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## ACCEPTED MANUSCRIPT



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# The preparation and cycloaddition reaction of 1-sulfonyl-1-trifluoromethyl allenes

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#### ARTICLE INFO

### ABSTRACT

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*Keywords:* trifluoromethyl allene isoxazolidine cycloaddition nitrone A series of 1-sulfonyl-1-trifluoromethyl allenes were prepared for the first time from commercial available 2-bromo-3,3,3-trifluoropropene. Cycloaddition reaction of these trifluoromethylated allenes with nitrones occured readily under mild conditions, giving the corresponding trifluoromethylated isoxazolidines in high yields.

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In the past few decades, allene chemistry has attracted considerable attention,<sup>1</sup> and allenes have proven themselves to be valuable building blocks toward complex molecular targets, revealing their novel applications in natural product synthesis, pharmaceutical chemistry and materials science.<sup>2</sup> Among various allenes, sulfonyl-containing allenes are special ones and important in organic synthesis,<sup>3</sup> and practical methods for their preparation are highly desirable.<sup>4</sup> Meanwhile, efforts have also been made to study the chemistry of allenic sulfones. For example, Ma's group has studied the hydrohalogenation of 1,2-allenic sulfones with aryl halides.<sup>5b</sup> Mukai *et al.* reported the intramolecular nucleophilic addition of 1,2-allenic sulfones.<sup>6</sup>

The introduction of fluorine atom or fluoroalkyl groups may modulate physical and electronic properties of a molecule, which further reflects on the reactivity and bioactivity of fluorinated organic compounds.<sup>7</sup> Because of their high hydrophobicities, metabolic activities and bioavailabilities, fluorinated compounds, especially trifluoromethylated compounds, have recently attracted significant interest and became very important synthetic targets in labs and industries.<sup>8</sup> So far, most methods for the preparation of trifluoromethylated allenes involve the transformation of trifluoromethylated alkynes.<sup>9</sup>

Previously, we reported the synthesis and application of some allenyl perfluoroalkyl sulfones,<sup>10</sup> and found that zwitterionic compounds can be obtained from the cycloaddition of allenyl perfluoroalkyl sulfones.<sup>10b</sup> The iodocyclization reaction of trifluoromethylallenic phosphonates was also achieved.<sup>11</sup> As an extension of our study on the chemistry of fluorine-containing allenes, we prepared a series of 1-sulfonyl-1-trifluoromethyl

allenes and studied their reaction with nitrones. The results are reported in this paper.

According to the literature,<sup>12</sup> allenic sulfones could be prepared via [2,3] sigmatropic rearrangement of propargylic sulfinates, which could be obtained by the reaction of propargylic alcohols with sulfinyl chlorides. Therefore, we started with the reaction of 2-bromo-3,3,3-trifluoropropene (1) with ketone or aldehyde in the presence of LDA (Lithium diisopropylamide).<sup>13</sup> As shown in Table 1, a series of propargylic alcohols 3 were obtained in moderate to good yields. Subsequent esterization of alcohols 3 with methanesulfinyl chloride in the presence of pyridine afforded the corresponding propargylic sulfinates, which underwent thermal rearrangement in CH<sub>3</sub>CN under reflux to give 1-sulfonyl-1-trifluoromethyl allenes 4. Results in Table 1 indicated that this method was an efficient approach toward 4 and tolerated many substituents. All acetylenic alcohols containing methyl, ethyl, propyl, phenyl or tert-butyl group were converted smoothly to the corresponding trifluoromethyl allenyl sulfones 4 in good yields (entries 1-7). Allenes 4h and 4i containing cyclohexyl or cyclopentyl group were also prepared by this method (entries 8-9). However, in the case of trisubstituted propargylic alcohol 3j, the desired product 4j was not obtained (entry 10).

#### Table 1. The preparation of allenes 4



1) CH<sub>3</sub>SOCI (1.4 equiv) SO<sub>2</sub>Me pyridine (1.4 equiv) CH<sub>2</sub>Cl<sub>2</sub>, rt 2) CH<sub>3</sub>CN, reflux

Entry	<b>2</b> , $R^{1}/R^{2}$	Yield ( <b>3</b> , %) <sup>[a]</sup>	Yield ( <b>4</b> , %) <sup>[a]</sup>
1	<b>2a</b> , Me/Me	<b>3a</b> , 55	<b>4a</b> , 83
2	<b>2b</b> , Et/Et	<b>3b</b> , 75	<b>4b</b> , 79
3	<b>2c</b> , Et/Me	<b>3c</b> , 74	<b>4c</b> , 86
4	<b>2d</b> , Me/ <sup>n</sup> Pr	<b>3d</b> , 68	<b>4d</b> , 87
5	2e, Me/ <sup>t</sup> Bu	<b>3e</b> , 78	<b>4e</b> , 88
6	<b>2f</b> , Ph/Ph	<b>3f</b> , 94	<b>4f</b> , 73
7	<b>2g</b> , Ph/Me	<b>3g</b> , 94	<b>4g</b> ,67
8	<b>2h</b> , -(CH <sub>2</sub> ) <sub>4</sub> -	<b>3h</b> , 82	<b>4h</b> , 80
9	<b>2i</b> , -(CH <sub>2</sub> ) <sub>5</sub> -	<b>3i</b> , 94	<b>4i</b> , 75
10	<b>2j</b> , Ph/H	<b>3j</b> , 93	<b>4j</b> , -

Tetrahedron OH PR<sup>1</sup>

R<sup>2</sup>

 $R^2$ 

temperature were needed for the trifluoromethylated allenic sulfones.<sup>14</sup> When unsymmetrical sulfonyl allene such as 4c was used, the reaction gave complex cycloadducts as indicated by NMR analysis.

Table 2. The reaction of allene 4 and nitrone 5				
SO <sub>2</sub> Me F <sub>3</sub> C	R <sup>1</sup> + H R <sup>3</sup>	benzene, rt, 1 h	$ \begin{array}{c}                                     $	
4	<b>5</b> , 1.4 equiv		6	
Entry <sup>[a]</sup>	$4 (R^{1}/R^{2})$	<b>5</b> , R <sup>3</sup>	Yield (6, %) <sup>[b]</sup>	
1	4a, Me/Me	5a, H	<b>6a</b> , 93	
2	4a, Me/Me	5b, Cl	<b>6b</b> , 93	
3	4a, Me/Me	<b>5c</b> , NO <sub>2</sub>	<b>6c</b> , 88	
4	4b, Et/Et	<b>5a</b> , H	<b>6d</b> , 93	
5	4b, Et/Et	<b>5b</b> , Cl	<b>6e</b> , 90	
6	<b>4b</b> , Et/Et	<b>5c</b> , NO <sub>2</sub>	<b>6f</b> , 86	
7	4i, -(CH <sub>2</sub> ) <sub>5</sub> -	<b>5</b> a, H	<b>6g</b> , 94	

<sup>a</sup> Isolated yields.

Both sulfonyl and trifluoromethyl are strongly electronwithdrawing and have activating effect on the carbon-carbon double or triple bond with respect to conjugate additions and cycloadditions. Therefore, allenes 4 were expected to undergo cycloaddition reaction with nitrone. To prove this hypothesis, the reaction of 4a with 1.4 equiv of nitrone 5a was carried out in benzene. Gratefully, the reaction occurred smoothly at room temperature without any catalyst and cycloaddition product 6a was obtained in 93% isolated yield after work-up of the reaction mixture (Scheme 1). In our previous study on the dipolar cycloaddition of allenyl perfluoroalkyl sulfones, it was found that homolytic cleavage of the N-O bond in the cycloadducts occured and the subsequent rearrangement of resulting diradical intermediate gave zwitterionic products.<sup>10b</sup> In this reaction, isoxazolidine 6a was very stable and no further rearrangement was observed.



Scheme 1. Reaction of 4a with nitrone 5a

Under similar conditions, the scope of the cycloaddition addition was investigated and the results are summarized in Table 2. All reactions took place readily at room temperature to afford the corresponding isoxazolidine 6 in high yields. Substituents in allenes 4 had little influence on the yields, while nitrones 5 containing a strong electron-withdrawing substituent (NO<sub>2</sub>) gave slightly lower yield. Generally, compared with their non-fluorine-containing analogs, less reaction time and lower

<sup>a</sup> Reaction condition: 4 (0.15 mmol), nitrone 5 (0.21 mmol), benzene (2 mL), room temperature, 1 h. b Isolated yield.

In summary, we have developed an efficient method for the synthesis of trifluoromethylated allenic sulfones. Starting from commercial available 2-bromo-3,3,3-trifluoroproprene, a series of 1-sulfonyl-1-trifluoromethyl allenes were prepared for the first time in good yields. Due to the presence of strongly electronwithdrawing sulfonyl and trifluoromethyl group, these trifluoromethylated allenic sulfones could react easily with nitrones under mild conditions to give the corresponding trifluoromethylated isoxazolidine products in high yields.

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#### Supplementary data

Supplementary data associated with this article can be found, the in online version. at http://dx.doi.org/10.1016/j.tetlet.201x.xx.xxx.

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## **Research highlights**:

A series of 1-sulfonyl-1-trifluoromethyl allenes were prepared for the first time.

Cycloaddition reaction of trifluoromethylated allenes with nitrones was investigated.

Trifluoromethylated isoxazolidines were obtained under mild conditions.

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Graphical abstract