Organic & Biomolecular Chemistry

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Journal:	*Organic & Biomolecular Chemistry*
Manuscript ID	OB-COM-12-2019-002713.R1
Article Type:	Communication
Date Submitted by the Author:	27-Feb-2020
Complete List of Authors:	Sugiishi, Tsuyuka; Gunma University, Faculty of Science and Technology Matsumura, Chihori; Gunma University, Science and Technology Amii, Hideki; Gunma University

COMMUNICATION

Synthesis of 3-Fluoro-2,5-disubstituted Furans through Ring Expansion of *gem*-Difluorocyclopropyl Ketones

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Tsuyuka Sugiishi,[a] Chihori Matsumura,[a] Hideki Amii*[a]

The synthesis of 3-fluoro-2,5-disubstituted furans from *gem*-difluorocyclopropyl ketones was accomplished using trifluoromethanesulfonic acid (CF_3SO_3H) through ring expansion owing to the activation of the carbonyl group in the starting material. The present synthesis of 3-fluorofurans tolerates substrates designed for products with aromatic substituents at the C-2 and C-5 positions.

Many bioactive molecules contain heterocycles. Furans are a ubiquitous type of heterocyclic compound and have been found in pharmaceuticals, agrochemicals, and materials.[1] However, a few organofluorine compounds can be found in natural products, and introducing fluorine atoms into organic molecules may improve the efficiency or alter the properties of non-fluorinated compounds in pharmaceutical, agricultural, and materials chemistry.[2] The installation of fluorine atoms on furan rings is significant in organic synthesis; hence, several useful syntheses of 3-fluorofurans from *gem*-difluorohomopropargyl alcohols,[3] 2-fluoroalk-3-yn-1-ones,[4] or *gem*-difluorinated phosphonium[5] have been reported. We sought an alternative method for the synthesis of fluorofurans using an original reagent as a fluorine source that would involve neither the cyclization of acetylenes[3,4] nor a radical reaction with a photocatalyst.[5] We previously reported a synthesis of *gem*-difluorocyclopropanes involving sodium bromodifluoroacetate ($BrCF_2CO_2Na$),[6] and the characteristics of *gem*-difluorocyclopropanes and the utilization of these compounds as materials for promising heterocyclic compounds containing fluorine atoms have recently attracted our attention. However, it is known that the ring of *gem*-difluorocyclopropanes are generally, rarely opened unless the substrates are designed adequately.[7] In our approach, it was found that a carbonyl group adjacent to the *gem*-difluorocyclopropane ring and a Brønsted acid were required to not only force *gem*-difluorocyclopropanes to open, but also enable ring expansion to produce 3-fluorofurans. 3-Fluorofurans have also been generated in low yields as byproducts in the acetal deprotection of the precursors of *gem*-difluorocyclopropyl ketones (Scheme 1a)[8] and in the hydrobromination of *gem*-difluorocyclopropyl ketones (Scheme 1b).[9] The ring opening of cyclopropyl ketones can occur through either distal or proximal C-C bond cleavage. Cyclopropyl ketones undergo hydrobromination through distal bond cleavage (Scheme 1b)[9] and react with nitriles through proximal bond cleavage (Scheme 1c).[10] Concerning with distal bond cleavages, there are a few examples of furan synthesis from geminal dichloro- or dibromo- cyclopropyl ketones.[11] In the synthesis of 3-fluorofurans that we will propose herein, the distal bond would be cleaved (Scheme 1d). Furthermore, the carbonyl group of a *gem*-difluorocyclopropyl ketone can be utilized for the preparation of a five-membered ring framework and the two fluorine atoms play a role in the conversion to a 3-fluorofuran.

First, we prepared starting materials **2**, featuring a carbonyl group adjacent to the cyclopropane ring, through cycloaddition of chalcone derivatives **1**, which were synthesized easily from benzaldehydes and acetophenones, with sodium bromodifluoroacetate ($BrCF_2CO_2Na$)[6] in diglyme at 180 °C for 20 min in 14–38% yields.

The results for the optimisation of the reaction conditions for the synthesis of 3-fluorofuran **3a** from *gem*-difluorocyclopropyl ketone **2a** are presented in Table 1. The effect of the solvent was investigated using 2.0 equiv of trifluoromethanesulfonic acid (CF_3SO_3H) at room temperature and a reaction time of 30 min. Desired compound **3a** was obtained in 24% yield when 2,2-difluoro-3-phenylcyclopropyl-phenylmethanone **2a** was exposed to CF_3SO_3H in acetonitrile (entry 1). Although the reaction condition was similar to that of the reported pyrrole synthesis,[10] the corresponding pyrrole product was not obtained at all in entry 1. Toluene and dichloromethane were suitable as solvents for this synthesis (entries 2 and 3), but

[a] *Division of Molecular Science, Graduate School of Science and Technology, Gunma University, 1-5-1 Tenjin-Cho, Kiryu, Gunma, 376-8515, Japan.*

† Footnotes relating to the title and/or authors should appear here.

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

dimethylformamide (DMF) and tetrahydrofuran (THF) were not (entries 4 and 5). When the reaction temperature was lower than room temperature, the yields of 3-fluorofuran **3a** were higher (entries 6–10), and the reaction performed at −20 °C afforded the highest yield (entry 9). When the amount of CF_3SO_3H was reduced to 0.5 equivalents to cyclopropyl ketone **2a**, a trace of 3-fluorofuran **3a** was generated with only 20% recovery of **2a** suggesting that a stoichiometric amount of fresh CF_3SO_3H is effective for this synthesis although CF_3SO_3H is considered to be regenerated in situ (entry 11). In the presence of H_2SO_4, desired compound **3a** was generated in a low yield (entry 12).[12]

Next, the substrate scope of the present synthesis of 3-fluorofurans **3** from cyclopropanes **2** was explored (Table 2). Corresponding furans **3** were synthesized in moderate yields when R^1 on the benzene rings was a 4-methyl, 4-bromo, 4-chloro, or 3-methoxy group (entries 2–5). Syntheses were also successful when R^2 on the benzoyl group of cyclopropyl ketones **2** was a 4-methyl, 4-bromo, 4-methoxy, or 3-methoxy group, affording disubstituted fluorofurans **3** in moderate to high yields (entries 6–9). Fluorofurans **3** with substituted aromatic groups at both C-2 and C-5, such as those with R^1 = 4-bromo and R^2 = 4-methyl (entry 10)[13] or R^1 = 4-bromo and R^2 = 4-methoxy (entry 11), were synthesized well using this method. When R^1 = 4-methyl and R^2 = 4-bromo (entry 12), that is, when the substituents at C-2 and C-5 on synthesized 3-fluorofuran **3** were reversed with respect to entry 10, the yield was not significantly different. The screening of substrates for 2,5-disubstituted 3-fluorofurans **3** revealed that we had complete control of the aromatic functional groups at the C-2 and C-5 positions, as can be seen from entries 2 and 6, 3 and 7, 5 and 9, and 10 and 12.

Scheme 3 shows a plausible mechanism for the above synthesis of fluorofurans **3**. CF_3SO_3H, which is a strong acid, would coordinate with the oxygen atom of the carbonyl group in cyclopropane **2** and then undergo a ring opening reaction to generate benzylic carbocation intermediate **4**. Subsequent attack of the oxygen atom of the enol on the carbocation would lead to the intramolecular cyclization of intermediate **4**. Finally, deprotonation and aromatization occur to furnish fluorofuran **3**. In the case that the substrate was (2,2-difluoro-3-heptylcyclopropyl)(phenyl)methanone, which has a normal alkyl group instead of Ar^1, the corresponding furan was not observed but unaromatized 3,3-difluoro-2,3-dihydrofuran. The result indicates that the aromatic substituents Ar^1 accelerate the aromatization in the end of the reaction mechanism.[14]

Conclusions

In summary, we have realized the regiospecific synthesis of 2,5-disubstituted 3-fluorofurans **3** from *gem*-difluorocyclopropane derivatives **2**. CF_3SO_3H is necessary for the low-temperature ring expansion of *gem*-difluorocyclopropane derivatives **2** containing a carbonyl group, affording 3-fluorofurans **3** in good yields. The regioselectivity in the present synthesis of 3-fluorofurans **3** is guaranteed when the starting material for the cyclopropanation step is synthesized. Ultimately, the functional groups of chalcones **1** determine the substituents at the 2- and 5-positions of 3-fluorofurans **3**.

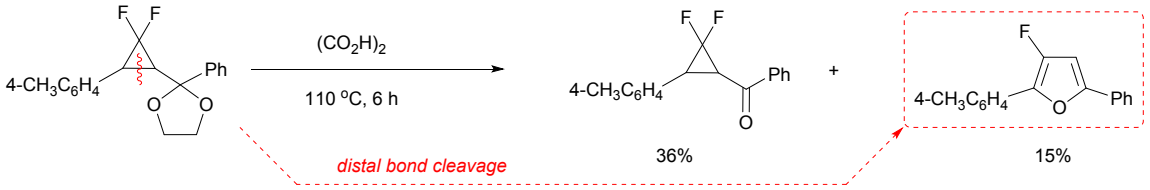
Conflicts of interest

There are no conflicts to declare.

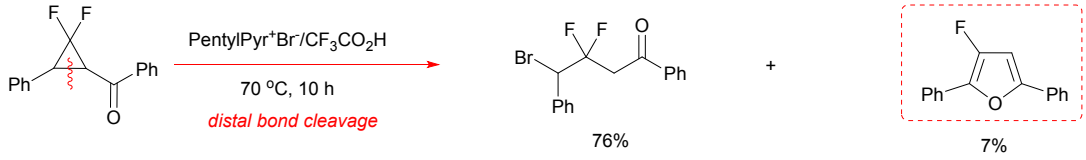
Acknowledgements

We would like to acknowledge Grants-in-Aid for Scientific Research, the financial support of Japan Society for the Promotion of Science (JSPS) KAKENHI Grant Number 17K14479 Grant-in-Aid for Young Scientists B, the Association for the Advancement of Science & Technology, Gunma University, the financial support of JSPS KAKENHI Grant Number JP 16H04143 Grant-in-Aid for Scientific Research B, JP18H04235 in Middle Molecular Strategy, 18H04381 in Precisely Designed Catalysts with Customized Scaffolding, and Japan Science and Technology Agency (JST) (ACT-C: Creation of Advanced Catalytic Transformation for the Sustainable Manufacturing at Low Energy, Low Environmental Load). We would like to thank Editage (www.editage.com) for English language editing. We would like to thank Technical Department, Tottori University for HRMS measurement.

Generation of 3-fluorofurans from *gem*-difluorocyclopropyl ketone derivatives (ref. 8,9)

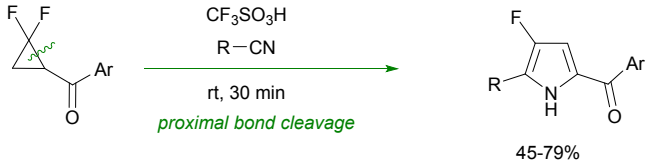


(a)



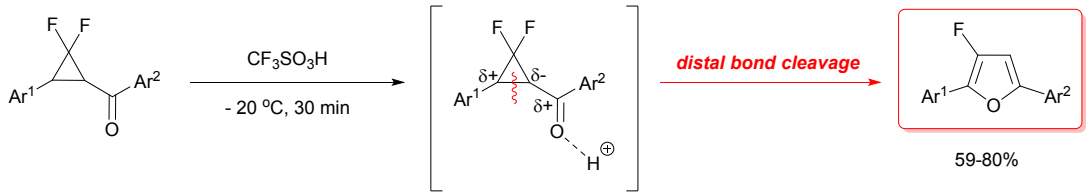
(b)

Cleavage of *gem*-difluorocyclopropyl ketones at the *proximal position* (ref. 10)



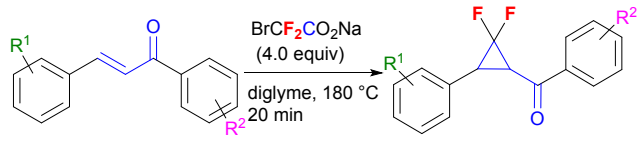
(c)

Synthesis of 3-fluorofurans from *gem*-difluorocyclopropyl ketones (this work)



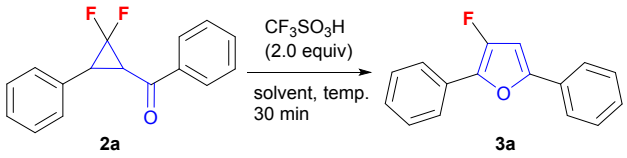
(d)

Scheme 1 Reactivities of *gem*-Difluorocyclopropane



Scheme 2 Preparation of Starting Materials **2** from Chalcones **1**

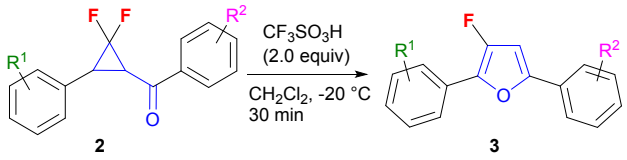
Table 1 Optimization of Reaction Conditions[a]



entry	solvent	temp. (°C)	yield of **3a** (%)	recovery of **2a** (%)
1	CH_3CN	rt	24[b]	0
2	toluene	rt	44[b]	0
3	CH_2Cl_2	rt	45[b]	0
4	DMF	rt	4[b]	95[b]
5	THF	rt	5[b]	0
6	CH_2Cl_2	10	52	0
7	CH_2Cl_2	0	68	0
8	CH_2Cl_2	−10	74	0
9	CH_2Cl_2	−20	80	0
10	CH_2Cl_2	−40	75	0
11[c]	CH_2Cl_2	−20	trace	20
12[d]	CH_2Cl_2	−20	19	77

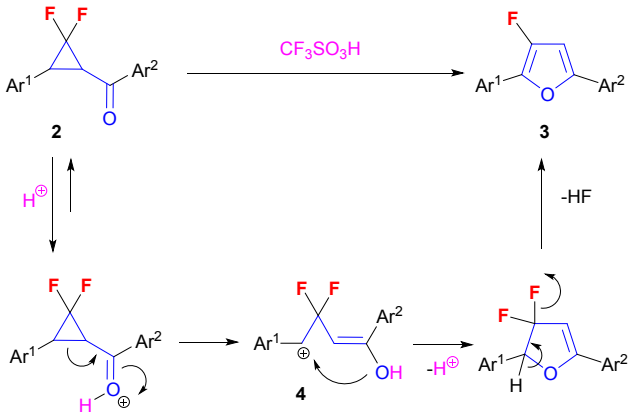
[a]Reaction conditions: the reactions were carried out with cyclopropane **2a** (0.2 mmol) and CF_3SO_3H (0.4 mmol) in a solvent (1.0 mL) for 30 min. Isolated yields. [b]Determined by ^{19}F NMR analysis using C_6F_6 as an internal standard. [c]CF_3SO_3H was reduced to 0.5 equiv to cyclopropane **2a**. [d]H_2SO_4 was used as the acid instead of CF_3SO_3H.

Table 2 Screening of Substrates



entry	R^1	R^2	yield of **3** (%)[b]
1	H	H	80
2	4-Me	H	64
3	4-Br	H	73
4	4-Cl	H	71
5	3-MeO	H	59
6	H	4-Me	76
7	H	4-Br	80
8	H	4-MeO	74
9	H	3-MeO	65
10	4-Br	4-Me	75
11	4-Br	4-MeO	77
12	4-Me	4-Br	70

[a]Reaction conditions: the reactions were carried out with *gem*-difluorocyclopropyl ketone **2** (0.1 mmol) and CF_3SO_3H (0.2 mmol) in CH_2Cl_2 (1.0 mL) at −20 °C for 30 min. [b]Isolated yields.



Scheme 3. Plausible Reaction Mechanism

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14 See Scheme S1 in Supporting Information.

The synthesis of 3-fluoro-2,5-disubstituted furans from *gem*-difluorocyclopropyl ketones was accomplished using trifluoromethanesulfonic acid in good yields at low temperature.