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MONOTHIOACETALIZATION OF ACETALS USING DIETHYLALUMINIUM THIOPHENOXIDE

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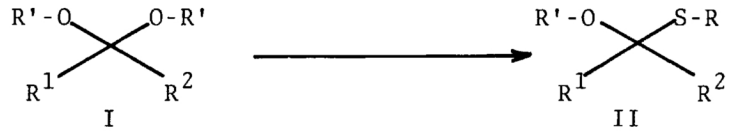
Reactions of diethylaluminium thiophenoxide (Et_2AlSPh) with acetals of several types, in which acyclic, cyclic, and bicyclic ones are involved, were examined in comparison with the known reaction using thiophenol in the presence of Lewis acid and found to provide a new and efficient method for preparation of monothioacetals.

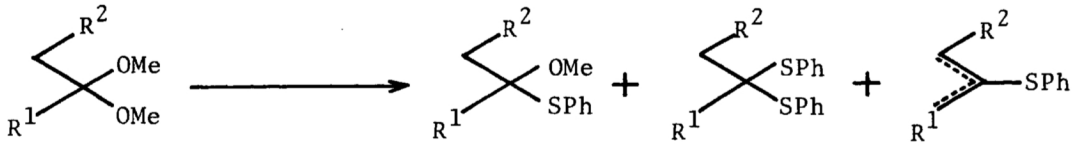
Monothioacetals (II) have been widely used as intermediates in organic synthesis, for example, reductive cleavage of the C-O bond providing thioethers[1a] and mixed acetalization with alcohols directly in the presence of oxidizing agent or by way of α-fluoro ethers, the method of which was effectively utilized in the construction of the O-glycoside linkage.[1b] For carbon-carbon bond formation, monothioacetals have been known to undergo selective substitution of the oxygen- and sulfur-containing group with allylsilanes in the presence of Lewis acids[1c] and base-promoted electrophilic substitution of the sulfur-containing group via the α-lithio ethers.[1d] One of the general methods for preparation of monothioacetals (II) is the transacetalization of acetals (I) by using limited amounts of thiols in the presence of Lewis acids in aprotic solvents such as CH_2Cl_2 (non-coordinating solvent) or 1,2-dimethoxyethane (DME) (coordinating solvent).[1d, 2)]



In our synthetic projects on optically active natural products starting with 6,8-dioxabicyclo[3.2.1]octanes (9), methods for selective cleavage of the bicyclic acetal system providing monothioacetals (10) were required. Attempts of trans-monothioacetalization of the system (9) using thiophenol with Lewis acid (BF_3-Et_2O, $AlCl_3$, and $TiCl_4$) under several reaction conditions have been unsuccessful yet in selective formation of 10.[3)] Recently, the organoaluminium reagent of type R_2AlX (X= OR', NR'_2, and SR') has been known to work as potent nucleophile in the reaction with oxygen functionalities.[4)] In this paper we wish to report a new method for preparation of monothioacetals (II) from various types of acetals including acyclic, cyclic, and bicyclic ones, by using diethylaluminium thiophenoxide (Et_2AlSPh).

Treatment of a cold (0 °C) solution of acetone dimethylacetal (1a) in toluene for 1.5 h with 1.2 equiv. of Et_2AlSPh[5)] (conditions A) gave the monothioacetal (2a)

in 78% yield. Use of 3 equiv. of Et_2AlSPh in the reaction, on the other hand, afforded the thioacetal (3a) and the vinyl sulfide (4a) respectively in 51% and 31% yields. Analogous reactions were observed for acyclic acetals (1b—1d) on treatment with Et_2AlSPh as shown in Table 1. These results were comparable to those obtained by the reactions under the reference conditions using 1.2 equiv. of thiophenol in the presence of Lewis acid (BF_3-Et_2O or $AlCl_3$) at 0 °C for 1.5 h in CH_2Cl_2 or DME (conditions B).[2)]



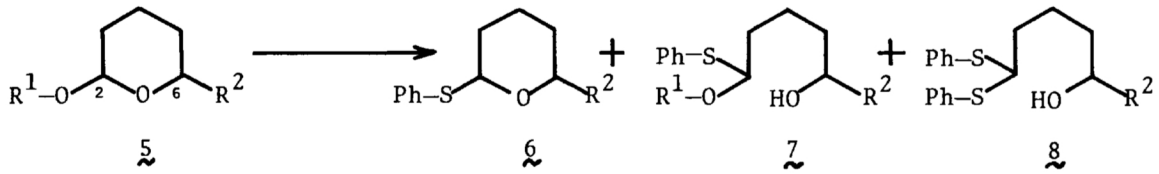
1 2 3 4

Table 1. Monothioacetalization of Acyclic Acetals

Reactant (1)			Conditions[a)]	Product (yield/%)		
	R^1	R^2		2	3	4
1a	Me	H	A	78	–	–
			A [–20 °C]	89	–	–
			A [Et_2AlSPh (3.0 equiv.)]	–	51	31
			B [BF_3 (0.2 equiv.)/CH_2Cl_2]	40	16	–
			B [BF_3 (1.0 equiv.)/CH_2Cl_2]	–	50	–
			B [BF_3 (0.2 equiv.)/DME]	74	–	–
1b	Me	Prenyl	A	71	–	9
			A [Et_2AlSPh (3.0 equiv.)]	5	40	38
1c	H	CH_2SO_2Tol	A [Et_2AlSPh (2.0 equiv.)]	72	–	–
1d	Me	CH_2SO_2Ph	A [Et_2AlSPh (2.0 equiv.)]	72	–	–

a) Reactions were carried out at 0 °C for 1.5 h using 1.2 equiv. of Et_2AlSPh in toluene under the conditions A, and using 1.2 equiv. of PhSH in the presence of Lewis acid in the solvent indicated under the conditions B, unless otherwise noted. BF_3 was used as the etherate.

Interesting differences in reactivities of cyclic acetals were observed between the conditions A and B. Although a tetrahydropyranyl ether (5e) afforded the cyclic monothioacetal (6e) in which the alcohol moiety was substituted with thiophenoxide group, as the product under the conditions either A or B, a cyclic acetal (5f) which has the oxygen functionality ($PhCH_2OCH_2$) at the C(6) position of the pyran ring yielded the different products depending upon the reaction conditions as shown in Table 2. Whereas the cyclic monothioacetal (6f) only or together with the thioacetal (8f) was produced under the reference conditions B, the acyclic monothioacetal (7f) was obtained exclusively under the conditions A. The tetrahydropyranyl ethers (5g and 5h) which also have the oxygen functionalities at the C(6) position, gave parallel results affording acyclic monothioacetals (7g and 7h), respectively.

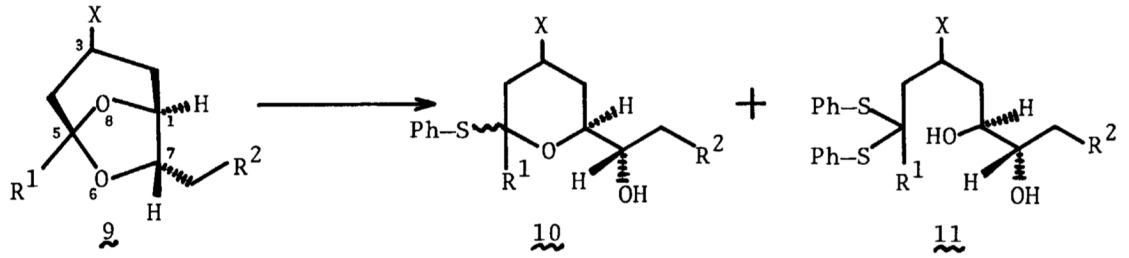


5 6 7 8

Table 2. Monothioacetalization of Cyclic Acetals

	Reactant (5) R^1	R^2	Conditions[a]	Product (yield/%) 6	7	8	
5e	$PhCH_2CH_2$	H	A	no reaction			
			A [15 °C/3 h]	32	–	–	SM (54%)[b]
			A [Et_2AlSPh (3.0 equiv.)/15 °C/2 h]	66	–	–	SM (14%)
			B [BF_3 (0.2 equiv.)/CH_2Cl_2]	70	–	–	
			B [$AlCl_3$ (0.2 equiv.)/CH_2Cl_2]	65	–	12	
5f	Me	CH_2OCH_2Ph	A	–	68	–	SM (8%)
			B [BF_3 (0.2 equiv.)/CH_2Cl_2]	71	–	–	
			B [$AlCl_3$ (1.0 equiv.)/CH_2Cl_2]	18	–	32	
5g	$PhCH_2$	CH(OMe)Me	A	–	55	–	SM (22%)
5h	Me	CH_2OMs	A	–	50	–	SM (21%)

a) See Table 1. b) Recovery of the starting material.



9 10 11

Table 3. Monothioacetalization of Bicyclic Acetals

	Reactant (9) R^1	R^2	X	Conditions[a]	Product (yield/%) 10	11	
9i	H	OMs	H	A	70	–	
				B [BF_3 or $AlCl_3$[c]/CH_2Cl_2]	25–39	16–12	SM (23–18%)[b]
				B [BF_3 or $AlCl_3$/DME]	no reaction		
9j	Me	OMs	H	A	78	–	
				B [BF_3 or $AlCl_3$/CH_2Cl_2]	no reaction		
9k	Me	S-Tol	H	A	72	–	
9l	Me	OMs	S-Tol	A [–40 °C]	56	–	SM (18%)
9m	H	OMs	SO_2Tol	A [45 °C/15 h]	no reaction		
9n	Me	OMs	SO_2Ph	A [45 °C/15 h]	no reaction		

a) and b) See Tables 1 and 2. c) 0.2 Equiv. of Lewis acid was used.

Application of the reaction conditions A to the bicyclic acetal system (9i) realized successfully the desired partial ring fission to give the monothioacetal (10i) in 70% yield. Thus, several bicyclic substrates (9) furnished the monothioacetals (10)[6] in moderate to good yields as shown in Table 3, although substrates which have arylsulfonyl group at the C(3) position resisted to react even at higher temperature. In striking contrast to the results, under the reference conditions B the 5-unsubstituted bicyclic compound (9i) afforded poor yields of the product mixture 10i and thioacetal (11i), in addition to the recovery of the unreacted substrate (9i), and the 5-methylated bicyclic substrate (9j) did not react at all.

In conclusion, the organoaluminium reagent of type R_2AlSPh proved to be a potential tool for regioselective monothioacetalization particularly of cyclic and bicyclic acetals and would enable us to perform stepwise cleavage of the acetal C–O bonds of the 5-alkylated bicyclic ones (9 R^1= alkyl) which has been otherwise unsuccessful.[3]

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3) Y. Masaki, Y. Serizawa, K. Nagata, and K. Kaji, Chem. Lett., 1984, 2105.

4) K. Oshima and H. Nozaki, Yuki Gosei Kagaku Kyokai Shi, 38, 460 (1980).

5) A solution of Et_2AlSPh in toluene was prepared from a solution of Et_3Al in toluene (ca. 1.1 M solution) and 1.2 equiv. of PhSH (0 °C/20 min).

6) Monothioacetals were obtained as diastereoisomeric mixture concerning the anomeric position.

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