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Journal of Fluorine Chemistry 104 (2000) 277–280

JOURNAL OF FLUORINE CHEMISTRY

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Fluorocyclization of unsaturated alcohols and carboxylic acids by iodotoluene difluoride and amine-HF complexes

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Received 15 October 1999; received in revised form 11 January 2000; accepted 16 February 2000

Abstract

In the presence of amine-HF complexes, iodotoluene difluoride reacted with unsaturated alcohols and carboxylic acids to give cyclic fluoroethers and fluorolactones, respectively.

Keywords: Iodotoluene difluoride; Cyclic fluoroethers; Fluorolactones; Amine-HF complexes

1. Introduction

Fluorinated carbohydrates have been of great interest because of their significant biological activity and usefulness in proving biochemical mechanisms [1–14]. Fluorocyclization reaction of unsaturated alcohols and carboxylic acids by electrophilic fluorinating reagents seems to be effective for the synthesis of fluorinated carbohydrates. However, such methodology for transformation has not been developed because the electrophilic fluorinating reagents are generally too reactive to control the fluorination–cyclization sequences. Recently, we found that iodotoluene difluoride (**1**) reacts with alkenes to give *vic*-difluorides as the electrophilic fluorinating reagents [15], and in an extension of that work, we applied **1** to the fluorocyclization reaction of unsaturated alcohols and carboxylic acids (Scheme 1).

2. Results and discussion

At first, the fluorocyclization reaction of 1-nonen-4-ol (**2a**) was examined. The reaction of **2a** with **1** was carried out in CH_2Cl_2 using various kinds of HF-amine complexes which are necessary for the activation of **1** [15]. Recently, Et_3N-3HF has been used as a mild and less-corrosive fluorinating reagent [16,17]. However, Et_3N-3HF did not effectively activate **1** and the starting **2a** remained unchanged after 24 h at room temperature. On the other hand, when a strongly acidic complex such as Et_3N-7HF or pyridine-9HF was used, **2a** was consumed even at −45°C in 1 h, but a complex mixture was formed. Consequently, a slightly acidic reagent such as Et_3N-5HF and pyridine-6HF was found to be suitable for the reaction and especially, in the presence of pyridine-6HF, the reaction was completed at −45°C in 3 h to give the desired fluorinated tetrahydrofuran derivative **3a** in 60% yield as a mixture of two stereoisomers[2] (Entry 1 in Table 1).

Under the same reaction conditions, 1-cyclohexyl-3-buten-1-ol (**2b**) and 1-decen-5-ol (**4**) gave the fluorinated tetrahydrofuran derivative (**3b**) and tetrahydropyran derivative (**5**), respectively, in moderate yields (Entries 2, 4). From 1-allylcyclohexanol (**2c**), which has an acid-sensitive *tert*-alcohol function, the expected spiro compound (**3c**) was obtained in lower yield (Entry 3). Consequently, the unsaturated alcohols (**2a**-**4**) gave *endo*-cyclized products in 40–60% yields. The fluorocyclization of unsaturated carboxylic acids (**6**, **8**) was more sluggish and was carried out at room temperature. In the reaction of 3-butenoic acid, the *endo*-cyclization product, γ-fluoro-γ-butyrolactone (**7**), was obtained. During the isolation, **7** partially changed to an unsaturated lactone by the loss of HF which caused a decrease in the yield (Entry 5). From the 4-pentenoic acids (**8**), unexpected *exo*-cyclization products, γ-fluoromethyl-γ-butyrolactones (**9**), were obtained instead of the expected δ-valerolactone derivatives (Entries 6, 7).

These results can be explained as follows: lodotoluene difluoride **1** activated by amine-HF adds to the double bond

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[2] The separation of the stereoisomers was possible by column chromatograhy but the determination of their structures were difficult.

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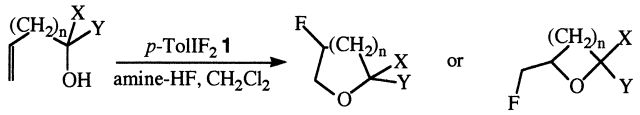
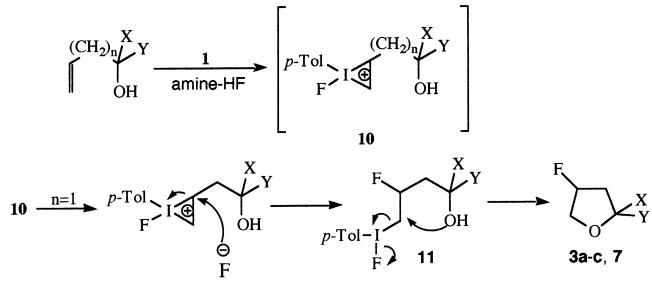
PII: S0022-1139(00)00241-4



Scheme 1.



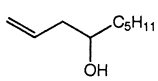
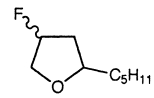
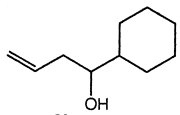
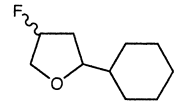
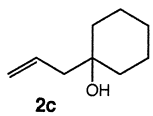
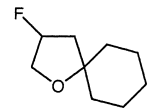
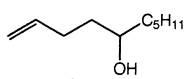
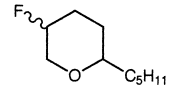
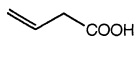
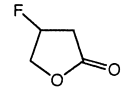
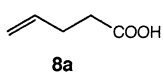
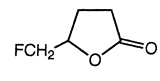
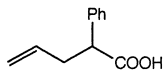
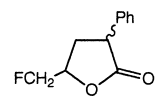
Scheme 2.

to give the intermediate (**10**). In the case of n=1, the attack of a fluoride on the C3 of **10** is faster than the formation of a four membered ring by the intramolecular attack of a hydroxy group. The resulting iodonium intermediate (**11**) cyclized to give the fluorinated tetrahydrofuran derivatives (**3a–c**) or γ-lactone (**7**) (Scheme 2).

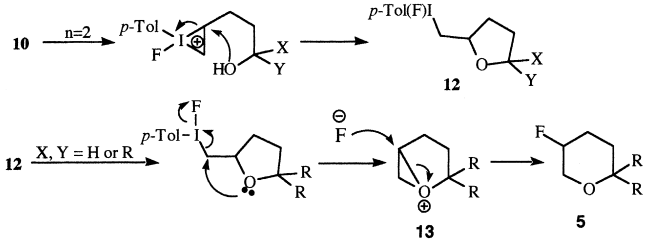
In the case of n=2, the formation of the five-membered intermediate (**12**) by the intramolecular attack of the hydroxy group on C4 of **10** is faster than the intermolecular fluoride attack. When the unsaturated alcohol (**4**) was used, the elimination of the *p*-Tol-I-F part was assisted by the lone pair electron on ethereal oxygen to give the bicyclic oxonium intermediate (**13**) [18], which was then converted to the fluorinated tetrahydropyran derivative (**5**) by the attack of a fluoride on C4. Therefore, from the unsaturated alcohols and 3-butenoic acid **6**, the formally *endo*-cyclized products were obtained (Scheme 3).

In the reaction of the 4-pentenoic acids, the oxygen attached to the carbonyl group is not so nucleophilic as to form an oxonium intermediate such as **13**, and the simple displacement of the *p*-Tol-I-F group of **12** by a fluoride took

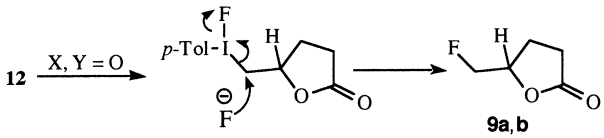
Table 1
Fluorocyclization of unsaturated alcohols and carboxylic acids[a]

Entry	Substrate	Reaction conditions	Product	Yield (%)[b]
1	 **2a**	−45°C, 3 h	 **3a**	60 (1:1)
2	 **2b**	−45°C, 2 h	 **3b**	55 (1:1)
3	 **2c**	−45°C, 3.5 h	 **3c**	40
4	 **4**	−45°C, 4 h	 **5**	50 (4:3)
5	 **6**	r.t., 3 h	 **7**	40
6	 **8a**	r.t., 3 h	 **9a**	40
7	 **8b**	r.t., 3 h	 **9b**	50 (2:1)

[a] The reaction was carried out as shown in an experimental part.
[b] Isolated yields based on substrates used. The ratio of stereoisomers is shown in parentheses.



Scheme 3.



Scheme 4.

place to provide the γ-fluoromethyl-γ-lactones (**9a**, **9b**) (Scheme 4).

3. Conclusion

The fluorocyclization reaction of unsaturated alcohols and carboxylic acids was carried out using iodotoluene difluoride **1** and pyridine-6HF. From the 1-alken-4-ols and 1-alken-5-ol, the formal *endo*-cyclization products, the 3-fluorotetrahydrofuran derivatives and 3-fluorotetrahydropyran derivative, were selectively obtained, respectively. On the other hand, the fluorinated γ-lactone derivatives were obtained from 3-butenoic acid and the 4-pentenoic acids.

4. Experimental details

IR spectra were recorded using a JASCO FT/IR-410. The ^{1}H NMR (400 MHz) and ^{19}F NMR (376 MHz) spectra were recorded in $CDCl_3$ on a JEOL JNM-A400II FT NMR. Chemical shifts, δ, are referred to TMS (^{1}H) and $CFCl_3$ (^{19}F), respectively. EI-low and high-resolution mass spectra were measured on a JEOL JMS-DX303. The pyridine-HF and Et_3N-HF complexes were prepared from freshly distilled pyridine or Et_3N and anhydrous HF [19]. The unsaturated alcohols **2a**, **2b** and **2c** were prepared by the reaction of allylmagnesium bromide with heptanal, cyclohexanecarboaldehyde, and cyclohexanone, respectively. Similarly, **4** was prepared from 3-butenylmagnesium bromide and hexanal. The unsaturated carboxylic acid **8b** was prepared by the reaction of the phenylacetic acid dianion with allyl bromide [20].

4.1. Preparation of iodotoluene difluoride *1*

Iodotoluene difluoride was prepared from iodotoluene dichloride [21] by a modification of the reported procedure [22]. Into a 300 ml three-necked round flask equipped with a dry ice condenser, a mechanical stirrer, and an inlet tube for the introduction of Cl_2, were placed iodotoluene (21.8 g, 100 mmol) and CH_2Cl_2 (75 ml). The Cl_2, generated from MnO_2 (30.5 g, 350 mmol) and conc. HCl (80 ml), was introduced to the reaction mixture under stirring. After the introduction of Cl_2, the mixture was stirred for 1 h at room temperature and then cooled to −78°C. The generated solid was separated by filtration, washed with a small amount of $CHCl_3$ and dried in air on filter paper to give iodotoluene dichloride (a yellow solid, 24.5 g) which was used for the next step.

Into a 500 ml vessel made of fluororesin, iodotoluene dichloride (24.5 g), HgO (23.8 g, 110 mmol) and CH_2Cl_2 (200 ml) were introduced and the mixture was vigorously stirred at room temperature. Then 46% hydrofluoric acid (60 ml) was added and the mixture was stirred vigorously again. After 10 min, a white solid ($HgCl_2$) was removed by filtration using an apparatus made of fluororesin, and the filtrate was extracted three times with CH_2Cl_2. The organic layer was dried over MgO and concentrated under reduced pressure to give a pale yellow solid of iodotoluene difluoride (21.3 g, 83 mmol). mp. 140–142°C. ^{1}H NMR δ: 2.47 (s, 3H), 7.56 (d, 2H, J=8.4 Hz), 7.84 (d, 2H, J=8.4 Hz) ppm. ^{19}F NMR δ: −147.30 (s, 2F) ppm.

4.2. Fluorocyclization reaction of unsaturated alcohols *2a–c, 4*

To a CH_2Cl_2 solution (5 ml) of an unsaturated alcohol (1 mmol) in a vessel made of fluororesin was added at −45°C, a pyridine-6HF solution (5 ml) of iodotoluene difluoride (332 mg, 1.3 mmol). The reaction was monitored by TLC and continued until the consumption of the starting material was confirmed. The mixture was then poured into water, and the product was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$. After concentration under reduced pressure, the product was isolated by column chromatography (silica gel/hexane-ether).

2-Pentyl-4-fluorotetrahydrofuran (**3a**, one isomer): IR: 1101, 1079, 962 cm^{-1}. ^{1}H NMR δ: 0.89 (t, 3H, J=6.8 Hz), 1.31–1.66 (m, 9H), 2.21–2.31 (m, 1H), 3.90–4.12 (m, 3H), 5.18–5.33 (m, 1H) ppm. ^{19}F NMR δ: −174.37 to −173.89 (m, 1F) ppm. HRMS (EI) calc. for $C_9H_{17}FO$ 160.1263 found 160.1253.

(**3a**, another isomer): IR: 1134, 1096, 962 cm^{-1}. ^{1}H NMR δ: 0.89 (t, 3H, J=6.8 Hz), 1.30–1.88 (m, 9H), 2.25–2.39 (m, 1H), 3.59–3.71 (m, 3H), 3.81–3.88 (m, 1H), 4.10–4.18 (m, 1H), 5.1–5.30 (m, 1H) ppm. ^{19}F NMR δ: −171.57 to −171.10 (m, 1F) ppm. HRMS (EI) calc. for $C_9H_{17}FO$ 160.1263 found 160.1276.

2-Cyclohexyl-4-fluorotetrahydrofuran (**3b**, one isomer): IR: 1450, 1080, 962 cm^{-1}. ^{1}H NMR δ: 0.95–1.76 (m, 11H), 1.92–1.96 (m, 1H), 2.15–2.25 (m, 1H), , 5.17–5.33 (m, 1H) ppm. ^{19}F NMR δ: −174.57 to −174.09 (m, 1F) ppm. HRMS (EI) calc. for $C_{10}H_{17}FO$ 172.1263 found 172.1269.

(**3a**, another isomer): IR: 1450, 1082, 963 cm^{-1}. ^1H NMR δ: 0.88–2.00 (m, 12H), 2.18–2.33 (m, 1H), 3.48–3.68 (m, 2H), 4.08–4.17 (m, 1H), 5.14–5.30 (m, 1H) ppm. ^{19}F NMR δ: −171,70 to −171.24 (m, 1F) ppm. HRMS (EI) calc. for $C_{10}H_{17}FO$ 172.1263 found 172.1248.

3-Fluoro-1-oxaspiro[4.5]decane (**3c**): IR: 1447, 1088, 965 cm^{-1}. ^1H NMR δ: 1.40–1.94 (m, 1H), 2.05–2.14 (m, 1H), 3.87–4.13 (m, 2H) 5.15–5.31 (m, 1H) ppm. ^{19}F NMR δ: −172.43 to −171.96 (m, 1F) ppm. HRMS (EI) calc. for $C_9H_{15}FO$ 158.1107 found 158.1110.

5-Fluoro-2-pentyltetrahydropyran (**5**, major isomer): IR: 1101, 1039 cm^{-1}. ^1H NMR: δ: 0.88 (t, J= 6.7 Hz, 3H), 1.21–1.82 (m, 11H), 2.18–2.24 (m, 1H), 3.19–3.30 (m, 1H), 4.42–4.62 (m, 1H) ppm. ^{19}F NMR: δ: −188.00 to −187.805 (m, 1F) ppm. HRMS calc. for $C_{10}H_{19}FO$ 174.1420 found 174.1418.

(**5**, minor stereoisomer): IR: 1118, 1061 cm^{-1}. ^1H NMR: δ: 0.89 (t, J=6.83 Hz, 3H), 1.24–1.80 (m, 11H), 2.09–2.18 (m, 1H), 3.26–3.30 (m, 1H), 3.47–3.60 (m, 1H), 4.07–4.15 (m, 1H), 4.51–4.64 (m, 1H) ppm. ^{19}F NMR: δ: −189.40 to −188.00 (m, 1F) ppm. HRMS calc. for $C_{10}H_{19}FO$ 174.1420 found 174.1423.

*4.3. Fluorocyclization reaction of unsaturated carboxylic acids **6**, **8a**, **b**.*

To a CH_2Cl_2 solution (5 ml) of unsaturated carboxylic acid (1 mmol) in a vessel made of fluororesin was added at room temperature, a pyridine-6HF solution (5 ml) of iodotoluene difluoride (332 mg, 1.3 mmol). The reaction mixture was stirred at room temperature for 3 h and then poured into water. The product was extracted with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$. After concentration, the product was isolated by column chromatography (silica gel/hexane-ether).

β-Fluoro-γ-butyrolactone (**7**): IR: 1786, 1165 cm^{-1}. ^1H NMR: δ: 2.75–2.86 (m, 2H), 4.40–2.52 (m, 1H), 4.53–4.62 (m, 1H), 5.36–5.43 (m, 1H); ^{19}F NMR: δ: −176.96 to −176.50 (1F, m) ppm. HRMS calc. for $C_9H_{17}FO$ 104.0274 found 104.0274.

γ-Fluoromethyl-γ-butyrolactone (**9a**): IR: 1778, 1187 cm^{-1}. ^1H NMR δ: 2.14–2.24 (m, 1H), 2.32–2.41 (m, 1H), 2.50–2.68 (m, 2H), 4.39–4.77 (m, 3H) ppm. ^{19}F NMR: δ: −233,09 to −232.77 (1F, m) ppm. HRMS calc. for $C_4H_5FO_2$ 118.0430 found 118.0426.

γ-Fluoromethyl-α-phenyl-γ-butyrolactone (**9b**, major isomer): IR: 1774, 1158 cm^{-1}. ^1H NMR: δ: 2.50–2.58 (m, 1H), 2.69–2.76 (m, 1H), 3.98–4.12 (m, 1H), 4.47–4.48 (m, 3H), 4.46–4.61 (m, 3H), 7.26–7.40 (m, 5H) ppm. ^{19}F NMR: δ: −233.90 to −233.50 (m, 1F) ppm. HRMS calc. for $C_{11}H_{11}FO_2$ 194.0743 found 194.0760.

(**9b**, minor stereoisomer): IR: 1764, 1498, 1458, 1172 cm^{-1}. ^1H NMR: δ: 2.31–2.40 (m, 1H), 2.69–2.76 (m, 1H), 3.91–3.97 (m, 1H), 4.44–4.60 (m, 1H), 4.65–4.81 (m, 2H), 7.26–7.40 (m, 5H) ppm. ^{19}F NMR: δ: −233.90 to −233.50 (m, 1F) ppm. HRMS calc for $C_{11}H_{11}FO_2$ 194.0743 found 194.0735.

Acknowledgements

This work was financially supported by a Grant-in-Aid for Scientific Research (B) from the Japanese Ministry of Education, Science, Sports and Culture.

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