

Competition for Regiochemical Control between Substituents of Some 2,3-Disubstituted Buta-1,3-dienes in the Diels–Alder Reactions

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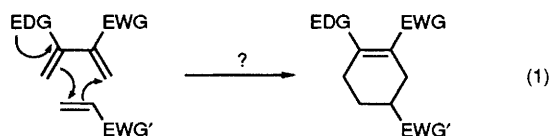
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Several 3,4-disubstituted 3-sulfolenes **1a–j**, the precursors for the corresponding 2,3-disubstituted 1,3-dienes **2a–j**, are conveniently prepared and undergo Diels–Alder reactions smoothly with methyl acrylate under thermal conditions where the order of *para*-directing ability of different substituents is OTBS≡CN > SPh > OMe≡CO₂Me > OTs > OAc.

The Diels–Alder reaction of a monosubstituted 1,3-diene with an unsymmetric dienophile is known to give, with very few exceptions, mainly the *para* or *ortho* cycloadduct.¹ Such regioselectivity makes Diels–Alder reactions useful in the construction of functionalized six-membered carbocycles.² The question of regiochemistry becomes more complicated for the reactions of 1,3-dienes containing two different substituents at the 1,4-,³ 1,2-⁴ or 2,3-positions⁵ because a competition for regiochemical control would appear. An understanding of the relative directing ability for the regioselectivity of different groups would raise the synthetic usefulness of Diels–Alder reactions. However, so far there is no systematic study on this topic,⁶ probably owing to the instability of many disubstituted 1,3-dienes and the lack of general methods for their preparation. It has been established that substituted buta-1,3-dienes can be conveniently obtained from the thermolysis of 3-sulfolenes.⁷ Such a strategy could be utilized in the preparation of unstable dienes and in the examinations of competitive control for regioselectivity of Diels–Alder reactions.

We were interested to study the Diels–Alder reaction of 2,3-disubstituted dienes bearing both an electron-donating group (EDG) and an electron-withdrawing group (EWD). These dienes have a special structural feature that the polarities of the substituents are reinforcing each other in the cycloaddition reaction [eqn. (1)]. It was considered likely that, in addition to the frontier molecular orbital coefficients,^{1,8} the polarities of the substituents might make some contribution to the regioselectivity of their Diels–Alder reactions.^{5c}

The requisite disubstituted 3-sulfolenes **1a–j**, which are stable precursors for the corresponding dienes **2a–j**, were conveniently prepared *via* three different routes. Compounds **1a**, **1c**, **1f** and **1h–j** were obtained from the *m*-chloroperbenzoic acid oxidation reactions of the corresponding 3,4-disubstituted 2,5-dihydrothiophene **4**, which in turn were prepared from **3a**⁹ and **3b**¹⁰ under appropriate conditions (Table 1).



Compound **1c**¹¹ is actually not a 3-sulfolene but a 2-sulfolene the structure of which is **1c'**. We were unable to isomerize its double bond to the 3-position. Fortunately, the thermal reaction of **1c'** with methyl acrylate (Table 2) under neutral conditions proceeded smoothly [eqn. (2)]. A rapid isomerization of **1c'** to **1c** must be taking place during the reaction.⁷

The method shown in Table 1 was not applicable to the synthesis of **1d**¹² nor **1e** because of undesired side reactions during the oxidation stage.¹¹ Alternatively, compounds **1d** and **1e** were prepared from 3-methoxycarbonyl-4-sulfolanone **5**¹³ by treatment with toluene-*p*-sulfonyl chloride (TsCl) or acetyl chloride (AcCl), respectively [eqn. (3)]. The phenylthio-containing 3-sulfolenes **1b** and **1g** were produced from the

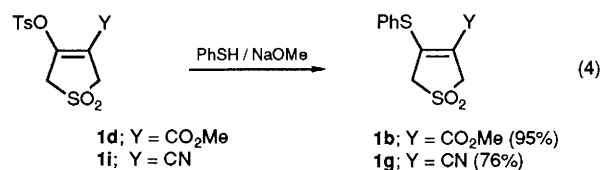
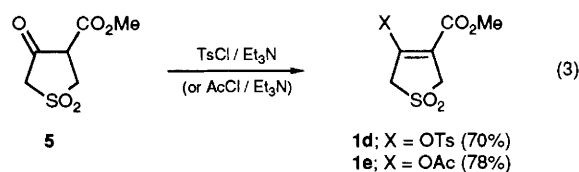
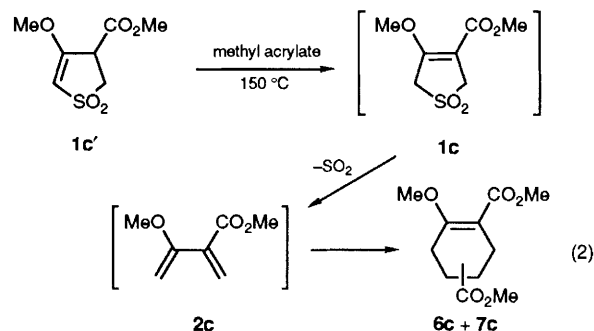


Table 1 Preparation of 3-sulfolenes **1a**, **1c**, **1f** and **1h–j**

Entry	Reactant	Reagent	X	Y	Intermediate and yield (%) ^a	Product and yield (%) ^a
1	3a	TBSCl/Et ₃ N	OTBS	CO ₂ Me	4a (82)	1a (93)
2	3a	CH ₂ N ₂	OMe	CO ₂ Me	4c (97)	1c (95)
3	3b ^b	TBSCl	OTBS	CN	4f (98)	1f (89)
4	3b	CH ₂ N ₂	OMe	CN	4h (77)	1h (95)
5	3b	TsCl/Et ₃ N	OTs	CN	4i (85)	1i (93)
6	3b	AcCl/Et ₃ N	OAc	CN	4j (98)	1j (84)

^a These are isolated yields after column chromatography. ^b The sodium-enolate of **3b** was used in this reaction.

Table 2 The Diels–Alder reactions of 2,3-disubstituted dienes with methyl acrylate

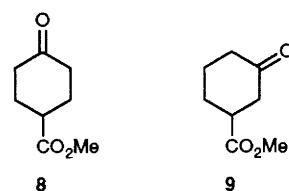
Entry	X	Y	Reactant	Products and total yield (%) ^a	(6 : 7)
1	OTBS	CO ₂ Me	1a	6a + 7a (51)	75 : 25
2	SPh	CO ₂ Me	1b	6b + 7b (62)	69 : 31
3	OMe	CO ₂ Me	1c	6c + 7c (75)	50 : 50
4	OTs	CO ₂ Me	1d	6d + 7d (82)	33 : 67
5	OAc	CO ₂ Me	1e	6e + 7e (91)	27 : 73
6	OTBS	CN	1f	6f + 7f (94)	50 : 50
7	SPh	CN	1g	6g + 7g (98)	42 : 58
8	OMe	CN	1h	6h + 7h (82)	36 : 64
9	OTs	CN	1i	6i + 7i (80)	33 : 67
10	OAc	CN	1j	6j + 7j (80)	23 : 77

^a These are isolated yields after column chromatography. The reaction conditions were not optimized.

corresponding tosyl-containing compounds **1d** and **1i**, respectively, by treatment with phenylthiolate¹² [eqn. (4)].

The thermolysis of **1e** at 150 °C in the absence of a dienophile resulted in the extrusion of SO₂.¹⁴ However, this reaction gave only a complex mixture and the corresponding diene **2c**, which should be the primary product, could not be isolated. This result indicates that **2c** is not stable at this high temperature. Therefore, no attempts were made to isolate the dienes from the thermolysis of other 3-sulfolenes **1**. When the mixture of a 3,4-disubstituted sulfolene **1a–j** and methyl acrylate in toluene was heated at 150 °C in a sealed tube for 8 h, the Diels–Alder reaction took place smoothly to yield a mixture of regioisomers of the cycloadducts **6** and **7**. The yields and ratios of the products are summarized in Table 2.

It is almost impossible to prepare all the disubstituted dienes to study the competition for regiocontrol among OTBS, SPh, OMe, OTs and OAc groups (TBS = *tert*-butyldimethylsilyl). Nevertheless, it was thought that, the comparison of the product ratios shown in Table 2 should give us a reasonable indication of the relative directing ability of each of the substituents. The ratio of **6c** to **7c** (50 : 50) in entry 3 indicates that CO₂Me group has about the same ability as a MeO group in controlling the regioselectivity. Other ratios show that OTs and OAc (entries 4 and 5) are lower while OTBS and SPh (entries 1 and 2) are higher than CO₂Me in directing ability. The steric bulkiness or the polarity of the substituents does not appear to influence the regiochemistry of the Diels–Alder reactions. The product ratios shown in entries 6 to 10 exhibit the same order of directing ability for the substituents. It should be noted that CN is a more powerful directing group than CO₂Me (entry 1 vs. entry 6). Based on these data, the order of directing ability of the substituents for regioselectivity in the Diels–Alder reaction of 2,3-disubstituted butadienes with methyl acrylate is suggested as: OTBS ≈ CN > SPh > OMe ≈ CO₂Me > OTs > OAc. An early study^{5a} of the Diels–Alder reactions of 2-alkoxy-3-(phenylthio)buta-1,3-dienes showed that SPh is a more powerful '*para*'-directing group than OMe and OAc. This result is in agreement with the order of directing ability listed above. However, another



study^{5d} indicated that OTBS is a weaker directing group than SAR exemplifying a contradiction to this study. Such a difference remains to be answered.

Although compounds **1a** and **1e** are structurally and electronically similar, they gave opposite regioselectivity in the Diels–Alder reactions with methyl acrylate (entry 1 vs. entry 5). Treatment of **6a**, the major product in entry 1, with HCl in refluxing MeOH gave 4-oxocyclohexanecarboxylate **8**. Similar treatment of **7e**, the major product in entry 5, gave the regioisomer of **8**, 3-oxocyclohexanecarboxylate **9**. In other words, one is able to prepare either regioisomer **8** or **9** from the same starting material **3a** via certain functionality transformation and regioselective Diels–Alder reactions. The sequence of hydrolysis/decarboxylation reactions of **6** and **7** not only illustrates the synthetic usefulness of the regioselective Diels–Alder reactions, but also constitutes a convenient and unambiguous method for the determination of the regiochemistry of the cycloadducts.

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