



Photoinduced sulfonylation of cyclic ethers



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ABSTRACT

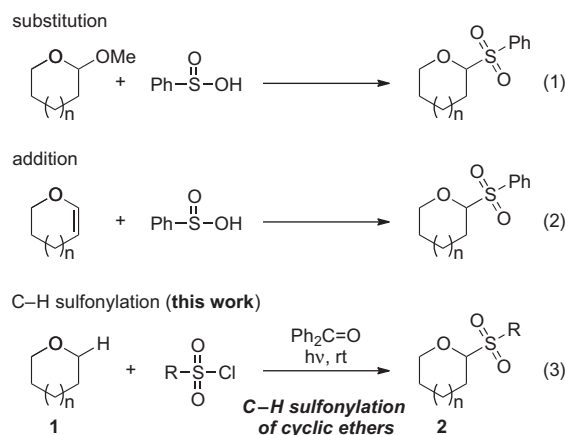
A one-step preparation of α -sulfonylated cyclic ethers has been achieved via the intermolecular sulfonylation of ethereal C–H bonds. In this process, the chemoselective cleavage of the ethereal C–H bond was achieved by hydrogen abstraction with photo-excited benzophenone, and the sulfonyl unit was provided by sulfonyl chloride. This protocol allows a direct transformation of ethereal C(sp³)–H bonds to C(sp³)–SO₂R bonds under photo-irradiation conditions at room temperature.

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The chemistry of sulfones has provided flexible synthetic strategies for the synthesis of organic molecules owing to their unique and diverse reactivities.¹ One of the most characteristic features of sulfones is that they can be utilized as both nucleophiles and electrophiles.² The electron-withdrawing nature of the sulfonyl group facilitates the generation of a nucleophilic α -sulfonylated carbanion by base treatment, whereas the inherent leaving group ability of the sulfonyl moiety allows sulfone to act as an electrophile. Consequently, a number of methods have been developed to prepare sulfones as a synthetically versatile building block.^{1,2} For example, conventional sulfone syntheses include oxidation of sulfides, substitution reactions using sulfinate salts as nucleophiles, and alkylation and/or arylation using sulfonic acid derivatives as electrophiles. Although various preparation methods have been established for sulfones,³ those for α -sulfonylated ethers are quite limited and efficient preparation methods are still desired.^{4,5} Representative preparation methods of α -sulfonylated cyclic ethers are illustrated in Scheme 1. The first example is the substitution of acetals with sulfinic acid (Eq. 1), and the second is the addition of sulfinic acid to enol ethers (Eq. 2), which were both described by Ley's group.⁴ On the other hand, almost no examples were found to prepare sulfones by the direct sulfonylation of ethereal C(sp³)–H bonds of readily available ethers as depicted in Eq. 3.⁶ We herein report a one-step preparation of α -sulfonylated cyclic ethers via the intermolecular sulfonylation of ethereal C(sp³)–H bonds under photo-irradiation conditions⁷ (Eq. 3). The capability to prepare

sulfones by ethereal C–H sulfonylation offers not only a new way for direct derivatization of ethers with a heteroatom-based functionality but also provides an efficient strategic approach for the synthesis of elaborate organic molecules having a cyclic ether moiety as a substructure.⁸

During our previous investigations on the direct functionalization of unreactive C(sp³)–H bonds using tosyl cyanide⁹ and tosyl acetylene¹⁰ as sources for installing the carbon unit, we noted in some cases the formation of a common minor side product con-

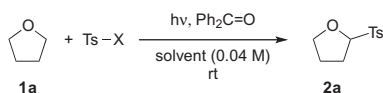


Scheme 1. Representative preparation methods of α -sulfonylated cyclic ethers.

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Table 1
Optimization of reaction conditions for tosylation of THF **1a**^a



Entry	1a (equiv)	Ts-X (equiv)	Solvent	Time (h)	Yield ^b (%)
1	8	TsTs, 1	CH ₃ CN	24	0 ^c
2	8	TsOTs, 1	CH ₃ CN	24	0 ^d
3	8	TsCl, 1	CH ₃ CN	6	92 (86) ^e
4	8	TsCl, 1	Acetone	6	90 (88) ^e
5	8	TsCl, 1	Benzene	6	70
6	8	TsCl, 1	<i>t</i> -BuOH	6	50
7 ^f	8	TsCl, 1	CH ₃ CN	6	34
8	4	TsCl, 1	CH ₃ CN	6	71
9	1	TsCl, 1.2	CH ₃ CN	24	44 ^g

^a The mixture of THF **1a**, TsX (Ts = *p*-toluenesulfonyl), and Ph₂C=O (1 equiv) in degassed solvent (0.04 M) was photo-irradiated using a medium-pressure Hg lamp at room temperature unless otherwise indicated.

^b Yield was calculated based on NMR analysis of the crude mixture unless otherwise noted.

^c Reaction was carried out in 0.02 M solution of CH₃CN. Recovery of TsTs was observed in 67% yield.

^d Recovery of TsOTs was observed in 37% yield.

^e Isolated yield is shown in parentheses.

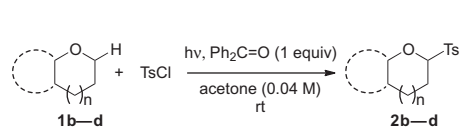
^f Ph₂C=O (0.5 equiv) was employed.

^g Recovery of TsCl was observed.

taining a tosyl group. We thus envisaged that the proper choice of a tosyl source would realize direct C(sp³)–H sulfonylation under photo-irradiation conditions. We initially selected tetrahydrofuran (THF, **1a**) as a starting material and screened the conditions for the direct sulfonylation of ethers (Table 1). Tosyl sources such as 1,1'-di(*p*-tolyl)disulfone (TsTs)¹¹ and *p*-toluenesulfonic anhydride (TsOTs) did not give the desired sulfone **2a** at all, and recovery of the sulfonylating agents was observed (entries 1 and 2). On the other hand, tosyl chloride (TsCl) was found to be an excellent sulfonylating agent (entry 3). A high yield of the tosylated product **2a** (86% isolated yield) was obtained by treating an excess amount of THF **1a** (8 equiv) with TsCl (1 equiv) in the presence of benzophenone (Ph₂C=O, 1 equiv) in CH₃CN under photo-irradiation using a medium-pressure Hg lamp at room temperature for 6 h.¹² Similar to the result obtained in CH₃CN solution, the reaction in acetone gave a high yield of **2a** as well (88% isolated yield, entry 4). Both benzene and *t*-BuOH solvent mediums provided the desired sulfone **2a** as the major product, though diminished product yields were observed (entries 5 and 6). The reaction employing 0.5 equiv of benzophenone did not go to completion within 6 h (entry 7), and decreasing the THF amount relative to TsCl had a negative effect on the yield of the desired adduct **2a** (entries 8 and 9). Thus, a stoichiometric amount of benzophenone was found to be essential for smooth completion of the present transformation, and an excess amount of the starting ether was required to obtain the desired sulfonylated product in high yield.

With the optimum conditions for the efficient photochemical ethereal C–H tosylation in hand, we then examined the reaction employing a variety of ethers to investigate their applicability as starting materials (Table 2). Not only five-membered cyclic ether **1a** but also six- and seven-membered cyclic ethers **1b** and **1c** were tosylated at the methylene carbon adjacent to the oxygen functionality to afford the corresponding sulfones **2b**¹³ and **2c** in moderate yields (entries 1 and 2).¹⁴ The tosylation of ambroxide **1d**, a fused tricyclic compound containing a five-membered cyclic ether, chemoselectively proceeded at the ethereal C–H bond to afford **2d** in quantitative yield with high diastereoselectivity, without touching other potentially reactive methine C–H bonds at the ring junctures (entry 3).^{9,10}

Table 2
Tosylation of cyclic ethers **1b–d**^a



Entry	Ether 1	Time (h)	Product 2	Yield ^b (%)
1	1b	7	2b	53 (79)
2 ^c	1c	8	2c	44 (47)
3	1d	5	2d	100 (100) [dr = 93:7] ^d

^a The mixture of ether **1b–d** (8 equiv), TsCl (1 equiv), and Ph₂C=O (1 equiv) in degassed acetone (0.04 M) was photo-irradiated using a medium-pressure Hg lamp at room temperature unless otherwise indicated.

^b Isolated yield. NMR yield is shown in parentheses.

^c CH₃CN was used as a solvent.

^d Ratio of diastereomers. The structure of the major isomer is shown in table.

We next investigated the applicability of various sulfonyl chlorides to the present transformation using THF **1a** and ambroxide **1d** as starting materials (Table 3). Both electron-donating methoxy- and electron-withdrawing bromo-substituted benzenesulfonyl chlorides furnished the corresponding sulfones **2e** (69%) and **2f** (49%)¹³, respectively. When 2,4,6-tri(isopropyl)phenylsulfonyl chloride was applied as a sulfonylating agent, the expected sulfonylated product **2g** was observed only in trace amounts along with multiple unidentified products.¹⁵ It is presumed that the steric bulkiness of the tri(isopropyl)phenylsulfonyl moiety hampered the reaction progress. Alkylsulfonyl chlorides also served as sulfonylating agents to produce the corresponding alkyl sulfones **2h** (74%) and **2i** (49%). In the same way, the chemoselective ether sulfonylations took place with ambroxide **1d** to afford both aryl sulfone **2j** (87%) and alkyl sulfone **2k** (84%) with high to good diastereoselectivities.

A main reaction pathway of the present sulfonylation of ethereal C–H bonds is proposed as shown in Scheme 2. The highly reactive oxyl radical species **A**, generated by the photo-excitation of benzophenone, abstracts an ethereal hydrogen from the starting molecule **1** to generate a carbon radical **B** along with the formation of ketyl radical **C**.^{9,10,16} The reaction of the derived carbon radical **B** with sulfonylating agent (RSO₂Cl) provides sulfone **2** as a product. Alternatively, chlorination of the radical **B** with RSO₂Cl to furnish α -chlorinated ether and substitution of the installed chlorine moiety with in situ generated sulfonic acid (RSO₂H) can account for the formation of sulfone **2**. To clarify the reaction pathway, we examined the substitution reaction between chlorinated ether, 2-chloro-tetrahydro-2H-pyran, and toluenesulfonic acid in the presence of benzophenone under photo-irradiation conditions. The corresponding tosylated ether **2b** was not obtained, indicating that the present transformation most probably proceeded via the direct sulfonylation of ethereal C–H bonds.¹⁷ The salient feature of the present transformation is that sulfonyl chlorides can act as a sulfonylating agent for α -alkoxy carbon radical although they are generally employed as a chlorinating agent in radical chemistry.¹⁸ Benzophenone would be regenerated by immediate abstraction

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