Pergamon

Tetrahedron Letters 40 (1999) 2797–2800

TETRAHEDRON LETTERS

Discrimination of Diastereotopic Sulfonyl Oxygens by Intramolecular Hydrogen Bonding: Stereoselective Hydrogenation of α-Sulfonyl Radicals

Nobuyuki Mase, Yoshihiko Watanabe, Takeshi Toru*

Department of Applied Chemistry, Nagoya Institute of Technology, Gokiso, Showa-ku, Nagoya 466-8555, Japan

Received 26 December 1998; revised 1 February 1999; accepted 5 February 1999

Abstract

Stereoselective intramolecular hydrogen bonding between the hydroxy group and a stereogenic sulfonyl oxygen led to high diastereoselectivity in the radical reaction of α-(1-hydroxyethyl)vinyl sulfone with alkyl iodides and tributyltin hydride in the presence of triethylborane as a radical initiator. Intramolecular hydrogen bonding was demonstrated to play an important role in controlling the diastereoselectivity.

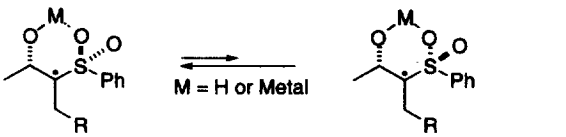
Keywords: Radicals and radical reactions; Hydrogen bonding; Hydrogenation; Sulfones

Giese *et al.* have shown the influence of an α-substituent in the 1,2-stereoinduction of α-substituted β-oxy-radicals:[1] Planar substituents such as COMe, CO_2Me, Ph, and NO_2 give rise to 1,2-stereoinduction according to the allylic strain model, whereas linear or tetrahedral substituents such as CN, Cl, Me, $PhSO_2$, Me_3Si, and Me_3Sn do not show significant 1,2-stereoinduction. Recently, Renaud *et al.* have reported high levels of stereoselectivity in the reaction of the α-sulfinylated β-oxy-radicals according to the Felkin-Anh model.[2] We communicated excellent stereocontrol in the hydrogenation of the α-sulfinylated β-hydroxy-radical generated from the radical addition to the α-(1-hydroxyethyl)vinyl sulfoxide, in which we demonstrated the significant role of intramolecular hydrogen bonding between the hydroxy group and the sulfoxide oxygen in the reactivity as well as the stereocontrol.[3] Moreover, we have clarified that the formation of intramolecular hydrogen bonding depends on the stereochemistry of the α-(1-hydroxyethyl)vinyl sulfoxide, *i. e.*, significant intramolecular hydrogen bonding exists only in the (2*S*)-isomer but not in the (2*R*)-isomer. From these

Phone: +81-52-735-5217, Fax: +81-52-735-5217, E-mail: toru@ach.nitech.ac.jp

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00297-X

results, we envisaged that the diastereotopic sulfonyl oxygen could be discriminated by selective intramolecular hydrogen bonding or chelation and the newly formed chiral sulfur would have influence on the stereoselectivity in the reaction of the α-sulfonyl radical as shown in Figure 1.

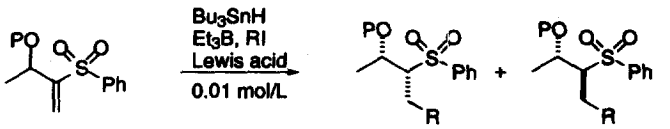


hydrogen bonding or chelation with *anti*-sulfonyl oxygen

hydrogen bonding or chelation with *syn*-sulfonyl oxygen

Fig. 1

We report herein the highly stereoselective reaction of α-sulfonyl radicals controlled by intramolecular hydrogen bonding as well as by chelation with Lewis acids. The α-(1-hydroxyethyl)vinyl sulfone **1** was prepared by the reaction of phenyl vinyl sulfone[4] with acetaldehyde in the presence of a catalytic amount of 1,4-diazabicyclo[2.2.2]octane.[5] The acetoxy- and triphenylsilyl-protected derivatives were prepared, when required. A solution of **1** was treated with an alkyl iodide (3 equiv), tributyltin hydride (3 equiv), and triethylborane (3 equiv) as a radical initiator.[6] The results are shown in Table 1. Reactions with *tert*-butyl radical gave the expected products in high yields. Higher diastereoselectivity was obtained, when the reaction was carried out at lower temperature (entries 1-3). Thus, the reaction at –78 °C afforded the addition-hydrogenation product **4** in a *syn* : *anti* ratio of 98 : 2 (entry 3). A polar solvent such as THF lowered the diastereoselectivity (entry 4). Cyclohexyl, isopropyl, butyl, and ethyl radicals, but not methyl radical,[7] successfully added to **1** (entries 5-9). In these reactions, the stereoselection was lowered, as the size of the alkyl radicals was sterically smaller. Addition of a Lewis acid such as $EtAlCl_2$ improved the diastereoselectivity (entry 10), and high diastereoselectivity was obtained even at room temperature (entry 11). The high diastereoselectivity obtained with $EtAlCl_2$ suggests the formation of a rigid chelating structure in the intermediate radical which is in accord with the results that the diastereoselectivity decreased with bulky monochelating methylaluminium bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD) (entries 12-13). The acetyl or triphenylsilyl protection of the hydroxy group lowered the diastereoselectivity (entries 14, 16). These results obtained in the reaction of **1** are in good accord with those obtained in the reaction of the α-(1-hydroxyethyl)vinyl sulfoxide.[3] The stereochemistry of the addition-hydrogenation product was determined by the ^1H NMR coupling constants between the hydrogens α and β to the sulfonyl, namely, the *anti* isomer shows larger $J_{\alpha\beta}$ values than the *syn* isomer in α-alkyl-β-hydroxy sulfones.[8]



1-3 *syn*-4-10 *anti*-4-10

1: P = H
2: P = Ac
3: P = $SiPh_3$

Table 1. Addition of Alkyl Radical to the α-(1-Hydroxyethyl)vinyl Sulfone 1 Followed by Hydrogenation with Tributyltin Hydride.

Entry	Substrate	R	Solvent	Lewis acid[a]	Temp (°C)	Time (h)	Product	Yield (%)	*syn* : *anti*
1[b]	1	*t*-Bu	PhH	none	80	0.5	4	93	74 : 26
2	1	*t*-Bu	CH_2Cl_2	none	rt	2	4	98	87 : 13
3	1	*t*-Bu	CH_2Cl_2	none	-78	2	4	91	98 : 2
4	1	*t*-Bu	THF	none	-78	2	4	84	81 : 19
5	1	*c*-Hex	CH_2Cl_2	none	-78	1	5	93	76 : 24
6	1	*i*-Pr	CH_2Cl_2	none	-78	1	6	91	69 : 31
7	1	*t*-Bu	CH_2Cl_2	none	-78 → rt	3	7	88	62 : 38
8	1	Et	CH_2Cl_2	none	-78 → rt	8	8	95	60 : 40
9	1	Me	CH_2Cl_2	none	-78 → rt	24	—[c]	—	
10	1	*t*-Bu	CH_2Cl_2	$EtAlCl_2$	-78	5	4	64	99 : 1
11	1	*t*-Bu	CH_2Cl_2	$EtAlCl_2$	rt	2	4	76	99 : 1
12	1	*t*-Bu	CH_2Cl_2	MAD	-78 → rt	24	4	93	88 : 12
13	1	*t*-Bu	CH_2Cl_2	MAD[d]	-78	7	4	93	68 : 32
14	2	*t*-Bu	CH_2Cl_2	none	-78	2	9	92	90 : 10
15	2	*t*-Bu	CH_2Cl_2	$EtAlCl_2$	-78	1	9	97	92 : 8
16	3	*t*-Bu	CH_2Cl_2	none	-78	2	10	99	67 : 33

[a] Lewis acid (1.1 equiv) was used unless otherwise noted. [b] AIBN was used as an initiator. [c] The sulfone 1 was recovered. [d] MAD (5 equiv) was used.

According to the results shown in Table 1, intramolecular hydrogen bonding seemed to be strongly related to the stereochemical outcome. Indeed, significant intramolecular hydrogen bonding is present in **1**, since only a small upfield shift of the chemical shift of the OH proton upon dilution is observed in the ^1H NMR (δ = 2.66 in 0.1 mol/L $CDCl_3$, δ = 2.58 in 0.01 mol/L). The infrared spectrum also supports the existence of intramolecular hydrogen bonding. These spectral data suggest that high diastereoselectivity can be ascribed to the fixed conformation of the radical intermediate with intramolecular hydrogen bonding. This was confirmed by semiempirical calculation of heat of formation of the intermediate radical **1-R** using the PM3 parameter set as implemented in MOPAC 93.[9] High diastereoselectivity is possibly derived from not only conformationally but also configurationally different radical intermediates (Figure 2). The most stable conformer was found to be a conformer **1-CR2** in which intramolecular hydrogen bonding exists between the hydroxy group and the *anti*-sulfonyl oxygen. The energy difference between **1-CR2** and **1-DR1** may be relatively small, but the upper face is more widely open in **1-CR2** to the attack of tributyltin hydride, *i. e.*, **1-CR2** should be kinetically more preferred intermediate. Thus, tributyltin hydride

approaches from the face opposite to the methyl and *tert*-butyl groups, leading to the addition-hydrogenation product *syn*-**4** with *syn* stereochemistry. As the alkyl radical is sterically bulkier, the lower face is more shielded by the newly formed alkyl group to cause higher diastereoselectivity (Table 1, entries 3, 5-8). These results were quite different from those obtained in the radical reaction of β-hydroxy and β-amino α-methylene esters,[10,11] in which diastereoselectivities decrease as the size of alkyl radicals becomes sterically larger, possibly because of the space-demanding difference between the tetrahedral sulfur structure of the sulfone and the trigonal structure of the ester.

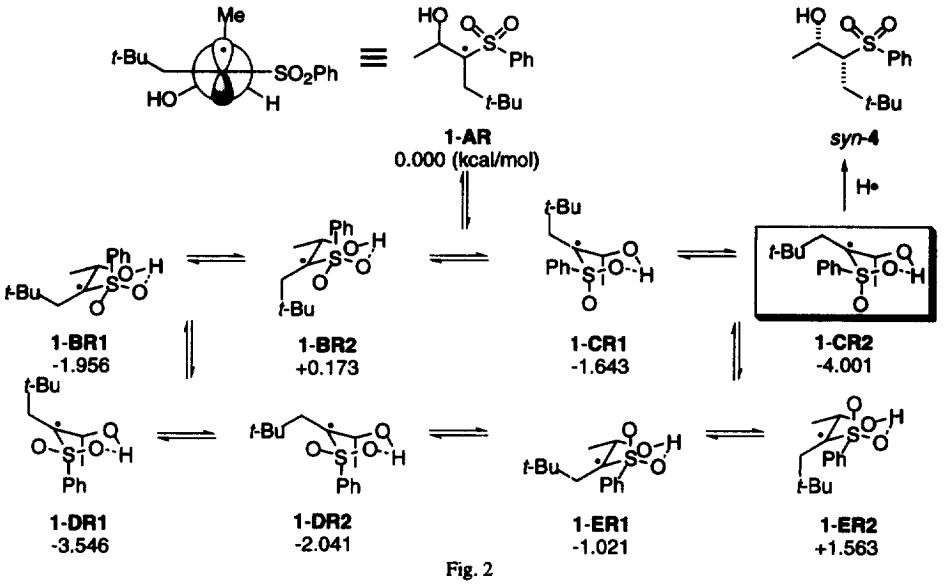


Fig. 2

The present reaction opens a way to the development of a new sulfonyl function: The sulfonyl group can be designed as a chiral template by selective intramolecular hydrogen bonding or by chelating coordination with one of the stereogenic oxygens of the sulfone, providing high stereoselectivity in the radical reaction.

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