pronounced in the less polar media in which the enolate must exist as a contact ion pair. For deprotonation with a strong base like LDA, the structure of the transition state may be close to the most stable conformer of **1a**. The observed high E-selectivity would suggest that both meso and dl ketones have stable conformations in which two chlorine atoms on C_α and C_α' lie in anti-clinal regions



Scheme 3.



Scheme 4.

to the carbonyl plane. This is supported by MM2 calculations which indicate that in a stable conformer, dihedral angles Cl-C_α-CO, Cl-C_α'-CO, Me-C_α-CO, and Me-C_α'-CO are 163.4, 106.6, 15.7, and 35.8° respectively for meso-**1a** and 144.0, 144.9, 89.4, and 88.6° for dl-**1a**.[9] Alternatively, diastereoselective formation of enolate might be accomplished by addition of R_3N to carbonyl group[10] followed by subsequent anti elimination of R_3NH^+, as shown in Scheme 3. The addition is presumably a diastereotopic face-differentiated process for meso-**1a**, while the additions from a and b faces are identical for dl-**1a** but the subsequent elimination step would be stereoselective if we assume the least motion. The diastereoselectivity in protonation of **2a** may be explained by assuming that the protonation occurs at the olefinic carbon of a preferred conformation of **2a** in which an allyllic Me group is anti to the double bond plane, as shown in Scheme 4.[11,12] A further study on mechanistic details is under way.

References

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2) C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn, and J. Lampe, J. Org. Chem., 45, 1066 (1980).
3) meso- and dl-**1a** were prepared according to the literature [G. Claeson and A. Thalen, Arkiv Kemi., 25, 321 (1965)].
4) Stereochemical assignment for Z-**2a** [NMR (CCl_4) δ=0.29 (9H, s), 1.57 (3H, d, J=6.5 Hz), 2.14 (3H, s), 4.87 (1H, q, J=6.5 Hz)] and E-**2a** [NMR δ=0.29 (9H, s), 1.53 (3H, d, J=6.5 Hz), 2.01 (3H, s), 5.30 (1H, q, J=6.5 Hz)] was confirmed by a stereospecific conversion to 2,4-dimethyl-2-chloro-8-oxabicyclo[3.2.1]oct-6-en-3-one promoted by silver perchlorate in the presence of furan in nitromethane [N. Shimizu, M. Tanaka, and Y. Tsuno, J. Am. Chem. Soc., 104, 1330 (1982)].
5) Prolonged heating under reflux caused elimination of HCl yielding 4-chloro-3-trimethylsiloxy-1,3-pentadiene.
6) H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, J. Org. Chem., 34, 2324 (1969).
7) Z. A. Fataftah, I. E. Kopka, and M. W. Rathke, J. Am. Chem. Soc., 102, 3959 (1980).
8) Reaction of **1a** with LDA in the presence of TMS-Cl in ether did not give **2a** appreciably but yielded 2,4-dichloro-3-trimethylsiloxypentane as the major product.
9) Enol silylation of **1b** with LDA at -78 °C in THF gave a 77/23 mixture of E- and Z-isomers consistent with MM2 calculations which suggest that a stable conformer of **1b** has a dihedral angle Cl-C_α-CO of 141.5°.
10) P. Y. Bruice, J. Am. Chem. Soc., 105, 4982 (1983).
11) M. H. Novice, H. R. Seikaly, A. D. Seiz, and T. T. Tidwell, J. Am. Chem. Soc., 102, 5835 (1980).
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