# Alkylation of 4*H*,6*H*-Thieno[3,4-*c*]furan 5,5-Dioxide and Its Use as a 3,4-Dimethylenefuran Synthon in Intramolecular Diels–Alder Reactions

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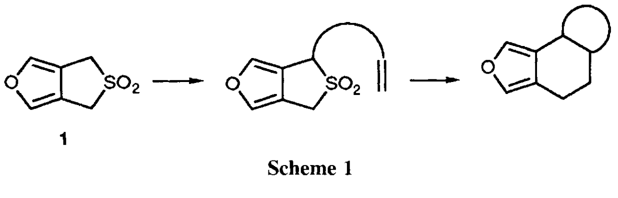
4*H*,6*H*-thieno[3,4-*c*]furan 5,5-dioxide **1** was readily converted to the 4-alkylated compounds **2** and the appropriate compounds **2** were submitted to intramolecular Diels–Alder reactions to afford fused furans **8a** and **b** in good yields.

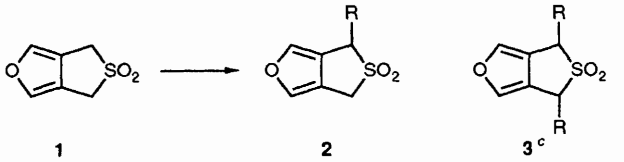
4*H*,6*H*-Thieno[3,4-*c*]furan 5,5-dioxide **1**[1] is a useful building block which contains furan and 3-sulfolene[2] moieties. Because both these moieties can be used as the diene component in Diels–Alder reactions, **1** could sequentially react with two different kinds of dienophiles and offer a rapid elaboration of multicyclic systems. We have already shown that **1** selectively undergoes Diels–Alder reactions on the furan moiety with several dienophiles containing two electron withdrawing groups.[1] We now report chemical modifications of **1** at the position α to the $SO_2$ group and its use as a 3,4-dimethylenefuran[3] synthon in the intramolecular Diels–Alder reaction (Scheme 1). This scheme should provide an efficient route to fused furan multicyclic systems, which are present in antifungal marine natural products such as euryfuran.

The alkylation studies are summarized in Table 1. When a solution of **1** in tetrahydrofuran–hexamethylphosphoric triamide (THF–HMPA) (4 equiv.) was treated with LiN-$(SiMe_3)_2$ (LiHMDS) (1.0 equiv.) at −78 °C and then the alkyl halide was added (entries 1,2), compounds **2** (R = Me, Bu) were obtained in low yields which showed that the anion from

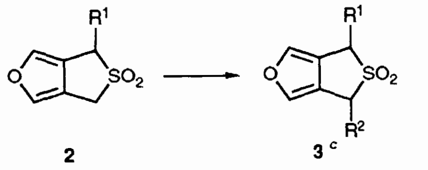


**Scheme 1**

**Table 1** Alkylation of 4*H*,6*H*-thieno[3,4-*c*]furan 5,5-dioxide **1**[a]



| Entry | RX | Method[b] | **2** (%)[d] | **3** (%)[d] | **1** (%)[d] |
|---|---|---|---|---|---|
| 1 | MeI | A | 26 | — | 49 |
| 2 | BuI | A | 20 | 21 | 7 |
| 3 | BuI | B | 58 | 21 | 21 |
| 4 | BuI | C | 36 | 36 | 28 |
| 5 | BuI | D | 18 | 68[e] | — |
| 6 | Pr$^i$I | B | 67 | 10 | 21 |
| 7 | $CH_2$=$CHCH_2Br$ | B | 34 | 26 | 35 |
| 8 | $CH_2$=$CHCH_2Cl$ | B | 44 | 21 | 36 |
| 9 | $PhCH_2Br$ | B | 19 | 25[e] | 39 |
| 10 | $PhCH_2Cl$ | B | 40 | 27 | 32 |
| 11 | MeI | B | 28 | 44 | 28 |
| 12 | $CH_2$=$CH[CH_2]_3Br$ | B | 59 | 16 | 21 |
| 13 | $CH_2$=$CH[CH_2]_4Br$ | B | 54 | 18 | 25 |

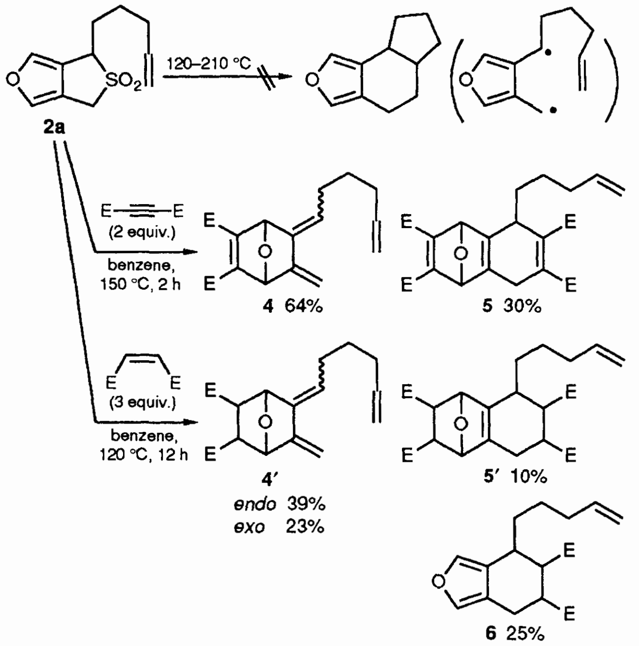


| Entry | R$^1$ | R$^2$X | Method[b] | **3** (%)[d] | **2** (%)[d] |
|---|---|---|---|---|---|
| 14 | Bu | MeI | B | 77 | 23 |
| 15 | $CH_2$=$CH[CH_2]_3$ | MeI | B | 97 | — |
| 16 | $CH_2$=$CH[CH_2]_3$ | $PhCH_2Cl$ | B | 56[e] | 22 |

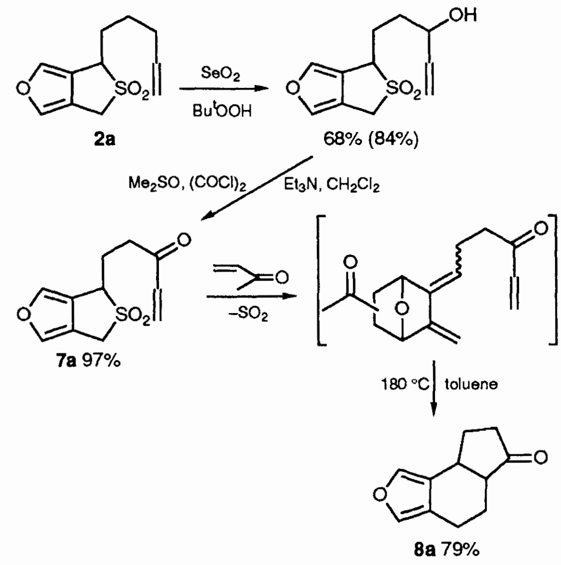
[a] *Reagents and conditions*: RX or R$^2$X (1 equiv.), THF–HMPA (4 equiv.), then LiHMDS (1 equiv.), −78 °C. [b] A: RX was added after lithiation (−78 °C, 30 min). A′: (−78 °C, 1 min). B: The carbanion was generated in the presence of RX at −78 °C. C: The carbanion was generated in the presence of RX at −105 °C. D: B except that 2 equiv. of RX and 2 equiv. of LiHMDS were used. [c] *cis–trans* mixture (1 : 1 to 1 : 5). [d] Isolated yield. [e] Other poly-alkylated products were obtained.

**1** was labile and decomposed to an unidentified complex mixture. Compound **1** can be successfully alkylated at the position α to the $SO_2$ group in good yields along with dialkylated products **3** by generating the carbanion in the presence of alkyl halides (entries 3–13). Pr$^i$I has a higher selectivity for monoalkylation (entry 6). On the other hand, the more reactive allyl, benzyl and methyl halides had lower selectivities. The alkylation of **2** was accomplished by the same method and gave **3** in good yields (entries 14–16).

Next we studied the intramolecular Diels–Alder reactions. When **2a** was heated, expecting the generation of a 3,4-dimethylenefuran intermediate, no reaction except decomposition occurred (120–210 °C) (Scheme 2). If **2a** was heated in the presence of dimethyl acetylenedicarboxylate, the Diels–Alder reaction occurred on the furan moiety to afford **4**† and **5**. The reaction with dimethyl maleate gave **6** along with **4′** and **5′**. Presumbly **6** was formed from **5′** by the retro-Diels–Alder reaction. We were interested in this result. If the furan moiety can be selectively protected, and then the intramolecular Diels–Alder reaction and the following deprotection occur, Scheme 1 could be realized.



**Scheme 2**



**Scheme 3** (Yield based on consumed **2a** in parentheses)

Finally methyl vinyl ketone was found to react only on the furan moiety at room temperature.[4] Compound **2a** was treated with methyl vinyl ketone at room temperature for one day to give a brown crude oil whose NMR spectrum showed no furan proton, but thermolysis of this crude oil at 180–200 °C did not give any of the intramolecular Diels–Alder products, so we decided to activate the alkene unit. Compound **2a** was oxidized with $SeO_2$–Bu$^t$OOH[5] and the resulting allyl alcohols were submitted to Swern oxidation[6] to afford the enone **7a**‡

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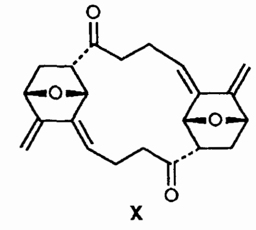
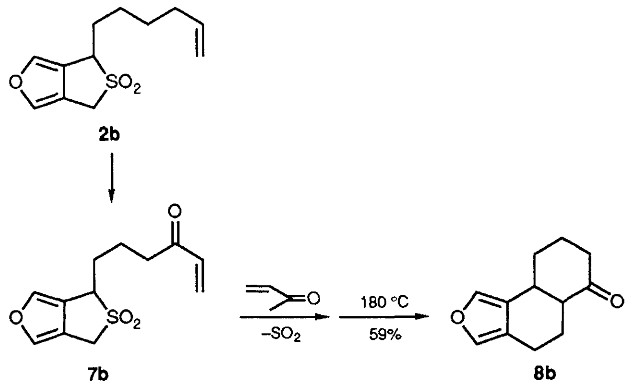
† When **4** was submitted to both thermal (200 °C; 2 h) and high-pressure conditions (12 kbar; 80 °C), expecting the intramolecular Diels–Alder reaction to occur, only a complex mixture was obtained.

‡ When the enone **7a** was heated (benzene; 120 °C), a dimer whose structure was tentatively assigned as **X** by NMR and mass spectroscopy was obtained in 52% yield.



**X**



**Scheme 4** *Reagents and conditions*: i, SeO$_2$–Bu$^t$OOH, 56% (67% based on consumed **2b**); ii, Me$_2$SO–(COCl)$_2$, Et$_3$N, 91%

(Scheme 3). The enone **7a** was treated with methyl vinyl ketone at room temperature and the crude oil obtained was heated at 180 °C for 8 h. The intramolecular Diels–Alder reaction and the subsequent retro-Diels–Alder reaction occurred to give **8a** (*cis–trans*-mixture; 3.2 : 1) in 79% isolated yield after chromatography on silica gel. By the same method, **8b** (*cis–trans*-mixture; 2 : 1) was obtained from **2b** in good yield (Scheme 4).

These results show that **1** is easily functionalized and offers a facile entry for fused furan multicyclic systems,[7] *i.e.* **1** is a useful functionalizable 3,4-dimethylenefuran synthon. Further studies on the furan-annelated sulfolene **1** are in progress in our laboratory.

All new compounds described in this paper were characterized by $^1$H NMR spectroscopy, and mass and high-resolution mass spectrometry.

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