A stereocontrolled syntheses of conjugated dienyl trifluoromethyl ketones *via* the Claisen rearrangement of allyl 2-phenylsulfanyl-1-(trifluoromethyl) vinyl ethers

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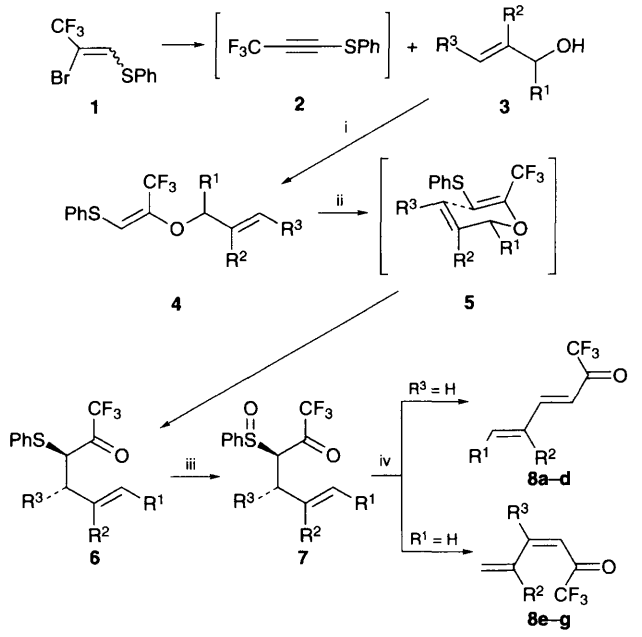
The stereocontrolled syntheses of buta-2,4-dienyl trifluoromethyl ketones are described which rely upon the Claisen rearrangement of allyl 2-phenylsulfanyl-1-(trifluoromethyl)vinyl ethers.

Organic molecules bearing a trifluoromethyl group have been attracting a great deal of interest due to their possible biological activities.[1] Trifluoromethyl ketones, in particular, have received considerable attention as transition-state analogue inhibitors for a variety of hydrolytic enzymes.[2] Therefore, much attention has been paid to the development of efficient synthetic routes leading to trifluoromethyl ketones that can be used not only as potential inhibitors themselves but also as versatile starting materials for synthesizing more complex fluorinated organic compounds.[3] Conventionally, alkyl or aryl trifluoromethyl ketones are prepared by the reaction of organolithium or Grignard reagents with trifluoroacetic acid or amide derivatives.[3,4] However, functionalized trifluoromethyl ketones, such as unsaturated trifluoromethyl ketones, are usually not readily accessible.[5] As we know, the Claisen rearrangement has found substantial utility in the synthesis of unsaturated carbonyl compounds.[6] However, difficulty in preparation of the C-1 trifluoromethyl-substituted vinyl allyl ether restricted its practical usefulness in the synthesis of trifluoromethyl ketones.[7] As part of our ongoing program aimed at producing new, versatile CF_3-containing building blocks, we present here a convenient and stereocontrolled syntheses of buta-2,4-dienyl trifluoromethyl ketones from allyl 2-phenylsulfanyl-1-(trifluoromethyl) vinyl ethers **4** *via* Claisen rearrangement.

1-Bromo-1-phenylsulfanyl-3,3,3-trifluoroprop-1-ene **1** could be readily obtained from 3,3,3-trifluoropropene in high yield.[8] We envisaged that **1** might serve as a precursor of 1-phenylsulfanyl-3,3,3-trifluoroprop-1-yne **2**, which could be produced from **1** by dehydrobromination and was found to be labile and difficult to isolate. We sought to use **2** directly in subsequent reactions after its formation. Thus, the reaction of **1** with 1 equiv. of a primary or secondary allyl alcohol **3** in the presence of 1.5 equiv. of sodium hydride in diethyl ether at room temperature for 1 h furnished allyl 2-phenylsulfanyl-1-(trifluoromethyl)vinyl ethers **4** in excellent yield. The products **4** were obtained with the 2-phenylsulfanyl-1-(trifluoromethyl)-vinyl moiety in the *E* geometry exclusively. The stereochemistry of the vinyl moiety in **4** is defined on the basis of absence of H–F coupling between the C-2 proton and C-1 CF_3 group in the ^1H NMR spectra (δ 6.50, s), and that only one single signal (δ −6.6) was observed in its ^{19}F NMR spectra.[9] In turn, the allyl vinyl ethers **4** smoothly rearranged to γ,δ-unsaturated ketone **6** simply on refluxing in CCl_4. As may be seen from Table 1, the ease of this particular Claisen variant depends markedly upon the alkyl substitution pattern on the



Scheme 1 *Reagents and conditions*: i, NaH, THF, room temp.; ii, CCl_4, reflux; iii, MCPBA, CH_2Cl_2, −20 °C; iv, CH_2Cl_2, reflux

Table 1 Reaction of 1-bromo-1-phenylsulfanyl-3,3,3-trifluoroprop-1-ene **1** with allyl alcohols **3** and sodium hydride followed by Claisen rearrangement, oxidation and dehydrosulfenylation

Entry	R^1	R^2	R^3	Yield of **4**[a,c] (%)	Reaction time/h[b]	Yield of **6**[a,c] (%)	Yield of **8**[a] (stereochemistry)[c]
a	H	H	H	98	2	100	83 (2*E*)
b	H	Me	H	97	6	100	87 (2*E*)
c	Me	H	H	98	1	100	83 (2*E*, 4*E*)
d	C_3H_7	H	H	95	1	98	83 (2*E*, 4*E*)
e	H	H	Me	97	2	100	82 (2*Z*)
f	H	H	C_3H_7	98	10	97	83 (2*Z*)
g	H	H	Ph	70	1	98	83 (2*Z*)

[a] Isolated yield. [b] Refluxing in CCl_4. [c] ^1H NMR spectrum shows the presence of only one isomer. Satisfactory spectral and microanalytical data obtained for all new compounds.

allyl moiety. In all cases, the Claisen products were obtained in almost quantitative yield. Oxidation of **6** (MCPBA–CH_2Cl_2, −20 °C), followed by elimination of benzenesulfenic acid by refluxing the resulting sulfoxide **6** in CH_2Cl_2, furnished the title compound **8** in good yield (Scheme 1, Table 1).

The stereochemical features of the butadienyl trifluoromethyl ketone products **8** were determined by ^1H NMR. The rearrangement of **4** derived from allyl alcohol or secondary allyl alcohols **3a–d** eventually yielded the (2*E*)- or (2*E*, 4*E*)-butadienyl trifluoromethyl ketones **8a–d**, while **4** derived from 3-substituted allyl alcohols **3e–f** yielded (2*Z*)-butadienyl trifluoromethyl ketones **8e–g**. The high stereoselectivity of the products is due to the chairlike transition state **5**, inherent in Claisen rearrangement,[6] and the *syn*-elimination mechanism accepted for the thermal extrusion of sulfenic acid.[10]

In conclusion, we have demonstrated the utility of 1-bromo-1-phenylsulfanyl-3,3,3-trifluoroprop-1-ene as a trifluoropropyne precursor and its use as a new CF_3-containing building block for the stereocontrolled syntheses of a variety of conjugated butadienyl trifluoromethyl ketones *via* Claisen rearrangement.

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