Unexpected Formation of Trifluoromethylated Spiro or Fused Cyclic Compounds from 4-Ethyloxy-1,1,1-trifluoro-3-buten-2-one and Silyl Enol Ethers

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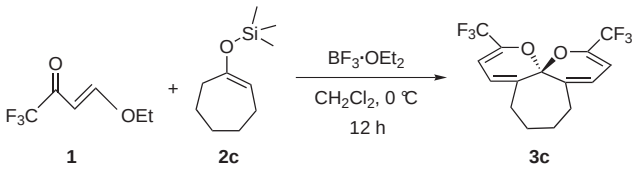
Abstract: Two kinds of trifluoromethylated spiro or fused cyclic compounds were synthesized via the unexpected direct α,α′-dialkylation of (*E*)-4-ethoxy-1,1,1-trifluoro-3-buten-2-one (**1**) with silyl enol ethers in the presence of boron trifluoride etherate.

Key words: trifluoromethylated spiro or fused cyclic compounds, silyl enol ethers, (*E*)-4-ethoxy-1,1,1-trifluoro-3-buten-2-one, boron trifluoride etherate

The aldol condensation has long been recognized to be one of the most versatile synthetic tools in organic chemistry.[1] It is well known that silyl enol ethers can be readily attacked by a carbonyl or an α,β-unsaturated compound in the presence of a Lewis acid. In most of these condensation reactions an electrophile was introduced regiospecifically onto one side of a silyl enol ether at the α-position.[2] However, to the best of our knowledge, very little is known about the α,α′-dialkylation of the silyl enol ether, although there are several related examples reported in the literature. α,α′-Bis(substituted-benzylidene)cycloalkanones and bis(trifluoroethylidene)cyclohexanone were synthesized through the reaction of arylaldehydes and silyl enol ether in the presence of SmI_3 and ZnI_2, respectively.[3,4] To our surprise, compound (*E*)-4-ethoxy-1,1,1-trifluoro-3-buten-2-one (**1**) reacted with silyl enol ethers in the presence of boron trifluoride etherate to afford, unexpectedly, α,α′-dialkylated products. More surprisingly, these α,α′-dialkylated products had spiro or fused cyclic structures, which are difficult to synthesize by other means. As reported in the literature, certain spiropyran derivatives exhibited remarkable thermochromism properties.[5] The interesting reversible color change of spiropyran derivatives was temperature-dependent; an intense violet color developed in polar solvents at high temperature, reverting to colorless at room temperature. Such a characteristic has become more and more important over the past few decades, because these compounds could be used as thermosensors. Though several methods were available for the preparation of these analogues, they suffered from some disadvantages.[6] Condensation of aldehydes and ketones catalyzed by traditional acids or bases was simple but reversible. Herein, we wish to report the unexpected formation of trifluoromethylated spiro or fused cyclic compounds and discuss the possible mechanism.

Although compound **1** and silyl enol ethers[7] failed to react in the absence of a catalyst, it was found that the reaction proceeded smoothly in the presence of one equivalent of boron trifluoride etherate. When equal amounts of silyl enol ether **2c**, derived from cycloheptanone, reacted with **1** in dichloromethane at 0 °C, there was not the expected traditional nucleophilic addition product isolated but instead a small quantity of **3c** was observed (Scheme 1). From the single crystal X-ray diffraction analysis of the product **3c** (Figure 1) it was clear that **3c** was a bis-trifluoromethylated spiropyran derivative with a completely symmetrical framework. There was only one peak observed in the ^{19}F NMR spectrum at –72.00 ppm, which was in agreement with its structure. Based on these experimental phenomena, we surmised that there should be two molecules of **1** participating in the reaction.

The unusual formation of the spiropyran derivative was extremely sensitive to solvents and catalysts. First, we examined the reaction of **1** and **2c** in the presence of $BF_3{\cdot}OEt_2$ (1.0 equiv) in various solvents and the results



Scheme 1

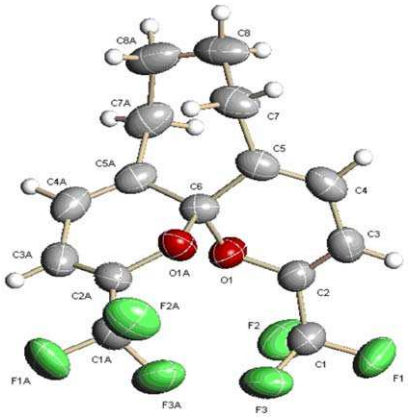


Figure 1 Crystal structure of compound **3c**.

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are summarized in Table 1. It was found that the reaction only proceeded readily in CH_2Cl_2. When using Et_2O as the solvent, the yield of **3c** decreased to 30%. However, very little product was found in the reaction mixture when CH_3CN or benzene was employed (Table 1, entries 5–7). Secondly, different catalysts were examined and it was found that other catalysts such as $TiCl_4$, KF or CsF could not promote this reaction and no product was obtained (Table 1, entries 8–10). Attempting to employ catalytic amounts of $BF_3{\cdot}OEt_2$ caused a drastic decrease in the yields (Table 1, entries 3 and 4).

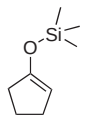
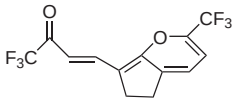
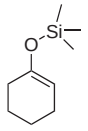
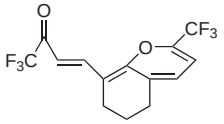
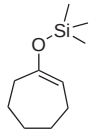
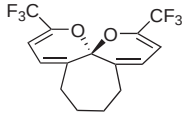
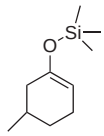
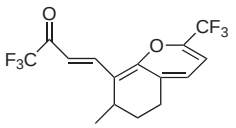
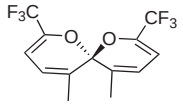
Table 1 Reaction of Compound **1** and **2c** under Several Conditions[a]

Entry	Catalyst	Solvent	**2c**/**1**	**3c** (%)
1	$BF_3{\cdot}OEt_2$ (1 equiv)	CH_2Cl_2	1:1	37[b]
2	$BF_3{\cdot}OEt_2$ (1 equiv)	CH_2Cl_2	1:2	71[b]
3	$BF_3{\cdot}OEt_2$ (0.5 equiv)	CH_2Cl_2	1:2	39[c]
4	$BF_3{\cdot}OEt_2$ (0.05 equiv)	CH_2Cl_2	1:2	5[c]
5	$BF_3{\cdot}OEt_2$ (1 equiv)	Et_2O	1:2	30[c]
6	$BF_3{\cdot}OEt_2$ (1 equiv)	CH_3CN	1:2	trace
7	$BF_3{\cdot}OEt_2$ (1 equiv)	benzene	1:2	trace
8	$TiCl_4$ (1 equiv)	CH_2Cl_2	1:2	–
9	KF (1 equiv)	CH_2Cl_2	1:2	–
10	CsF (1 equiv)	CH_2Cl_2	1:2	–

[a] Reactions were carried out in solvent (5 mL) with **1**, **2c**, and $BF_3{\cdot}OEt_2$ under a nitrogen atmosphere at 0 °C for 12 h.
[b] Isolated yields.
[c] According the NMR spectrum.

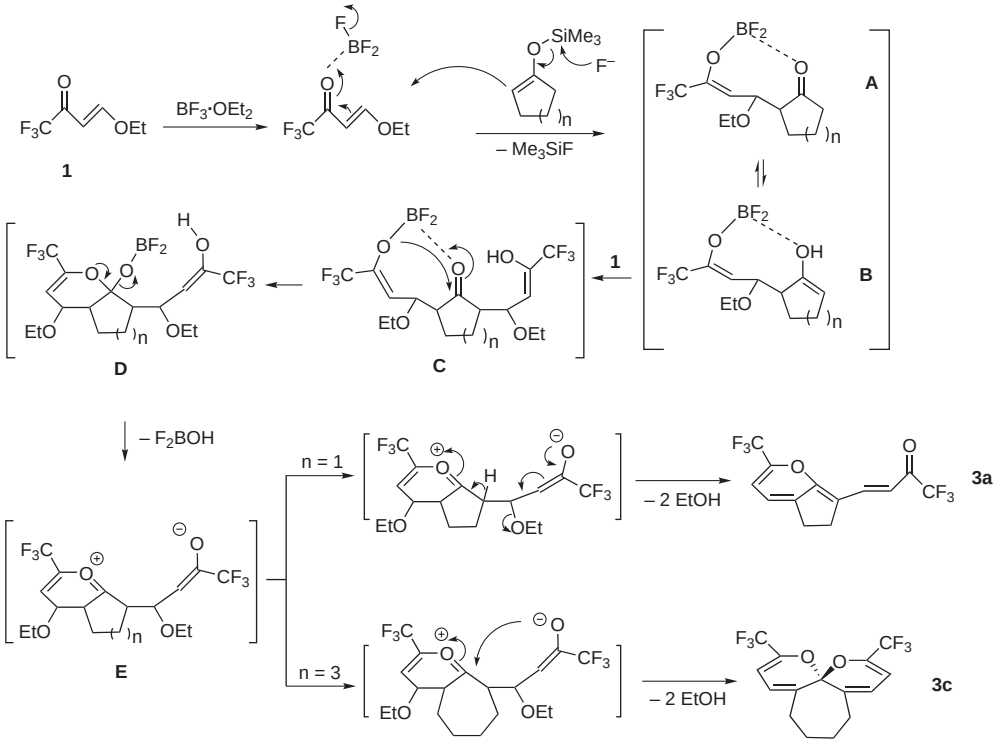
A similar spiro structure was also formed when the silyl enol ether **2e** derived from pentan-3-one reacted with **1** (Table 2, entry 5). However, when two equivalents of the six-membered ring silyl enol ether **2b** was added into the reaction mixture, there was no corresponding spiro product obtained. The ^{19}F NMR spectrum revealed two peaks at –71.92 and –77.37 ppm, of equivalent intensity. Thus, it was clear that there must be a trifluoroacetyl in its structure, and the other trifluoromethyl should connect to a cyclic structure. Based on these data, it was clear that it possessed a fused cyclic structure (Table 2, entry 2, **3b**). Similarly, five- or methylated six-membered ring silyl enol ether furnished only fused cyclic compounds (Table 2, entries 1 and 4). However, other silyl enol ethers derived from pinacolone or a-tetralone failed to form either the simple aldol reaction products or the polycyclic products under the same reaction conditions. To establish the generality of this process, we tried to employ non-fluorinated compound (*E*)-1,3-diethoxy-2-propen-1-one under the same conditions. To our disappointed, there was no useful product isolated and most of the material decomposed.

Table 2 Reaction of **1** with Silyl Enol Ethers[a,9]

Entry	Silyl enol ether	Products	Yield (%)[b]
1	 **2a**	 **3a**	92
2	 **2b**	 **3b**	68
3	 **2c**	 **3c**	71
4	 **2d**	 **3d**	64
5	 **2e**	 **3e**	67

[a] Reactions were carried out in CH_2Cl_2 (10 mL), with silyl enol ether (2 mmol), **1** (4 mmol), and $BF_3{\cdot}OEt_2$ (4 mmol) under a nitrogen atmosphere overnight, at 0 °C to r.t.
[b] Isolated yield based on the amount of silyl enol ethers employed.

Although the exact mechanism for the formation of new spiro or fused cyclic compounds is not known, we propose that **1** undergoes a $BF_3{\cdot}OEt_2$-catalyzed reaction with silyl enol ethers to form intermediate **A**, which is in equilibrium with intermediate **B**. Intermediate **B** is attacked by a second molecule of **1** to form **C**, which could undergo an intramolecular nucleophilic reaction to form **D**. The intermediate **D** could eliminate difluorohydroxyborane to form zwitterionic intermediate **E**. Subsequently, when n = 1, intramolecular electron transfer takes place and two molecules of ethanol are eliminated to form **3a** as the sole product. This elimination of ethanol would be promoted by the formation of a conjugated system and the strong electron-withdrawing trifluoromethyl group.[8] However, when n = 3, an intramolecular nucleophilic reaction could occur again followed by elimination of ethanol to form spiro compound **3c**. It is interesting to note that when seven-membered and linear silyl enol ethers are employed, the spiropyran derivatives are formed due to their lower activation energy for cyclization. Based on the single crystal X-ray diffraction analysis of **3c**, the dihedral angle of C5–C6–O1 and the plane of the C5′–C6–O1′ was 87°,



Scheme 2 Proposed mechanism for forming compound **3a** and **3c**.

almost a right angle. Seven-membered or linear silyl enol ether could easily form spiropyran structures without increasing the strain energy significantly. On the other hand, spiropyran structures formed from the five- and six-membered ring silyl enol ethers may have high strain energy, prohibiting their formation. Therefore, fused cyclic products **3a**, **3b**, and **3e** are favored.

In summary, two kinds of unexpected trifluoromethylated products are obtained in good yields through the reaction of (*E*)-4-ethoxy-1,1,1-trifluoro-3-buten-2-one with silyl enol ethers under very mild conditions. Seven-membered and linear silyl enol ethers give the spiropyran derivatives, while six-, and five-membered silyl enol ethers form fused cyclic compounds, which are difficult to synthesize by other methods. This unusual transformation may have great potential in synthesis, complementing the existing methods for the synthesis of the substitutional spiro or fused compounds. Further studies to develop new analogues are underway in our laboratories.

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(9) **General Procedure.** $BF_3{\cdot}OEt_2$ (1.6 mL, 6 mmol) was added dropwise to a mixture of **1** (1.01 g, 6 mmol) and silyl enol ether (3 mmol) in CH_2Cl_2 (5 mL) at 0 °C under a nitrogen atmosphere. After 12 h TLC analysis showed the reaction was complete. H_2O (10 mL) was added to the reaction

mixture to quench the reaction, and then the organic layer was extracted with CH_2Cl_2 and dried over Na_2SO_4. The residue was subjected to column chromatography on silica gel (hexane–EtOAc, 60:1) to provide pure products.

(*E*)-1,1,1-Trifluoro-4-(2-trifluoromethyl-5,6-dihydrocyclopenta[*b*]pyran-7-yl)but-3-en-2-one (3a): Yield: 92%; red solid; mp 88–89 °C. IR: 2976, 1687, 1587, 1515, 1252, 1078, 1018, 834 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.95 (1 H, d, $^3J_{HH}$ = 15.0 Hz, CH), 6.21 (1 H, d, $^3J_{HH}$ = 6.3 Hz, CH), 6.20 (1 H, d, $^3J_{HH}$ = 15.0 Hz, CH), 6.10 (1 H, d, $^3J_{HH}$ = 6.3 Hz, CH), 2.71 (2 H, m, CH_2), 2.69 (2 H, m, CH_2). ^{13}C NMR ($CDCl_3$): δ = 174.9 ($C_{3'}$, $^2J_{CF}$ = 34.7 Hz), 159.99 (C_{4a}), 146.02 (C_{7a}), 142.5 (C_2, $^2J_{CF}$ = 38.8 Hz), 139.31 (C_4), 118.8 ($C_{1''}$, $^1J_{CF}$ = 271.5Hz), 116.8 ($C_{4'}$, $^1J_{CF}$ = 292.5 Hz), 116.22 (C_7), 115.78 ($C_{2'}$), 112.88 (C_3), 107.50 ($C_{1'}$), 25.49 (C_6), 24.89 (C_5). ^{19}F NMR ($CDCl_3$, CHF_3 as internal standard): δ = –71.12, –77.18 (s, CF_3). LRMS: *m*/*z* (%) = 310 (M^+, 64.38), 291 (M^+ – F, 4.69), 263 (1.33), 241 (M^+ – CF_3, 100), 213 (M^+ – $COCF_3$, 17.80), 115 (30.22), 69 (CF_3, 8.09). Anal. Calcd for $C_{13}H_8F_6O_2$ (310.195): C, 50.33; H, 2.60. Found: C, 49.98; H, 2.68.

(*E*)-1,1,1-Trifluoro-4-(2-trifluoromethyl-6,7-dihydro-5*H*-1-benzopyran-8-yl)but-3-en-2-one (3b): Yield: 68%; red solid; mp 99–101 °C. IR: 2925, 1689, 1533, 1307, 1143 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 8.22 (1 H, d, $^3J_{HH}$ = 15.3 Hz, CH), 6.31 (1 H, d, $^3J_{HH}$ = 15.6 Hz, CH), 6.20 (2 H, s, CH), 2.54 (2 H, t, $^3J_{HH}$ = 5.7 Hz, CH), 2.45 (2 H, t, $^3J_{HH}$ = 6 Hz, CH_2), 1.81 (2 H, m, CH_2). ^{13}C NMR ($CDCl_3$): δ = 179.2 ($C_{3'}$, $^2J_{CF}$ = 33.6 Hz), 155.3 (C_{4a}), 143.9 (C_2, $^2J_{CF}$ = 38.5 Hz), 142.8 (C_{8a}), 134.7 (C_4), 122.1 (C_8), 116.9 ($C_{1''}$, $^1J_{CF}$ = 269.6 Hz), 116.9 ($C_{4'}$, $^1J_{CF}$ = 288.8 Hz), 112.5 ($C_{2'}$), 110.6 (C_3), 105.7 ($C_{1'}$), 29.7 (C_7), 24.4 (C_5), 19.7 (C_6). ^{19}F NMR ($CDCl_3$, CHF_3 as internal standard): δ = –71.92, –77.37. LRMS: *m*/*z* (%) = 324 (M^+, 29.59), 305 (M^+ – F, 2.33), 255 (M^+ – CF_3, 100), 199 (7.47), 69 (CF_3, 13.18). HRMS: *m*/*z* calcd for $C_{14}H_{10}F_6O_2$: 324.059; found: 324.062.

2,11-Ditriflouromethyl-5,6,7,8-tetrahydrocyclohepta[1,2-*b*;1,7-*b*]di(dihydropyran) (3c): Yield: 71%; colorless solid; mp 123–125 °C. IR: 2948, 1683, 1449, 1349, 1306, 1189, 1070 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 6.22 (2 H, d, $^3J_{HH}$ = 6.3 Hz, CH), 6.05 (2 H, d, $^3J_{HH}$ = 6.3 Hz, CH), 2.48 (2 H, m, CH_2), 2.34 (2 H, m, CH_2), 2.03 (2 H, m, CH_2), 1.48 (2 H, m, CH_2). ^{13}C NMR ($CDCl_3$): δ = 137.43 ($C_{2,11}$, $^2J_{CF}$ = 37.7 Hz), 134.28 ($C_{4a,8a}$), 119.54 (CF_3, $^1J_{CF}$ = 271.8 Hz), 120.28 ($C_{8,9}$), 103.46 (C_{13}), 102.69 ($C_{3,10}$), 33.423 ($C_{7,6}$), 31.81 ($C_{5,8}$). ^{19}F NMR ($CDCl_3$, CHF_3 as internal standard): δ = –72.00 (s, CF_3). LRMS: *m*/*z* (%) = 338 (M^+, 27.94), 319 (M^+ – F, 3.27), 291 (3.98), 269 (M^+ – CF_3, 100), 115 (11.52), 69 (CF_3, 5.64). Anal. Calcd for $C_{15}H_{12}F_6O_2$ (338.248): C, 53.26; H, 3.57. Found: C, 53.18; H, 3.57. X-ray data $C_{15}H_{12}F_6O_2$: FW = 338.25; temperature 293 K; monoclinic,C2/c; wavelength 0.71 Å; *a* = 14.504 (4) Å, *b* = 13.383 (4) Å, *c* = 9.806 (3) Å, *α* = 90°, *β* = 130.413 (34)°, *γ* = 90°; V = 1449.2 (8) $Å^3$; Z = 4, Dc = 1.550 mg/m^3; absorption coefficient 0.153 mm^{-1}; F(000) = 688; size 0.515 × 0.371 × 0.128 mm; 2.39<θ<27.00; reflections collected 4052; absorption correction empirical; transmission 1.00_{mix} – 0.602_{min}; goodness-of-fit on F^2 1.026; final R indices R_1 = 0.0518, wR_2 = 0.1294.

(*E*)-1,1,1-Trifluoro-4-(7-methyl-2 trifluoromethyl-6,7-dihydro-5*H*-1-benzopyran-8-yl)but-3-en-2-one (3d): Yield: 64%; colorless solid; mp 70–72 °C. IR: 3096, 1689, 1534, 1142 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 8.20 (1 H, d, $^3J_{HH}$ = 15.6 Hz, CH), 6.30 (1 H, d, $^3J_{HH}$ = 15.0 Hz, CH), 6.21 (2 H, m, CH), 2.55 (2 H, m, CH_2), 2.50 (1 H, m, CH_2), 2.05 (1 H, m, CH_2), 2.00 (1 H, m, CH_2), 1.08 (3 H, d, $^3J_{HH}$ = 6.3 Hz, CH_3). ^{13}C NMR ($CDCl_3$): δ = 179.7 ($C_{3'}$, $^2J_{C\text{-}F}$ = 30 Hz), 152.2 (C_{4a}), 143.7 (C_2, $^2J_{CF}$ = 38.5 Hz), 142.8 (C_{8a}), 134.5 (C_4), 122.1 (C_8), 116.7 ($C_{1''}$, $^1J_{CF}$ = 269.4 Hz), 116.5 ($C_{4'}$, $^1J_{CF}$ = 288.6 Hz), 112.6 ($C_{2'}$), 111.3 (C_3), 105.4 ($C_{1'}$), 37.5 (C_7), 32.6 (C_5), 26.1 (C_6), 20.7 (CH_3). ^{19}F NMR ($CDCl_3$, CHF_3 as internal standard): δ = –71.85, –77.39 (s, CF_3). LRMS: *m*/*z* (%) = 338 (M^+, 32.12), 319 (M^+ – F, 2.78), 269 (M^+ – CF_3, 100), 270 (16.35), 69 (CF_3, 11.55). Anal. Calcd for $C_{15}H_{12}F_6O_2$ (338.248): C, 53.26; H, 3.58. Found: C, 53.26; H, 3.84.

5,5′-Dimethyl-2,2′-trifluoromethyl-6,6′-spirobis-dihydropyra (3e): Yield: 67%; red solid; mp 109–110 °C. IR: 2998, 1688, 1347, 1306, 1187, 1061, 911, 838 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 6.18 (2 H, d, $^3J_{HH}$ = 5.1 Hz, CH), 5.96 (2 H, d, $^3J_{HH}$ = 6 Hz, CH), 1.92 (6 H, s, CH_3). ^{13}C NMR ($CDCl_3$): δ = 138.69 ($C_{2,10,}$ $^2J_{CF}$ = 36.5 Hz), 128.5 ($C_{5,7}$), 119.94 (CF_3, $^1J_{CF}$ = 269.6 Hz), 120.28 ($C_{4,8}$), 109.46 (C_6), 101.21 ($C_{3,9}$), 43.41 (CH_3). ^{19}F NMR ($CDCl_3$, CHF_3 as internal standard): δ = –72.19 (s, CF_3). LRMS: *m*/*z* (%) = 312 (M^+, 86.06), 297 (29.52), 265 (9.90), 245 (100), 215 (30.13), 146 (35.40), 69 (30.27). Anal. Calcd for $C_{13}H_{10}F_6O_2$ (312.210): C, 50.01; H, 3.28. Found: C, 49.71; H, 3.30.