



Stereoselective reactions of a thioester butanediactal with various electrophiles



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ABSTRACT

The reactions of the lithium enolate of *S*-ethyl (2*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-[1,4]-dioxane-2-carbothioate were investigated in the presence or absence of hexamethylphosphoramide (HMPA). Fluorination gave a single isomer with a much better yield than for the corresponding methyl ester. Alkylation with alkyl halides strongly depended upon their structure. Without HMPA, only methyl iodide reacted with moderate yield and gave a single isomer. In the presence of HMPA, all of the alkyl halides reacted almost quantitatively (81–98% yield) with moderate stereoselectivity and preferentially gave products with the alkyl chain attached at the equatorial position. The silyl enol ether obtained from the thioester had the opposite geometry to that obtained from the methyl ester, which thus explains the difference in stereoselectivity between these two compounds.

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1. Introduction

Butanediacetals are extremely useful building blocks in the synthesis of both small and very complex natural compounds.^{1–3} They can be obtained in a large scale from cheap and readily available starting materials, such as *L*-ascorbic acid, *D*-mannitol or (*S,S*)- and (*R,R*)-dimethyl tartrate.^{4–7} The key derivatives of butanediacetals can be assembled using flow chemistry methods.^{8,9} Butanediacetals with a rigid chair conformation induce excellent diastereoselectivity in many types of reactions, including alkylations with alkyl halides, aldol reactions with aldehydes, addition of zinc alkynylides or Grignard reagents to butanediacetals derivatives with an aldehyde group, or radical alkylations.^{10–15}

In the butanediacetals obtained from dimethyl tartrate, the ester groups were replaced with thioesters to give compound **1** (Fig. 1), which improved the stability of the enol ions and gave

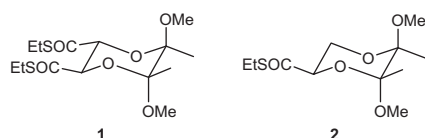


Figure 1. Thioester butanediactal derivatives **1** and **2**.

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better results in the alkylation reactions with halides and aldol reactions with aldehydes,¹⁶ compared to the enol ions obtained from diester butanediacetals, which gave mixtures of products.¹⁷ However, the reactivity of thioester **2** (Fig. 1) has not been investigated in the alkylation reactions. We therefore decided to study the reactions of this compound and compare the results with those previously obtained with methyl ester **3**.¹⁰

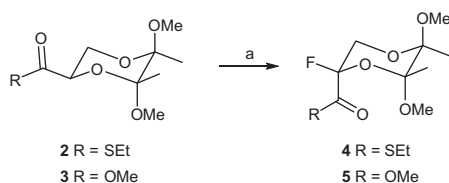
2. Results and discussion

For the synthesis of the thioester we chose the same procedure as for the tartrate derivative.^{15,18} In the reaction with trimethyl aluminum and ethanethiol, compound **2** was obtained in 98% yield (Scheme 1). Next, electrophilic fluorination was investigated for both substrates: methyl ester **3** and ethyl thioester **2**. First, the Selectfluor[®] was applied as a fluorinating reagent for the methyl ester, but was unsuccessful. A mixture of products was obtained from which the desired product could not be isolated. When Selectfluor[®] was replaced with *N*-fluorobenzenesulfonamide (NFSI), both substrates **2** and **3** gave products **4** and **5**, in which



Scheme 1. Reagents and conditions: (a) EtSH, (Me)₃Al, CH₂Cl₂.

the fluorine atom was located at the equatorial position (Scheme 2). Methyl ester derivative **5** was obtained in 52% yield and was accompanied with by-products. The thioester analog **4** was produced as a single product in a much better yield (82%). For both substrates **2** and **3**, the reactions gave better results when they were carried out without the addition of hexamethylphosphoramide (HMPA).



Scheme 2. Reagents and conditions: (a) 1.5 equiv LDA, NFSI, -78°C . The stereochemistry of the products was assumed by analogy to the alkylation products **6a–6c**.

Since the butanediactal with the thioester group **2** gave a higher yield than its methyl ester analog **3** in the reaction with an electrophilic fluorinating reagent, we decided to investigate its reactivity in the alkylation reactions with alkyl halides and compare it with the results obtained for the methyl ester **3** described in the literature.¹⁰ For this comparison, the following alkyl halides were chosen: allyl iodide, iodomethane, and benzyl bromide. First, the same conditions as for the methyl ester **3** were used in the reactions of thioester **2** with allyl iodide (Table 1, entry 1). Only substrate **2** and its diastereoisomer with the thioester group at the axial position were present in the mixture after the reaction was stopped, whereas the methyl ester analog **3** gave the product in 61% yield.¹⁰ When the allyl iodide diluted in HMPA was added to the enol ion, almost complete conversion of the substrate into products **6a** and **7a** occurred (Table 1, entry 2). Under these conditions the products with the allyl group at the equatorial **6a** and axial **7a** positions were produced in a ratio of 4.7:1, respectively. The mixture of diastereoisomers **6a** and **7a** could be separated by

Table 1
Results of the alkylation reactions of **2** with alkyl halides^a

Entry	Halide	HMPA (%)	Yield (%)	Product ^b	dr ^c
1	$\text{CH}_2=\text{CHCH}_2\text{I}$	0	0	—	—
2	$\text{CH}_2=\text{CHCH}_2\text{I}$	10	99	6a:7a	4.7:1
3	$\text{CH}_2=\text{CHCH}_2\text{Br}$	10	0	—	—
4	CH_3I	0	27	6b	1:0
5	CH_3I	10	84	6b:7b	2.7:1
6	PhCH_2Br	0	0	—	—
7	PhCH_2Br	10	81	6c:7c	5.5:1

^a 1.5 equiv LDA, -78°C ; 5 equiv halide.

^b Stereochemistry determined by 2D NOE NMR signals.

^c Based on the ^1H NMR spectra of the crude product.

column chromatography on silica gel. In order to verify the influence of the electrophile on the alkylation reaction, the allyl iodide was replaced by allyl bromide (Table 1, entry 3). In this case, no product was obtained. Next, lithium hexamethyldisilazide was used as a base instead of lithium diisopropylamide, but only substrate **2** was recovered from the reaction mixture, thus suggesting that the enol ion was not formed. When iodomethane was used without the addition of HMPA, a single product **6b** with methyl group at the equatorial position was produced, but in only 27% yield (Table 1, entry 4). The addition of HMPA caused the formation of both diastereoisomers **6b** and **7b** in a ratio of 2.7:1, respectively, (Table 1, entry 5). Reaction with a more bulky electrophile, benzyl bromide diluted in HMPA, gave both isomers **6c** and **7c** in a ratio of 5.5:1, respectively (Table 1, entry 7). When the reaction of benzyl bromide was carried out without addition of HMPA, no products were obtained (Table 1, entry 6).

A stable enolate equivalent, silyl enol ether **8**, was obtained in an attempt to understand the differences in diastereoselectivity between these reactions and to determine the configuration of the enol ion (Fig. 2). The silyl derivative was prepared from the enol ion generated in the presence and absence of HMPA. The silyl enol ether obtained in both cases had the same geometry. When 1 equiv of trimethylsilyl chloride was applied in this reaction, only a small amount of the silyl enol ether **8** was formed. Complete conversion of thioester **2** into silyl enol ether **8** was achieved when 5 equiv of trimethylsilyl chloride were used. A 2D NOE NMR experiment allowed the determination of the geometry of **8** as *Z* (Fig. 2), which is opposite to the geometry of derivative **9** obtained from the methyl ester **2** (Fig. 2).¹²

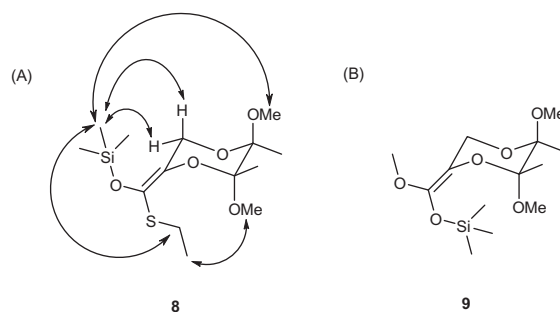


Figure 2. (A) The interactions detected in the 2D NOE NMR spectrum of **8**; (B) the structure of the silyl enol ether **9**.

The ratio of diastereoisomers obtained in the alkylation reactions depended on the structure of the alkyl halides used. The smallest alkyl electrophile, methyl iodide, gave the lowest ratio of diastereoisomers **6b:7b** in the presence of HMPA, but it was reactive in the absence of HMPA and gave a single isomer. In the case of methyl ester **3**, no product was obtained in the absence of HMPA, although the reaction was selective in its presence.¹⁰ In general, higher yields of the alkylation were obtained in the presence of HMPA for thioester **2** (Table 1) than for the methyl ester **3**,¹⁰ but the stereoselectivity was lower for thioester **2**, although it increased with the size of the alkyl chain. This lower selectivity may be explained by the reversed geometry of the enol ion generated from the thioester **2**. In the lithium enolate of **2**, the convex side is more hindered when the lithium ion is coordinated by HMPA than when HMPA is not present. Although the reactivity of this enolate increases with the addition of HMPA, the stereo preference for the formation of products with the alkyl chain attached in the equatorial position is smaller. For the lithium enolate of **3**, coordination of the lithium ion by HMPA does not influence the accessibility of the convex side. On the contrary, it most

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