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Practical synthesis of *gem*-difluorides from cyclohexanone: Synthesis of *gem*-bistrifluoroacetates and their reactions with fluoride nucleophiles

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ABSTRACT

Formation of ketone acylals bearing trihaloacetoxy groups and their nucleophilic geminal disubstitution by fluoride ions were investigated. Cyclohexanone reacted with trifluoroacetic anhydride without catalyst to give *gem*-bistrifluoroacetates via a concerted bimolecular reaction. Treatment with hydrogen fluoride under mild conditions efficiently yielded the corresponding *gem*-difluorides. In this reaction process, trifluoroacetic acid was recovered and converted to trifluoroacetic anhydride using P_2O_5. Since *gem*-difluorides were derived from ketones, HF and P_2O_5, this constitutes a practical synthesis of *gem*-difluorides.

1. Introduction

Aldehyde acylals are readily synthesized from aldehydes and acid anhydrides with the aid of various catalysts [1,2]. They are successfully used as protecting groups of aldehydes [3] and substrates for nucleophilic substitution [1,4]. On the other hand, only a limited number of ketones react with substituted acid anhydrides having electron withdrawing groups such as trichloroacetic anhydride [5] and trifluoroacetic anhydride to give ketone acylals [6]. Since it was found that some ketone acylals are subject to hydrolysis [2d] and elimination of carboxylic acids [7], their derivatives bearing two acyloxy groups on the same carbon atom can serve as reactive intermediates for nucleophilic geminal disubstitution to give *gem*-difluorides.

gem-Difluorides have been synthesized as potential pharmaceuticals [8] and functional organic materials [9] by various methods [10]. Direct fluorination of carbonyl compounds was reported using SF_4, diethylaminosulfur trifluoride (DAST) [11], carbonyl fluoride [12], fluoroalkylamino reagent (FAR) [13], and 2,2-difluoro-1,3-dimethylimidazolidine (DFI) [14]. Indirect fluorination of carbonyl compounds with IF or BrF_3 [15] and oxidative desulfurization-fluorination of *ortho*-thioesters, dithiolanes, and thiocarbonyl derivatives with electrophilic halonium species were also developed [16]. Since the employed fluorinating agents and oxidizing agents were not re-used easily, these methods were not applicable in industrial processes. Furthermore, sophisticated reactions were required in which hydrogen fluoride and metal fluorides worked as nucleophilic fluorinating agents. We have previously reported the synthesis of *gem*-bistrifluoroacetoxy derivatives from ketones and trifluoroacetic anhydride. The obtained ketone acylals efficiently reacted with fluoride anion to give *gem*-difluorides [6]. Herein, we report the chemical reactivity and reaction mechanism of ketone acylals, the formation of *gem*-bistrifluoroacetates, and their subsequent reaction with several fluorides to give *gem*-difluorides. Cyclohexanone was demonstrated to react with trifluoroacetic anhydride to give *gem*-bistrifluoroacetates via a concerted bimolecular reaction even in the absence of catalyst. Further treatment with hydrogen fluoride or pyridinium poly(hydrogen fluoride) yielded *gem*-difluorides under mild conditions with the aid of catalyst. We successfully recovered the trifluoroacetic acid from the reaction mixture and converted it to trifluoroacetic anhydride using P_2O_5. Therefore, the present method provides a practical synthesis of *gem*-difluorides.

2. Results and discussion

2.1. Formation of ketone acylals

We first compared the reactivity of acid anhydrides **2a**–**2c** in the formation of ketone acylals **3a**–**3c**. In order to characterize the

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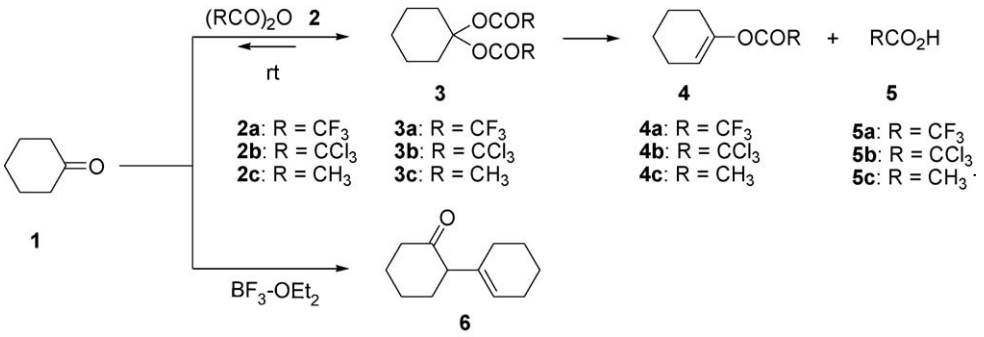
Table 1
Reaction of cyclohexanone **1** with acid anhydrides **2**.



Entry	$(RCO)_2O$ (equiv.)	BF_3-OEt_2 (mol%)	Time (h)	Yield[a]			Initial rate[b] (% h^{-1})	K[c] (L mol^{-1})
				3 (%)	**4** (%)	**6** (%)		
1	**2a** (1)	0.8	4	36	1	3	9.0	
			72	73	4	6		9.8
2	**2a** (1)	0	5	44	2	0	8.8	
			43	76	4	0		8.4
3	**2a** (3)	0	4	32	0.5	0	8.0	
			72	92	2	0		6.6
4	**2b** (3)	0	72	1	0	0		
5[d]	**2b** (3)	0	4	17	5	22		
6	**2c** (3)	0	72	0	0	0		
7	**2c** (3)	0.8	4	12	9	3		

[a] Determined by gas-liquid chromatography.
[b] Initial formation rate: yield (**3**, %)/time(h).
[c] K = [**3a**]/[**1**][**2a**].
[d] Carried out at 100 °C.

reaction profiles, three kinds of acid anhydrides having $-CF_3$, $-CCl_3$, and $-CH_3$ groups were compared. Cyclohexanone **1** was reacted with acid anhydrides **2** at room temperature. Reaction conditions and selected results are summarized in Table 1. When trifluoroacetic acid anhydride **2a** was employed (Entries 1–3), 1,1-bistrifluoroacetoxycyclohexane **3a** was formed as the major product.

When the reaction was carried out without catalyst at room temperature for 72 h, *gem*-diacyloxycyclohexane **3** was obtained in 92% yield with **2a** (Entry 3), 1% with **2b** (Entry 4) and 0% with **2c** (Entry 6). Since **2a** was the most reactive acid anhydride, the trifluoromethyl group with its smaller bulkiness and higher electron-withdrawing ability was suggested to be more effective than trichloromethyl and methyl groups. In addition to the main product **3**, a small amount of cyclohexenyl acylate **4** was detected as a by-product, which was derived from **3** by elimination of carboxylic acid **5**. Addition of BF_3-OEt_2 slightly influenced the initial rate of **3a** (9.0 [% h^{-1}] with BF_3-OEt_2 and 8.8 [% h^{-1}] without catalyst), indicating that it did not catalyze the main reaction but did catalyze the condensation of **1** to form by-product **6** [17]. Acylal **3b** was obtained in 17% yield at 100 °C as reported earlier [5], though considerable amounts of **4b** and **6** were formed (Entry 5). BF_3-OEt_2 seemed to work in the case of **2c** and promoted the formation of **4c** and **6** (Entry 7).

The product/reactant ratios (K = [**3a**]/[**1**][**2a**]) were calculated after equilibrium was reached (Entries 1–3 in Table 1). They ranged from 6.6 to 9.8 [L mol^{-1}] depending on the concentrations of **2a** and BF_3-OEt_2. The yield of acylal **3a** reached 92% with three equivalents of **2a**, while the formation of by-product **4a** decreased (Entry 3). These observations indicate that the equilibrium between **1** and **3a** was far to the right at room temperature.

The unreacted **2a** was first distilled from the reaction mixture of Entry 3 under reduced pressure (20 mmHg), and then acylal **3a** was distilled under reduced pressure (bp 84–86 °C/19 mmHg). When the distillation was conducted at higher pressure (bp 107–110 °C/70 mmHg), acylal **3a** decomposed gradually to starting materials **2a** and **1**. This indicates that the acylal formation reaction occurred reversibly. Since acylal **3a** was successfully isolated by distillation, a practical synthetic process was developed.

2.2. Mechanism for ketone acylal formation

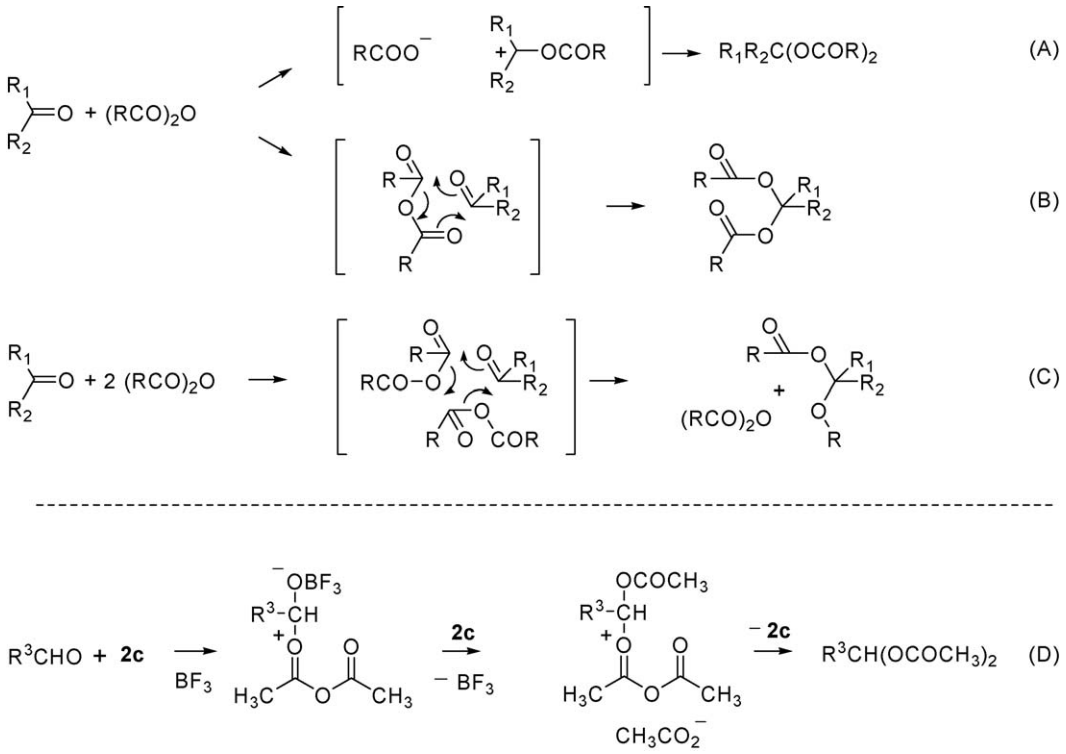
There are several mechanisms which can explain the non-catalytic reaction of ketone (or aldehyde) and trihaloacetic anhydride **2** (Scheme 1). Route A involves nucleophilic attack by the ketone carbonyl group on **2** to form a carbocation and a trihaloacetate anion [18]. Routes B and C involve dipolar concerted reactions via intermolecular rearrangement through 6-centered transition states [5,18]. Route B comprises a one-step addition of **2** to the carbonyl compound via bimolecular reaction, while Route C comprises a two-step addition of **2** to the carbonyl compound via trimolecular reaction [5]. Route D involves the participation of two anhydride molecules in the acid-catalyzed aldehyde acylal formation [19,1b].

We characterized kinetic profiles of the reaction between ketone **1** and acid anhydrides **2** to elucidate the mechanism (Fig. 1). The addition reaction occurred reversibly, but the reverse reaction could be disregarded during the initial reaction period (<10 h). If the reaction follows second-order kinetics in **1** and **2**, integral representations of the reaction rates are:

$$\frac{1}{[\mathbf{1}]} - \frac{1}{[\mathbf{1}]_0} = k_2 t \quad (\text{when } [\mathbf{1}]_0 = [\mathbf{2}]_0) \tag{1}$$

$$\ln\left(\frac{[\mathbf{2}]_0[\mathbf{1}]}{[\mathbf{1}]_0[\mathbf{2}]}\right) = k_2 t \quad (\text{when } [\mathbf{1}]_0 \neq [\mathbf{2}]_0) \tag{2}$$

where $[\mathbf{1}]_0$ and $[\mathbf{2}]_0$ are the initial concentrations of **1** and **2**.



Scheme 1. Possible mechanism of acylal formation.

If the reaction follows first-order kinetics in **1**, integral representation of the reaction rate is:

$$\ln[\mathbf{1}] - \ln[\mathbf{1}]_0 = k_1 t \quad (3)$$

Second-order plots (left) and first-order plots (right) of Entries 1 and 3 are shown in Fig. 1. To disregard the reverse reaction, the data were taken at <10 h. As plotted in Fig. 1 (left), the calculated $(1/[\mathbf{1}] - 1/[\mathbf{1}]_0)$ of Eq. (1) and the calculated $\{\ln([\mathbf{2a}]_0[\mathbf{1}]/[\mathbf{1}]_0[\mathbf{2a}])\}$ of Eq. (2) were found to have linear relationships with time. The second-order rate constants k_2 were calculated from the slopes of the linear plots to be 0.034 L mol^{-1} h^{-1} for Entry 1, and 0.035 L mol^{-1} h^{-1} for Entry 3. Since the two obtained k_2 values are almost identical, second-order kinetics are applicable to the present reaction system. For comparison, first-order rate constants k_1 for the different initial concentration conditions were calculated based on a linear relationship between $(\ln[\mathbf{1}] - \ln[\mathbf{1}]_0)$ and time as shown in Fig. 1 (right). Different k_1 values were obtained (Entry 1: 0.28 h^{-1}; Entry 3: 0.17 h^{-1}), indicating that first-order kinetics are inapplicable to the present reaction system. Thus, the addition reaction of **1** with **2a** was demonstrated to occur via a bimolecular reaction. BF_3-OEt_2 catalyst was reported to promote the formation of the aldehyde acylal [2a,4b,4d] and ketone acylal from **2c** [2b], but did not influence the reactions of **2a** and **2b** [5,17]. Our studies suggest that the formation of the acylal bearing trihaloacetoxy groups involves a dipolar concerted reaction via intermolecular rearrangement through a 6-centered bimolecular transition state as illustrated in Route B of Scheme 1.

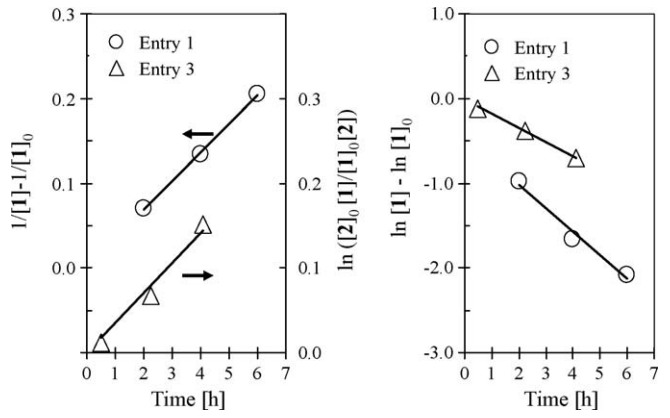


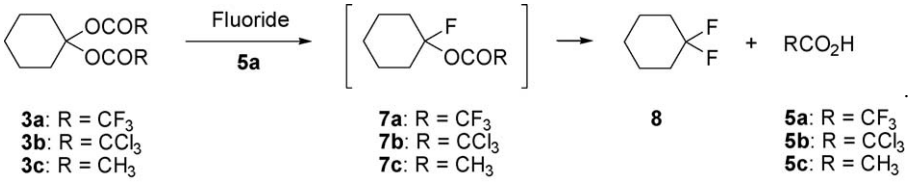
Fig. 1. Kinetic profiles of the reaction between ketone **1** and acid anhydride **2a**. Second-order plots of $1/[\mathbf{1}] - 1/[\mathbf{1}]_0$ vs time for Entry 1, and $\ln([\mathbf{2a}]_0[\mathbf{1}]/[\mathbf{1}]_0[\mathbf{2a}])$ vs time for Entry 3 (left); first-order plots of $\ln[\mathbf{1}] - \ln[\mathbf{1}]_0$ vs time for Entries 1 and 3 (right). Conditions: see Table 1.

2.3. Reaction of ketone acylals with fluoride ion

The nucleophilic fluorination of the isolated acylals **3** was carried out next (Table 2). When acylal **3a** was treated with HF-pyridine (HF-Py) without catalyst at −60 °C to room temperature for 2 h, a precipitate appeared and the reaction did not proceed (Entry 1). Addition of trifluoroacetic acid **5a** initiated the reaction, and 1,1-difluorocyclohexane **8** was obtained in 94% yield (Entry 2). The yield of **8** depended on the amount of HF-pyridine (Entries 2 and 3), though a possible intermediate 1-fluoro-1-trifluoroacetoxycyclohexane **7** was not observed in the reaction. Other ketone acylals **3b** and **3c** reacted with HF-pyridine in the presence of **5a** to give **8** in 26% yield from **3b** and 0.5% yield from **3c** (Entries 4 and 5), showing that **3a** was the most reactive acylal. Anhydrous hydrogen fluoride (AHF) also worked as a fluorinating agent (Entry 7) without **5a** (Entry 8). Metal fluorides were also examined as nucleophilic fluorinating agents, but KF and CsF did not promote the reaction (Entries 9 and 10).

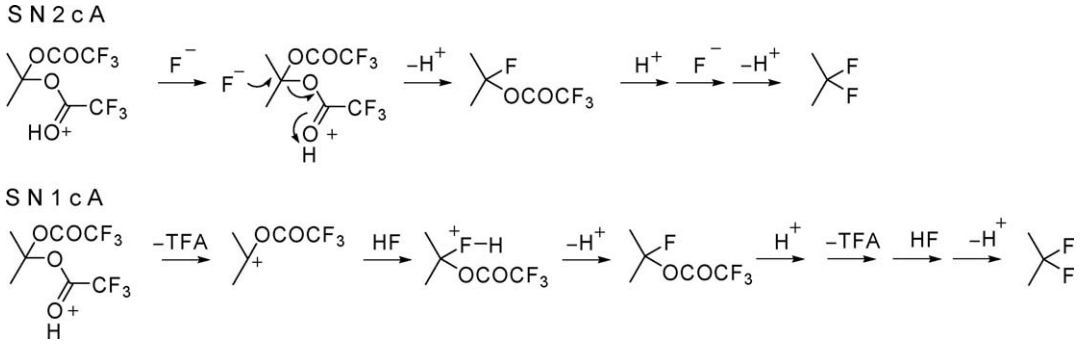
Since addition of an acid catalyst initiated the reaction, the reaction may begin with protonation of the carbonyl group of substrate **3** (Scheme 2). The trihaloacetoxy group itself did not work as a good leaving group, but came off when the protonation occurred via a SN2cA or SN1cA mechanism. This enhanced the reactivity of the ketone acylal enough for it to be attacked by a weak nucleophile such as a fluoride ion even at low temperature.

Table 2
Formation of *gem*-difluorides from *gem*-bistrifluoroacetates.



Entry	3[a]	Fluoride (equiv.)	5a (mol%)	Solvent (wt%)	Temperature	Time (h)	Isolated yield of 8 (%[b])
1	3a	HF-Py (39)	0	None	−60 °C to rt[d]	2	0
2	3a	HF-Py (39)	7	None	−60 °C to rt	2	94
3	3a	HF-Py (23)	7	None	−30 °C to rt	2	83
4	3b	HF-Py (39)	7	None	−30 °C to rt	5	26
5	3c	HF-Py (39)	7	None	−30 °C to rt	5	0.5
6	3a[c]	HF-Py (39)	5	None	−30 °C to rt	5	99
7	3a	AHF (23)	7	None	−30 °C to rt	12	88
8	3a	AHF (23)	0	None	−30 °C to rt	12	81
9	3a	KF (20)	200	Sulfolan (63)	80–90 °C	8	0
10	3a	CsF (10)	7	Sulfolan (58)	80–90 °C	10	0

[a] Distilled **3** (99.5% purity) was used.
[b] Yield is based on **3**.
[c] A mixture containing **3a** (93%) and **4a** (3%) was prepared from the reaction mixture of Entry 3 in Table 1.
[d] When the acylal was added to the HF-pyridine solution at −60 °C, a precipitate appeared.

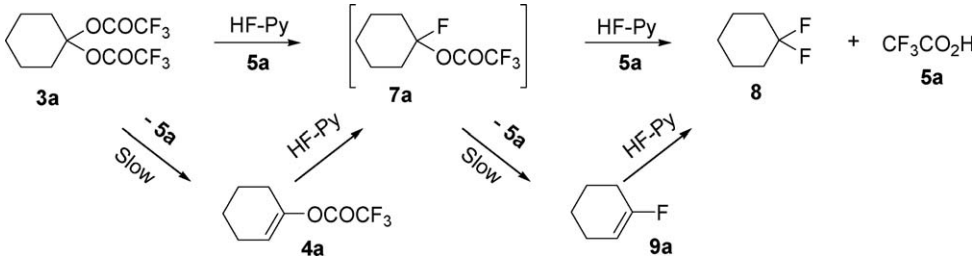


Scheme 2. Possible mechanism for *gem*-difluoride formation from acylal: nuclephilic substitution.

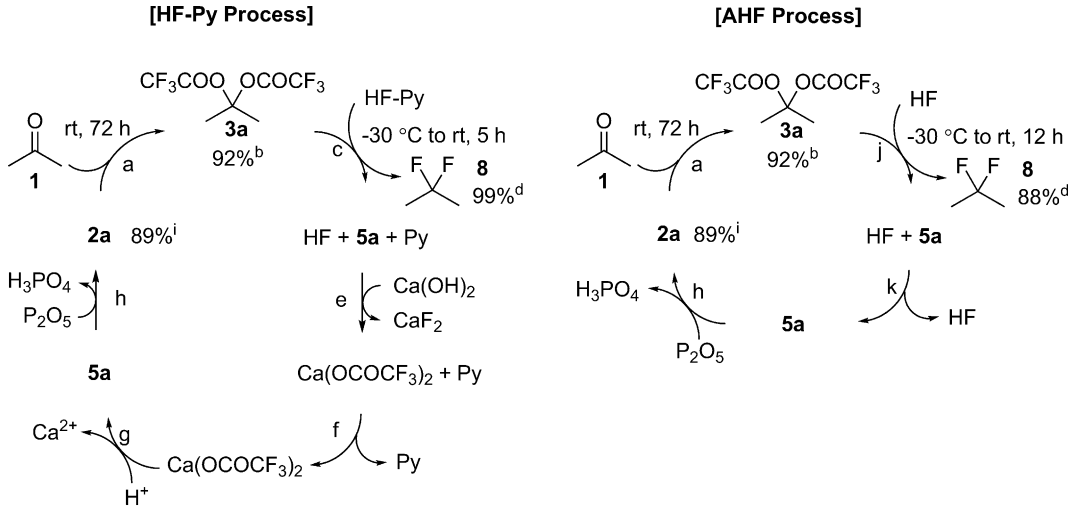
A mixture containing **3a** (93%) and **4a** (3%) was prepared from the reaction mixture of Entry 3 in Table 1. This gave **8** in 99% yield under the employed conditions (Entry 6 in Table 2). Since contaminant **4a** was not detected in the reaction mixture, **4a** was converted to possible intermediate **7a** en route to **8**. This means that **4a** is not a by-product but one of the intermediates for **8** via an elimination-addition mechanism. The isolated **9a** also reacted with HF to afford **8**, indicating that the addition of HF to **4a** and **9a** occurred. However, the conversion of **3a** to **4a** occurred very slowly with or without acid catalyst (Entries 1 and 2 in Table 1), suggesting that the elimination of **5a** from trifluoroacetates **3a** and **7a** occurred slowly (Scheme 3). Thus, fluorine disubstitution proceeded mainly via nucleophilic substitution as shown in Scheme 2.

*2.4. Recovery of trifluoroacetic acid anhydride **2a** for recycling synthesis of gem-difluorides*

Two recycle synthesis systems of *gem*-difluoride **8** were compared in Scheme 4. In the HF-Py process, trifluoroacetic acid **5a** was recovered via calcium trifluoroacetate in order to separate it from HF-Py. In the AHF process, **5a** was recovered by distillation. The recovered **5a** was dehydrated to **2a** using P_2O_5 in both processes. Both HF-Py and AHF fluorinated the ketone acylals, but AHF is a more favorable reagent from an industrial perspective because AHF does not yield by-product except H_3PO_4, and HF is easily recovered by distillation when AHF is used.



Scheme 3. Possible mechanism for *gem*-difluoride formation from acylal: elimination–addition.



[a] Entry 3 in Table 1. [b] Yield based on **1**. [c] Entry 6 in Table 2: A mixture (93% of **3a**, 3% of **4a**) was used. [d] Yield based on **3a**. [e] CaF_2 was filtered off. [f,k] Separated by distillation. [g] Passed by cation-exchange column. [h] Dehydration followed by distillation. [i] Yield based on treated **5a**. [j] Entry 7 in Table 2: Distilled **3a** (99.5%) was used.

Scheme 4. Recycling synthesis systems of *gem*-difluoride **4**.

3. Conclusions

We described the formation and nucleophilic geminal disubstitution of ketone acylals **3**. Acylals having trihaloacetoxy groups **3** easily reacted with HF to give *gem*-difluorides **4** in good yields under mild conditions without any active fluorinating agents and oxidizing agents. This two-step *gem*-difluorination procedure was applicable to a variety of ketones and aldehydes [6d]. Since the formed **5a** was recycled to **2a** using P_2O_5 as a dehydrating agent, the present method provides a practical synthesis of *gem*-difluorides from ketones, HF and P_2O_5.

4. Experimental

4.1. Synthetic procedure of ketone acylals **3** (Table 1)

To the magnetically stirred solution of carboxylic anhydride **2** (0.1–1.35 mol) and BF_3-etherate (0.8 mmol), cyclohexanone **1** (0.1–0.45 mol) was added slowly at room temperature under nitrogen atmosphere, and the mixture was stirred for up to 72 h. Only trichloroacetic anhydride **2b** was reacted at 100 °C for 4 h. All the reaction mixtures were analyzed using gas-liquid chromatography every 2–10 h. After the unreacted carboxylic anhydride was evaporated under reduced pressure, the crude product was distilled under reduced pressure to give **3**. Products **4a**, **4b**, **4c** and **6** were also separated by gas-liquid chromatography and characterized spectroscopically.

4.1.1. 1,1-Bis(trifluoroacetoxy)cyclohexane **3a** [6a]

Colorless liquid, bp 84–86 °C/19 mmHg, 107–110 °C/70 mmHg (slightly decomposed). MS (EI): *m/z* 308 (M^+, 1%), 195 (27), 194 (38), 81 (100), 80 (83). ^{1}H NMR ($CDCl_3$): δ 1.2–1.8 (m, 6H), 2.1–2.7 (m, 4H).

4.1.2. 1,1-Bis(trichloroacetoxy)cyclohexane **3b** [5]

Colorless liquid, bp 105–107 °C/0.04 mmHg (Ref. [5] 110–112 °C/0.05 mmHg). MS (EI): *m/z* 245 (M^+ –$OCOCCl_3$, 20%). ^{1}H NMR ($CDCl_3$): δ 1.2–1.8 (m, 6H), 2.0–2.8 (m, 4H).

4.1.3. 1,1-Diacetoxycyclohexane **3c** [2c,2d,7b]

Colorless liquid, bp 98–100 °C/5 mmHg. MS (EI): *m/z* 200 (M^+, 5%). ^{1}H NMR ($CDCl_3$): δ 1.35–1.5 (m, 6H), 1.7–1.8 (m, 4H), 2.1 (s, 6H).

4.1.4. 1-Trifluoroacetoxycyclohexene **4a** [20]

MS (EI): *m/z* 194 (M^+, 25%). ^{1}H NMR ($CDCl_3$): δ 1.6–2.0 (m, 4H), 2.0–2.4 (m, 4H), 5.5 (m, 1H).

4.1.5. 1-Trichloroacetoxycyclohexene **4b** [5]

Colorless liquid, bp 50–52 °C/0.09 mmHg (Ref. [5] 53–56 °C/0.11 mmHg). MS (EI): *m/z* 226 (M^+, 10%). ^{1}H NMR ($CDCl_3$): δ1.6–1.8 (m, 4H), 2.1–2.3 (m, 4H), 5.4–5.6 (m, 1H).

4.1.6. 1-Acetoxycyclohexene **4c** [21]

Colorless liquid, bp 84–85 °C/25 mmHg (Ref. [21b] 74–76 °C/17 mmHg). MS (EI): *m/z* 98 (M^+ –42, 100%). ^{1}H NMR ($CDCl_3$): δ 1.4–2.4 (m, 8H), 2.1 (s, 3H), 5.2–5.4 (m, 1H).

4.1.7. 2-(1-Cyclohexenyl)cyclohexanone **6** [17]

MS (EI): *m/z* 178 (M^+, 57%). ^{1}H NMR (CCl_4): δ 0.7–3.0 (m, 17H), 5.4–5.5 (m, 1H).

4.2. Synthetic procedure of 1,1-difluorocyclohexane **4** (Table 2, Entries 1–6)

4.2.1. 1,1-Difluorocyclohexane **8** [22]

70% HF-Pyridine[1] (60 g, 2.1 mol) and **5a** (1.9 mmol or 1.4 mmol) were mixed in a 1-L polyethylene bottle and cooled to −60 or −30 °C.[2] 1,1-Diacyloxycyclohexane **3** (27 mmol) was added slowly at −30 °C with stirring, and the mixture was further stirred for 2 h while warming to room temperature. The resulting mixture was

[1] Caution: HF-pyridine is corrosive and should be handled in a well ventilated hood with protection.

[2] When the acylal was added to the HF-pyridine solution at − 60 °C, a solid material precipitated. As they were both soluble at − 30 °C, addition of the residual acylal rarely gave precipitation, suggesting that the solid materials were the unsolubilized acylal.

extracted with diethyl ether (20 mL × 5). The extract was washed with water (20 mL × 2), saturated aq. $NaHCO_3$ (20 mL × 3), and water (20 mL × 2). The combined organic layers were dried over $MgSO_4$, and the solvent was evaporated. The residue was distilled under atmospheric pressure to give 1,1-difluorocyclohexane **8** [22]: colorless liquid, bp 99–101 °C/760 mmHg (Ref. [22b] 99–100 °C/760 mmHg). ^1H NMR ($CDCl_3$): δ 1.9–2.3 (m, 10H). MS (EI): m/z 120 (M^+, 9%), 100 (63), 80 (12), 57 (98), 41 (100). Fluoride anion and trifluoroacetate anion were detected by ion chromatographic analysis of the combined aqueous layer.

*4.2.2. Synthetic procedure of authentic sample **8***

1-Fluorocyclohexene **9** was synthesized according to literature procedures [23]. 1-Fluorocyclohexene **9** [22c,24]: MS (EI): m/z 100 (M^+, 47%). ^1H NMR (CCl_4): δ 1.7–2.0 (m, 4H), 2.1–2.4 (m, 4H), 5.1 (d, 1H). Authentic sample **8** was derived from **9** [25]. HF-Pyridine (71 g, HF 2.5 mol) was added in a polyethylene bottle and cooled to −30 °C. **9** (200 mmol) was added slowly at −30 °C with stirring, and the mixture was further stirred for 2 h while warming to room temperature. The resulting mixture was worked up as described above to give **8**: yield 15.1 g (63%). The obtained **8** showed identical ^1H NMR spectra to the reported one [22c,23].

*4.2.3. Conversion of **5a** to **2a***

2a was typically recovered from the aqueous extracts and washings of the reaction mixture in Entry 6 in Table 2. One half of the aqueous mixture (105 g) containing trifluoroacetate anion (28 mmol) was added to a 500-mL polyethylene bottle and cooled to 0 °C. $Ca(OH)_2$ (45 g, 0.61 mol) was added slowly at 0 °C with vigorous stirring, and the mixture was further stirred for 2 h while warming to room temperature. After the formed CaF_2 and excess of $Ca(OH)_2$ were filtered off, the filtrate was distilled at atmospheric pressure to recover pyridine and diethyl ether as azeotropic mixtures with water, and then passed through a polystyrenesulfonic acid type cation-exchange column (exchange capacity: 1.2 equiv./L, 100 mL) to convert calcium trifluoroacetate to its acid solution. The column was washed by water (100 mL), and the washing was added to the acid solution. The concentrated **5a** solution (**5a**: 64 wt%, 27 mmol) was obtained after adding distilled water. Phosphorus pentoxide (5.7 g, 40 mmol) was added with cooling to the concentrated **5a** solution, and the mixture was stirred at room temperature for 8 h [26]. Distillation under reduced pressure yielded a mixture of **2a** and **5a** (2.8 g, **2a**: 88 wt%, 12 mmol), which means that 89% of **2a** was recovered.

*4.2.4. Synthetic procedure of **8** (Table 2, Entry 7) and recovery of **2a***

The reaction was carried out in a Hastelloy C reactor equipped with a distillation column, a thermometer, a pressure gauge and a safety valve. **3a** (15.4 g, 0.05 mol) and **5a** (7 mol%, 3.5 mmol) were introduced in the reactor, followed by AHF (46 g, 2.3 mol) *in vacuo* after cooling down the reactor (−76 °C). The reaction mixture was fractionated under atmospheric pressure without further work-up, and separated into a first fraction boiling up to 30 °C (45 g, HF: 99 wt%, **5a**: 0.9 wt%), a second fraction boiling up to 101 °C (12 g, **5a**: 96 wt%, **8**: 4 wt%) and a final fraction with a boiling point in the range of 102 to 104 °C (5.3 g, **8**: 99.9%, yield: 88%). To the second fraction described above, phosphorus pentoxide (4.3 g, 30 mmol) was added with cooling, and the mixture was stirred at room temperature for 8 h. Distillation under reduced pressure yielded a mixture of **2a**, **8**, and **5a** (11 g, **2a**: 89 wt%, 47 mmol). This shows that 94% of **2a** was recovered.

*4.2.5. Synthesis of **4** (Table 2, Entries 9 and 10)*

Metal fluoride (KF: 20 equivalent; CsF: 10 equivalent) was used in place of HF-Pyridine in sulfolan solution. The reaction mixture was extracted with diethyl ether and analyzed by gas–liquid chromatography.

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