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Hydrolysis of Difluorocyclopropenes: the Role of the Cyclopropenyl Cation and the Effects of Substituents

Abstract

Monosubstituted *gem*-difluorocyclopropenes undergo hydrolysis yielding cyclopropenones and acrylic acid derivatives. Herein, we investigate the reaction routes of hydrolysis for both aromatic and alkyl derivatives. The study supports the idea that the formation of a cyclopropenyl cation controls the reactivity of *gem*-difluorocyclopropenes, and aromatic substituents accelerate the hydrolysis *via* the resonance stabilization. Reaction conditions, including the solvent composition and temperature, significantly affect the conversion and the product selectivity. This information facilitates the preparative synthesis and improves understanding of the fluorinated cyclopropene reactivity.

Keywords: difluorocyclopropenes; cyclopropenyl cation; hydrolysis

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Гідроліз дифтороциклопропенів: роль циклопропенільного катіона та ефекти замісників

Анотація

Монозаміщені *гем*-дифтороциклопропени піддаються гідролізу з утворенням циклопропенонів і похідних акрилової кислоти. У цій роботі ми досліджуємо реакційні шляхи гідролізу як ароматичних, так і алкільних похідних. Дослідження підтверджує ідею про те, що реакційною здатністю *гем*-дифтороциклопропенів керує утворення циклопропенільного катіона, а ароматичні замісники прискорюють гідроліз через резонансну стабілізацію. Умови реакції, зокрема склад розчинника та температура, значно впливають на конверсію і вибірковість утворення продукту. Ці відомості полегшують препаративний синтез і покращують розуміння реакційної здатності фторованого циклопропену.

Ключові слова: дифтороциклопропени; циклопропеніл-катіон; гідроліз

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Introduction

Difluorocyclopropenes, particularly 3,3-difluorocyclopropenes, are compact, strained, three-membered cyclic compounds bearing two fluorine atoms on a single carbon atom of an unsaturated cyclopropene framework. Their unique electronic and steric properties render them valuable building blocks for organic synthesis in a broad range of transformations [1–3]. The recent studies have shown that many compounds of this class can be viewed as bench-stable reagents [4], which enhanced the overall interest to *gem*-difluorocyclopropenes and facilitated further research.

Upon exposure to water, difluorocyclopropenes undergo a rapid hydrolysis, leading predominantly to the formation of cyclopropenones and, under certain conditions, to acrylic acid derivatives [5]. The hydrolytic instability is particularly marked in aromatic monosubstituted derivatives where the presence of aromatic rings appears to accelerate the process. This enhanced reactivity is attributed to electronic effects that promote the formation of a cyclopropenyl cation intermediate [6], which is a highly stabilized, aromatic species characterized by the 2π electron system [7].

The mechanistic pathway is hypothesized to involve the nucleophilic attack of water at the cyclopropene ring, leading to the elimination of fluoride ions and the transient formation of the cyclopropenyl cation [8]. The subsequent reaction steps yield cyclopropenones [9] as the primary hydrolysis products, although further transformation to acrylic acid derivatives can occur, particularly under conditions that favor ring opening [5]. The precise nature of this pathway remains a subject of further research, with yet no direct experimental evidence that would clarify whether the cationic species is a discrete intermediate or part of a more complex reaction cascade.

Substituent effects play a critical role in modulating the hydrolysis rate of *gem*-difluorocyclopropenes. Aromatic substituents appear to facilitate the reaction by stabilizing the cyclopropenyl cation *via* the resonance delocalization, thereby lowering the activation energy for the hydrolysis. In contrast, alkyl substituents offer significantly less stabilization, resulting in slower reaction rates [4]. Understanding these substituent-dependent reactivity patterns is essential not only for elucidating the mechanistic details of the *gem*-difluorocyclopropenes hydrolysis process, but also for the potential optimization of preparative approaches to the synthesis of cyclopropenone and acrylic acid derivatives.

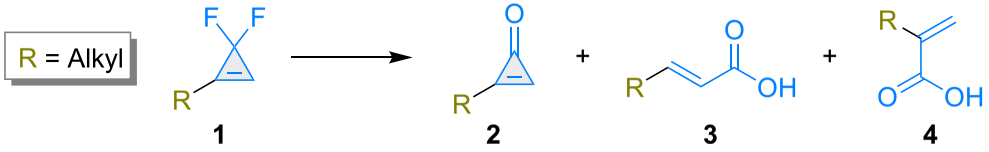
In this study, we systematically investigate the hydrolysis of monosubstituted *gem*-difluorocyclopropenes containing both aromatic and alkyl substituents. Our research focuses on identifying the scope and limitations of these hydrolytic reactions while assessing the potential of substrates for practically valuable preparative transformations.

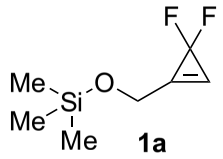
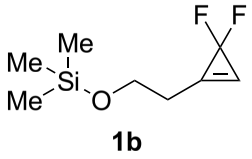
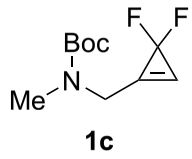
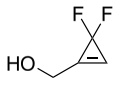
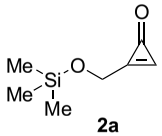
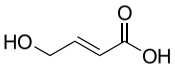
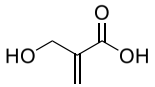
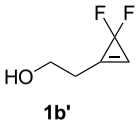
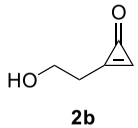
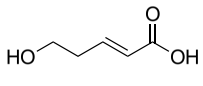
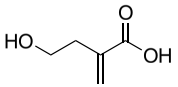
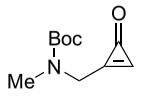
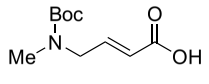
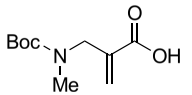
Results and discussion

The hydrolysis of 1-alkyl-3,3-difluorocyclopropenes was evaluated under several reaction conditions (**Table 1**). Under mild conditions (**Table 1**, *entry 1*: DCM/SiO_2 on air, 18 h), the substrates remained largely unchanged, affording primarily the starting materials (**1a, 1b, 1c, Table 1**). When the controlled amount of water was introduced (**Table 1**, *entry 2*: DCM/SiO_2/H_2O, 5 equiv., 18 h), a partial conversion occurred, yielding mixtures of products (e.g., **1a/1a′** and **1b/1b′**, **Table 1**), while substrate **1c** showed the minimal conversion. A similar outcome was observed with a DCM/MeOH (2:1) mixture on SiO_2 (**Table 1**, *entry 3*). In contrast, the application of the MeOH/H_2O (10:1) solvent system on SiO_2 for 18 h (**Table 1**, *entry 4*) led to a more complex distribution: intermediate products appeared alongside nascent hydrolysis products (e.g., **1a′**, **2a**, **3a** for substrate **a**; similar profiles were seen for substrates **b** and **c**, **Table 1**). Increasing the reaction time to 72 h in the same solvent system (**Table 1**, *entry 5*), or carrying out the reaction at a higher water ratio (MeOH/H_2O, 5:1) at 60 °C for 18 h (**Table 1**, *entry 6*) led to the fact that the conversion was almost completed, resulting in mainly the final products of hydrolysis (**3a/4a**, **3b/4b**, **3c/4c**, **Table 1**). Notably, basic conditions (using MeOH/K_2CO_3 or MeOH/NaOH, **Table 1**, *entries 7* and *8*) led to degradation of the substrates to unidentifiable mixtures, emphasizing that silica gel played a crucial role in binding the eliminating HF and stabilizing the reaction environment. These results highlight the significant effect of the solvent composition, reaction time, and temperature on the efficiency and selectivity of the hydrolysis process.

The MeOH/H_2O solvent system on SiO_2, particularly with either extended reaction times or a higher water ratio at moderate temperatures emerged as the most promising preparative approach for efficiently converting alkyl *gem*-difluorocyclopropenes into acrylic acid derivatives.

Table 1. The hydrolysis of 1-alkyl *gem*-difluorocyclopropenes **1a–c** under different reaction conditions



Reaction Conditions	Substrates, products, and product ratio		
	 **1a**	 **1b**	 **1c**
	 **1a'**  **2a**  **3a**  **4a**	 **1b'**  **2b**  **3b**  **4b**	 **2c**  **3c**  **4c**
1. DCM/SiO_2/Air, 18 h	**1a**	**1b**	**1c**
2. DCM/SiO_2/H_2O (5 equiv.), 18 h	**1a**(70%) + **1a'** (30%)[a]	**1b**(75%) + **1b'** (25%)[a]	1c
3. DCM/MeOH (2:1) SiO_2, 18 h	**1a**	**1b**	**1c**
4. MeOH/H_2O (10:1) SiO_2, 18 h	**1a'** (60%), **2a** (25%), **3a** (15%)	**1b'** (40%), **2b** (45%), **3b** (12%), **4b** (3%)	**1c** (55%), **2c** (35%), **3c** (20%)
5. MeOH/H_2O (10:1) SiO_2, 72 h	**3a** (95%), **4a** (5%)	**3b** (72%), **4b** (28%)	**3c** (84%), **4c** (16%)
6. MeOH/H_2O (5:1) SiO_2, 60C 18 h	**3a** (95%), **4a** (5%)	**3b** (72%), **4b** (28%)	**3c** (85%), **4c** (15%)
7. MeOH/K_2CO_3	complex mixture	complex mixture	complex mixture
8. MeOH/NaOH	complex mixture	complex mixture	complex mixture

Note: [a]**1a'**, **1b'** – products where the CF_2 moiety remains unchanged, while the $SiMe_3$ protection group degrades

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In the case of 1-aryl-3,3-difluorocyclopropenes (**Table 2**), the hydrolysis proceeded under considerably milder conditions compared to their alkyl counterparts. Under ambient conditions (DCM/SiO_2/Air, 18 h, **Table 2**, *entry 1*) even slight exposure to the atmospheric moisture initiated hydrolysis, as evidenced by the formation of hydrolysis products (**2e** (80%) and **3e** (20%), **Table 2**, *entry 1*) in case of the substrate containing the strongest donating aromatic group in the series (**1e**, **Table 2**). Notably, the electron-donating 4-methoxyphenyl fragment of the substrate **1e** (**Table 2**) had the most significant potential to effectively stabilize the cyclopropenyl cation intermediate, which was an indirect indication of the key role that the cyclopropenyl cation formation had for the *gem*-difluorocyclopropene hydrolysis rate and course. In contrast, such substrates as **1d**, **1f**, and **1g** (**Table 2**) showed lower reactivity under these conditions, with **1d** remaining largely unconverted. When the reaction medium was changed to a DCM/MeOH (1:1) mixture (**Table 2**, *entry 2*), the conversion of substrate **1d** improved (yielding 40% of **2d** and 60% of **3d**), while substrate **1e** further progressed to yield predominantly **3e** (82%) alongside a minor quantity of **4e** (16%) (**Table 2**, *entry 2*). For substrates **1f** and **1g**, the DCM/MeOH conditions resulted only in a partial conversion, forming small amounts of the "first stage" hydrolysis product – cyclopropenones **2f** (25%) and **2g** (20%), respectively (**Table 2**, *entry 2*).

These observations underscore that the electronic properties of aromatic substituents critically dictate the hydrolysis rate, with donor groups markedly enhancing the reaction *via* better stabilization of the cyclopropenyl cation, while substrates with less favorable (electron withdrawing) characteristics display the reduced reactivity.

■ Conclusion

Our study strongly supports the concept that the hydrolysis of *gem*-difluorocyclopropenes is controlled by the formation of a cyclopropenyl cation intermediate, which stability plays a central role in determining both the reaction rate and the product distribution. Our experimentations show that 1-aryl-*gem*-difluorocyclopropenes display divergent behavior depending on the electronic nature of the substituents attached to the aromatic ring. When electron-donating groups, such as methoxy or alkyl groups, are present, they engage in resonance with the cyclopropene framework, effectively delocalizing the positive charge of the cyclopropenyl cation. This stabilization presumably lowers the energy barrier for the hydrolysis reaction, leading to a faster conversion and a more efficient formation of cyclopropenones under milder conditions. Conversely, aromatic systems containing electron-withdrawing groups, such as fluorine or carboxyl functionalities, offer limited resonance stabilization for the cationic intermediate. The reduced stabilization leads to an increase in the activation energy, thereby slowing down the hydrolysis process and requiring more stringent conditions to achieve notable conversion.

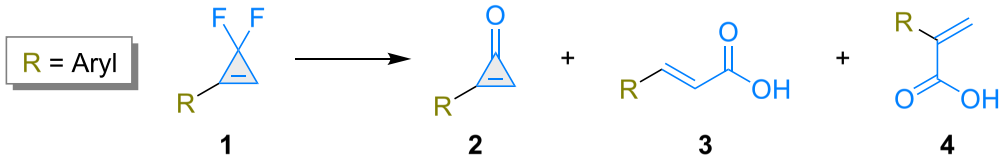
Furthermore, the use of silica gel to bind the evolving HF proves essential in both scenarios as it prevents degradation pathways and helps to maintain the integrity of the reaction environment. 1-Alkyl-*gem*-difluorocyclopropenes, lacking the conjugative effects of an aromatic ring, require more rigorous conditions, such as an increased water content or higher temperatures, to achieve an effective hydrolysis. Together, these findings not only provide a nuanced understanding of how the substituent effects modulate the stability of key intermediates, but also inform the optimization of the reaction conditions for the preparative synthesis of cyclopropenones, and acrylic acid derivatives using *gem*-difluorocyclopropenes as substrates, thereby advancing the scope of potentially valuable transformations of this accessible class of building blocks.

■ Experimental part

The general information and materials

The solvents were purified according to the standard procedures. All starting materials were obtained from Enamine Ltd. Melting points were measured on an automated melting point system. ^1H, ^{19}F, and ^{13}C NMR spectra were recorded on a Bruker Avance 500 spectrometer (at 500 MHz for ^1H, 470 MHz for ^{19}F, and 126 MHz for ^{13}C) and Varian Unity Plus 400 spectrometers (at 400 MHz for ^1H, 376 MHz for ^{19}F and 101 MHz for ^{13}C). The NMR chemical shifts are referenced using the solvent signals at 7.26 and 77.1 ppm for ^1H and ^{13}C nuclei, respectively, in $CDCl_3$ and 2.48 and 39.5 ppm for ^1H and ^{13}C nuclei, respectively, in DMSO-d_6; C_6F_6 was used as the internal standard for ^{19}F NMR spectra. HPLC analyses were done on an Agilent 1200 instrument. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (APCI)).

Table 2. The hydrolysis of 1-aryl *gem*-difluorocyclopropenes **1d–g** under different reaction conditions



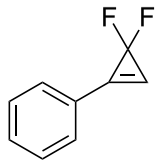
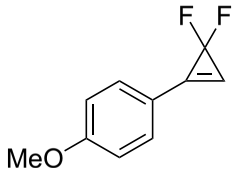
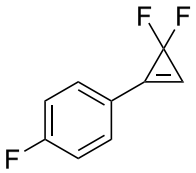
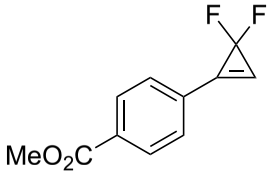
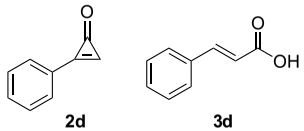
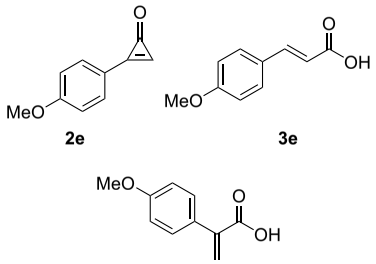
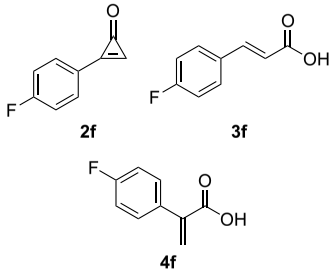
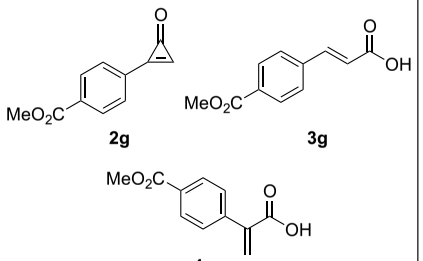
Reaction Conditions	Substrates, products, and product ratio			
	 **1d**	 **1e**	 **1f**	 **1g**
	 **2d** **3d** **4d**	 **2e** **3e** **4e**	 **2f** **3f** **4f**	 **2g** **3g** **4g**
1. DCM/SiO_2/Air, 18h	**1d**	**2e** (80%), **3e** (20%)	**1f**	**1g**
2. DCM/MeOH (1:1) SiO_2, 18h	**2d** (40%), **3d** (60%)	**3e** (82%), **4e** (16%)	**1f** (75%), **2f** (25%)	**1g** (80%), **2g** (20%)

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Table 3. Hydrolysis protocol details for the hydrolysis of 1-alkyl-*gem*-difluorocyclopropenes **1a–c**

Table 1 entries	Hydrolysis protocol details
1. DCM/SiO_2/Air, 18 h	A difluorocyclopropene (1 equiv.) was dissolved in dichloromethane (20 mL g^{-1}) and SiO_2 (5 equiv.) was added. The reaction mixture was stirred in an open flask for 18 hours at room temperature. The reaction mixture was then filtered and evaporated
2. DCM/SiO_2/H_2O (5 equiv), 18 h	A difluorocyclopropene (1 equiv.) was dissolved in dichloromethane (20 mL g^{-1}), SiO_2 (5 equiv.), and water (5 equiv.) were added. Then the reaction mixture was stirred for 18 hours at room temperature. The reaction mixture was then filtered, dried over sodium sulfate, and evaporated
3. DCM/MeOH (2:1), SiO_2, 18 h	A difluorocyclopropene (1 equiv.) was dissolved in a 2-to-1 dichloromethane/methanol mixture (20 mL g^{-1}), SiO_2 (5 equiv.) was added, and the reaction mixture was stirred for 18 hours at room temperature. Then water was added to the reaction mixture and extracted twice with dichloromethane, the organic layer was dried over sodium sulfate and evaporated
4. MeOH/H_2O (10:1), SiO_2, 18 h	A difluorocyclopropene (1 equiv.) was dissolved in a 10-to-1 methanol/water mixture (20 mL g^{-1}), SiO_2 (5 equiv.) was added, and the reaction mixture was stirred for 18 (entry 4) or 72 (entry 5) hours at room temperature. Then methanol was evaporated, water was added to the reaction mixture, and extracted twice with dichloromethane. The organic layer was dried over sodium sulfate and evaporated
5. MeOH/H_2O (10:1), SiO_2, 72 h	
6. MeOH/H_2O (5:1), SiO_2, 60°C 18 h	A difluorocyclopropene (1 equiv.) was dissolved in a 5-to-1 methanol/water mixture (20 mL g^{-1}), SiO_2 (5 equiv.) was added, and the reaction mixture was stirred for 18 hours at 60°C. Then, the reaction mixture was cooled, methanol was removed *in vacuo*, and water was added. The mixture was extracted twice with dichloromethane, the organic layer was dried over sodium sulfate and evaporated
7. MeOH/K_2CO_3	A difluorocyclopropene (1 equiv.) was dissolved in methanol (20 mL g^{-1}), K_2CO_3 (entry 7) or NaOH (entry 8) (2 equiv.) was added, and the reaction mixture was stirred for 18 hours at room temperature. Then, the methanol was evaporated, water was added, and the mixture was acidified with sodium hydrogen sulfate to pH 3 and extracted twice with dichloromethane. The organic layer was dried over sodium sulfate and evaporated
8. MeOH/NaOH	

Table 4. Hydrolysis protocol details for the hydrolysis of 1-aryl-*gem*-difluorocyclopropenes **1d–g**

Table 2 entries	Hydrolysis protocol details
1. DCM/SiO_2/Air, 18 h	Similarly to **Table 1**, conditions for **entry 1**
2. DCM/MeOH (1:1), SiO_2, 18 h	A difluorocyclopropene (1 equiv.) was dissolved in a 1-to-1 dichloromethane/methanol mixture (20 mL g^{-1}), SiO_2 (5 equiv.) was added, and the reaction mixture was stirred for 18 hours at room temperature. Then, water was added, and the mixture was extracted twice with dichloromethane, the organic layer was dried over sodium sulfate and evaporated

The column chromatography was performed with silica gel (200–300 mesh).

Tables 3 and **4** contain experimental protocols used during experimentation and reflect the results highlighted in **Tables 1** and **2**.

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