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β-Acyloxysulfonyl Tethers for Intramolecular Diels–Alder Cycloaddition Reactions

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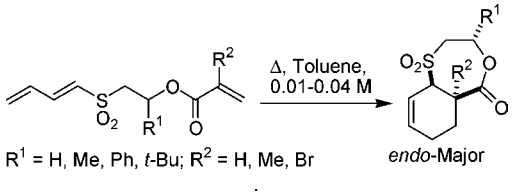
ABSTRACT



β-Hydroxy sulfone-based tethers were employed for the first time to achieve thermally mediated intramolecular Diels–Alder cycloaddition. The reactions proceeded with complete regioselectivity and high (10/1) to complete *endo/exo*-selectivity and resulted in the preferential formation of one of the two possible *endo*-cycloadducts. The yields and stereoselectivities were proportional to the bulk of the R^1 substituent on the β-acyloxysulfonyl tether.

It is known that temporary tethers can be used to control the regio- and stereoselectivity in Diels−Alder cycloaddition reactions.[1] However, to the best of our knowledge, only two types of tethers based on sulfur-containing functional groups have been reported, involving the use of sulfonate esters[2] and sulfonamides.[3] On the other hand, the intermolecular Diels−Alder reactivity of sulfonyl-substituted dienes and dienophiles has been studied. 1-Sulfonyl-1,3-dienes (the data are scarce and restricted to cyclic dienes)[4−6] and 2-sulfonyl-1,3-dienes[7−13] are prone to self-dimerization[4,8−10] through Diels−Alder reactions. They also undergo highly regioselective cycloaddition with electron-rich[5,9−11] dienophiles and less regioselective reactions with electron-deficient[6,9,10,12,13]

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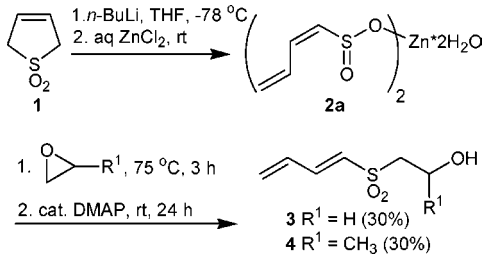
alkenes. If a 2-sulfonyl-1,3-diene bears an electron-donating group at C-3, the regioselectivity of the cycloaddition with α,β-unsaturated carbonyl compounds is increased in the presence of Lewis acids.[13] However, this is not the case for nonsubstituted 2-sulfonyl butadienes.[10] Connecting a sulfone-bearing diene and an electron-deficient dienophile by a tether bearing a stereogenic center might be expected not only to improve the regioselectivity but also to cause the cycloaddition to proceed in a diastereoselective manner. The presence of a sulfone group in the final cycloadduct provides various possibilities for further transformations. We have begun to explore the potential utility of sulfone-based tethers for cycloaddition reactions and present here our preliminary results.[14]

We considered the (*Z*)-butadienyl sulfinate anion, readily available from butadiene sulfone (**1**),[15] as an attractive building block to prepare 1-sulfonyl-1,3-dienes. We found[16] that Zn (*Z*)-sulfinate **2a**, freshly prepared from the corresponding Li (*Z*)-sulfinate in aqueous medium, reacted with ethylene oxide or propylene oxide regioselectively to produce the corresponding β-hydroxy sulfones as (*E*)-/(*Z*)-mixtures.

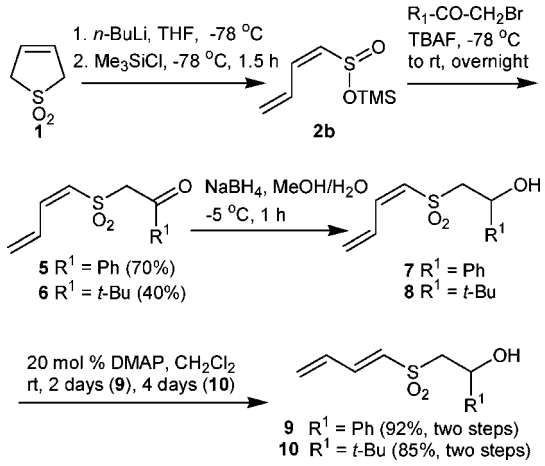
Isomerization to the (*E*)-stereoisomers occurred readily in the presence of DMAP to give cleanly (*E*)-butadienyl β-hydroxy sulfones **3** and **4** in 30% isolated yield from **1** (Scheme 1).

Scheme 1



As an alternative approach to β-hydroxy sulfone tethers, we attempted to employ α-halo ketones as electrophiles to trap the (*Z*)-butadienyl sulfinate anion. However, Zn, Li, or K butadienyl sulfinates, freshly prepared from **1** in THF, failed to react with α-bromo ketones, which were recovered unreacted. Bouchez and Vogel reported[17] that allyl or β-carboxyalkyl sulfinate anions, produced in situ from the corresponding silyl sulfinates, reacted with α-bromo esters to generate the corresponding sulfones. To our delight, this approach worked well for the reaction of (*Z*)-butadienyl silyl sulfinate **2b** with α-bromo ketones to furnish (*Z*)-β-oxo sulfones **5** and **6**, which were reduced in high yield to produce the corresponding (*Z*)-β-hydroxy sulfones **7** and **8**. DMAP-mediated isomerization required longer times than were employed for the preparation of sulfones **3** and **4** but still provided quantitative yields of the corresponding (*E*)-β-hydroxy sulfones **9** and **10** (Scheme 2).

Scheme 2



The esterification of (*E*)-β-(dienesulfonyl) alcohols **3**, **4**, **9**, and **10** with methacrylic acid (**11**) and acrylic acid (**12**) proceeded in good yield using conventional DCC/DMAP methods to afford the corresponding acrylate esters **14a**−**f**,**i** (Scheme 3, Table 1, method A). No alcohol decomposition was observed under the reaction conditions. Not surprisingly,[18] esterification using α-bromoacrylic acid (**13**) was

Table 1. Esterification of (*E*)-β-(Dienylsulfonyl) Alcohols **3**, **4**, **9**, and **10** to Afford Acrylate Esters **14a**−**i**

product	R^1	R^2	method[a]	yield (%)[b]
14a	H	Me	A	85
14b	Me	Me	A	93
14c	Ph	Me	A	81
14d	*t*-Bu	Me	A	50[c]
14e	Me	H	A	83
14f	Ph	H	A	81
14g	Me	Br	A	28[c]
14h	Ph	Br	B	47[c] (59[d])
14i	H	H	A	85

[a] A: DCC, DMAP, CH_2Cl_2, rt. B: 2,4,6-Trichlorobenzoyl chloride, Et_3N, LiCl, THF, rt. [b] Isolated yields after purification by silica chromatography. [c] Nonoptimized yields. [d] Based on consumed β-hydroxy sulfone.

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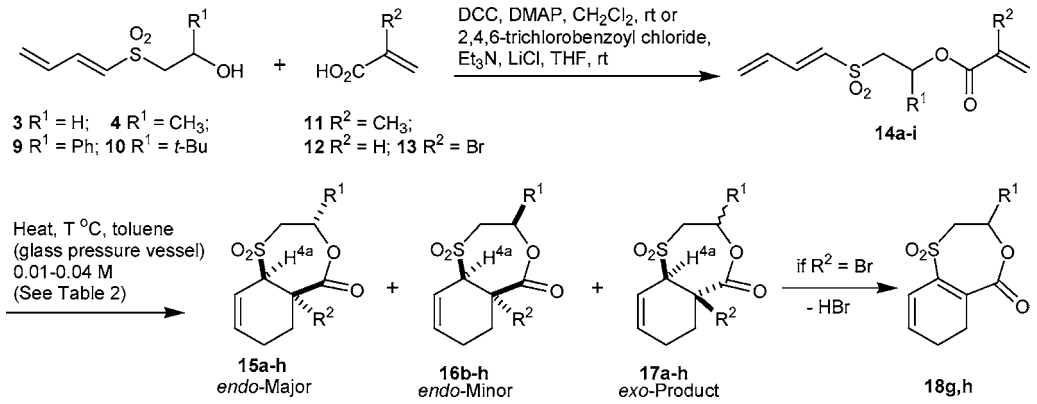
Scheme 3



problematic. The best yield to date was achieved when alcohol **9** was treated with the mixed anhydride derived from α-bromoacrylic acid (**13**) and 2,4,6-trichlorobenzoyl chloride in the presence of LiCl and triethylamine (Scheme 3, Table 1, method B).

Thermally mediated intramolecular Diels−Alder cycloaddition (IMDA) reaction of **14a**−**h** (Scheme 3, Table 2) occurred with complete regioselectivity and high (10/1) to complete *endo*/*exo*-selectivity (except when R^1 = H (**14a**)) and resulted in the preferential formation of one of the two possible *endo*-cycloadducts. For substrates **14a**−**d**, derived from methacrylic acid (**11**), the major *endo*-cycloadducts **15a**−**d** were separated as single diastereomers after crystallization, while the minor *exo*-cycloadducts **17a**,**d** and *endo*-cycloadducts **16b**−**d** were characterized by ^{1}H and ^{13}C NMR analysis of the residual mother liquors. For cycloadditions involving the substrates **14e**,**f**, derived from acrylic acid (**12**), both the major *endo*-cycloadducts **15e**,**f** and the minor *endo*-cycloadducts **16e**,**f** were cleanly separated as single diastereomers by column chromatography. For cycloadditions involving substrates **14g**,**h**, derived from 2-bromoacrylic acid (**13**), the major *endo*-cycloadducts **15g**,**h** were purified by silica chromatography. Unfortunately, the minor *endo*-cycloadducts **16g**,**h** underwent partial dehydrobromination on exposure to silica to afford the corresponding dienes **18g**,**h**. In the case of **16g**, we were able to obtain a sample of diastereomerically pure material from the silica column; however, the dehydrobromination of **16h** was too fast to permit its isolation. The presence and relative amount of **16h**, as well as the *exo*-products **17b**,**c** (derived from methacrylic acid (**11**)) and **17g**,**h** (derived from 2-bromoacrylic acid (**13**)), were tentatively determined on the basis of the integration of H^{4a} in the ^{1}H NMR of the crude reaction mixtures. The absence of the formation of *exo*-products **17e**,**f** in the Diels−Alder cycloaddition of acrylate substrates **14e**,**f** might have been expected, while the high *endo*/*exo*-selectivity observed for methacrylate substrates **14a**−**d**, as well as bromoacrylate substrates **14g**,**h**, was a pleasant surprise. It is well-documented that dienophiles derived from methacrylic acid (**11**) give poor stereoselectivity in Diels−Alder reactions and often show a proclivity to undergo *exo*-cycloaddition.[19,20]

Table 2. Diels−Alder Cycloaddition Reactions of **14a**−**h**

entry	compd	*T* (°C)	time (h)	ratio of **15**/**16**/**17**/**14**[a]	yield of **15a**−**h** (%)
1	**14a**	130	29.5	100/- - -/33/20	42 of **15a** + **17a**
2	**14b**	128	32.5	100/25/12/22	47 of **15b** + **16b**
3	**14b**	140	41	100/25/12/- - -	36
4	**14c**	138	28	100/25/10/20	49
5	**14c**	145	50	100/25/10/- - -	49
6	**14d**	138	47	100/4/12/- - -	65
7	**14e**	130	43	100/30/- - -/- - -	54 + 18 of **16e**
8	**14f**	127	43	100/25/- - -/23	57 + 16 of **16f**
9	**14g**	115	21	100/27/9/- - -[b]	58
10	**14h**	127	21	100/12/8/- - -[b]	63

[a] Determined from ^{1}H NMR analysis of the crude reaction mixtures. [b] Ratio can only be estimated because **16** and **17** are unstable.

We observed that increasing the bulk of the substituent R^1 on the tether backbone is beneficial for avoiding side reactions during the IMDA reaction. The nonsubstituted substrate **14i**, derived from acrylic acid (**12**), failed to give any intramolecular cycloaddition product and was completely polymerized on heating (120 °C) in toluene. Large amounts of polymerization byproducts were produced in IMDA reactions of the other nonsubstituted (**14a**) and Me-substituted (**14b**,**e**,**g**) substrates, while for Ph- (**14c**,**f**) and *t*-Bu-substituted (**14d**) substrates, no significant tar formation was observed during the IMDA reaction.

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The *endo*-major (**15**)/*endo*-minor (**16**) diastereoselectivity in IMDA reactions involving Me- (**14b**,**e**,**g**) and Ph-substituted (**14c**,**f**) substrates was comparable (∼4/1), while for *t*-Bu-substituted substrate **14d**, the diastereoselectivity was improved to ∼25/1.

endo/exo-Diastereoselectivity was significantly increased (from 3/1 to 10/1) on introducing a substituent R^1 (Me) in place of a hydrogen atom on the tether backbone (Table 2, compare entries 1 and 2). Interestingly, it remained the same (∼9/1 to ∼14/1) on changing R^1 from a relatively small Me group to the larger Ph and *t*-Bu substituents (see Table 2, entries 2−6, 9, and 10).

The cycloaddition of α-bromoacrylate substrates **14g**,**h** proceeded faster than for the analogous methacrylate (**14b**,**c**) and acrylate substrates (**14e**,**f**) and required ∼10 °C lower reaction temperatures.

Furthermore, the fact that the acrylate substrate **14i** failed to give any IMDA reaction products, while the corresponding methacrylate derivative **14a** was converted into IMDA products in 42% yield, contradicts the conventional wisdom that normal-electron demand Diels−Alder reactions of methacrylate dienophiles are usually more difficult than for the corresponding acrylate substrates.[19,20]

We propose a transition state for the above cycloaddition reactions (Figure 1) in which (i) steric interactions between R^1 and the carbonyl group and (ii) the stereoelectronically preferred s-trans ester conformation[19] are responsible for the observed diastereoselectivity.

In conclusion, the linkage of 1-sulfonyl-1,3-butadiene and various acrylate dienophiles by a two-carbon tether bearing a large Ph or *t*-Bu substituent allowed efficient diastereoselective formation of the corresponding *endo*-IMDA cycloadducts. Our current efforts are directed toward the synthesis of enantiomerically pure cycloadducts and exploring their synthetic utility. Our results along these lines will be reported in due course.

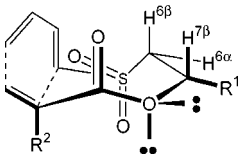

Figure 1. Proposed transition state for Diels−Alder cycloaddition of **14b**−**h**.

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Supporting Information Available: Full experimental procedures and spectroscopic data for compounds **3**−**10**, **14**−**17**, and **18g**, along with copies of ^{1}H and ^{13}C NMR spectra of major cycloadducts **15a**−**h**, minor cycloadducts **16e**,**f**, and mixtures **17a/15a** and **16/15(b**,**c**,**g)**. This material is available free of charge via the Internet at http://pubs.acs.org.

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