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Regioselective Substitution Reactions of Zinc Sulfolenylates

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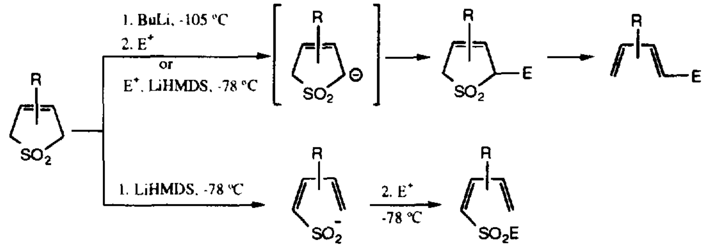
Abstract. Zinc sulfolenylates **2a-c** have been generated by metal exchange processes from lithium sulfolenylate. These organozinc compounds show very interesting regioselectivity in the reactions with electrophiles.

It has been well established that lithium sulfolenylates could be generated from 3-sulfolenes and BuLi at 105 °C and they react with electrophiles to produce substituted 3-sulfolenes which are stable precursors for substituted 1,3-dienes.[1] It is also known that the cycloreversion of a metal sulfolenylate which takes place readily at -78 °C [2] can be suppressed if an electrophile is already present when the sulfolenylate is generated.[1] These deprotonation/substitution reactions find broad applications in the preparation of various substituted 1,3-dienes (scheme I). However, this strategy would be more useful if the ring opening of the sulfolenylate does not occur at -78 °C in the absence of an electrophile.

Scheme I



One approach to achieve this goal is to attach an electron-withdrawing group on the 3-sulfolene so as to stabilize the anion.[3] Another approach is to perform a metal exchange reaction on the lithium sulfolenylate so as to generate a more covalent, and thus more stable, sulfolenylate.[4] A few years ago, we were successful in generating a zinc sulfolenylate by treating 4-bromo-2-sulfolene with zinc metal under ultrasonic irradiation at room temperature and we used this organozinc *in situ* to react with aldehydes or ketones to produce 4-(1-hydroxyalkyl)-2-sulfolenes.[5] The regioselectivity of this reaction is different from that of the reactions of lithium sulfolenylates with electrophiles where essentially 2-substituted 3-sulfolenes are obtained.[1] We were therefore interested to look further into the substitution reactions of zinc sulfolenylates. Since the zinc sulfolenylates prepared from 4-bromo-2-sulfolenes react only with aldehydes or ketones which must be added to the reaction vessel prior to the generation of the organozinc species, we seeked another route to prepare zinc sulfolenylates in a hope to overcome these limitations.

When a solution of lithium sulfolenylate, generated by treating 3-sulfolene with *n*-BuLi at -105 °C, was treated with a solution of anhydrous $ZnCl_2$ in THF, the metal exchange reaction took place immediately as indicated by the change of color from dark red to light yellow. Electrophiles were then added at -78 °C for substitution reactions. The organozinc species **2a** could remain stable for days when stored in a freezer.

To test the completion of the metallation of 3-sulfolene and the reactivity of **2a**, D_2O was used as the electrophile. 2-Deuterated 3-sulfolene **3**, a good precursor for monodeuterated 1,3-butadiene, was obtained as the only product in almost quantitative yield (entry 1, Table I). In contrast, when D_2O was added to lithium sulfolenylate, a mixture **3** and multideuterated 3-sulfolenes was obtained. This is due to the basicity of LiOD which causes further deuterium exchange of **3** to take place.

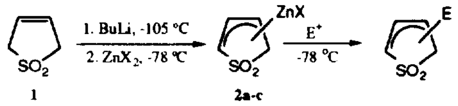
A series of reactions were then performed on the zinc sulfolenylate **2a** with different electrophiles and the results are summarized in Table I.[6] The reaction with TMSCl (entry 2) gave 2-silylated 3-sulfolene **4**. It has been reported that the reaction of lithium sulfolenylate with TMSCl gave 3-silylated 3-sulfolene; whereas the reaction of lithium sulfolenylate with TMSCl in the presence of NaI gave **4** in fair yield.[7] The procedure shown in Table I provides an improved method for the preparation of **4** and, consequently, 1-silylated 1,3-butadiene.

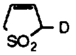
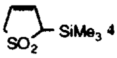
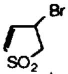
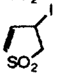
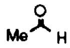
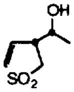
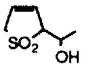
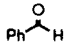
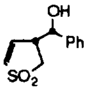
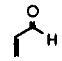
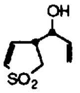
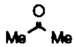
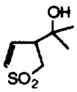
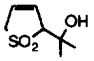
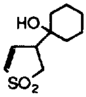
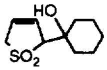
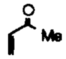
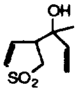
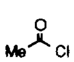
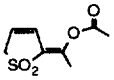
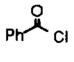
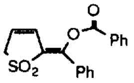
Reactions of **2a** with Br_2 and I_2 (entries 3 and 4) gave the 4-halo-2-sulfolenes **5** and **6**, respectively, in good yields. These reactions are of practical value because it is an improvement for the preparation of **5** which are usually obtained from **1** *via* bromine addition and subsequent partial dehydrobromination.[8] To the best of our knowledge, compound **6** has never been prepared before.

When an aldehyde was used as the electrophile (entries 5-7), only the γ-substituted 2-sulfolene was obtained, except that in the case of using acetaldehyde as the reactant a 2-substituted 3-sulfolene **8** was detected in trace amount. In general, the yields of the products in these reactions are better than those obtained from the reactions of aldehydes with 4-bromo-2-sulfolene and activated zinc under ultrasonic irradiation.[5] In principle, the reactions with aldehydes should produce mixtures of two possible diastereomers. However, only a single isomer was obtained in each case, indicating a very high stereoselectivity in these reactions. To determine the relative configuration of the two chiral centers, a single crystal of compound **7** was obtained and analyzed with X-ray diffractometry. A chair conformation of the transition state as shown in **A** where the R-group stays at the equatorial position can be used to explain the stereoselectivity of the reaction (eq 1). Presumably the reactions of **2a** with other aldehydes would proceed *via* a similar transition state so that the stereochemistry of those products should be the same as that in compound **7**.

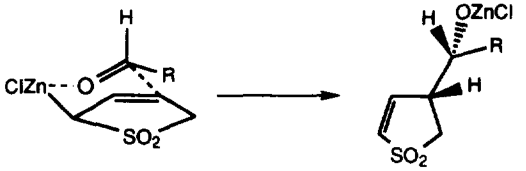
The reaction of **2a** with acetone (entry 8) gave mainly the α-substituted product **12** which is different from the result of using 4-bromo-2-sulfolene and Zn as the source of organozinc where only γ-substitution product **11**[5] was observed. It has been reported that the reaction of lithium sulfolenylate[9] or magnesium sulfolenylate[5] with acetone gave **12**, the α-substitution product. These results indicate that the regiochemistry of the substitution reactions is influenced by the metal counterion of the sulfolenylate. Apparently there is a subtle

Table I. Reactions zinc sulfolenylate, generated by metal exchange, with electrophiles.



entry	electrophile	product(s)	yield(%) and ratio		
			X=Cl (**2a**)	X=Br (**2b**)	X=I (**2c**)
1	D$_2$O	 3	99	99	97
2	Me$_3$SiCl	 4	72	73	67
3	Br$_2$	 5	92	61	70
4	I$_2$	 6	91	71	73
5		 7 +  8	86 (13:1)	85 (1:0)	85 (1:0)
6		 9	95	90	87
7		 10	95	97	97
8		 11 +  12	92 (1:10)	88 (1:19)	91 (1:24)
9		 13 +  14	90 (3:2)	87 (1:3)	95 (1:3)
10		 15	91	93	92
11		 16	0	0	20
12		 17	0	0	21

structural difference between the zinc sulfolenylate generated by metal exchange process and that generated by ultrasound-induced allylzincation process.



(eq 1)

We therefore studied the reactivity and selectivity of the zinc sulfolenylates **2b** and **2c** generated from metal exchange of lithium sulfolenylate with $ZnBr_2$ and ZnI_2, respectively (Table I). Not much difference was observed among the reactions of **2a**, **2b** and **2c** except that the α- to γ- selectivity in the reactions with acetone and cyclohexanone (entries 8 and 9) varies to some extent. It seems that the α-substitution is more favored in the reactions with **2b** and **2c**. One distinct difference is that no reactions took place when **2a** or **2b** were treated with acyl chlorides, whereas compounds **16** and **17** were obtained, albeit in low yields, when **2c** was used as the reagent (entries 11 and 12). No reactions took place when any of **2a-c** was treated with MeI.

The regiochemistry of the zinc sulfolenylate **2** with electrophiles agrees well with the hard and soft acids and bases (HSAB) principle.[10] The α-position of **2**, being the harder nucleophilic center, prefers to react with hard electrophiles such as D_2O and TMSCl. On the other hand, the γ-position, being the softer nucleophilic center, prefers to react with soft electrophiles such as halogens and carbonyl compounds.

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6. ^{1}H NMR spectral data (300 MHz) of new products: compound **6**, δ 3.53 (1H, dd, J = 3.3, 11.7 Hz), 3.76 (1H, dd, J = 7.2, 14.7 Hz), 5.17-5.21 (1H, m), 6.61 (1H, d, J = 6.3 Hz), 6.89 (1H, dd, J = 3.3, 6.3 Hz); compound **10**, δ 2.67 (1H, br s), 3.20-3.34 (3H, m), 4.29 (1H, t, J = 6.0 Hz), 5.31 (1H, d, J = 10.2 Hz), 5.37 (1H, d, J = 17.4 Hz), 5.83 (1H, ddd, J = 6.0, 10.2, 17.4 Hz), 6.70 (2H, s); compound **11**, δ 1.49-2.15 (10H, m), 3.10 (1H, br s), 3.74 (3H, s), 6.16 (2H, s).
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