JOC Note

Ring-Opening Reactions of Difluoro(methylene)cyclopropanes with Halogens and Amines

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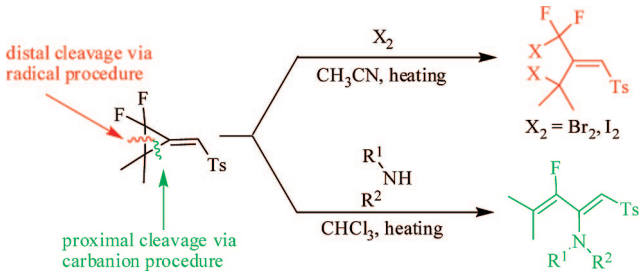
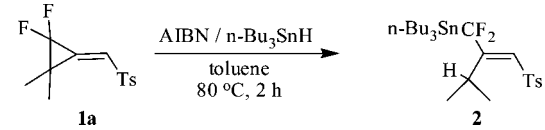


The distal and proximal bond of difluoro(methylene)cyclopropanes (F_2MCPs) could be cleaved, respectively, under different conditions to give the corresponding ring-opening products. The reaction mechanisms are discussed.

Methylenecyclopropane derivatives (MCPs), which are relatively stable but highly strained molecules, have been proved to be useful building blocks in organic synthesis for their remarkable chemical reactivity over the past decades.[1] Among the various reactions of MCPs, the reactions related to the ring-opening process are most attractive to chemists,[2] as one of the fluorinated MCPs, difluoro(methylene)cyclopropanes (F_2MCPs), may possess many interesting properties derived from both steric and electronic effects of the fluorinated cyclopropanes.[3b] However, ring-opening reactions of F_2MCPs are seldom disclosed due to the difficulty in their synthesis.[3] Recently, we found that F_2MCPs could be readily prepared from the direct difluorocyclopropanation of allenes.[4a] It was shown that the difluorocyclopropane rings in F_2MCPs are quite stable under many reaction conditions, such as Pd-catalyzed Heck reaction, *t*-BuLi-induced hydrogen abstraction, and retro-Diels−Alder reaction.[4] However, we found that the cycloadducts of F_2MCPs and nitrones could rearrange to give the ring-opened 3,3-difluorinated tetrahydropyridinols at elevated temperature.[5] As an extension of our interest in the stability of the difluorocyclopropane rings in F_2MCPs, we investigated their ring-opening reactions under different conditions.

SCHEME 1. Reaction of 1a with Tin Radicals



Under thermal reaction conditions, nonfluorinated MCPs could generate diradical intermediates by homolytic cleavage of the cyclopropane rings.[2c,6] In the case of 1,1-difluoro-2-methylenecyclopropane, the simplest homologue of F_2MCPs, the similar ring-opening rearrangement was experimentally investigated by Dolbier and computationally studied by Borden.[7] They found that the presence of two fluorine atoms in the cyclopropane ring improved the ring strain.[7a,c] Therefore, we postulated that the difluorocyclopropane ring might be cleaved under radical conditions. Herein, we present the results.

Treatment of F_2MCPs **1a** with *n*-Bu_3SnH in the presence of 2,2′-azobisisobutyronitrile (AIBN) in toluene gave the ring-opening product **2** in 42% yield (Scheme 1). The distal bond of F_2MCPs **1a** was cleaved under this radical condition. In view of the easy generation of halogen radicals under thermal conditions, we reinvestigated the CuI-catalyzed ring-opening reactions of F_2MCPs **1a** with I_2.[4a] Unexpectedly, this reaction can proceed smoothly even without the presence of CuI (Table 1, entries 2, 4, 6). Bromine was found to react equally well to give the ring-opening products at lower temperature (entries 1, 3, 5), whereas in the case of ICl, the ring-opening product could not be obtained and **1a** was fully recovered (entry 7).

To gain more insight into the reaction mechanism of F_2MCPs **1** with halogen, inhibition experiment was carried out. Addition of the free radical inhibitor hydroquinone (20 mol %) to the reaction mixture of **1a** and Br_2 decreased the yield of **3a** from 50% (entry 1) to 13% (entry 8). On the basis of these experiments it appears that bromine radical was involved in the reaction, suggesting a reaction mechanism as shown in Scheme 2. Homolytic cleavage of Br_2 resulted in the formation of

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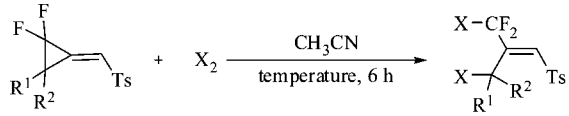
TABLE 1. Ring-Opening Reaction of 1 with Halogens

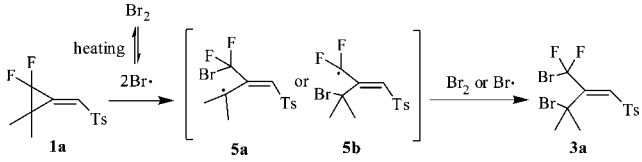


1a-c **3** X = Br, **4** X = I

entry	F_2MCPs	R^1/R^2	X_2 (equiv)	T (°C)[a]	product (%)[b]
1	**1a**	CH_3/CH_3	Br_2 (2)	50	**3a** (50)
2	**1a**	CH_3/CH_3	I_2 (3)	80	**4a** (61)
3	**1b**	CH_3/C_2H_5	Br_2 (4)	50	**3b** (63)
4	**1b**	CH_3/C_2H_5	I_2 (3)	80	**4b** (85)
5	**1c**	$-(CH_2)_5-$	Br_2 (4)	50	**3c** (49)
6	**1c**	$-(CH_2)_5-$	I_2 (3)	80	**4c** (80)
7	**1a**	CH_3/CH_3	ICl (4)	80	*c*
8	**1a**	CH_3/CH_3	Br_2 (2)	50	**3a** (13)[d]

[a] Reaction temperature. [b] Isolated yield. [c] **1a** was fully recovered. [d] 20% hydroquinone was added, and the yield was determined by ^{19}F NMR.

SCHEME 2. Proposed Mechanism of 1a with Br_2



bromine radical. Its attack on **1a** led to the opening of the difluorocyclopropane ring. Subsequent reaction with bromine or bromine radical afforded the final product **3a**.

The distal bond of F_2MCPs **1a** was cleaved under radical conditions, while the proximal bond remains intact. In an attempt to increase the diversity of the ring opening of F_2MCPs **1a**, we investigated their proximal bond-cleavage reactions. Kobayashi found that the bond opposite to the difluorinated carbon can be cleaved through an α-carbanion intermediate,[8] which suggested that the difluorocyclopropane ring of F_2MCPs **1a** might be similarly opened. In order to obtain an α-carbanion intermediate, we investigated the nucleophilic addition of **1a** with several nucleophiles.

Ethanol was first used as the nucleophile. Among various conditions investigated, only the addition product **6a** was formed (Table 2, entries 1−4). Similar results were obtained when phenolate, thiophenolate, or malonate anion were employed as the nucleophiles (entries 5−7). However, the difluorocyclopropane ring in F_2MCPs **1a** was opened in its reaction with benzylamine, giving a monofluorinated butadiene derivative **7a** as the sole product (entry 8). The structure of **7a** was assigned by ^{1}H and ^{19}F NMR spectroscopy, mass spectrometry, and elementary analysis and further comfirmed by X-ray crystallography (see Supporting Information).

Although various solvents such as methanol, benzene, tetrahydrofuran could be used for the reaction, $CHCl_3$ was found to be the most suitable solvent. A series of amines were applicable to the reaction in $CHCl_3$ (Table 3). Primary amines gave better yields than secondary amines and ammonia. No desired products were obtained in the case of *t*-butylamine and aniline, which might be a result of the steric hindrance of amines (entries 6 and 7).

The reaction of benzylamine with **1a** was chosen to probe the reaction mechanism. ^{19}F NMR measurement of the reaction

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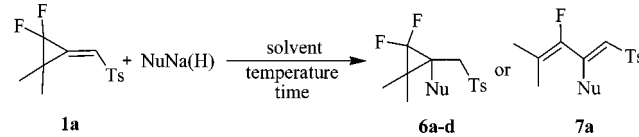
TABLE 2. Reaction of F_2MCPs 1a with Nucleophiles

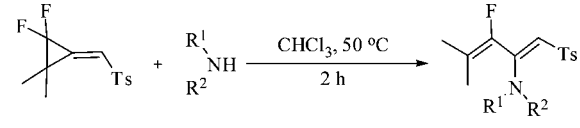


1a **6a-d** **7a**

entry	NuNa(H) (equiv)	solvent	T (°C)[a]	t (h)[b]	product (%)[c]
1	EtONa (0.5)	EtOH	rt[g]	1	**6a** (79)
2	EtONa (2)	EtOH	rt[g]	5	**6a** (54)
3	EtONa (2)	EtOH	80	2	*d*
4	EtONa (1.2)	THF[h]	50	2	**6a**[e]
5	PhONa (1.2)	THF	50	4	**6b** (52)
6	PhSNa (1.1)	THF	50	2	**6c** (59)
7	$C_7H_{11}O_4Na$[f] (1.2)	THF[h]	50	1	**6d** (85)
8	$BnNH_2$ (1.2)	$CHCl_3$	50	1.5	**7a** (59)

[a] Temperature. [b] Time. [c] Isolated yield. [d] Reaction was complicated, and no main product was isolated. [e] Only a trace of **6a** was detected by ^{19}F NMR. [f] Sodium salts of diethyl malonate. [g] Room temperature. [h] Anhydrous THF that was distilled from sodium wires.

TABLE 3. Reaction of F_2MCPs 1a with Amines[a]

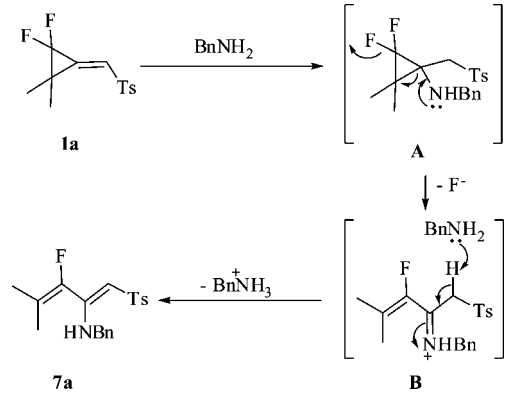


1a **7a-e**

entry	R^1	R^2	product	yield (%)[b]
1	H	$PhCH_2$	**7a**	80
2	H	C_5H_5O[c]	**7b**	83
3	CH_3	CH_3	**7c**	56
4	$CH_2CH_2CH_2CH_2$		**7d**	56
5	H	H	**7e**	52
6	H	$(CH_3)_3CH$	*d*	*d*
7	H	Ph	*d*	*d*

[a] 2.5 equiv of amines was used. [b] Isolated yield. [c] Furfuryl. [d] No reaction and **1a** was recovered.

SCHEME 3. Proposed Mechanism of 1a with Benzylamine



course showed an AB peak appearing at −147.1 and −150.0 ppm while being performed at −10 °C. Further ^{1}H NMR and mass spectral mesurements revealed the formation of simple addition product similar to **6**, which could be transformed to **7a** at elevated temperature in the presence of excess amount of benzylamine (see Supporting Information). Thus, the simple nucleophilic adduct **A** was considered to be the intermediate of the reaction (Scheme 3). Similar to α-carbanion promoted ring-opening reaction of the difluorocyclopropane,[8] the nitrogen lone pair in **A** would initiate the proximal bond cleavage with simultaneous removal of fluoride ion. Subsequent rearrangement

of **B** in the presence of benzylamine resulted in the formation of **7a**, whereas for those adducts with ethanol, phenol, etc. (Table 2, entries 1−7), the lone electron pair on oxygen or sulfur in **6a**−**d** could not cause the opening of the difluorocyclopropane ring. Therefore, no further rearrangement occurred. However, the cyclopropane ring in F_2MCPs **1a** was relatively easier to open as compared with the nonfluorinated MCPs. It is often necessary to use specific catalysts in the ring-opening reactions of MCPs with nucleophiles.[9]

In summary, the distal bond of difluoro(methylene)cyclopropanes can be cleaved under radical reaction conditions, while its proximal bond can be opened with the addition of amines. As a result of the ready availability of F_2MCPs and the ease of operation of these ring-opening reactions, a number of fluorine-containing compounds that were prepared with difficulty by the traditional method might be synthesized in this way, making them potential fluorine-containing building blocks. Efforts to determine the scope and limitations of these reactions are currently underway in this laboratory.

Experimental Section

(*Z*)-1-(3-Bromo-2-(bromodifluoromethyl)-3-methylbut-1-enylsulfonyl)-4-methylbenzene (3a). A 5 mL sealed tube was charged with **1** (54 mg, 0.20 mmol), bromine (96 mg, 0.40 mmol), and acetonitrile (1.5 mL). The sample was stirred at 50 °C for 6 h. After cooling to room temperature, the solvent was removed under reduced pressure. The residue was directly purified by chromatography on a silica gel column (petroleum ether/ethyl acetate = 10:1) to yield **3a** as a viscous oil, 43 mg, 50%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.84 (s, 6H), 2.45 (s, 3H), 7.37 (d, J = 8.6 Hz, 2H), 7.56 (s, 1H), 7.88 (d, J = 8.6 Hz, 2H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −99.1 (s, 2F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.7, 29.3, 61.1 (t, J_{FC} = 28.5 Hz), 117.8 (t, J_{FC} = 254.9 Hz), 127.3 (m), 128.3, 130.0, 136.5, 140.2(t, J_{FC} = 5.9 Hz), 145.7. IR (film): 3036, 1597, 1466, 1394, 1333, 1213, 1152, 1110, 1086, 1063, 923, 879, 815, 558 cm^{-1}. MS (ESI): m/z 449.9 [M + NH_4^+]. HRMS (ESI) calcd for $C_{13}H_{14}Br_2F_2O_2S$ + Na^+ 452.8942, found 452.8940.

(*Z*)-*N*-Benzyl-3-fluoro-4-methyl-1-tosylpenta-1,3-dien-2-amine (7a). A 5 mL sealed tube was charged with **1a** (54 mg, 0.20 mmol), benzylamine (54 mg, 0.50 mmol), and chloroform (1 mL). The sample was stirred at 50 °C for 2 h. After cooling to room temperature, the solvent was removed under reduced pressure. The residue was directly purified by chromatography on a silica gel column (petroleum ether/ethyl acetate = 10:1) to yield **10a** as a white solid, 57 mg, 80%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.46 (d, J = 2.4 Hz, 3H), 1.66 (d, J = 2.4 Hz, 3H), 2.42 (s, 3H), 4.30 (d, J = 6.2 Hz, 2H), 4.88 (s, 1H), 7.11−7.44 (m, 7H), 7.71 (d, J = 8.4 Hz, 2H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −112.9 (s, 1F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.8 (d, J = 7.5 Hz), 18.2 (d, J = 3.0 Hz), 21.5, 48.4 (d, J = 3.6 Hz), 95.4 (d, J = 5.1 Hz), 118.0 (d, J = 15.4 Hz), 126.0, 127.1, 127.4, 128.6, 129.5, 138.6, 140.9, 143.2, 145.9 (d, J = 243.5 Hz), 148.5 (d, J = 25.5 Hz). IR (film): 3362, 3096, 2951, 2855, 1706, 1664, 1592, 1582, 1455, 1414, 1353, 1283, 1137, 1120, 1081, 1042, 834, 820, 665, 605, 540 cm^{-1}. MS (ESI): m/z 360.0 [M + H^+]. Anal. Calcd for $C_{20}H_{22}FNO_2S$: C 66.83, H 6.17, N, 3.90. Found: C 66.76, H 6.17, N, 3.68.

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Supporting Information Available: Experimental details, characterization data for new compounds, and crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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