Difluorocarbene Chemistry: Synthesis of *gem*-Difluorocyclopropenyl Ketones and *gem*-Difluorinated Dihydrofurans

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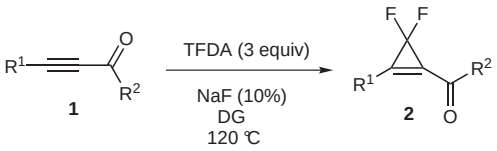
Abstract: The cycloaddition reactions of difluorocarbene, generated by the decomposition of $FSO_2CF_2CO_2SiMe_3$, with α,β-acetylenic ketones give *gem*-difluorocyclopropenyl ketones in good yields. Treatment of these *gem*-difluorocyclopropenyl ketones with aqueous potassium carbonate results in the formation of *gem*-difluorinated dihydrofurans.

Key words: difluorocarbene, *gem*-difluorocyclopropenes, *gem*-difluorocyclopropenyl ketones, *gem*-difluorinated dihydrofurans

The cycloaddition of difluorocarbene to carbon–carbon double or triple bonds is one of the most important methods for the synthesis of organofluorine compounds.[1] As the smallest cyclic organofluorine, *gem*-difluorocyclopropene derivatives command much attention on account of their theoretical interest and synthetic application.[2]

During the course of our studies on difluorocarbene chemistry, we conducted cyclopropanation reactions using our difluorocarbene precursor, i.e., trimethylsilyl fluorosulfonyldifluoroacetate (TFDA), with 1-iodoalkynes[3] and α,β-unsaturated aldehydes or ketones.[3] It was found that introduction of an iodine atom into the alkyne of the former leads to the formation of stable 3,3-difluoro-1-iodocyclopropene, whereas carbonyl groups in the latter should be protected as 1,3-dioxolanes, otherwise the reaction did not occur. Furthermore, deprotection of these fluorinated compounds with oxalic acid either gave the corresponding *gem*-difluorocyclopropyl ketones or 2-aryl-3-fluorofurans. In connection with the above, we were interested in the cycloaddition reaction of difluorocarbene with α,β-acetylenic ketones; herein, we present the results.

Unlike α,β-unsaturated aldehydes and ketones, α,β-acetylenic ketone **1a**, without protection, reacted smoothly with TFDA (3 equiv) in diglyme (DG) in the presence of 10 mol% anhydrous NaF at 120 °C for about three hours to give the corresponding adduct 3,3-*gem*-difluorocyclopropenyl ketone (**2a**), in 83% conversion and 89% yield (Scheme 1). The use of more TFDA (5 equiv) did not increase the conversion or yield significantly. Similarly, other α,β-acetylenic ketones[4] reacted under the same conditions[5] (Table 1).



Scheme 1 Cycloaddition of difluorocarbene to **1**

Table 1 Cycloaddition of Difluorocarbene to **1**[a]

Entry	Substrate **1**	Product **2**	Yield[b] (%)
1	**1a** (R^1 = Ph, R^2 = Ph)	**2a**	89
2	**1b** (R^1 = Ph, R^2 = 4-*t*-BuC_6H_4)	**2b**	85
3	**1c** (R^1 = Ph, R^2 = 4-MeC_6H_4)	**2c**	80
4	**1d** (R^1 = Ph, R^2 = 4-BrC_6H_4)	**2d**	71
5	**1e** (R^1 = Ph, R^2 = 4-$CF_3C_6H_4$)	**2e**	65
6	**1f** (R^1 = 4-MeOC_6H_4, R^2 = Ph)	**2f**	95
7	**1g** (R^1 = 4-MeC_6H_4, R^2 = Ph)	**2g**	90
8	**1h** (R^1 = 4-BrC_6H_4, R^2 = Ph)	**2h**	88
9	**1i** (R^1 = 3-$CF_3C_6H_4$, R^2 = Ph)	**2i**	55
10	**1j** (R^1 = *n*-C_5H_{11}, R^2 = Ph)	**2j**	50
11	**1k** (R^1 = Ph, R^2 = *n*-C_4H_9)	**2k**	88

[a] Reagents: **1**/NaF/TFDA, 1:0.1:3, 120 °C, 3 h.
[b] Isolated yield based on conversion of **1**.

As shown in Table 1 the yields of *gem*-difluorocyclopropenyl ketones **2** varied from modest to good. When R^1 or R^2 was a phenyl with electron-donating groups such as OMe or Me, the yields of **2** were higher than those substrates with electron-withdrawing groups such as Br, CF_3 (Table 1, entries 2, 3 vs 4, 5 and entries 6, 7 vs 8, 9). When R^1 was an alkyl group, the yield of **2** was lower than when R^1 was an aryl group (Table 1, entry 10 vs 11).

The structures of all *gem*-difluorocyclopropenyl ketones **2** were confirmed by ^1H and ^{19}F NMR spectroscopy, MS, and elemental analysis or HRMS. The structure of **2a** was further determined by single-crystal X-ray analysis (Figure 1), which suggests that the molecule is almost planar. Notably the length of C1–C2 is 1.33 Å, similar to that of a normal carbon–carbon double bond (1.34 Å).[6]

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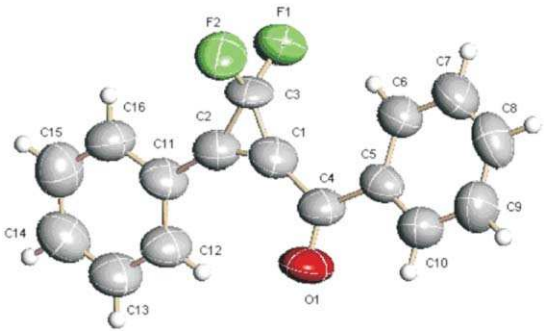


Figure 1 X-ray structure of **2a**

To compare *gem*-difluorocyclopropenyl ketones **2** with *gem*-difluorocyclopropenes,[3] we studied the ring-opening reactions of compounds **2**. Using **2a** as an example, it was found that acids such as HCl or $BF_3{\cdot}OEt_2$ as catalyst in various solvents always resulted in a complex reaction. To our surprise, when treating **2a** with aqueous 10% K_2CO_3 in MeOH, a new product was obtained in high yield and was characterized as 3,3-difluoro-2-methoxy-2,5-diphenyl-2,3-dihydro-furan **3a** (Figure 2).[8] The X-ray analysis of **3a** shows that the torsion angle of C(1)–C(2)–C(3)–C(4) and C(1)–O(1)–C(4)–C(3) are –6.3° and 5.64°, indicating that the fluorinated dihydrofuran ring is almost coplanar. To our knowledge, this is the first X-ray structure of difluorinated dihydrofuran.

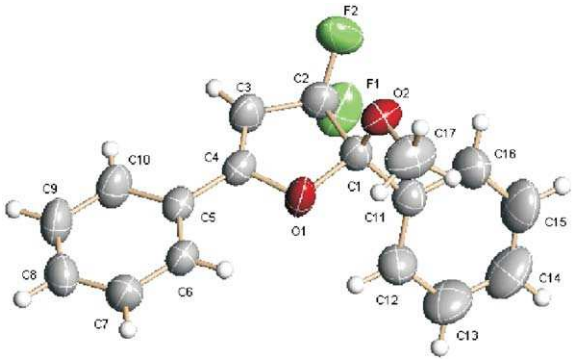
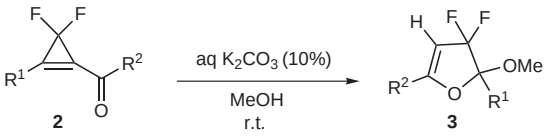


Figure 2 X-ray structure for **3a**

In a similar fashion, other *gem*-difluorocyclopropenyl ketones **2** were converted to *gem*-difluorinated dihydrofurans[7] (Scheme 2, Table 2).

The data in Table 2 demonstrate that when R^1 and R^2 were aryl groups having either electron-donating or electron-withdrawing groups, the reactions proceeded smoothly to furnish **3** in good yields (Table 2, entries 2–9), but alkyl substituents resulted in a slightly lower yield of **3**.



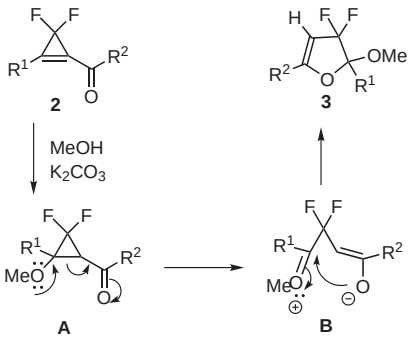
Scheme 2 Synthesis of *gem*-difluorinated dihydrofurans

Table 2 Synthesis of Difluorinated Dihydrofurans[a]

Entry	Substrate **2**	Product **3**	Yield[b] (%)
1	**2a** (R^1 = Ph, R^2 = Ph)	**3a**	75
2	**2b** (R^1 = Ph, R^2 = 4-*t*-BuC_6H_4)	**3b**	88
3	**2c** (R^1 = Ph, R^2 = 4-MeC_6H_4)	**3c**	80
4	**2d** (R^1 = Ph, R^2 = 4-BrC_6H_4)	**3d**	97
5	**2e** (R^1 = Ph, R^2 = 4-$CF_3C_6H_4$)	**3e**	89
6	**2f** (R^1 = 4-MeOC_6H_4, R^2 = Ph)	**3f**	88
7	**2g** (R^1 = 4-MeC_6H_4, R^2 = Ph)	**3g**	92
8	**2h** (R^1 = 4-BrC_6H_4, R^2 = Ph)	**3h**	90
9	**2i** (R^1 = 3-$CF_3C_6H_4$, R^2 = Ph)	**3i**	75
10	**2j** (R^1 = *n*-C_5H_{11}, R^2 = Ph)	**3j**	70
11	**2k** (R^1 = Ph, R^2 = *n*-C_4H_9)	**3k**	75

[a] Excess aq K_2CO_3 was used.
[b] Isolated yield after silica gel column chromatography.

The formation of **3** may be rationalized as follows: addition of methanol to cyclopropene gives **A**. The carbon bearing methoxy group in **A** is then subjected to intramolecular attack by the enolate ion generated by collapse of the cyclopropane **B** (Scheme 3).



Scheme 3 A possible mechanism for the formation of **3**.

In conclusion, we have accomplished the synthesis of *gem*-difluorocyclopropenyl ketones by the cycloaddition of difluorocarbene to α,β-acetylenic ketones. These ketones can be converted into *gem*-difluorinated dihydrofurans easily in high yields under basic conditions.

Acknowledgment

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References and Notes

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(5) ***gem*-Difluorocyclopropenyl Ketone 2a**: α,β-Acetylenic ketone **1a** (0.73 g, 3.55 mmol), NaF (19 mg, 10 mol%), and DG (2 mL) were added under a N_2 atmosphere to a Schlenk tube charged with a magnetic stirring bar and a pressure-equalized dropping funnel. After the mixture was heated to about 120 °C (oil bath), TFDA (2.71 g, 3 equiv) was added dropwise. The mixture was stirred at this temperature for about 3 h. Then the mixture was cooled to r.t. and purified by flash column chromatography on silica gel; yield: 0.67 g (89%) [recovered **1a**: 0.12 g (conversion 83%)]; solid; mp, 80–85 °C. IR (film): 1759, 1681, 1650, 1597,1577, 1494, 1450, 1313, 1299, 1226 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 8.15–8.18 (m, 2 H), 8.01–8.05 (m, 2 H), 7.52–7.72 (m, 6 H). ^{19}F NMR ($CDCl_3$, 282 MHz): δ = –103.74 (s, 2 F). MS: *m*/*z* (%) = 256 (M^+, 11.37), 228 (6.99), 151 (6.11), 105 (100), 77 (40.21). Anal. Calcd for $C_{16}H_{10}OF_2$: C, 75.00; H, 3.93; F, 14.83. Found: C, 75.06; H, 3.82; F, 14.86. X-ray crystallographic data for **2a**: crystal system, monoclinic; space group, P2 (1)/n; unit cell dimensions: *a* = 8.4778 Å, *b* = 9.0567 Å, *c* = 17.022 Å, *α* = 90°, *β* = 103.462°, *γ* = 90°, Z = 4, F(000) = 528, *R*1 = 0.0623, w*R*2 = 0.1635 (all data), CCDC No. 287907.

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(7) **Difluorinated Dihydrofuran 3c**: To a solution of **2c** (50 mg, 0.18 mmol) in MeOH (5 mL) was added 10% aq K_2CO_3 (0.1 mL). The mixture was stirred at r.t. and the progress of the reaction was monitored by ^{19}F NMR spectroscopy. When the reaction had reached completion, H_2O (10 mL) was added and the reaction was extracted with EtOAc (3 × 10 mL). The combined organic layer was dried over $MgSO_4$. After the solvent was removed under reduced pressure, the residue was purified by flash column chromatography on silica gel; yield: 45 mg (80%); white solid. IR (film): 3117, 2935, 1650, 1616, 1579, 1515, 1494, 1452, 1343, 1285, 1271, 1149, 1071, 1047, 968, 731 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.40 (s, 3 H), 3.39 (s, 3 H), 5.69 (s, 1 H), 7.23–7.50 (m, 7 H), 7.75–7.80 (m, 2 H). ^{19}F NMR ($CDCl_3$, 282 MHz): δ = –82.27 (d, *J* = 247 Hz, 1 F), –111.31 (d, *J* = 248 Hz, 1 F). MS: *m*/*z* (%) = 302 (M^+, 10.13), 283 (12.21), 282 (10.24), 271 (24.50), 243 (14.40), 177 (9.80), 152 (100), 151 (65.65), 119 (59.20), 105 (93.95), 84 (99.36). Anal. Calcd for $C_{18}H_{16}O_2F_2$: C, 71.51; H, 5.33. Found: C, 71.52; H, 5.64.

(8) X-ray crystallographic data for **3a**: $C_{17}H_{14}F_2O_2$, *M* 288.28; monoclinic; space group, P2 (1)/n; unit cell dimensions: *a* = 13.6673 Å, *b* = 7.1944 Å, *c* = 14.8156 Å, *α* = 90°, *β* = 92.034°, *γ* = 90°, Z = 4, D_{calcd} = 1.315 g/cm^3, F(000) = 600, *R*1 = 0.0812, w*R*2 = 0.1246, CCDC No. 287908.