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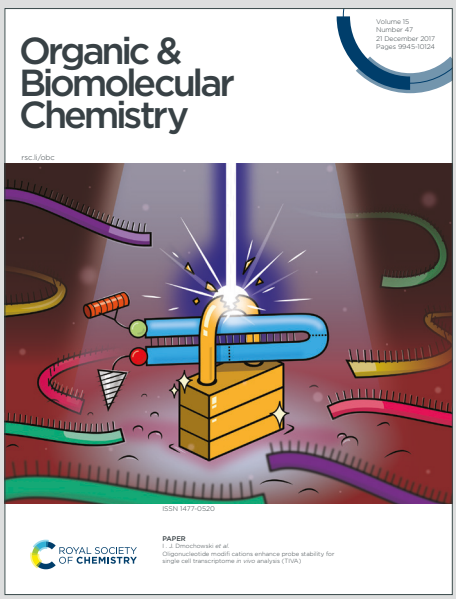

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COMMUNICATION

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

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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

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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

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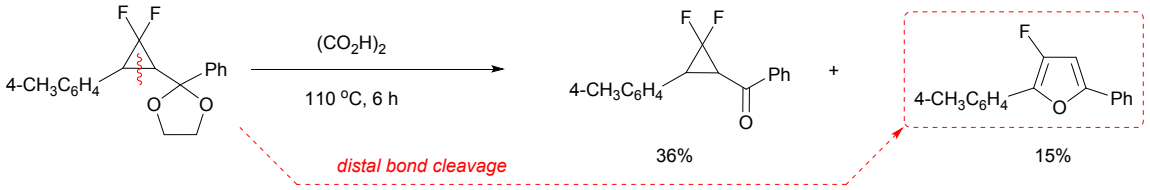
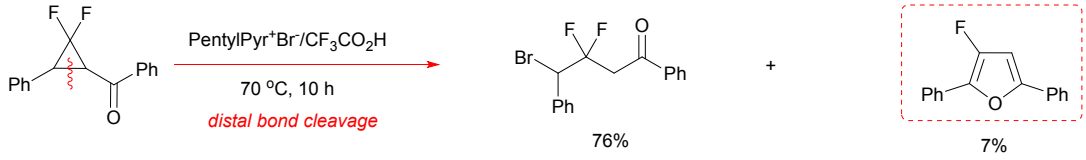
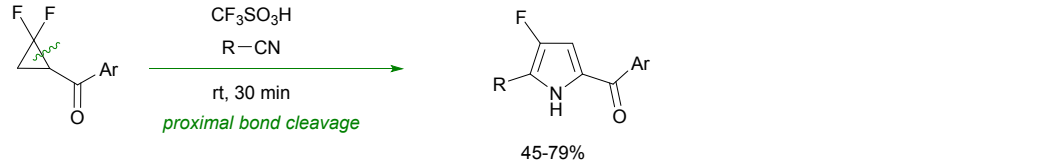
Generation of 3-fluorofurans from *gem*-difluorocyclopropyl ketone derivatives (ref. 8,9)

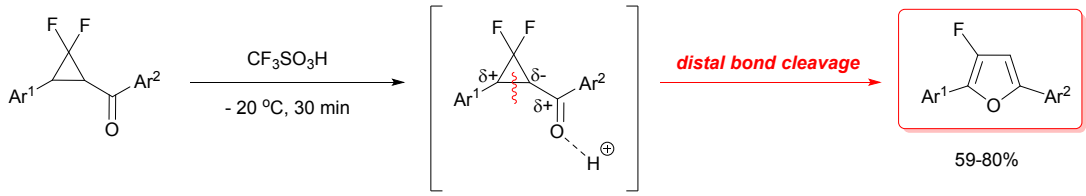




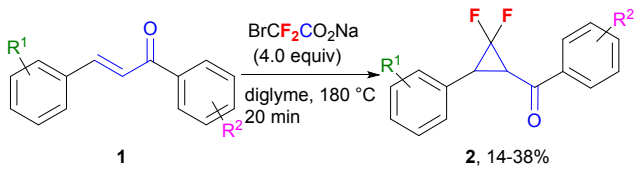
Cleavage of *gem*-difluorocyclopropyl ketones at the *proximal position* (ref. 10)



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

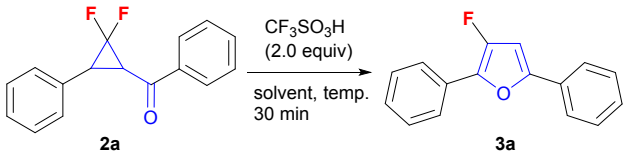


Scheme 1 Reactivities of *gem*-Difluorocyclopropane



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

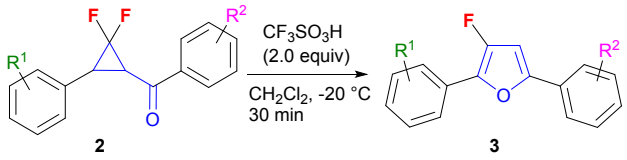
Table 1 Optimization of Reaction Conditions[a]



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

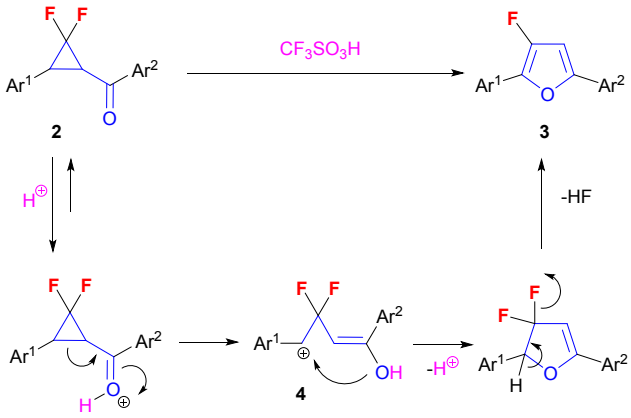
[a]Reaction conditions: the reactions were carried out with cyclopropane **2a** (0.2 mmol) and CF_3SO_3H (0.4 mmol) in a solvent (1.0 mL) for 30 min. Isolated yields. [b]Determined by ^{19}F NMR analysis using C_6F_6 as an internal standard. [c]CF_3SO_3H was reduced to 0.5 equiv to cyclopropane **2a**.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

Notes and references

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12 Other acids, such as CH_3CO_2H, $(CO_2H)_2$, *p*-TsOH, CF_3CO_2H, and aqueous HCl, were screened, but did not work at all in the reaction, and starting material **2a** was recovered. The yield of desired compound **3a** was lower when H_2SO_4 was used at a temperature higher than the highest one applied for CF_3SO_3H (see Supporting Information).

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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.