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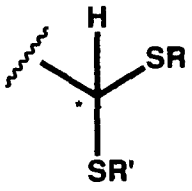
A NOVEL DIASTEREOSELECTIVE SYNTHESIS OF CHIRAL, NON-RACEMIC UNSYMMETRICAL THIOACETALS USING SILICON-INDUCED PUMMERER-TYPE REACTION

Norio Shibata[a], Shigekazu Fujita[a], Michiyo Gyoten[a], Keita Matsumoto[b], and Yasuyuki Kita*[a]

[a] Faculty of Pharmaceutical Sciences, Osaka University, 1-6 Yamada-oka, Suita, Osaka 565, Japan
[b] Research Center, Taisho Pharmaceutical Co., Ltd., 1-403 Yoshino-cho, Omiya, Saitama 330, Japan

Abstract: Chiral, non-racemic sulfoxides were reacted with thiols and BSA in the presence of a catalytic amount of TMSOTf in MeCN at rt overnight to give the corresponding chiral, non-racemic *anti*-thioacetals with high diastereoselectivity.

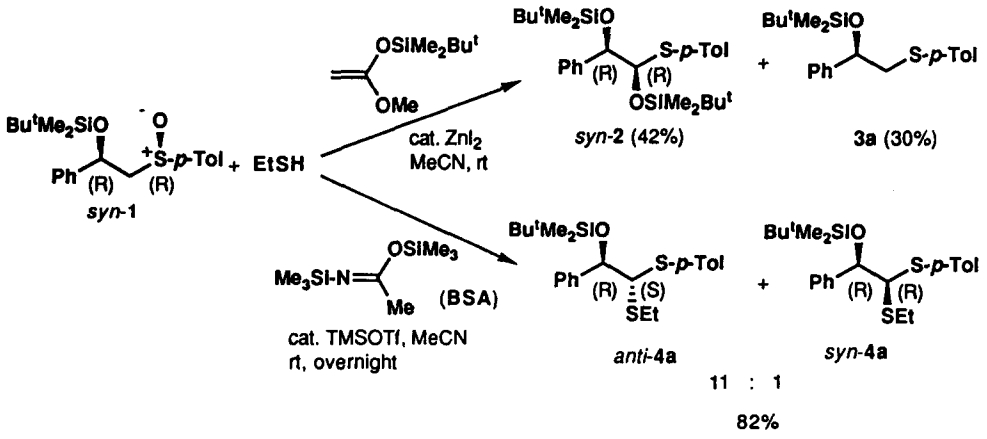
Although several methods for the synthesis of racemic unsymmetrical thioacetals have been reported, there is no useful method for the synthesis of chiral, non-racemic unsymmetrical thioacetals,[1] which are expected to be useful precursors[2,3] for an asymmetric synthesis. Among the methods for racemic thioacetals; the reaction of α-chlorosulfides[4] or *O*, *S*-acetals with thiolate anions,[5] the sulfenylation of α-lithiosulfides,[6] the Grignard reaction of thiocarbonyl compounds,[7] the thiophilic allylation of dithioesters or trithiocarbonyl compounds,[8] and the Pummerer reaction of sulfoxides in the presence of thiols,[9, 10] the Pummerer reaction seems to be an efficient method for the synthesis of the chiral, non-racemic unsymmetrical thioacetals because of the ready availability of the starting optically active sulfoxides[11] and mild reaction conditions. Thus, Tanikaga reported[10] the synthesis of unsymmetrical thioacetals by the reaction of sulfoxides with thiols in the presence of trifluoroacetic anhydride (TFAA). This procedure, however, is limited to the synthesis of simple thioacetals.[12] We also observed that some chiral, non-racemic sulfoxides reacted with TFAA to give the deoxygenated product exclusively[13] without producing the desired thioacetals. As an extension of our silicon-induced asymmetric Pummerer-type reaction,[14-16] we now undertook the asymmetric synthesis of chiral, non-racemic unsymmetrical thioacetals using silylating agents and found that the use of *N*, *O*-bistrimethylsilylacetoamide (BSA) in the presence of thiols gave the chiral, non-racemic thioacetals with high diastereoselectivity.



chiral, non-racemic
unsymmetrical thioacetals

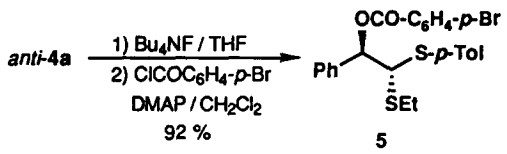
At first, we examined the reaction of the chiral, non-racemic sulfoxide with thiol using our silicon-induced Pummerer-type rearrangement conditions.[15] The treatment of the optically active sulfoxide (*syn*-**1**) with EtSH and *O*-methyl-*O*-*tert*-butyldimethylsilyl ketene acetal in the presence of a catalytic amount of ZnI_2 in MeCN gave a mixture of the chiral, non-racemic *O*, *S*-acetal (*syn*-**2**, a normal Pummerer-type rearrangement product) and the sulfide (**3a**, a reduction product). We then investigated the reaction of *syn*-**1** with EtSH in the presence of various other silylating agents. The desired chiral, non-racemic unsymmetrical thioacetals (*anti*- and *syn*-**4a**) were obtained from *syn*-**1** by the reaction with BSA in the presence of a catalytic amount of

TMSOTf. Treatment of *syn*-**1** (1 eq.) with EtSH (1.5 eq.) and BSA (5 eq.) in the presence of TMSOTf (0.1 eq.) in MeCN at rt overnight gave an 11:1 diastereomixture of *anti*-**4a** and *syn*-**4a** in 82% yield (Scheme 1).



Scheme 1

The stereochemistry of the products (*anti*- and *syn*-**4a**) was determined using X-ray crystallographic analysis[17] of the *p*-bromobenzoylester (**5**) of the major isomer (Scheme 2, Fig. 1).



Scheme 2

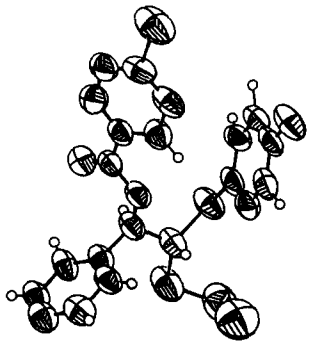
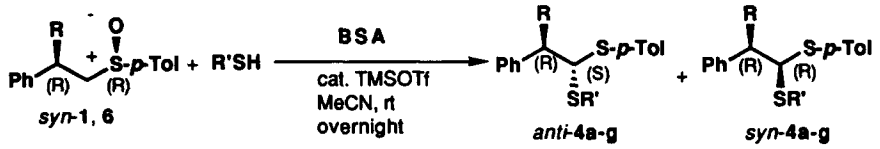


Fig. 1 X-Ray crystallographic structure of **5**.

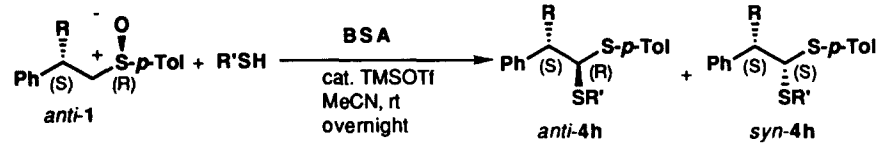
Similarly, chiral, non-racemic sulfoxides (**1** and **6**) were reacted with various types of thiols and BSA under the same conditions. All reactions proceeded with good chemical yields (Table 1). A high *anti*-selectivity of the product was observed for both the *syn* and *anti*-sulfoxides. Although the mechanism of the predominant formation of the *anti*-isomer is not well understood, it may proceed by the cyclic Cram model of the silicon coordinated intermediate[18,19] or the Cram model of the thionium intermediate[20] (Scheme 3).

In conclusion, we report the novel stereoselective synthesis of chiral, non-racemic thioacetals using the silicon-induced Pummerer-type reaction. Application of these optically active thioacetals to an asymmetric synthesis is now under investigation.[21]

Table 1. Diastereoselective Synthesis of Chiral, Non-racemic Thioacetals

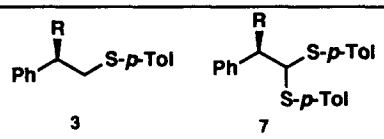


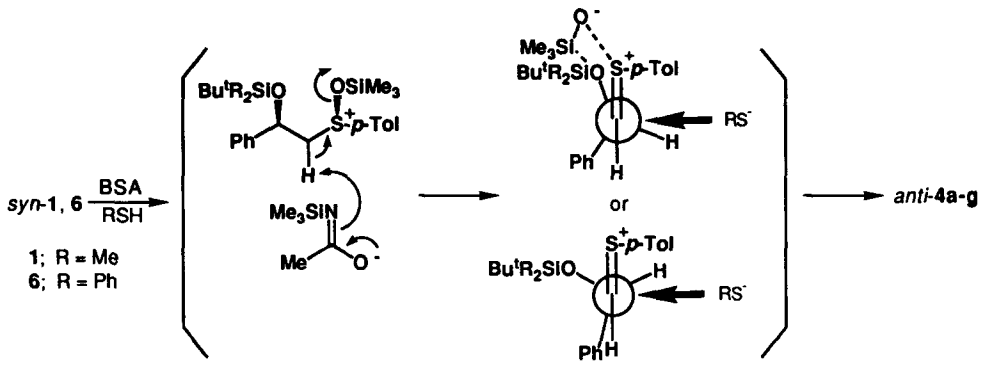
entry	sulfoxide	R'SH	product[a]	R	R'	yield (%)[b]	anti : syn[c]
1	*syn*-1 R = $OSiMe_2Bu^t$	EtSH	4a	$OSiMe_2Bu^t$	Et	82	11:1
2		PrSH	4b		Pr	75	10:1
3		Pr^iSH	4c		Pr^i	68	13:1
4		Bu^tSH	4d		Bu^t	62	6:1
5		AllylSH	4e		Allyl	75	9:1
6		BnSH	4f		Bn	75	11:1
7	*syn*-6 R = $OSiPh_2Bu^t$[d]	EtSH	4g	$OSiPh_2Bu^t$	Et	41[e]	23:1



entry	sulfoxide	R'SH	product[a]	R	R'	yield (%)[b]	anti : syn[c]
8	*anti*-1 R = $OSiMe_2Bu^t$	EtSH	4h	$OSiMe_2Bu^t$	Et	66	11:1

a) Small amounts (0-20%) of sulfides (3) and symmetrical thioacetals (7) were produced as by-products. b) Isolated yields. c) Determined from ^{1}H-NMR data. d) Racemic sulfoxides were used. e) Sulfide (3) was produced in 36% yield.





Scheme 3

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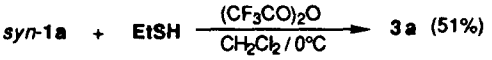
13. For example, the reaction of *syn*-**1a** with EtSH using Tanikaga's procedure gave the deoxygenated compound in 51 % yield.



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17. The crystal data for **5** are as follow: orthorhombic; $P2_12_12_1$ with a=13.932(3), b=27.308(5), c=6.079(2) Å, V=2312.7(8) Å^3, Z=4, and μ(Cu Kα)=40.18cm^{-1} by Mac Science MXC 18 instrument. Final R value was 0.068 for 1381 reflections. The supplementary materials have been deposited at the Cambridge Crystallographic Data Centre.
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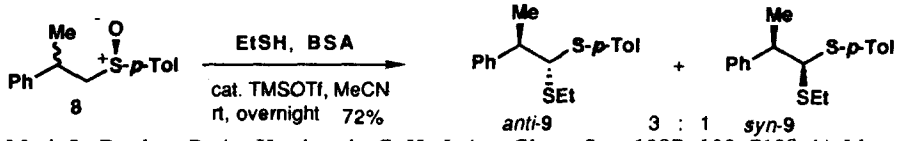
19. The reaction of β-alkyl substituted sulfoxide **8** under the same conditions showed low *anti* -selectivity.



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21. From a preliminary experiment, a site-selective sulfoxidation (-S(O)R) of *anti*-**4a** was observed by the treatment with *m*-chloroperbenzoic acid.

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