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# The regio- and stereoselective addition of carbon nucleophiles to trifluoromethyl phenylsulfanyl acetylene: a novel and expeditious approach to 3-trifluoromethyl furans

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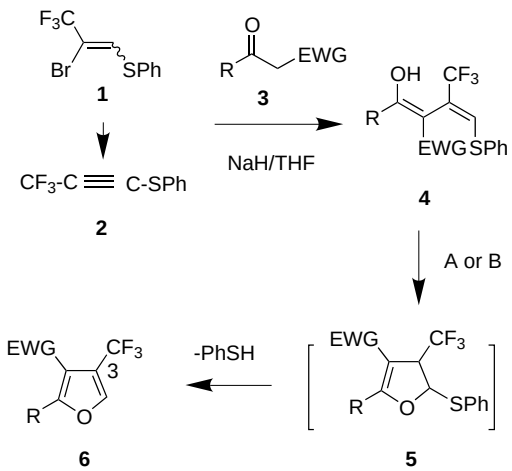
**Abstract**—A convenient generation of trifluoromethyl phenylsulfanyl acetylene was realized from 2-bromo-1-phenylsulfanyl-3,3,3-trifluoropropene. The reagent was reacted with carbanions to give (1*E*,3*E*)-2-trifluoromethylbutadienyl phenyl sulfides regio- and stereoselectively, which underwent intramolecular cyclization in decalin at 190°C or in acetic acid with 1,4-benzoquinone and sodium acetate to afford 3-trifluoromethyl-substituted furans in high yields. 

The development of synthetic methodologies for the selective introduction of trifluoromethyl groups into heteroaromatic compounds has gained growing interest in recent years since many such products exhibit unique biological activities,[1] for example 2-aryl-5-trifluoromethylpyrroles are a new class of insecticides.[2] However, there are a limited number of regiospecific syntheses of $CF_3$-substituted heteroaromatic compounds in good yields.[3] In the case of trifluoromethylated furans, only a few synthetic concepts have been developed. Reductive fluoride elimination of β,β-bis(trifluoromethyl)-α,β-unsaturated ketones with $SnCl_2$ and 1,5-electrocyclization with elimination offered a versatile access to trifluoromethylfurans.[4] Pyrolysis of the adducts of the Diels–Alder reaction of trifluoromethyl-substituted acetylenic dienophiles with furan gave an alternative pathway for the preparation of trifluoromethylfurans.[5] In addition, the introduction of a trifluoromethyl group in low yield was achieved by direct fluorination of furan dicarboxylic acid with sulfur tetrafluoride.[6] Although several reagents and reaction sequences have been developed for the introduction of this group in the furan system, there are remaining problems to be solved, such as the handling of the materials, availability of reagents and selectivity. The search for a simple and efficient access to heteroaromatic compounds with a trifluoromethyl group at a specific position is highly desirable in this area. Herein we describe a novel and expeditious approach to the formation of 3-trifluoromethylfurans in excellent yields (Scheme 1).

2-Bromo-2-trifluoromethylethenyl phenyl sulfide **1** which is easily obtainable from the inexpensive trifluoropropene in high yield,[7] can serve as a useful and economical precursor for the preparation of trifluoromethyl phenylsulfanyl acetylene **2**.[8] In a previous communication, we showed that **1** easily underwent dehydrobromination followed by a regio- and stereoselective nucleophilic addition reaction with sodium




**Scheme 1.** *Reagents and conditions*: (A) decalin/190°C; (B) $CH_3CO_2H$/NaOAc/1,4-benzoquinone/reflux.

*Keywords*: acetylene; regio- and stereoselection; dienes; furans.

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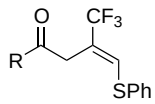
**Table 1.** Reaction of **1** with active methylene compounds **3** and NaH followed by intramolecular cyclization and dehydrosulfination

| Entry | R | EWG | Temp. (°C)/Time (h) | Yield (%) of **4**[a] (stereochemistry) | Yield (%) of **6** | | |
|---|---|---|---|---|---|---|---|
| | | | | | A[b] | B[c] | |
| 1 | $CH_3$ | $CO_2Et$ **3a** | 60/6 | 91 (1*E*,3*E*) **4a** | 81 | 0 | **6a** |
| 2 | $C_2H_5$ | $CO_2Et$ **3b** | 60/9 | 90 (1*E*,3*E*) **4b** | 86 | 0 | **6b** |
| 3 | *n*-$C_3H_7$ | $CO_2Et$ **3c** | 60/9 | 89 (1*E*,3*E*) **4c** | 87 | 0 | **6c** |
| 4 | Ph | $CO_2Et$ **3d** | 60/4 | 87 (1*E*,3*E*) **4d** | 91 | 0 | **6d** |
| 5 | Ph | CN **3e** | 80/10 | 85 (1*E*,3*E*) **4e** | 90 | 85 | **6e** |
| 6 | *p*-$CH_3C_6H_4$ | CN **3f** | 80/16 | 81 (1*E*,3*E*) **4f** | 93 | 93 | **6f** |
| 7 | *p*-$CH_3OC_6H_4$ | CN **3g** | 80/24 | 90 (1*E*,3*E*) **4g** | 92 | 85 | **6g** |
| 8 | *m*-$CH_3C_6H_4$ | CN **3h** | 80/26 | 93 (1*E*,3*E*) **4h** | 90 | 91 | **6h** |
| 9 | *p*-$MeO_2CC_6H_4$ | CN **3i** | 80/26 | 80 (1*E*,3*E*) **4i** | 92 | 90 | **6i** |
| 10 | *o*-Ph-$C_6H_4$ | CN **3j** | 80/30 | 15 (1*E*,3*E*) **4j** | 91 | 85 | **6j** |

[a] The reaction was carried out with 1 equiv. **1**, 1.2 equiv. NaH and 1 equiv. **3** in THF.
[b] Refluxing in decalin.
[c] Refluxing in acetic acid/sodium acetate/1,4-benzoquinone.

alkoxides to form trifluoromethylvinyl ethers. Based on this fact, we sought a method for carbon–carbon bond formation via nucleophilic addition of carbanions to the acetylene **2**. We found that compound **2** ($^{19}F$ NMR $\delta_{TFA}$: −27.5, s), generated in situ from 2-bromo-2-trifluoromethylethenyl phenyl sulfide **1** by treatment with 1.2 equiv. of NaH in THF, smoothly reacted with active methylene compounds **3** to give the Michael addition products **4**.[9] The carbanion attacked the acetylene **2** in the β-position regioselectively to afford diene **4** with (1*E*,3*E*)-geometry stereoselectively. Due to the presence of the strong electron-withdrawing group (EWG) in the molecule, the enol form was produced exclusively. The stereochemistry was defined on the basis of $^1H$ NMR, $^{19}F$ NMR ($\delta_{TFA}$: −13.8, s) and IR spectra. The IR spectrum contained a broad band (3300–3100 $cm^{-1}$) assigned to an O–H stretch. Further confirmation of the structure was afforded by an X-ray structure analysis of compound **4e**. As shown in Table 1, the reaction of compound **1** with alkyl keto-acetates (entries 1–3) or benzoylacetate (entry 4) with NaH in THF gave dienes **4a–4d** within 6–8 h at 60°C, while the reactions of aryl keto-acetonitriles (entries 5–10) proceeded sluggishly at 80°C, but could be readily completed in 10–30 h to afford dienes **4e–4j** in high yields.

Taking advantage of the ease of preparation of (1*E*,3*E*)-2-trifluoromethyl-4-hydroxy-dienes, we have demonstrated the possibility of making $CF_3$-substituted furans by intramolecular cyclization. Initially, we tried to prepare furan **6** via cyclization of **4** in acetonitrile promoted by the Lewis acid, $TiCl_4$.[10] The reaction was however unsuccessful. We found that if compounds **4** were heated in decalin at 190°C for 3 h, the expected intramolecular cyclization products, 3-trifluoromethylated furans **6**, could be isolated in high yields with concurrent elimination of thiophenol (Table 1).[11] Using acetic acid as a proton source, compounds **4e–4j** were heated with sodium acetate and 1,4-benzoquinone at 100°C for 24 h to yield the furans **6e–6j** in excellent yields, while compounds **4a–4d** gave the decarboxylated product **7**, quantitatively.




R=$CH_3$, $C_2H_5$, n-$C_3H_7$, Ph

**7**

In summary, the addition of carbon nucleophiles to trifluoromethyl phenylsulfanyl acetylene provides an efficient method for the regio- and stereoselective synthesis of a wide range of functionalized (1*E*,3*E*)-trifluoromethylated 1,3-diene derivatives in high yields. The synthetic utility of trifluoromethylated 1,3-dienes lies in a novel and easy approach to 3-trifluoromethylated furans. This method has the advantage of ready accessibility of the reagent, mild conditions as well as its simplicity in manipulation.

## Acknowledgements

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9. **General procedure for the preparation (1*E*,3*E*)-trifluoromethyl butadienes 4**. For example: To a suspension of NaH (2.4 g, 12 mmol) in THF (50 mL) was added **1** (2.9 g, 10 mmol) and benzoylacetonitrile (4 mL, 10 mmol) at room temperature for 1 h. The mixture was heated at 80°C for 10 h. After cooling to room temperature, the mixture was poured into ice water (20 mL) and extracted with ethyl acetate (3×10 mL). The (1*E*,3*E*) combined organic phase was washed with 10% HCl, brine and dried over $Na_2SO_4$. After removal of the solvent, the residue was subjected to flash chromatography to afford **4e** (3.0 g, 85%). Mp 124.5–126.8°C; [found: C, 62.29; H, 3.13; N, 3.75. $C_{18}H_{12}F_3NOS$: requires C, 62.25; H, 3.46; N, 4.03%]; $\nu_{max}$ (KBr) 3300–3100 (OH), 2205 (CN) $cm^{-1}$; $\delta_F$ ($CDCl_3$) −13.8 (3F, s C<u>F</u>$_3$); $\delta_H$ ($CDCl_3$) 6.47 (1H, s, C=C<u>H</u>), 7.41–7.90 (10H, m, Ph-<u>H</u>); *m*/*z* (EI, 70 eV) 347 (15, $M^+$), 327 (23, $M^+$−F), 105 (100%).
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11. **General procedure for the preparation of 4-trifluoromethylated furans 6**. For example: Method A: **4e** (0.7 g, 2 mmol) in decalin (5 mL) was refluxed for 3 h. After removal of the solvent under reduced pressure, the crude product was purified on a short silica gel column to afford **6e** (0.43 g, 90%). Method B: A solution of **4e** (0.7 g, 2 mmol), 1,4-benzoquinone (0.43 g, 4 mmol) and sodium acetate (0.7 g, 8 mmol) in acetic acid (10 mL) was heated at 100°C for 24 h. The mixture was diluted with diethyl ether (20 mL). The organic phase was washed with water, saturated aqueous $NaHCO_3$ and dried over $Na_2SO_4$. After removal of the solvent in vacuum, the residue was purified by column chromatography on silica gel to give **6e** (0.4 g, 85%) as colorless crystals: mp 89.8–92.6°C; [found: C, 60.67; H, 2.69; N, 5.84. requires $C_{12}H_6NO$: C, 60.77; H, 2.55; N, 5.91%]; $\nu_{max}$ (KBr): 3129, 2232 (CN) 1676, 1141 $cm^{-1}$; $\delta_F$ ($CDCl_3$) −18 (3F, s, C<u>F</u>$_3$); $\delta_H$ ($CDCl_3$) 7.48–7.54 (3H, m, Ph-<u>H</u>), 7.84 (1H, s, furan-<u>H</u>), 8.00 (2H, m, Ph-<u>H</u>); *m*/*z* (EI, 70 eV) 237 (100, $M^+$).