1,3-Sulfanyl Group Migration: Formation of Unexpected Trifluoromethyl-Containing Bridged Heterocycles

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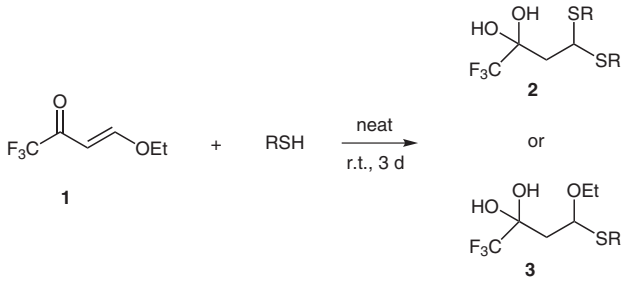
Received 14 November 2007

Abstract: Concentrated sulfuric acid promoted the intramolecular dehydration and 1,3-sulfanyl migration of 1,1,1-trifluoro-4,4-bis(arylthio)butane-2,2-diol; this afforded, in addition to the expected unsaturated ketone, an unexpected trifluoromethyl-containing bridged heterocycle.

Key words: 4-ethoxy-1,1,1-trifluorobut-3-en-2-one, thio nucleophiles, indium trichloride, Michael addition, dehydration

Bridged heterocycles have attracted much attention due to their importance in the fields of natural products and medicinal chemistry.[1,2] These structural frameworks are found in some alkaloids and they can also be elaborated into more functionalized systems.[3] Efforts have been directed to the development of efficient methods to synthesize such bridged heterocycles. The classic methods for preparing bridged heterocycles include the inter- and intramolecular condensation of polyphenols such as catechins,[4] the Pd-catalyzed intramolecular coupling of vinyl halides with ketone enolates,[5] and three-component reaction of salicylaldehyde, β-naphthol, and ethyl acetoacetate under $BF_3{\cdot}OEt_2$ catalysis.[6] Recently, there have been an increasing number of applications of ring-closing metathesis (RCM) reactions to prepare bridged bicyclic oxygen heterocycles.[7] In the above approaches, expensive transition-metal catalysts are usually used to activate unsaturated bonds and promote the ring-closing process. Herein, we wish to report a novel cyclization leading to trifluoromethyl-containing bridged heterocycles by H_2SO_4-promoted dehydration and 1,3-sulfanyl migration of 1,1,1-trifluoro-4,4-bis(arylthio)butane-2,2-diol **2** (Scheme 1). The significant benefit of this cyclization procedure, which does not need expensive transition-metal-complex participation, is that it provides a direct route to constructing the bridged framework. The driving force in this cyclization is the 1,3-sulfanyl migration.

Gerus and we have continuously studied the chemical transformation of the 4-ethoxy-1,1,1-trifluorobut-3-en-2-one (**1**) with various nucleophiles, such as Grignard reagents,[8] terminal alkynes,[9] alcohols,[10] amines,[11] and phosphorous nucleophiles,[12] and a series of trifluoromethyl-containing heterocycles, were synthesized. Naturally, as part of our systematic study, we also attempted the reaction of **1** with thio nucleophiles.



Scheme 1 Reaction of compound **1** with thiols

In general, thiols can react readily with unsaturated compounds when catalyzed by metal salts[13] under very mild conditions, yielding the corresponding Michael addition products. In consideration of environmentally friendly effects, we attempted the reaction of **1** with thiophenol in the absence of catalyst. Interestingly, a double thio-Michael addition reaction was observed and **2a** was obtained as the sole product, a yellow solid with a melting point of 62–63 °C (Table 1, entry 1).[14] The MS data (M^+, $m/z = 360$) for this product also confirmed that two equivalents of thiophenol participated in the reaction. The yield was increased to 72% by using more equivalents of thiophenol. Subsequently, reaction of 4-methylthiophenol or 4-methoxythiophenol with **1** afforded similar products **2b**,**c** in 47–62% yields (Table 1, entries 2 and 3). However, in the reaction of **1** with 4-chlorothiophenol, only one single nucleophilic adduct **3** was obtained (Table 1, entry 4). Furthermore, the less nucleophilic 4-nitrothiophenol

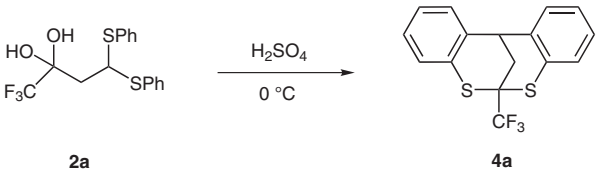
Table 1 Reaction Results for Compound **1** with Thiols

Entry	Thiol (RSH)	Time (d)	Product **2** or **3**	Yield (%)[a]
1	PhSH	3	**2a**	72
2	4-MeC_6H_4SH	4	**2b**	47
3	4-$MeOC_6H_4SH$	4	**2c**	65
4	4-ClC_6H_4SH	2	**3**	64
5	4-$N_2OC_6H_4SH$[b]	6	n.r.	–

[a] Isolated yields.
[b] PTSA (20 mg) was added to the reaction mixture as a catalyst.

SYNLETT 2008, No. 6, pp 0871–0874
Advanced online publication: 11.03.2008
DOI: 10.1055/s-2008-1042909; Art ID: W20107ST

Scheme 2 Reaction of **5** with thiols



Scheme 3 Reaction of **5** with thiols

could not react with **1**, even after prolonged reaction time in the presence of *p*-toluenesulfonic acid as the catalyst (Table 1, entry 5).

In order to prepare the similar bis(arylthio) products bearing electron-withdrawing groups, **1** was converted into 4,4-diethoxy-1,1,1-trifluorobutane-2,2-diol (**5**) in the presence of KOH.[15] Subsequently, **5** was allowed to react with excess 4-chlorothiophenol or 4-nitrothiophenol and the expected bisarylthio products **2d**,**e** were obtained in 73–82% yields (Scheme 2).

Interestingly, subsequent treatment of **2a** with concentrated sulfuric acid yielded a bridged cyclic product **4a**, which had a melting point of 169–171 °C (Scheme 3).[16] The MS data (M^+, *m/z* = 324) for this product indicated that only two molecules of H_2O were removed. Its bridged cyclic structure was further confirmed by single crystal X-ray diffraction analysis (Figure 1).[17]

When we treated other bisarylthio compounds **2b–e** with concentrated sulfuric acid in the same manner, we obtained two different products (Scheme 4, Table 2). It was clear that the electronic properties of the substituent groups had an important influence on the reaction outcome. When reactants carried electron-donating groups such as methyl or methoxy substituents, bridged heterocycles **4b**,**c** were formed together with a small amount of α,β-unsaturated product **6** (Table 2, entries 2 and 3). However, the corresponding α,β-unsaturated ketone was not found in the case of compound **2a**. In contrast, only α,β-unsaturated compounds **6d**,**e** were isolated in good yield

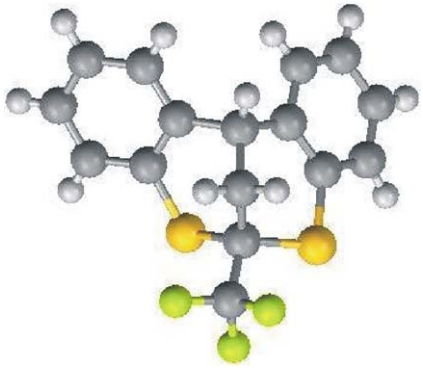


Figure 1 Crystal structure of **4a**

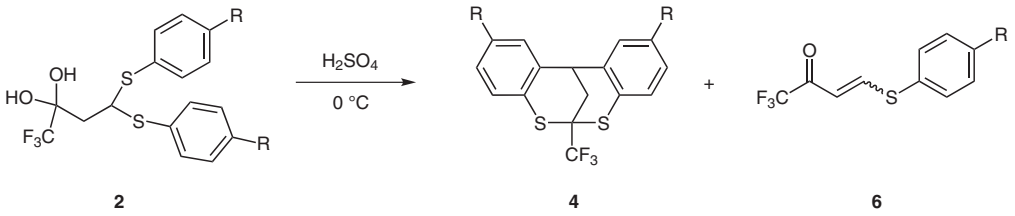
Table 2 Dehydration of **2a–e** with Concentrated H_2SO_4

Entry	**2** (R)	Time (h)	Yield of **4** (%)[a]	Yield of **6** (%, *E*/*Z*)[a]
1	**2a** (Ph)	1.5	**4a** (>99)	–
2	**2b** (4-MeC_6H_4)	1	**4b** (83)	**6b** (trace)
3	**2c** (4-$MeOC_6H_4$)	1	**4c** (26)	**6c** (42, 3:2)
4	**2d** (4-ClC_6H_4)	1	–	**6d** (78, 3:2)
5	**2e** (4-$O_2NC_6H_4$)	1	–	**6e** (82, 3:2)

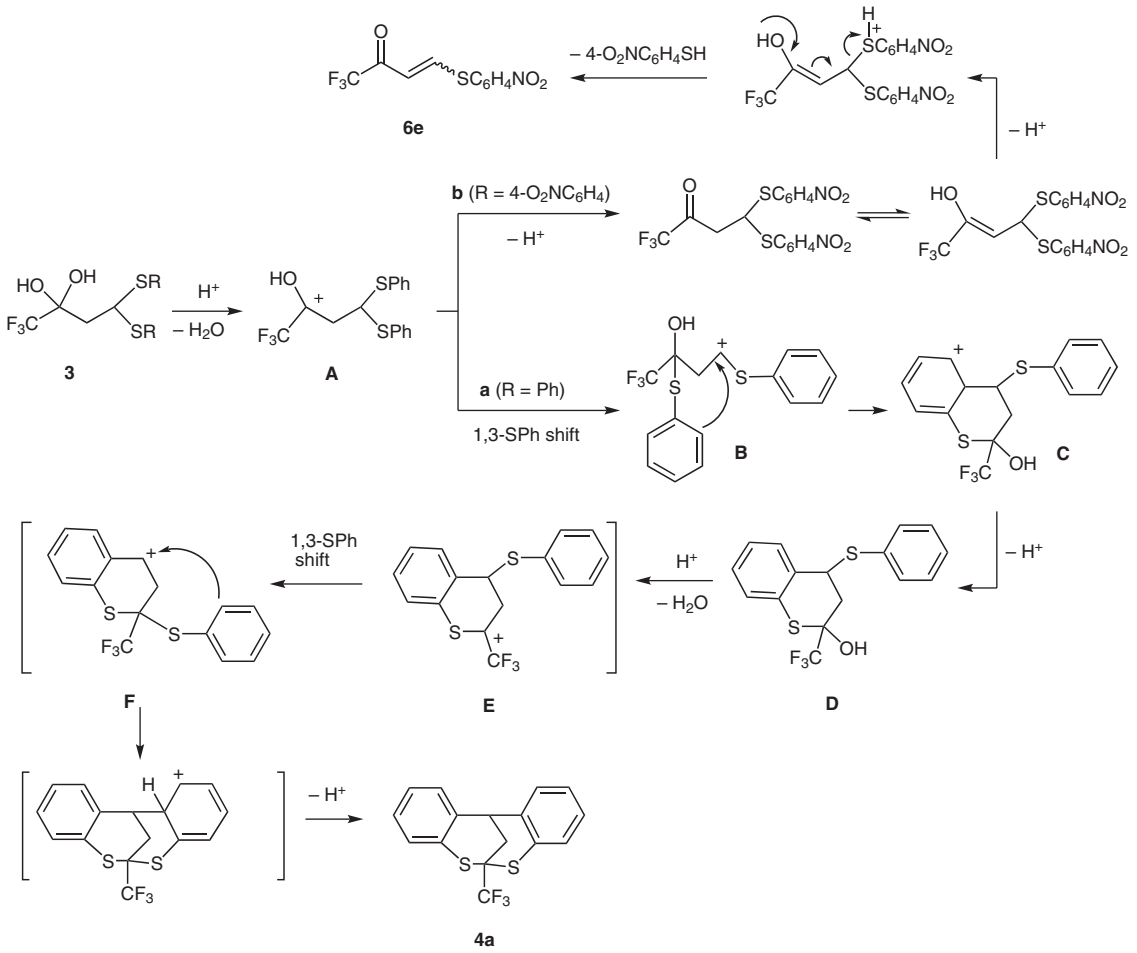
[a] Isolated yields.

when compound **2d**,**e** were treated under the same reaction conditions (Table 2, entries 4 and 5).

The formation of two different products could be explained by the mechanism as shown in Scheme 5. Initially, **2** underwent dehydration in the presence of concentrated sulfuric acid to form cationic intermediate **A**, which could undergo either a 1,3-SPh shift or a subsequent proton-elimination reaction, depending on the electronic character of the substituent groups. When compound **2** carried an electron-donating group or did not have any substituents, such as in **2a**, a 1,3-SPh shift occurred to form an intermediate **B**, followed by intramolecular nucleophilic attack to form cation **C**, which subsequently lost a proton to form intermediate **D**. Then another H_2O was eliminated and intermediate **E** was created, which underwent a second 1,3-SPh shift to form intermediate **F**, followed by a second intramolecular nucleophilic attack and proton elimination. The final bridged heterocycle **4a** was then formed. On the other



Scheme 4 Dehydration of **2a–e** with concd H_2SO_4



Scheme 5 Proposed mechanism for the formation of compounds **4a** and **6e**

hand, when compound **2** carried an electron-withdrawing group, such as a nitro group which significantly reduced the nucleophilicity of the carbon atom on the phenyl, it was more favorable to eliminate H_2O and thiol to afford an unsaturated compound **6e** than to undergo intramolecular cyclization.

In summary, we have developed an intramolecular dehydration and cyclization of 1,1,1-trifluoro-4,4-bis(arylthio)butane-2,2-diol promoted by concentrated sulfuric acid, which afforded trifluoromethyl-substituted bridged heterocycles and unsaturated ketones. This methodology affords a new entry into bridged cyclic systems. Utilization of this synthetic methodology for the generation of other bridged heterocycles is currently under way.

Acknowledgment

Financial support for this project was provided by The National Natural Science Foundation of China (NNSFC) (Nos. 20472106 and 20532040).

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(14) **Typical Procedure and Spectroscopic Data of Compounds 2 and 3**

4-Ethoxy-1,1,1-trifluoro-3-buten-2-one (**1**, 0.336 g, 2 mmol) was added into a 10 mL flask containing thiol (4 mmol), which was stirred at r.t.; TLC analysis was used to monitor the reaction progress. After 2–4 d, the reaction was deemed complete, and the reaction mixture was purified by column chromatography on silica gel (hexane–EtOAc, 200:3) to give the products **2** or **3**.

1,1,1-Trifluoro-4,4-bis(phenylthio)butane-2,2-diol (2a)

Yellow solid, mp 62–63 °C; yield 72%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.54–7.28 (10 H, m, 2 C_6H_5), 4.92 (1 H, t, $^3J_{HH}$ = 7.0 Hz, CH), 4.68 (2 H, br, OH), 2.37 (2 H, d, $^3J_{HH}$ = 7.0 Hz, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 42.63 (CH_2), 51.97 (CH), 115.17 (q, $^1J_{CF}$ = 233.3 Hz, CF_3), 129.91 (Ph), 130.14 (q, $^2J_{CF}$ = 43.6 Hz, CF_3C), 130.69 (Ph), 135.05 (Ph), 135.38 (Ph). ^{19}F NMR (298 MHz, $CDCl_3$): δ = –87.38 (s, CF_3). MS: *m/z* (%) = 360 (2.57) [M^+], 342 (15.59) [$M^+ – H_2O$], 251 (28.10) [M^+ – SPh], 233 (100) [$M^+ – H_2O$ – SPh], 109 (46.63) [SPh], 69 (5.42) [CF_3]. IR: ν = 3421, 3062, 1766, 1538, 1211, 1144, 1063 cm^{-1}. Anal. Calcd for $C_{16}H_{15}F_3O_2S_2$ (%): C, 41.32; H, 4.20. Found: C, 41.39; H, 4.20.

4-(4-Chlorophenylthio)-4-ethoxy-1,1,1-trifluorobutane-2,2-diol (3)

Yellow solid; mp 106–107 °C; yield 64%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.28 (4 H, m, C_6H_4Cl), 5.69 (1 H, br, OH), 5.22 [1 H, dd, $^3J_{HH}$ = 3.0 Hz, 11 Hz, CH(OH)OEt], 4.21–4.16 (1 H, m, OCH_2), 3.67–3.62 (1 H, m, OCH_2), 3.38 (1 H, br, OH), 2.32–2.27 (1 H, m, CH_2), 2.13–2.08 (1 H, m, CH_2), 1.32 (3 H, t, $^3J_{HH}$ = 7.0 Hz, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 36.87 (CH_3), 42.84 (CH_2), 51.31 (OCH_2), 51.90 (CH), 117.27 (q, $^1J_{CF}$ = 234.0 Hz, CF_3), 128.78 (C_6H_4Cl), 129.26 (C_6H_4Cl), 132.95 (q, $^2J_{CF}$ = 82.0 Hz, CF_3C), 133.34 (C_6H_4Cl), 133.64 (C_6H_4Cl). ^{19}F NMR (298 MHz, $CDCl_3$): δ = –87.15 (s, CF_3). MS: *m/z* (%) = 330 (1.36) [M^+], 312 (2.22) [$M^+ – H_2O$], 285 (0.53) [M^+ – OEt], 267 (3.21) [$M^+ – H_2O$ – OEt], 187 (45.82) [$M^+ – SC_6H_4Cl$], 169 (74.74) [$M^+ – H_2O$ – SPhCl], 141 (100) [$M^+ – SC_6H_4Cl$ – EtOH], 143 (44.78) [SC_6H_4Cl], 69 (34.39) [CF_3]. IR: ν = 3354, 1417, 1189, 1117, 1083, 1053 cm^{-1}. Anal. Calcd for $C_{12}H_{14}F_3O_3SCl$ (%): C, 43.58; H, 4.27. Found: C, 43.56; H, 4.26.

(15) **Typical Procedure and Spectroscopic Data for Diols**

4,4-Diethoxy-1,1,1-trifluorobutane-2,2-diol (**5**, 0.1 g, 0.5 mmol) was added into a 10 mL flask containing thiol (2 mmol), which was stirred at r.t.; TLC analysis was used to monitor the process. After 3 d, the reaction finished, and the reaction mixture was purified by column chromatography on silica gel (hexane–EtOAc, 100:1) to give the products **2d** or **2e**.

4,4-Bis(4-chlorophenylthio)-1,1,1-trifluorobutane-2,2-diol (2d)

Yellow solid, mp 66–67 °C; yield 73%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41 (4 H, d, $^3J_{HH}$ = 6.0 Hz, C_6H_4), 7.34 (4 H, d, $^3J_{HH}$ = 6.0 Hz, C_6H_4), 4.83 (1 H, t, $^3J_{HH}$ = 6.0 Hz, CH), 4.53 (2 H, s, OH), 2.31 (2 H, d, $^3J_{HH}$ = 8.0 Hz, CH_2). ^{19}F NMR (298 MHz, $CDCl_3$): δ = –86.99 (s, CF_3). MS: *m/z* (%) = 268 or 266 (27.12 or 97.86) [$M^+ – H_2O$ – *p*-$ClC_6H_4S^+$], 250 or 248 (25.14 or 58.83) [$M^+ – 2H_2O$ – *p*-$ClC_6H_4S^+$], 119 or 197 (28.55 or 58.47) [$M^+ – 2H_2O – CF_3$ – *p*-$ClC_6H_4S^+$], 146 or 144 (23.92 or 55.17) [*p*-ClC_6H_4SH], 108 or 106 (100) [$M^+ – 2H_2O$ – 2*p*-$ClC_6H_4S^+$], 69 (52.11) [CF_3]. IR: ν = 3823, 3753, 1477, 1168, 814 cm^{-1}. Anal. Calcd for $C_{16}H_{13}F_3O_2S_2$ (%): C, 44.77; H, 3.05. Found: C, 44.83; H, 3.01.

(16) **Typical Procedure and Spectroscopic Data for Bridged Cyclic Compounds**

Compound **2** was added to the cold concd H_2SO_4 (3 mL) with efficient stirring. The temperature of the reaction during the addition was kept below 10 °C and the reaction mixture was stirred at 0 °C for 1 h. Then it was poured to the chipped ice and set aside for 2 h in the refrigerator. The aqueous acid solution was extracted with CH_2Cl_2 (3 × 10 mL). The solvent was evaporated in vacuum to give the crude products, which were purified by recrystallization (CH_2Cl_2–hexane) to give the final product **4** and/or **6**.

Compound **4a**: white solid, mp 169–171 °C; yield >99%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45–7.14 (8 H, m, 2 C_6H_4), 4.48 (1 H, s, CH), 2.61 (2 H, d, $^3J_{HH}$ = 4.0 Hz, CH_2). ^{19}F NMR (298 MHz, $CDCl_3$): δ = –73.73 (s, CF_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.03 (C_6H_4), 130.33 (C_6H_4), 129.67 (C_6H_4), 127.56 (q, $^1J_{CF}$ = 286.0 Hz, CF_3), 127.41 (C_6H_4), 126.62 (C_6H_4), 125.81 (C_6H_4), 39.40 (CF_3C), 31.75 (CH), 29.71 (CH_2). MS: *m/z* (%) = 324 (100) [M^+], 255 (31.34) [$M^+ – CF_3$], 215 (63.32) [M^+ – Ph], 69 (7.29) [CF_3]. IR: ν = 1470, 1440, 1270, 1176, 1156, 760 cm^{-1}. HRMS: *m/z* calcd for $C_{16}H_{11}F_3S_2$: 324.030; found: 324.027.

X-ray Crystal Data: $C_{16}H_{1}{}_{1}F_3S_2$: *FW* = 324.37; 293 (K); monoclinic, *P*2/*c*; *l* = 0.71 Å; *a* = 9.482(9) Å, *b* = 16.180(19) Å, *c* = 9.482(9) Å, α = 90°, β = 109.203(10)°, γ = 90°; *V* = 1373.8(2) Å3; *Z* = 4, D_c = 1.568 mg/m^3; absorption coefficient 0.410 mm^{-1}; *F*(000) = 664; size 0.501 × 0.290 × 0.078 mm; 2.27 < θ < 26.99; reflections collected 7979; Absorption correction Empirical; transmission 1.00 mix-0.741 min; goodness of fit on *F*2 0.98; final *R* indices *R*1 = 0.0491, *wR*2 = 0.1190.

4-(4-Chlorophenylthio)-1,1,1-trifluorobut-3-en-2-one (6d)

Yellow solid; mp 79–81 °C; yield 78%. ^{1}H NMR (300 MHz, $CDCl_3$): δ (*E*-isomer) = 8.22 (d, $^3J_{HH}$ = 15.0 Hz, =CH), 7.48–7.40 (m, C_6H_4), 6.25 (d, $^3J_{HH}$ = 15.0 Hz, =CH). ^{19}F NMR (298 MHz, $CDCl_3$): δ (*E*-isomer) = –77.71 (s, CF_3). ^{1}H NMR (300 MHz, $CDCl_3$): δ (for Z) = 7.80 (d, $^3J_{HH}$ = 10.0 Hz, =CH), 7.48–7.40 (m, C_6H_4), 6.67 (d, $^3J_{HH}$ = 10.0 Hz, =CH). ^{19}F NMR (298 MHz, $CDCl_3$): δ (for *Z*) = –78.10 (s, CF_3). MS: *m/z* (%) = 266 (36.22) [M^+], 197 (100) [$M^+ – CF_3$], 143 (53.24) [$M^+ – {}^+SC_6H_4Cl$], 69 (28.63) [CF_3]. IR: ν = 1675, 1516, 1306, 1151, 1069, 898. Anal. Calcd for $C_{10}H_6ClF_3OS$ (%): C, 45.04; H, 2.27. Found: C, 44.84; H, 2.24.

(17) Single-crystal X-ray structural data for **4a** have been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 644817.