“*Syn-Effect*” in the Conversion of (*E*)-α,β-Unsaturated Esters to the Corresponding β,γ-Unsaturated Esters

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The stereochemistry in the conversion of (*E*)-α,β-unsaturated esters to the corresponding β,γ-unsaturated esters by treatment with lithium hexamethyldisilazide in the presence of HMPA was investigated. The Z/E ratios of the resulting β,γ-unsaturated esters varied according to the γ-substituents of the (*E*)-α,β-unsaturated esters. This phenomenon was rationalized by “*syn-effect*” which may be attributed primarily to $\sigma \rightarrow \pi^*$ interaction and/or 6π-electron homoaromaticity.

It is well known that treatment of dienolates derived from α,β-unsaturated carbonyl compounds with electrophiles, such as proton or alkyl halides, afforded deconjugated β,γ-unsaturated carbonyl compounds.[1,2] The reaction of ethyl (*E*)-2-alkenoates with lithium amides in the presence of HMPA was reported to give sterically unfavored (*Z*)-3-alkenoates as main products. The stereoselectivity was explained by the stability of the produced anion or cyclic transition model at the deprotonation.[1a-c] Furthermore, the deconjugative α-alkylation of (*E*)-4-methoxy-2-butenoate gave (*Z*)-4-methoxy-3-butenoate selectively[2b] and (*E*)-4-methylthio-2-butenoate produced a mixture of (*E*)- and (*Z*)-4-methylthio-3-butenoate.[2a] However, there was no explanation about the stereochemical outcomes. The rational elucidation for the origin of these puzzling phenomena has been strongly desired.

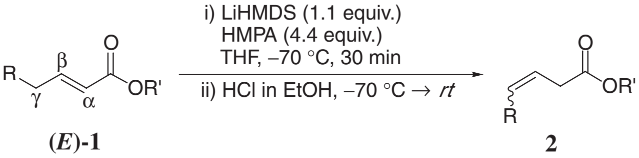
Previously we investigated the stereochemistry in the isomerization of α-unsubstituted (*E*)-vinylic sulfones to the corresponding allylic sulfones and the desulfonylation reaction of α,α-dialkylated allylic sulfones with a base.[3a,b] In both cases, the sterically unfavorable (*Z*)-allylic sulfones and (*Z*)-alkadienes were predominantly formed, respectively. These results were rationalized by “*conformational acidity*” which essentially implies “*syn-effect*.”[4] We proposed that the “*syn-effect*” was primarily caused by 6π-electron homoaromaticity and/or $\sigma \rightarrow \pi^*$ interaction.[3b] Very recently we have investigated the “*syn-effect*” in the conversion of α-fluorinated (*E*)-vinylic sulfones to the corresponding allylic sulfones and have shown that $\sigma \rightarrow \pi^*$ interaction is the most important factor for the “*syn-effect*.”[3c] In the present study, we precisely investigated the stereochemistry in the conversion of (*E*)-α,β-unsaturated esters to the corresponding β,γ-unsaturated esters by treatment with a base. The Z/E ratios of the resulting β,γ-unsaturated esters were rationalized by “*syn-effect*,” which mainly arose from the $\sigma \rightarrow \pi^*$ interaction in the transition state of deprotonation.

In order to investigate the “*syn-effect*” for (*E*)-α,β-unsaturated esters (***E***)-**1** bearing various substituents at the γ-position,[5] they were converted to the corresponding β,γ-unsaturated esters **2** by treating with lithium hexamethyldisilazide (LiHMDS) in the presence of HMPA, followed by quenching with diluted aq. HCl in EtOH. The results were summarized in Table 1.

(*Z*)-Selectivity among the γ-alkyl substituents decreased along with their bulkiness; CH_3- > CH_3CH_2- > $(CH_3)_2CH$- > $(CH_3)_3C$- (Entries 1, 3–5). For example, methyl group realized high (*Z*)-selectivity, whereas (*E*)-product was exclusively obtained in the case of ^{t}Bu substituent. In the case of γ-phenyl substituent, high (*E*)-selectivity was observed (Entry 6). γ-Fluoro and γ-benzyloxy groups have been found to show the complete (*Z*)-selectivity (Entries 7, 8), while γ-benzylthio substituted 2-alkenoate **1i** afforded almost 1/1 mixture of (*Z*)- and (*E*)-3-alkenoates **2i** (Entry 9). In the cases of γ-methyl and γ-fluoro substituted esters **1a**,**g**, the isolated yields of the products **2a**,**g** were a little lower compared with other γ-substituents (Entries 1, 7). This is due to the high volatility of those products. In fact, the use of ester **1b** derived from a higher alcohol realized better chemical yield (Entry 2). The relative degree of “*syn-effect*” depending on the γ-substitutents R of (*E*)-α,β-unsaturated esters **1** was found for their conversion to the corresponding β,γ-unsaturated esters **2** as follows;

$$\text{F-} \cong \text{BnO-} > \text{CH}_3\text{-} > \text{CH}_3\text{CH}_2\text{-} > (\text{CH}_3)_2\text{CH-} > \text{BnS-} > \text{Ph-} > (\text{CH}_3)_3\text{C-}$$

Table 1. Conversion of the (*E*)-α,β-unsaturated esters (*E*)-**1** to the corresponding β,γ-unsaturated esters **2**



(***E***)-**1** **2**

Entry	R	R'		**1**/**2**[a]	Z/E of **2**[a]	Yield[b] of **2** / %
1	CH_3	CH_2CH_3	**a**	0/100	91/9	42
2	CH_3	$(CH_2)_7CH_3$	**b**	0/100	94/6	69
3	CH_2CH_3	CH_2CH_3	**c**	0/100	85/15	70
4	$CH(CH_3)_2$	CH_2CH_3	**d**	0/100	70/30	68
5	$C(CH_3)_3$	CH_2CH_3	**e**	28/72	0/100	47
6	Ph	CH_2CH_3	**f**	0/100	16/84	99
7	F	CH_2CH_3	**g**	0/100	100/0	55
8[c]	OBn	CH_2CH_3	**h**	0/100	100/0	78
9	SBn	CH_2CH_3	**i**	7/93	44/56	84

[a] The ratios were determined by 400 MHz ^{1}H NMR spectra.
[b] Isolated yield.
[c] Quenched with $Et_3N \cdot HCl$ in EtOH instead of aq. HCl in EtOH to avoid the hydrolysis of a vinyl ether moiety of the product **2h**.

The relative degree of Z/E ratios seems to be possible to rationalize by “*syn-effect*” in the transition state of deprotonation. It was reported that C–CH_3 eclipsed conformation of ethyl (*E*)-2-pentenoate (**1a**) was preferred due to the hyperconjugation of C–H bond at γ-position to $\pi^*_{C=C}$ orbital of electron deficient olefin moiety.[6] In the transition state of deprotonation, hyperconjugation of developing anion generated by the interaction of H_{γ} with a base becomes more effective in the eclipsed conformations **A** and **B**, in both of which the developing anion is aligned with the $\pi^*_{C=C}$ orbital and other conformations could be neglected (Figure 1). Our recent proposal that $\sigma \rightarrow \pi^*$ interaction is the most probable explanation for the "*syn-effect*" is well consistent with this consideration. At the deprotonation of γ-alkyl-2-butenoates **1a**-**e**, the C–C eclipsed *syn*-conformation **A** might be preferred rather than C–H eclipsed form **B** because hyperconjugative electron donation by C–H_{γ_2} bond is more effective than that by C–C bond,[6,7] since H_{γ_2} can also interact with a base to afford the developing anion. In the cases of γ-fluoro- and γ-benzyloxy substituted α,β-unsaturated esters **1g**,**h**, C–H eclipsed form **B** is unfavorable due to low donor ability of C–F and C–O bonds[7c,8] resulting in the exclusive (*Z*)-selectivities.

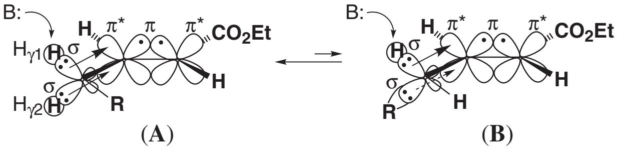
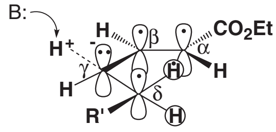
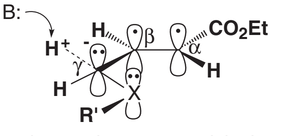


Figure 1. $\sigma \rightarrow \pi^*$ interaction in two eclipsed conformations **A** and **B**.

In the cases of **1a**–**c**,**g**,**h**, it is also possible to stabilize the *syn*-conformation at the transition state by 6π-electron homoaromaticity (as another origin of "*syn-effect*") involving the developing charge at the γ-position and a pseudo *p*-orbital of the δ–CH_2 (Figure 2a, R = R′CH_2), or a lone pair of electrons in a *p*-orbital of the hetero atom (Figure 2b), respectively.[4,9]



a) 6π-electron homoaromaticity in γ–alkyl-substituted system.



b) 6π-electron homoaromaticity in γ–heteroatom-substituted system.

Figure 2.

In the case of ^{i}Pr substituted ester **1d**, 6π-electron homoaromaticity is difficult to be considered, however, the sterically unfavorable (*Z*)-isomer was still obtained as the major products. So, it is clear that the "*syn-effect*" is arisen from the $\sigma \rightarrow \pi^*$ interaction. In the case of ^{t}Bu and Ph substituted esters **1e**,**f**, (*E*)-β,γ-unsaturated esters **2e**,**f** were obtained as the major products. This result is probably due to the bulkiness of the ^{t}Bu group, which excludes *syn*-conformation at the transition state from consideration. Steric interaction between α-proton of ester and *o*-proton of benzene ring also avoids C–C eclipsed form in the case of Ph group (Figure 3).

In the case of γ-benzylthio substituted ester **1i**, the contribution of the empty *d*-orbital of S-atom, such as $\sigma_{C\text{-}H} \rightarrow d$, is still unclear, but $\sigma_{C\text{-}S} \rightarrow \pi^*$ interaction (Figure 4) might be responsible for the predominance of the C–H eclipsed form **B** (R = BnS) in Figure 1 to increase (*E*)-selectivity.[10] The order in the relative degree of "*syn-effect*" of benzylthio substituent was different from the previous result observed in the conversion of vinylic sulfones to the corresponding allylic sulfones, probably due to the difference between the present electron deficient conjugated olefinic system and the non-conjugated olefinic system in vinylic sulfones.

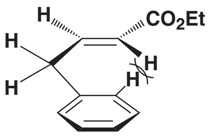


Figure 3.

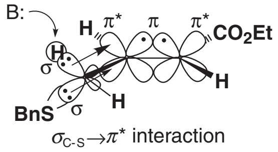


Figure 4.

In conclusion, the stereochemistry in the conversion of (*E*)-α,β-unsaturated esters to the corresponding β,γ-unsaturated esters is well rationalized by "*syn-effect*" in the transition state of deprotonation, which arose from the $\sigma \rightarrow \pi^*$ interaction and/or 6π-electron homoaromaticity. In the reaction using γ-fluoro and γ-benzyloxy substituted esters, the complete (*Z*)-selectivity was observed.

References and Notes

1 a) E.-P. Krebs, *Helv. Chim. Acta*, **64**, 1023 (1981). b) A. S. Kende and B. H. Toder, *J. Org. Chem.*, **47**, 163 (1982). c) P. Galatsis, J. J. Manwell, and S. D. Millan, *Tetrahedron Lett.*, **37**, 5261 (1996). d) K. Tomooka, A. Nagasawa, S.-Y. Wei, and T. Nakai, *Tetrahedron Lett.*, **37**, 8895 (1996). e) K. Tomooka, A. Nagasawa, and T. Nakai, *Chem. Lett.*, **1998**, 1049 and references cited therein.

2 a) A. S. Kende, D. Constantinides, S. J. Lee, and L. Liebeskind, *Tetrahedron Lett.*, **16**, 405 (1975). b) M. P. Zimmerman, *Synth. Commun.*, **7**, 189 (1977).

3 a) T. Hirata, Y. Sasada, T. Ohtani, T. Asada, H. Kinoshita, H. Senda, and K. Inomata, *Bull. Chem. Soc. Jpn.*, **65**, 75 (1992). b) A. Shibayama, T. Nakamura, T. Asada, T. Shintani, Y. Ukaji, H. Kinoshita, and K. Inomata, *Bull. Chem. Soc. Jpn.*, **70**, 381 (1997). c) T. Nakamura, S. K. Guha, Y. Ohta, D. Abe, Y. Ukaji, and K. Inomata, *Bull. Chem. Soc. Jpn.*, **75**, 2031 (2002).

4 "*Syn-effect*" is herein defined as an effect which stabilizes the *syn*-conformation against the steric hindrance: a) D. Cremer, *J. Am. Chem. Soc.*, **101**, 7199 (1979). b) K. N. Houk, R. W. Strozier, N. G. Rondan, R. R. Fraser, and N. Chuaqui-Offermanns, *J. Am. Chem. Soc.*, **102**, 1426 (1980). c) E. Block, R. E. Penn, A. A. Bazzi, and D. Cremer, *Tetrahedron Lett.*, **22**, 29 (1981) and references cited therein.

5 (*E*)-α,β-Unsaturated esters **1a**–**e**,**h** were prepared by Horner-Emmons-Wadsworth reaction. Compounds **1g**,**i** were prepared from ethyl 4-bromocrotonate by treating with AgF or BnSH in the presence of triethylamine, respectively. γ-Phenyl substituted (*E*)-α,β-unsaturated ester **1f** was prepared as follows: Ethyl (phenylthio)acetate was treated with sodium hydride, followed by the addition of (2-bromoethyl)benzene, oxidizing with *m*-CPBA, and finally refluxing in toluene to afford **1f**.

6 B. W. Gung and M. M. Yanik, *J. Org. Chem.*, **61**, 947 (1996).

7 Although there were debates on the relative donor ability of C–H and C–C, recently the former is reported to be better than the latter: a) T. Laube and H. U. Stilz, *J. Am. Chem. Soc.*, **109**, 5876 (1987). b) T. Laube and T.-K. Ha, *J. Am. Chem. Soc.*, **110**, 5511 (1988). c) P. R. Rablen, R. W. Hoffmann, D. A. Hrovat, and W. T. Borden, *J. Chem. Soc., Perkin Trans. 2*, **1999**, 1719.

8 Y. Apeloig, P. v. R. Schleyer, and J. A. Pople, *J. Am. Chem. Soc.*, **99**, 5901 (1977).

9 P. v. R. Schleyer, J. D. Dill, J. A. Pople, and W. J. Hehre, *Tetrahedron*, **33**, 2497 (1977).

10 The significance of the $\sigma_{C\text{-}S} \rightarrow \pi^*$ interaction in α-alkylthio carbonyl compounds was pointed out: P. R. Olivato, S. A. Guerrero, Y. Hase, and R. Rittner, *J. Chem. Soc., Perkin Trans. 2*, **1990**, 465 and references cited therein.

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