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UNUSUAL SUBSTITUTION REACTION OF 5-ALKYL-6,8-DIOXABICYCLO[3.2.1]OCTANES BEARING 3-SULFUR-CONTAINING SUBSTITUENTS WITH MERCAPTANS

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5-Alkyl-6,8-dioxabicyclo[3.2.1]octanes with sulfur-containing substituents at the C(3)-position were found to undergo an unusual substitution reaction with mercaptans in the presence of the Lewis acids providing the corresponding 3-sulfenyl derivatives.

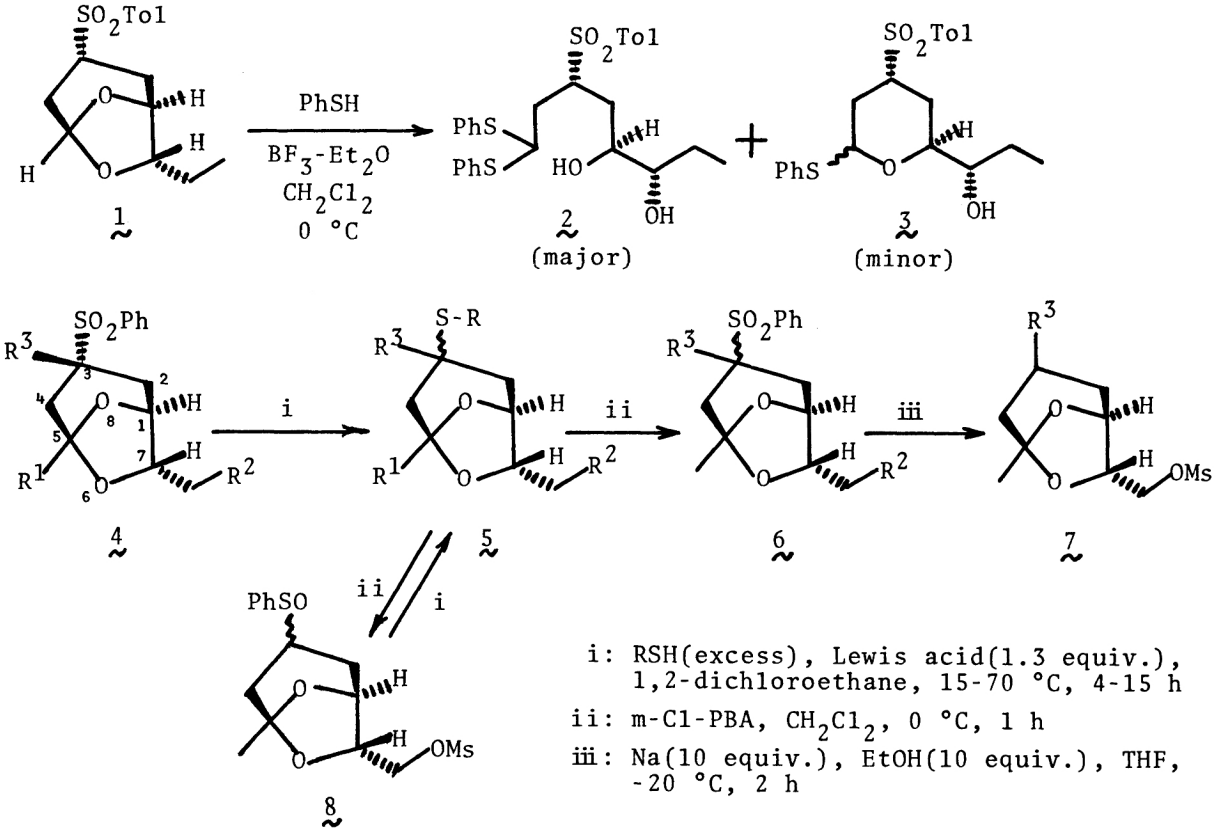
It is well known that acetals are converted into the corresponding thioacetals with excess of mercaptans in the presence of various acids.[1] In the course of synthetic study on pyranoid natural products utilizing the optically active cyclic acetals, 6,8-dioxabicyclo[3.2.1]octanes,[2] we encountered interesting behaviors of the ring system toward mercaptans in the presence of Lewis acids. Here we report a Lewis acid promoted novel substitution reaction of 5-alkyl-6,8-dioxabicyclo[3.2.1]-octane derivatives [4(6), 5, 8] bearing the sulfur-containing substituents at the C(3)-position by treatment with mercaptans (RSH), resulting in the corresponding 3-sulfenylated bicyclic compounds (5) in which the sulfur-containing substituents at the C(3)-position were derived from the mercaptans used.

Reaction of a 5-non-alkylated bicyclic compound (1) with an excess of thiophenol in the presence of 1.2 equiv. of BF_3-Et_2O in CH_2Cl_2 (0 °C/1 h) gave the thioacetal (2) in 76% yield together with a minor amount of the monothioacetal (3) (13%). On the contrary, the corresponding 5-methyl derivative (4a) resisted to the trans-acetalization reaction with thiophenol even at the room temperature for 15 h and was recovered unchanged. When the bicyclic compound (4a) was warmed in 1,2-dichloroethane at 70 °C with an excess of thiophenol and 1.3 equiv. of BF_3-Et_2O for 15 h, the corresponding 3-benzenesulfenyl derivative (5a) was unexpectedly obtained in 67% yield. The structure of the product (5a) was characterized and confirmed by its MS and ^{1}H-NMR analyses and by spectral comparison of the sulfone (6a) derived from the sulfide (5a) with the starting sulfone (4a).[3] This unusual transformation leading to the 3-benzenesulfenyl derivatives (5) was found to occur generally for other 5-alkyl-substituted compounds (4) and the results are summarized in Table 1 (entries 1—5).

Details of the reaction were investigated. First of all, the reaction turned out not to be the reduction of the sulfone to sulfide but to be the substitution on the basis of the following evidence. The 3-benzenesulfonyl derivative (4c) was treated with p-thiocresol under the same reaction conditions and the corresponding

3-p-toluenesulfenyl derivative (5g) was obtained in 66% yield. Reactions of 4c with other mercaptans, i-PrSH, t-BuSH, and EtSH, analogously provided the 3-sulfenyl derivatives (5h,i,j) in which each mercaptan used was introduced at the C(3)-position of the bicyclic system. The results are summarized in Table 1 (entries 6—14). As shown in Table 1, the other Lewis acid $TiCl_4$ was also effective for the transformation.

As for the stereochemical aspects of the reaction, we could obtain clear information on the 3-benzenesulfonyl-3-methyl derivative (4f) (entry 15). Treatment of the stereochemically pure sulfone (4f)[4] with thiophenol under the identical conditions as described above brought about a mixture composed of almost equal amounts of a pair of the C(3)-epimeric sulfides (5f).[5] ^{1}H-NMR Analysis of the sulfone (6f)[5] derived from the sulfide (5f) also revealed non-stereoselectivity of the substitution reaction. Retention of the bicyclic carbon skeleton throughout the reaction was verified by identification of the desulfonylated compounds (7c,f) derived respectively from the starting sulfones (4c,f) and from the corresponding



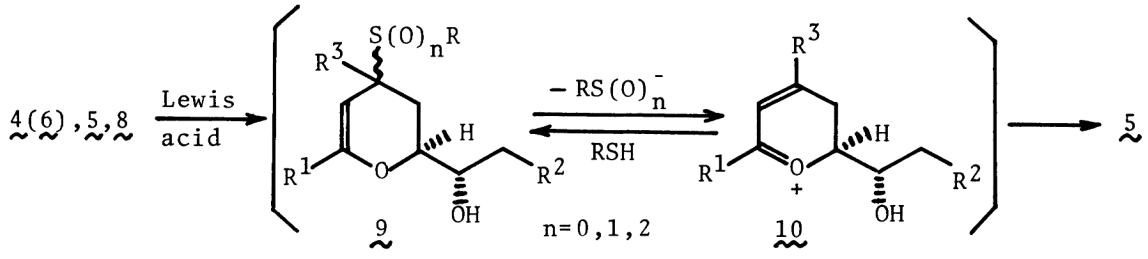
	a	b	c	d	e	f	g	h	i	j
R^1:	Me	Me	Me	i-Pr	i-Pr	Me	Me	Me	Me	Me
R^2:	Me	OTs	OMs	Me	OTs	OMs	OMs	OMs	OMs	OMs
R^3:	H	H	H	H	H	Me	H	H	H	H
R (5):	Ph	Ph	Ph	Ph	Ph	Ph	p-Tol	i-Pr	t-Bu	Et

Table 1. Reaction of 5-Alkyl-6,8-dioxabicyclo[3.2.1]octanes (4, 5, 8) Bearing the Sulfur-containing Substituents at the C(3)-position with Mercaptans in the Presence of Lewis Acids[a)]

Entry	Substrate	Mercaptan	Lewis Acid	Conditions	Product	Yield/%
1	4a	PhSH	BF_3-Et_2O	70 °C, 15 h	5a	67
2	4b	"	"	"	5b	70
3	4c	"	"	"	5c	83
4	4d	"	"	"	5d	86
5	4e	"	"	"	5e	91
6	4c	p-thiocresol	"	"	5g	66
7	"	"	$TiCl_4$	15 °C, 15 h	"	28
8	"	PhSH	"	"	5c	35
9	"	i-PrSH	BF_3-Et_2O	70 °C, 15 h	5h	78
10	"	"	$TiCl_4$	15 °C, 4 h	"	58
11	"	"	"	15 °C, 15 h	"	59
12	"	"	"	70 °C, 15 h	"	62
13	"	t-BuSH	"	"	5i	49
14	"	EtSH	"	15 °C, 15 h	5j	64
15	4f	PhSH	BF_3-Et_2O	"	5f	69
16	5c	p-thiocresol	"	70 °C, 15 h	5g	55
17	8	"	"	"	"	61
18	5c	i-PrSH	"	"	5h	82
19	8	"	"	"	"	84
20	"	EtSH	$TiCl_4$	15 °C, 15 h	5j	33

a) Reactions were carried out in 1,2-dichloroethane using 1 equiv. of the substrates, large excesses of RSH, and 1.2-1.3 equiv. of Lewis acids.

epimeric mixtures (6c,f)[6)] obtained through the substitution reaction. The non-stereoselectivity observed was ascribed to the fact that not only the C(3)-sulfonyl group but also the other C(3)-sulfur-containing substituents, i.e. sulfinyl and sulfenyl groups, undergo the displacement accompanied by racemization of the C(3)-asymmetric center with mercaptans used. Entries 16—20 in Table 1 indicate the results from reactions of the 3-sulfenyl- and 3-sulfinyl-substituted derivatives, (5c) and (8), with mercaptans.



A suggestion concerning the reaction mechanism was given by the fact that an acyclic β-sulfonyl acetal, 4-benzenesulfonyl-2-pentanone dimethyl acetal, on treatment with an excess of thiophenol (1.2 equiv. BF_3-Et_2O/$ClCH_2CH_2Cl$/70 °C/15 h) afforded, though in minor amounts, 4-phenylthio-2-pentanone and the corresponding phenylthioacetal. Although the mechanistic pathway of this type of reaction is not so unambiguous as to explain the striking difference between the behaviors of the 5-non-alkylated (1) and the 5-alkylated bicyclic system [4(6), 5, 8], the reaction may proceed via elimination of the sulfur-containing group at the C(4)-position of the intermediary pyranoid (9) followed by addition of mercaptans to the generated dihydropyrylium ion (10). Unfortunately, any such conceivable intermediate, which supports the mechanism, has not been isolated yet.

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2) Y. Masaki, K. Nagata, Y. Serizawa, and K. Kaji, Tetrahedron Lett., 23, 5553 (1982) and 25, 95 (1984); Y. Masaki, Y. Serizawa, K. Nagata, and K. Kaji, Chem. Lett., 1983, 1601; Y. Masaki, K. Nagata, and K. Kaji, ibid., 1983, 1835.

3) In spite of the C(3)-epimeric mixture, spectral properties (MS, IR, ^{1}H-NMR) and the TLC-behavior of 6a were indistinguishable from those of 4a.

4) The sulfone (4f) was prepared by the 4-steps sequence of reactions from 4-benzenesulfonyl-2-pentanone dimethyl acetal and dimethyl (+)-(R,R)-tartrate according to the reported method.[2] 4f (Mp 105-108 °C) appeared to be a single stereoisomer with respect to the C(3)-position on the basis of ^{1}H-NMR ($CDCl_3$) spectrum: δ 1.49 (3H, s, C(5)CH_3), 1.57 (3H, s, $CH_3C(SO_2Ph)$), 1.40-1.90, 2.25-2.92 (each 2H, m, C(2)- and C(4)-H_2), 2.98 (3H, s, CH_3SO_2), 3.86-4.25 (3H, m, $(O)_2CHCH_2OMs$), 4.50 (1H, bd, J=4.0 Hz, C(1)-H), 7.40-7.90 (5H, m, arom-H).

5) ^{1}H-NMR ($CDCl_3$) data for the epimeric mixture of 5f and 6f follow:
5f: δ 1.23, 1.52 (overall 3H, each s, $CH_3C(SPh)$), 1.41, 1.45 (overall 3H, each s C(5)CH_3), 2.96, 3.02 (overall 3H, each s, CH_3SO_2), 4.34 (br), 5.17 (dd, J=7.0, 5.5 Hz) (overall 1H, C(1)-H).
6f: δ 1.43, 1.57 (overall 3H, each s, $CH_3C(SO_2Ph)$), 1.49 (3H, s, C(5)CH_3), 2.98, 3.00 (overall 3H, each s, CH_3SO_2), 4.45 (bd, J=6.0 Hz), 4.50 (bd, J=4.0 Hz) (overall 1H, C(1)-H).

6) Spectral data (MS, IR, ^{1}H-NMR) of the desulfonylated products (7f), which were derived either from 4f or from 6f with Na and EtOH in THF at -20 °C, were indistinguishable from each other.

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