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A Convenient Access to Allylic Triflones with Allenes and Triflyl chloride in the Presence of $(EtO)_2P(O)H$

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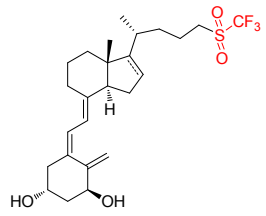
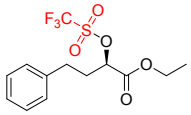
A simple method for the preparation of allylic triflones from allenes and triflyl chloride in the presence of $(EtO)_2P(O)H$ has been developed. The features of this reaction are catalyst-free and simple starting substrates. This method tolerates diverse functional groups and substituted allylic triflones are obtained in moderate to good yields.

For several years, organofluorines in chemistry have experienced a strong acceleration of interest.[1] Among them, the trifluoromethanesulfonyl (CF_3SO_2) group has attracted substantial attention both from the academic community and the pharmaceutical industry, because it substantially improve durg's chemical, physical, and biological properties.[2, 3] For instance, compound **I** has been developed as potential antiproliferative agent[4] and Compound **II** has been used as an API intermediate of potential pharmaceutiacal chemicals.[5]



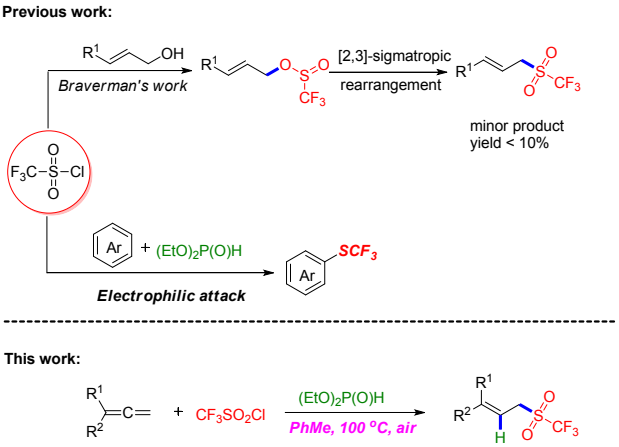
I. (+)-3 AU-16-ene-25-SO_2-CF_3



II. Ethyl (R)-4-phenyl-2-[[(trifluoro-methyl)sulfonyl]oxy]butyrate

Fig. 1 Pharmaceutical and bioactive compounds contain CF_3SO_2 moiety.

To meet the growing demand for CF_3SO_2-containing compounds, few successful strategies have been developed to introduce the CF_3SO_2 group into molecules.[6] In those transformations, some different trifluoromethylthiolating



Scheme 1 The reactions of trifluoromethylthiolation and fluoroalkylthiolation.

reagents have been used, such as sodium trifluoromethanesulfinate, lithium/sodium/potassium trifluoromethanesulfonate, trifluoromethyl sulfinic acid, and trifluoromethane sulfonyl chloride.[7] The trifluoromethane sulfonyl chloride as a readily accessible substrate is received extensive attentions and then significant progress has been developed in the trifluoromethylthiolation. The Braverman's group reported a method for the preparation of allylic triflones through rearrangement of cinnamyl triflinate which synthesized from allylic alcohol with trifluoromethane sulfonyl chloride.[8] The group of Yi developed a method of the fluoroalkylthiolation the electron-rich arenes and thiols with the $CF_3SO_2Cl/(EtO)_2P(O)H$ reaction system via electophilic fluoroalkylthiolation.[9] The related reports on trifluoromethylthiolation with trifluoromethane sulfonyl chloride are very rare and the reaction system of $CF_3SO_2Cl/(EtO)_2P(O)H$ is used for introducing the SCF_3 group. So using the reaction system of $CF_3SO_2Cl/(EtO)_2P(O)H$ that provides the trifluoromethanesulfonyl moiety through radical pathway is still a great challenge so far. Herein, we disclose a regioselective radical addition of $CF_3SO_2Cl/(EtO)_2P(O)H$ with

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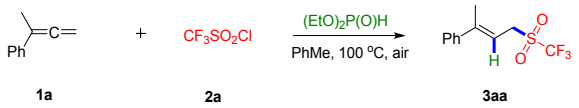
Table 1 Optimization of reaction conditions [a]



1a 2a 3aa

Entry	Variation from the "standard conditions"	Yield of **3aa** [%][b]
1	standard conditions	75
2	Ar instead of Air	61
3	$Ph_2P(O)H$ instead of $(EtO)_2P(O)H$	12
4	Without $(EtO)_2P(O)H$	0
5	**1a : 2a** = 1 : 1.5	54
6	at 80 °C	45
7[c]	THF instead of toluene	20

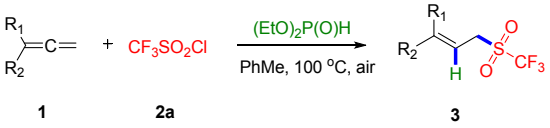
[a] Standard conditions: **1a** (0.3 mmol, 1.0 equiv), **2a** (0.9 mmol, 3.0 equiv), additive (0.6 mmol, 2.0 equiv) in 2 mL toluene at 100 °C for 8 h, under air. [b] Isolated yields. [c] THF = tetrahydrofuran.

allenes to form the allylic triflones through direct allylic trifluoromethanesulfonylation.

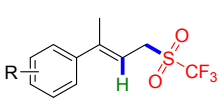
The reaction of buta-2,3-dien-2-ylbenzene **1a** and trifluoromethane sulfonyl chloride **2a** was chosen as the model reaction to optimize the reaction conditions (Table 1). The reaction was found to be facile with 3.0 equiv of **2a** in the presence of $(EtO)_2P(O)H$ (2.0 equiv) in toluene at 100 °C under air and it afforded the (*E*)-(4-((trifluoromethyl) sulfonyl)but-2-en-2-yl)benzene **3aa** in 75% isolated yield (Table 1, entry 1). However, the use of Ar in place of Air could lead to the formation of the desired product **3aa** in 61% yield. When $Ph_2P(O)H$ was employed in place of $(EtO)_2P(O)H$, the yield declined significantly from 61% to 12% (Table 1, entry 3). What was more, synthesis of **3aa** was not be observed without $(EtO)_2P(O)H$ (Table 1, entry 4). Unfortunately, changing the ratio of two components **1a** and **2a** to 1:1.5 reduced the yield (Table 1, entry 5). At a lower temperature of 80 °C, the result was found inferior than those observed under the standard conditions (Table 1, entry 6). The THF instead of toluene delivered a lower yield (Table 1, entry 7). Other trifluoromethylthiolating reagents, such as sodium trifluoromethanesulfinate/trifluoromethanesulfonate were also employed for this transformation and no desired product was detected. Finally, we found that solvents, temperature and other factors highly influence the yield of **3aa** (see the Supporting Information for details).

Having identified the optimized conditions, preliminary investigation of the scope of allenes was performed in Table 2. Gratifyingly, a broad range of allenes with different substitution patterns was used in this reaction, affording the corresponding products from moderate to excellent yields. Substrates **1a-1b, 1d-1f, 1h** bearing electron-rich groups on the phenyl ring of allenes reacted smoothly with trifluoromethane sulfonyl chloride and provided the desired products in 70-80% yields. Moreover, **1i-1k** with electron-poor groups, such as F, Cl, Br, were also well tolerated and the corresponding products

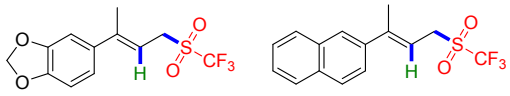
Table 2 Scope of substituted allenes [a]



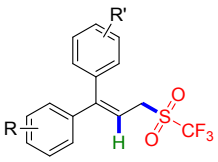
1 2a 3



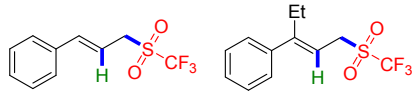
3aa (75%, E) R = H
3ba (71%, E) R = 4-Me
3ca (43%, E) R = 2-OMe
3da (80%, E) R = 4-OMe
3ea (70%, E) R = 4-OEt
3fa (72%, E) R = 3,4-diMe
3ga (60%, E) R = 3,4-diOMe
3ha (73%, E) R = 4-Ph
3ia (50%, E) R = 4-F
3ja (43%, E) R = 4-Cl
3ka (40%, E) R = 4-Br



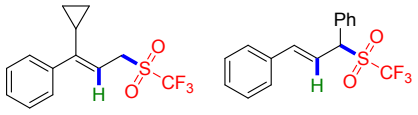
3la (52%) **3ma (56%)**



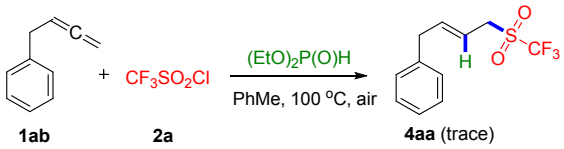
3na (81%) R = H, R' = H
3oa (70%, E/Z = 61/39)[b] R = 4-Me, R' = H
3pa (61%, E/Z = 72/28)[b] R = 4-OMe, R' = H
3qa (63%, E/Z = 65/35)[b] R = 3,4-diMe, R' = H
3ra (58%, E/Z = 65/35)[b] R = 4-Ph, R' = H
3sa (41%, E/Z = 50/50)[b] R = 4-Cl, R' = H
3ta (40%, E/Z = 49/51)[b] R = 4-Br, R' = H
3ua (69%) R = 4-Me, R' = 4-Me
3va (50%, E/Z = 65/35)[b] R = 4-F, R' = 4-OMe



3wa (trace) **3xa** (20%, E)



3ya (trace) **3za** (trace)



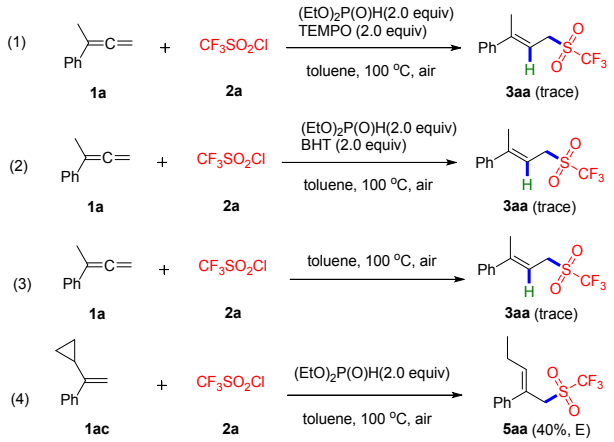
1ab **2a** **4aa** (trace)

[a] Reaction conditions: **1** (0.3mmol), **2a** (0.9mmol), $(EtO)_2P(O)H$ (0.6mmol) in 2mL of toluene at 100 °C under air for 8h. [b] E/Z selectivity of the allylic triflones determined by ^1H NMR analysis of the crude reaction mixture and nuclear overhauser effect.

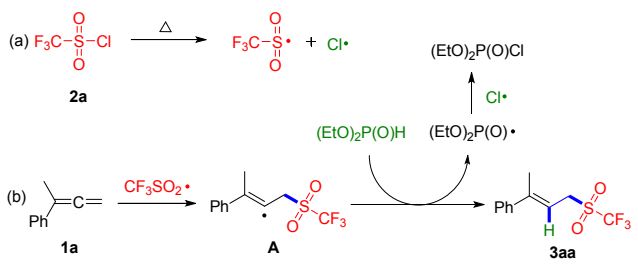
3ia-3ka were obtained with moderate yields. The substrates **1l-1m** were also subject to the optimized conditions and the target products **3la-3ma** were isolated in 52-56% yields. Even changing R^1 from alkyl to aryl, the aimed products **3na-3va** were also generated from moderate to good yields with moderate *E/Z* selectivity. Disappointingly, the substrates **1w-1z, 1ab** failed to undergo with this process, no desired products were detected except the product **3xa** obtaining in 20% yield.

To shed light on the mechanism of this transformation, several control experiments were carried out as described in Scheme 2. Only a trace amount of desired product **3aa** was detected when TEMPO was employed for this reaction. Meanwhile, the hydrogen radical was captured by TEMPO and the important intermediate of m/z = 157 was detected by the GCMS, which was 2,2,6,6-tetramethylpiperidin-1-ol (Figure S1). When BHT was added to the reaction system, none of the desired product was observed. Thus, this result suggested that the reaction was a radical process. As the only trace amount of the target product **3aa** was detected without $(EtO)_2P(O)H$, this result demonstrated that hydrogen was derived from $(EtO)_2P(O)H$. And the GC-MS measurement was also performed with **A** by following the standard conditions for 60 min. The important peaks at m/z = 172 was observed and the $(EtO)_2POCl$ was also confirmed (Figure S2). These results indicated that $(EtO)_2P(O)Cl$ and hydrogen radical exist in this transformation. Significantly, submitting (1-cyclopropylvinyl)benzene to the standard conditions afforded (*E*)-(1-((trifluoromethyl)sulfonyl)pent-2-en-2-yl)benzene **5aa** in 40% yield, which meant that the trifluoromethane sulfonyl radical existed in this transformation.

Scheme 2 Control experiments.



Scheme 3 Proposed mechanism.



Based on these experimental results and previous mechanistic studies, a possible mechanism is proposed in Scheme 3. Initially, trifluoromethane sulfonyl chloride **2a** is transformed into trifluoromethane sulfonyl radical and chlorine radical under the standard conditions. Then the trifluoromethane sulfonyl radical adds to the substrate **1a** to form radical intermediate **A**. Finally, the intermediate **A** converts to the desired product **3aa** through the capture hydrogen radical from the $(EtO)_2P(O)H$.

In conclusion, we develop a convenient and efficient method to achieve the allylic triflylation. In the presence of $(EtO)_2P(O)H$, various substituted groups on allenes proceed smoothly, and the desired products are afforded with moderate to good yields.

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