REGIOSELECTIVE ALKYLATION OF 3-SUBSTITUTED 3-SULFOLENES

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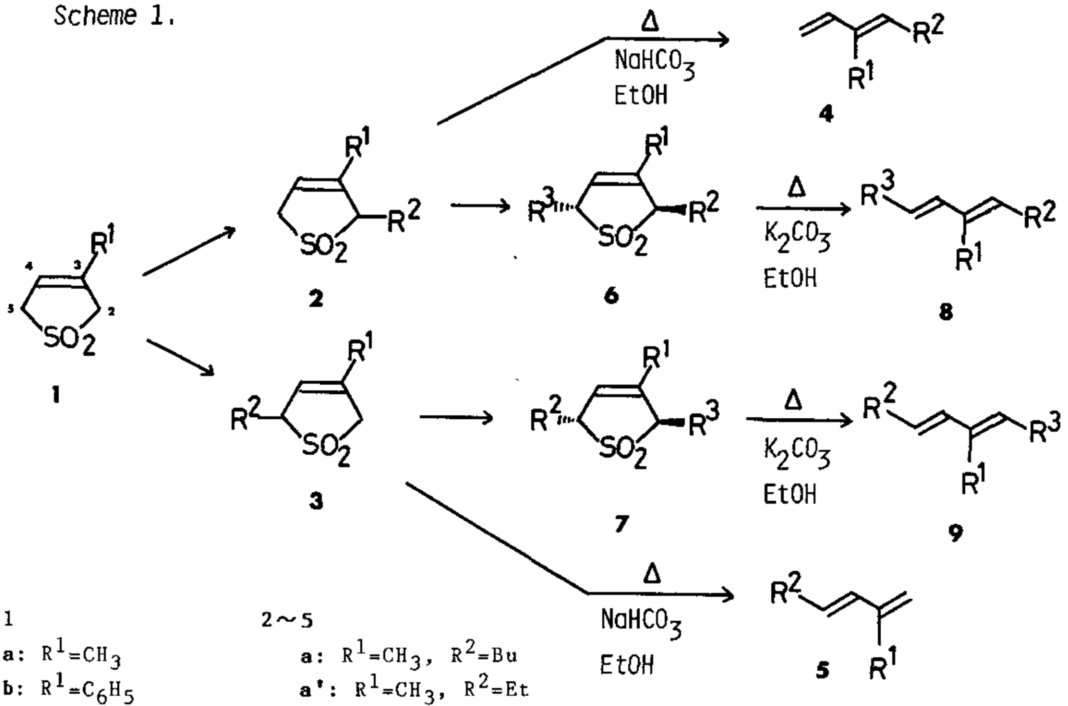
Abstract——Remarkable directing effect of the substituent on the double bond of 3-sulfolene was found in the reaction with alkyl iodides under basic conditions; electron donating groups effect selective substitution at the 2-position while electron withdrawing groups effect exclusive substitution at the 5-position.

Recently we have established a general method for direct alkylation of 3-sulfolene.[1,2] The method in combination with reversible thermal cheletropic reaction opened a new route to functionalize conjugated dienes.[3] In the course of studying the scope and limitation of the alkylation of 3-sulfolene, we found a remarkable substituent effect on the alkylation of 3-substituted 3-sulfolene in the synthesis of (±)-lupinine.[4] As we already reported,[1] the alkylation of 2-substituted 3-sulfolenes gave exclusively the corresponding 5-substituted products. It was found in the present study that the nature of the substituent on the double bond of 3-sulfolene greatly influences the reaction pathway of the 3-substituted 3-sulfolene, especially the regioselectivity of the alkylation.

Reactions of 3-substituted 3-sulfolenes (1) with alkyl iodides were carried out under the general alkylation conditions of 3-sulfolenes (LiHMDS, THF-HMPA, -78 °C).[1] 3-Methyl-3-sulfolene (**1a**) reacted with alkyl iodides to give only 2-substitution products (**2a** and **2a'**) in high yields (ca. 70%) with no detectable 5-substitution products (**3a** and **3a'**) (entry 1 and 2).[5] The regiochemistry of the products was confirmed by converting **2** to the corresponding (E)-dienes by thermal desulfonylation; (E)-3-methyl-1,3-octadiene (**4a**) and (E)-3-methyl-1,3-hexadiene (**4a'**) were obtained from **2a** and **2a'**, respectively, in quantitative yields and with 100% stereoselectivity. However, alkylation of the resulting 2-alkyl-3-methylsulfolenes (2a and **2a'**) (entry 7 and 8), occurred exclusively at the 5-position yielding trans-2,3,5-trisubstituted 3-sulfolenes (**6a** and **6a'**) in high yields. Since 3-methyl-3-sulfolene (**1a**) is a masked isoprene unit,[5] it is possible by using regioselective alkylation of the sulfolene to introduce a desirable alkyl group to either the head or the tail of the isoprene unit. For example, by changing the order of sequential two alkylations, butylation and

Scheme 1.



1
a: $R^1=CH_3$
b: $R^1=C_6H_5$
c: R^1=p-$MeOC_6H_4$
d: $R^1=CF_3$
e: $R^1=C_6H_5CH_2$

2～5
a: $R^1=CH_3$, R^2=Bu
a': $R^1=CH_3$, R^2=Et
b: $R^1=C_6H_5$, R^2=Bu
c: R^1=p-$MeOC_6H_4$, R^2=Bu
d: $R^1=CF_3$, R^2=Bu
e: $R^1=C_6H_5CH_2$, R^2=Me

6～9
a: $R^1=CH_3$, R^2=Bu, R^3=Et
a': $R^1=CH_3$, R^2=Et, R^3=Bu
b: $R^1=C_6H_5$, R^2=Bu, R^3=Et

Table 1. Reaction of 3-substituted 3-sulfolenes with alkyl iodides[a)]

entry	sulfolene	alkyl iodide	products (yield %)[b)]
1	**1a**	BuI	**2a** (71), **3a** (0)
2	**1a**	EtI	**2a'** (71), **3a'** (0)
3	1b	BuI	**2b** (0), **3b** (72)
4	**1c**	BuI	**2c** (12), **3c** (49)
5	**1d**	BuI	**2d** (0), **3d** (0)
6	**1e**	MeI	**2e** (0), **3e** (0)
7[c)]	**2a**	EtI	**6a** (73)
8[c)]	**2a'**	BuI	**6a'** (56)
9[c)]	3b	EtI	**7b** (14)[d)]

a) To a solution of 3-sulfolene (**1**) (2 equiv.), alkyl iodide (1 equiv.), and HMPA (4 equiv.) in THF was added a solution of LiHMDS (1 equiv.) in THF in one portion at -78 °C. b) Based on alkyl iodide. c) The reaction was carried out using equimolar amounts of 3-sulfolene (**2** or **3**) and alkyl iodide. d) The reaction was carried out at -7 °C.

ethylation, (E,E)-5-methyl-3,5-decadiene (**8a**) and (E,E)-4-methyl-3,5-decadiene (**8a'**) were synthesized in 3 steps in about 45% overall yield starting from the alkyl iodide used for the first alkylation[6] (Scheme 1).

Phenyl group at the 3-position exhibits completely inversed effect on the regioselectivity of the alkylation reaction; the reaction of 3-phenyl-3-sulfolene (**1b**) with butyl iodide gave only the 5-substitution product, 2-butyl-4-phenyl-3-sulfolene (**3b**)[7] (entry 3). In this case, second alkylation was very sluggish and no alkylation product was obtained under the standard conditions. The reaction of **3b** with ethyl iodide occurred under forced conditions (LiHMDS, THF-HMPA, -7° C) to give 5-butyl-2-ethyl-3-phenyl-3-sulfolene (**7b**) in low yield (14%) (entry 9). The reaction of 3-(p-methoxyphenyl)-3-sulfolene (**1c**) having electron donating group on the phenyl group with butyl iodide gave two monoalkylation products, 5-substituted derivative (**3c**) as the major product (49%) and 2-substituted derivative (**2c**) as the minor product (12%) [7] (entry 4).

Introduction of trifluoromethyl group to the 3-position caused spontaneous decomposition of the starting sulfolene (**1d**) under the general alkylation conditions. It is noteworthy that 3-benzyl-3-sulfolene (**1e**) was completely inert to the reaction with methyl iodide even at an elevated temperature (0 °C), nonetheless the starting sulfolene seems to be sufficiently stable to tolerate under the alkylation conditions.[8]

The effect of the substituents at the double bond on the regioselectivity of the alkylation of 3-sulfolene is considered to be electronic in nature. The electron donating methyl group made the protons at the 5-position less acidic and the only carbanion generated at the 2-position could react with the alkyl iodide. On the other hand, electron withdrawing phenyl group made the protons at the 5-position more acidic leading to selective formation of the carbanion at the 5-position. The fact that introduction of an electron donating methoxyl group on the phenyl group increases the proportion of the substitution at the 2-position supports the postulation. It is assumed from the results of benzyl substitution, that the carbanion formed at the 2-position could not react with the alkyl iodide because of the steric congestion on the carbanion caused by the adjacent benzyl group. In the reaction of 3-trifluoromethyl-3-sulfolene (**1d**), the carbanion formed selectively at the 5-position due to the effect of electron withdrawing trifluoromethyl group is supposed to decompose quite readily via the elimination of a fluorine atom situated γ-position of the carbanion.

It is concluded from the results of the present study that alkylation of sulfolene occurs at one of the positions α to the sulfonyl group which carries more acidic protons, and that if the position is so sterically hindered that an electrophile cannot approach, no alkylation occurs even under forced conditions. Applications of the regioselective alkylation of 3-sulfolenes to the syntheses of natural products are currently progressing.

REFERENCES AND NOTES

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5. Regioselective alkylation of 3-methyl-3-sulfolene has been reported from other laboratory: T. S. Chou, H. H. Tso, and L. J. Chang, J. Chem. Soc., Chem. Commun., 1984, 1323.
6. Stereoselective desulfonylation of trans-2,5-substituted sulfolenes to (E,E)-conjugated dienes was carried out according to our method reported previously.[1]
7. Regiochemistry was confirmed by converting the sulfolene to the corresponding diene by thermal desulfonylation.
8. 3-Sulfolene α-carbanions are generally unstable and decompose unless they can react with an electrophile present in the reaction mixture as they are generated. In the case of 3-trifluoromethyl-3-sulfolene, dark brown color was developed when LiHMDS was added to a mixture of the sulfolene and alkyl iodide indicating spontaneous decomposition of the sulfolene, while in the case of 3-benzyl-3-sulfolene, pale yellow color typical of sulfolene α-carbanion was developed showing transient existence of the carbanion.

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