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New synthesis of allylidenecyclobutanes by the reaction of cyclobutylmagnesium carbenoids with vinyl sulfones

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ABSTRACT

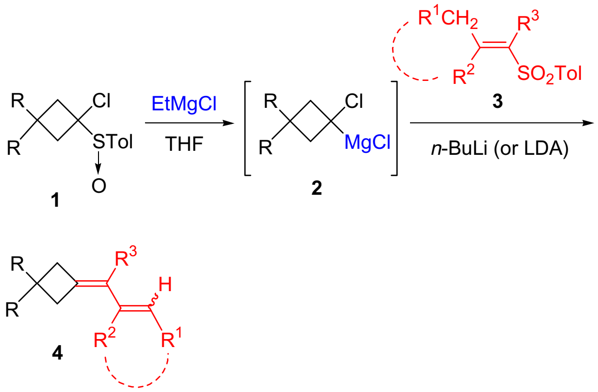
The reaction of cyclobutylmagnesium carbenoids, which were generated from 1-chlorocyclobutyl *p*-tolyl sulfoxides with EtMgCl via the sulfoxide–magnesium exchange reaction at low temperature, with carbanions derived from vinyl sulfones with *n*-BuLi or LDA resulted in the formation of allylidenecyclobutanes in moderate to good yields. The actual reactive species of the sulfones in this reaction were proved to be the lithium α-sulfonyl carbanion of allyl sulfones derived from the vinyl sulfones by double bond migration with the bases used. Mono- and di-substituted allylidenecyclobutanes can be obtained by using a variety of vinyl sulfones.

Introduction

Small ring strained molecules such as cyclopropanes and cyclobutanes, and their derivatives, have been known as versatile intermediates in organic synthesis for long time.[1] Small ring compounds reveal characteristic reactivity by their strain release. Innumerable studies for the chemistry, synthesis, and synthetic uses of cyclopropanes have been carried out; however, those for cyclobutanes are still limited.[2] Alkylidenecyclobutanes are also very interesting highly strained cyclobutane derivatives and often used in organic synthesis[3]; however, adequate methods for their synthesis are still lacking.[4]

We recently started to investigate the chemistry and synthetic uses of cyclobutylmagnesium carbenoid (carbenacyclobutane) and many interesting reactions have appeared.[5,6] Synthesis of alkylidenecyclobutanes by the reaction of cyclobutylmagnesium carbenoids with lithium α-sulfonyl carbanions as nucleophiles was one of the most interesting results from the investigations.[6] In continuation of our studies concerning the reaction of cyclobutylmagnesium carbenoids with nucleophiles, we recently found that the reaction of cyclobutylmagnesium carbenoids with the carbanions derived from vinyl sulfones with *n*-BuLi (or LDA) resulted in the formation of allylidenecyclobutanes in moderate to good yields (Scheme 1).

Thus, treatment of 1-chlorocyclobutyl *p*-tolyl sulfoxide **1** in THF with EtMgCl at −90 °C resulted in the generation of cyclobutylmagnesium carbenoid **2** via the sulfoxide–magnesium exchange reaction.[7] In an another flask, vinyl sulfone **3**[8] in THF at low temperature was treated with *n*-BuLi (or LDA) and this solution was transferred to the solution of cyclobutylmagnesium carbenoid **2** through a cannula and the whole reaction mixture was slowly allowed to warm to 0 °C to afford allylidenecyclobutane **4** in moderate to good yield. This is an unprecedented new method for the synthesis of allylidenecyclobutanes **4** from easily available 1-chlorocyclobutyl *p*-tolyl sulfoxides **1**.[6] Preliminary results of this study and mechanistic discussion of this reaction are reported in this Letter.



Scheme 1.

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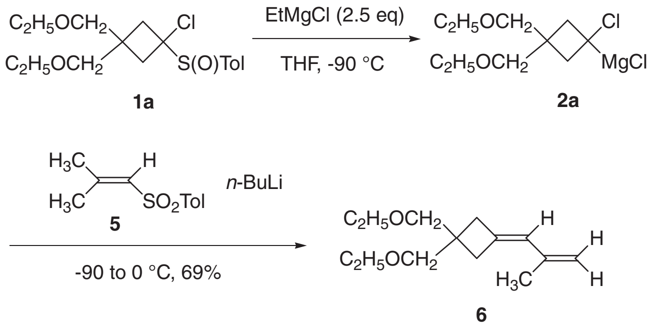


Scheme 2.

Results and discussion

As a representative example for this investigation, the reaction using 1-chlorocyclobutyl *p*-tolyl sulfoxide **1a** and 2-methyl-1-propenyl *p*-tolyl sulfone **5**[9] is reported (Scheme 2). In our previous studies, we reported the reactions of cyclobutylmagnesium carbenoids with carbon nucleophiles, including lithium α-sulfonyl carbanions, followed by electrophiles to give multi substituted cyclobutanes.[6] Based on the experiences of these studies, we treated cyclobutylmagnesium carbenoid **2a**, generated from **1a** with EtMgCl in THF at −90 °C, with 3 equiv of an anion generated from vinyl sulfone **5** with *n*-BuLi. The temperature of the reaction mixture was slowly allowed to warm to 0 °C.

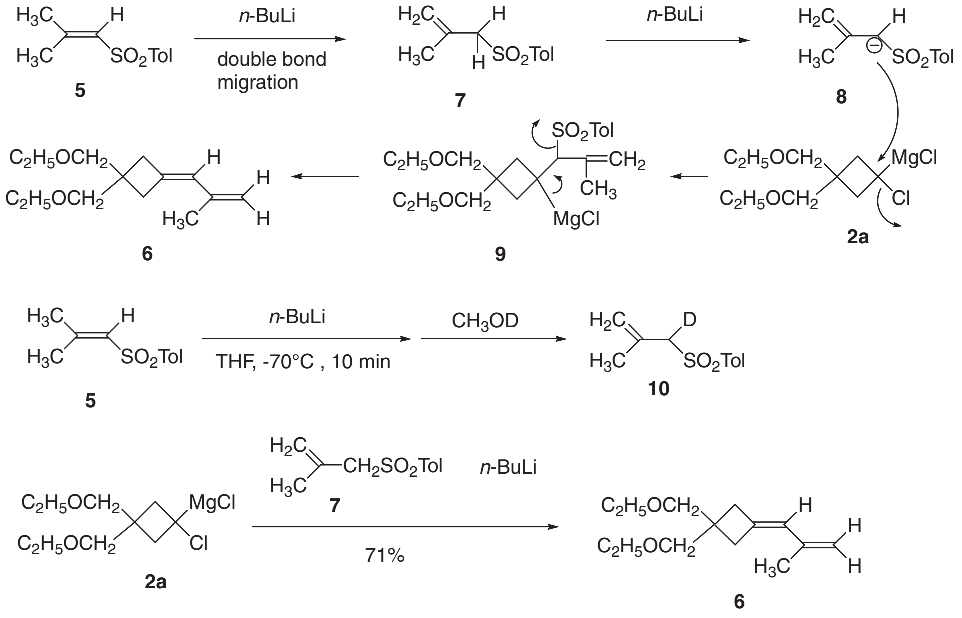
This reaction cleanly gave a product, which has $C_{14}H_{24}O_2$ as the molecular formula, in 69% yield as colorless oil. The product had three olefin protons (δ 4.74, 2H, broad singlet and δ 5.83, 1H, quintet, J=2.3 Hz) and one olefinic methyl group (δ 1.85, broad singlet). The structure of this product was easily assigned to be allylidenecyclobutane **6** as shown in Scheme 2. We investigated to find better conditions for this reaction; however, the conditions mentioned above were found to be the best.

A plausible mechanism of this quite interesting reaction is proposed as follows (Scheme 3). Thus, as the double bond migration of vinyl sulfones to allyl sulfones by a base was reported to occur relatively easily,[10] vinyl sulfone **5** must be isomerized to allyl sulfone **7** by *n*-BuLi in the reaction medium. α-Hydrogen of allyl sulfone **7** was easily deprotonated to give lithium α-sulfonyl carbanion **8**. Carbenoid **2a** was attacked from back side of the chlorine atom by α-sulfonyl carbanion **8** to give cyclobutylmagnesium chloride intermediate **9**,[11] from which β-elimination must have occurred to afford allylidenecyclobutane **6**.

The double bond migration of vinyl sulfone **5** to allyl sulfone **7** was confirmed from the experiment shown in Scheme 3. Thus, treatment of vinyl sulfone **5** with *n*-BuLi at −70 °C for 10 min followed by CH_3OD gave α-deuterio allyl sulfone **10** in 85% yield with over 99% deuterium content. In order to make sure that this reaction proceeds via α-sulfonyl carbanion of allyl sulfones, cyclobutylmagnesium carbenoid **2a** was reacted with 3 equiv of lithium α-sulfonyl carbanion generated from allyl sulfone **7** under the same conditions described above. As expected, this reaction gave allylidenecyclobutane **6** in 71% yield, which was almost the same as that of the reaction with vinyl sulfone **5** (69%, see Scheme 2).

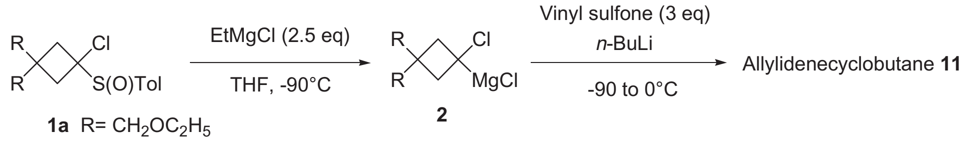
As we recognized that this reaction is unprecedented and would become a new method for the synthesis of allylidenecyclobutanes, generality was investigated and the results are summarized in Table 1. The result shown in entry 1 has been mentioned above. The reaction of **1b** with the carbanion derived from **5** gave allylidenecyclobutane **11a** in somewhat better yield (77%, entry 2). When the vinyl sulfone has a phenyl group at the β-position, yield of the reaction markedly diminished (entries 3 and 4).

Disubstituted allylidenecyclobutanes **11d** and **11e** were synthesized from **1a** and **1b** with 2,2-diethylvinyl sulfone in moderate yields (entries 5 and 6). Interestingly, only the geometrical isomer depicted in Table 1 was obtained and the structures of **11d** and **11e** were determined from their NOESY spectra. The vinyl sulfones synthesized from cyclopentanone and cyclohexanone gave allylidenecyclobutanes bearing a cyclopentene- and cyclohexene ring, respectively, in moderate to good yields (entries 7–10). In order to make sure that this reaction is not affected by the substituents on the 3-position of the cyclobutane ring, we investigated the reaction starting from 1-chlorocyclobutyl *p*-tolyl sulfoxide bearing no substituent **1c** and the vinyl sulfone having higher molecular weight, 2-benzyl-3-phenyl-1-propenyl *p*-tolyl sulfone, which was synthesized

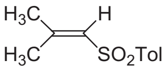
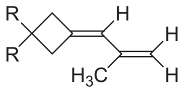
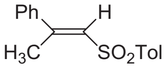
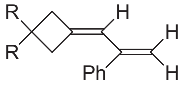
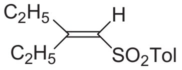
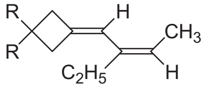
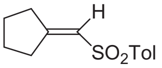
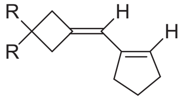
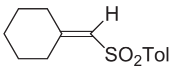
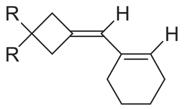
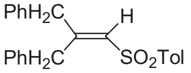
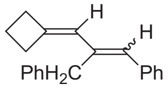


Scheme 3. A plausible mechanism for the reaction of cyclobutylmagnesium carbenoid **2a** with the carbanion generated from vinyl sulfone **5** with *n*-BuLi giving allylidenecyclobutane **6**.

Table 1
Synthesis of allylidenecyclobutanes **11** from 1-chlorocyclobutyl *p*-tolyl sulfoxides **1** with vinyl sulfones

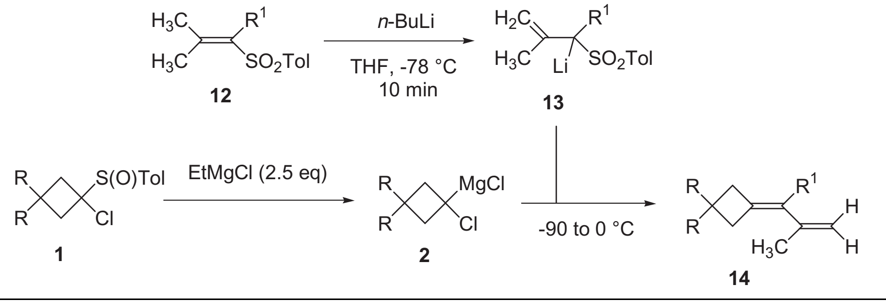


1a R= $CH_2OC_2H_5$
1b R= $CH_2O(CH_2)_3Ph$
1c R= H

Entry	1	Vinyl sulfone	11	
			Yield (%)	
1 2	**1a** **1b**			**6** (69) **11a** (77)
3 4	**1a** **1b**			**11b** (39) **11c** (47)
5 6	**1a** **1b**			**11d** (49) **11e** (59)
7 8	**1a** **1b**			**11f** (58) **11g** (66)
9 10	**1a** **1b**			**11h** (83)[a,b] **11i** (53)[b]
11	**1c**			**11j** (64)[c]

[a] Five equivalents of vinyl sulfone were used.
[b] Carbanion was generated with LDA at 0 °C for 1.5 h.
[c] About 30:1 mixture of two geometrical isomers; the configuration not determined.

Table 2
Synthesis of disubstituted allylidenecyclobutanes **14** from **1** with fully substituted vinyl sulfones **12**



Entry	Sulfoxide/**1** R	**12** R_1	**14** Yield (%)
1	**1a** $CH_2OC_2H_5$	**12a** CH_3	**14a** (79)
2	**1b** $CH_2O(CH_2)_3Ph$	**12a** CH_3	**14b** (83)
3	**1a** $CH_2OC_2H_5$	**12b** Ph	**14c** (20)
4	**1b** $CH_2O(CH_2)_3Ph$	**12b** Ph	**14d** (26)
5	**1a** $CH_2OC_2H_5$	**12c** COO*t*-Bu	**14e** (32)[a]
6	**1b** $CH_2O(CH_2)_3Ph$	**12c** COO*t*-Bu	**14f** (33)[a]
7	**1c** H	**12b** Ph	**14g** (17)
8	**1c** H	**12c** COO*t*-Bu	**14h** (28)[a]

[a] Carbanion **13** was generated with LDA at 0 °C.

from dibenzyl ketone. As shown in entry 11, the reaction gave the desired product **11j** in 64% yield without any problem.

Finally, we examined this reaction with the α-sulfonyl carbanions generated from the vinyl sulfones bearing a substituent at the α-position and the results are summarized in Table 2. Thus, at first, 3-methyl-2-butenyl *p*-tolyl sulfone **12a** ($R^1 = CH_3$, 3 equiv; synthesized from acetone and ethyl *p*-tolyl sulfone) was treated with *n*-BuLi in THF at −78 °C for 10 min. This solution was transferred into a solution of cyclobutylmagnesium carbenoid **2a** ($R = CH_2OCH_2CH_3$) through a cannula and the temperature of the reaction mixture was slowly allowed to warm to 0 °C. Gratifyingly, we obtained the desired allylidenecyclobutane **14a** in 79% yield (entry 1).[12] The same reaction starting from **1b** gave the desired **14b** in better yield of 83% (entry 2).

Other results are summarized in entries 3–8. Vinyl sulfone bearing a phenyl group at the α-position **12b** again gave allylidenecyclobutanes **14c** and **14d** in low yields. Vinyl sulfone bearing a *tert*-butyl ester group **12c** can be used in this reaction; however, at present, the yields were not satisfactory (entries 5 and 6). The reaction of **1c** with the carbanions derived from **12b** and **12c** also gave the desired product; however, the yields again were not satisfactory (entries 7 and 8).

In conclusion, we found that the reaction of the lithium carbanions derived from easily synthesized vinyl sulfones with cyclobutylmagnesium carbenoids, derived from 1-chlorocyclobutyl *p*-tolyl sulfoxide with EtMgCl via the sulfoxide–magnesium exchange reaction, resulted in the formation of allylidenecyclobutanes in variable yields. The chemistry presented herein is unprecedented and will contribute to the synthesis of various kinds of allylidenecyclobutanes in relatively short steps.

Acknowledgments

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9. 2-Methyl-1-propenyl *p*-tolyl sulfone **5** was synthesized from acetone and methyl *p*-tolyl sulfone as follows. Methyl *p*-tolyl sulfone was treated with LDA followed by acetone to give adduct. The hydroxyl group in the adduct was acetylated with Ac_2O-pyridine-DMAP to afford an acetate, which was treated with *N*-lithio piperidone to give **5** via β-elimination. Each step gave almost quantitative yield. Other vinyl sulfones except **12c** were synthesized from ketones with corresponding sulfones in the same manner in high overall yields.
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12. Experimental procedure for the synthesis of **14a**: Ethylmagnesium chloride (2 mol/L solution in THF; 0.13 mL; 0.25 mmol) was added to a solution of **1a** (34.5 mg; 0.1 mmol) in 1 mL of dry THF in a flame-dried flask at −90 °C under Ar atmosphere dropwise with stirring. In an another flame-dried flask, *n*-BuLi (1.65 mol/L solution in hexane; 0.18 mL; 0.3 mmol) was added to a solution of vinyl sulfone **12a** (67.3 mg; 0.3 mmol) in 1 mL of dry THF at −70 °C with stirring to give light yellow solution. After being stirred for 15 min, this solution was cooled to −90 °C and was transferred to a solution of the cyclobutylmagnesium carbenoid through a cannula. The reaction mixture was stirred and slowly allowed to warm to 0 °C. The reaction was quenched by adding satd aq NH_4Cl solution. The whole was extracted with $CHCl_3$ and the organic layer was dried over $MgSO_4$ and concentrated. The product was purified by silica gel column chromatography to give **14a** (19 mg; 79%) as colorless oil. IR (neat) 2975, 2931, 2865, 1606, 1445, 1375, 1112, 877 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.19 (6H, t, $J = 7.0$ Hz), 1.63 (3H, m), 1.90 (3H, br s), 2.51 (2H, m), 2.71 (2H, m), 3.43 (4H, s), 3.51 (4H, q, $J = 7.0$ Hz), 4.77 (1H, br s), 4.82 (1H, br s); ^{13}C NMR ($CDCl_3$) δ 15.08 ($CH_3 \times 2$), 15.51 (CH_3), 22.75 (CH_3), 36.71 (CH_2), 37.94 (C), 38.33 (CH_2), 66.64 ($CH_2 \times 2$), 73.64 ($CH_2 \times 2$), 110.81 (CH_2), 129.05 (C), 133.69 (C), 144.42 (C). MS *m*/*z* (%) 238 (M^+, 13), 133 (100), 105 (19), 91 (18). Calcd for $C_{15}H_{26}O_2$: *M*, 238.1933. Found: *m*/*z* 238.1935.