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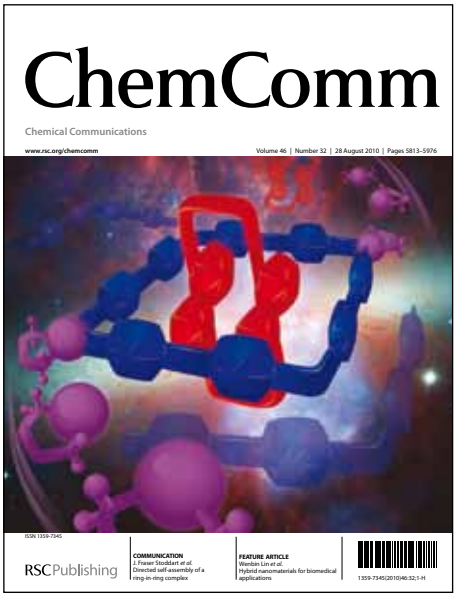

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ARTICLE TYPE

A novel reaction of *gem*-difluorocyclopropyl ketones with nitriles leading to 2-fluoropyrroles

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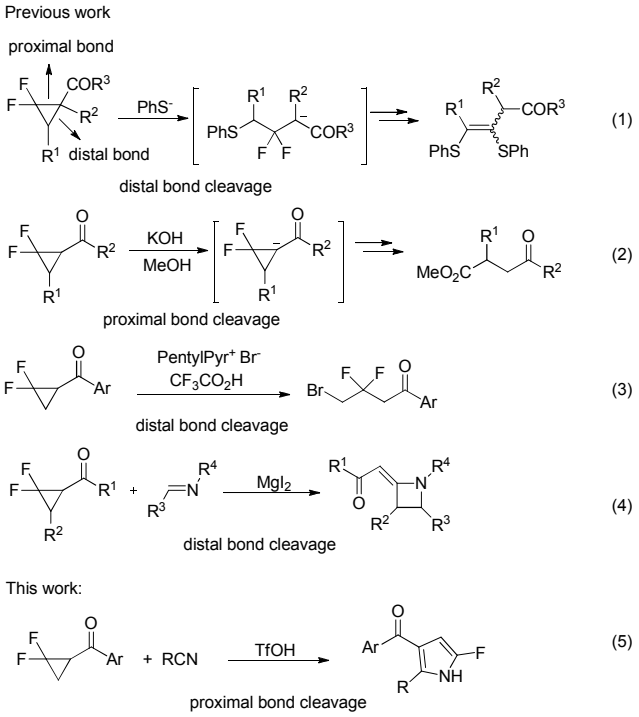
The CF_3SO_3H-promoted ring-opening of *gem*-difluorocyclopropyl ketones prefers to undergo proximal bond cleavage and the subsequent cyclization with nitriles occurred smoothly to give 2-fluoropyrroles.

The sharp increase in the number of fluorine-containing pharmaceuticals and agrochemicals clearly demonstrates the exceptional importance of fluorinated compounds.[1] As one of the important classes of fluorinated molecules, *gem*-difluorocyclopropanated derivatives have attracted much attention due to the unique biological activities of the *gem*-difluorocyclopropyl group.[2] Despite the significance of this moiety, only limited number of reports has been published about the studies on its reactivity, especially the ring-opening chemistry,[3] which would be expected to be an efficient approach for the synthesis of unique partially fluorinated compounds. As part of our continuing interest in *gem*-difluorocyclopropanes chemistry,[4] we described the regioselectivie ring-opening reaction of *gem*-difluorocyclopropyl ketones prompted by Brønsted acid in the presence of nitrile derivatives, allowing the synthesis of fluoropyrroles,[5] which are valuable subunits of many pharmacologically active compounds.[6]

In the study on ring-cleavage of *gem*-difluorocyclopropyl ketones, the regioselectivity was found to be an interesting issue. The ring-opening reaction could be promoted by nucleophiles, base and acids.[3a-b, 3d-e] Kobayashi and coworkers found that strong nucleophiles with low basicity would cause distal bond scission because the carbanion intermediate could be stabilized by both the carbonyl and β-difluoromethylene groups (eq. 1, Scheme 1).[3a-b] While strong base would result in deprotonation followed by defluorination and a series of transformation to lead to proximal bond cleavage (eq. 2).[3a-b] The interesting results disclosed some reactivity of *gem*-difluorocyclopropanes but both of these two routes lead to complete loss of fluorine. Dolbier et al reported Brønsted acid-mediated ring-opening reactions with ionic liquid reagent proceeding via S_N2-like process to give 3-bromo-2,2-difluoropropyl ketones resulting from distal bond scission (eq. 3).[3d] Soon after this report, they found that *gem*-difluorocyclopropyl ketones would also undergo distal bond cleavage upon the treatment with MgI_2 and further react with imine to give non-fluorine products (eq. 4).[3e] Dolbier's results show that distal bond prefers to cleave in the presence of acids. In this communication, we found the regioselectivity was different in the absence of soft nucleophiles and the proximal bond would be readily cleaved in the presence of strong Brønsted acid. The ring-opening of *gem*-difluorocyclopropyl ketones and the subsequent cyclization with nitriles proceeded smoothly to give 2-fluoropyrroles (eq. 5).



Scheme 1 The regioselectivity of ring-opening

The first attempt for the cyclization of phenyl *gem*-difluorocyclopropyl ketone (**1a**) with acetonitrile was made in the presence of triflic acid. Acetonitrile was used as the substrate and solvent. The reaction proceeded fast to give the desired product in 50% yield determined by ^{19}F NMR with the use of trifluoromethyl benzene as internal standard (Table 1, entry 1). A variety of other acids including Brønsted acids and Lewis acids were subjected to this transformation (entries 2-7). Even though TMSOTf have been reported to be able to efficiently promote cyclization of non-fluorinated cyclopropanes with nitriles to afford pyrroles,[7] this Lewis acid was not effective enough to convert *gem*-difluorocyclopropane into 2-fluoropyrrole. The conversion of the substrate (**1a**) was complete in 2h but very low

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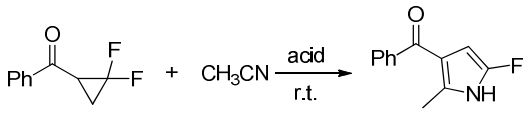
yield of product was obtained (entry 4). $Yb(OTf)_3$ and $In(OTf)_2$ were found to be good catalysts for cyclization of non-fluoroiated cyclopropanes with nuclephiles.[8] Nevertheless, both of them failed to mediate the desired conversion (entries 5 and 6). CF_3SO_3H was proved to be the suitable acid for this reaction.

It is necessary to determine if the reaction could proceed in organic solvent with the use of less amount of acetonitrile (entries 8-10). It turned out that the reactions in toluene, THF or dichloromethane became complicated and no expected product could be detected by ^{19}F NMR.

The amount of CF_3SO_3H and the reaction temperature were next examined for optimal conditions (entries 11-17). Catalytic amount of triflic acid led to trace amount of the desired product with much of the *gem*-difluorocyclopropyl ketone remained even prolonging the time to 2 h (entry 11). When 2 equivalents of triflic acid were used, the yield increased slightly to 62% (entry 12). Considering that the pyrroles are prone to polymerization in the presence of acid,[9] we tried to improve the yield by decreasing the acid concentration. However, no further improvement was achieved (entries 13 and 14). To our delight, higher yield (71%) of 2-fluoropyrrole could be obtained when the reaction was quenched at lower temperature (entry 15). When the reaction was conducted at 0 °C, longer time was needed for the complete conversion without increasing the yield (entry 16). The lower reaction temperature resulted in sluggish reaction (entry 17). Therefore, room temperature is the suitable temperature for the transformation.

Table 1 Screening of The Reaction Conditions[a]



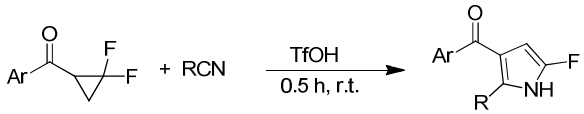
1a **2a**

Entry	Acid (equiv.)	Time (h)	Yield (%)[b]
1	CF_3SO_3H (1.0)	0.75	50%
2	CF_3COOH (1.0)	12	N.R.
3	TsOH (1.0)	12	N.R.
4	TMSOTf (1.0)	2	28%
5	$Yb(OTf)_3$ (1.0)	12	N.R.
6	$In(OTf)_2$ (1.0)	12	N.R.
7	$Cu(OTf)_2$ (1.0)	12	N.R.
8[c]	CF_3SO_3H (1.0)	12	N.D.
9[d]	CF_3SO_3H (1.0)	12	N.D.
10[e]	CF_3SO_3H (1.0)	12	N.D.
11	CF_3SO_3H (0.1)	2	trace
12	CF_3SO_3H (2.0)	0.5	62%
13[f]	CF_3SO_3H (2.0)	0.5	57%
14[g]	CF_3SO_3H (2.0)	0.5	56%
15[h]	CF_3SO_3H (2.0)	0.5	71%
16[h, i]	CF_3SO_3H (2.0)	0.75	71%
17[h, j]	CF_3SO_3H (2.0)	6	trace

[a] Reaction conditions: **1a** (0.2 mmol), CF_3SO_3H (0.2 mmol) in CH_3CN (1mL) at r.t. under N_2; [b] Determined by ^{19}F NMR with the use of trifluoromethyl benzene as internal standard, N.D.= not detected, N.R.= no reaction; [c] 0.4 mmol of CH_3CN was used in toluene (1 mL); [d] 0.4 mmol of CH_3CN was used in THF (1 mL); [e] 0.4 mmol of CH_3CN was used in CH_2Cl_2 (1 mL); [f] 5 mL of CH_3CN was used; [g] 10 mL of CH_3CN was used; [h] Quenched at -20 °C; [i] The reaction was performed at 0 °C; [j] The reaction was performed -10 °C.

With the optimized conditions (Table 1, entry 15) in hand, we investigated the scope of the substrates. As can be seen from Table 2, the yields were relatively lower for those *gem*-difluorocyclopropyl ketones with electron-donating substituent on the para position of the phenyl ring (entry 2 and entry 3). However, meta-methoxy substituted *gem*-difluorocyclopropyl ketone could react well with acetonitrile to give higher yield (entry 4). In the case of halogen substituted aryl *gem*-difluorocyclopropyl ketones (entries 5-9), similar tendency was also observed (entry 6 vs 7, 8 vs 9). Moderate yields were obtained for other examples, such as highly electron-deficient ketone and naphthyl ketone (entries 10 and 11). Besides acetonitrile, the reaction worked equally well for benzonitrile, which means the transformation is applicable to both aliphatic and aromatic nitriles (entry 12).

Table 2 The Reaction of *gem*-Difluorocyclopropyl Ketones with Nitriles[a]



1a-k **2a-l**

Entry	Ar	R	Product, Yield[b]
1	Ph (**1a**)	Me	**2a**, 64%
2	4-$CH_3C_6H_4$ (**1b**)	Me	**2b**, 49%
3	4-$CH_3OC_6H_4$ (**1c**)	Me	**2c**, 54%
4	3-$CH_3OC_6H_4$ (**1d**)	Me	**2d**, 74%
5	4-FC_6H_4 (**1e**)	Me	**2e**, 60%
6	3-ClC_6H_4 (**1f**)	Me	**2f**, 66%
7	4-ClC_6H_4 (**1g**)	Me	**2g**, 57%
8	4-BrC_6H_4 (**1h**)	Me	**2h**, 65%
9	3-BrC_6H_4 (**1i**)	Me	**2i**, 79%
10	4-$NO_2C_6H_4$ (**1j**)	Me	**2j**, 61%
11	Naphthyl (**1k**)	Me	**2k**, 52%
12	Ph (**1a**)	Ph	**2l**, 45%

[a] *gem*-Difluorocyclopropyl ketone (0.2 mmol), CF_3SO_3H (0.4 mmol) in RCN (1mL) at r.t. for 0.5 h under N_2; quenched at -20°C; [b] Isolated yields.

The structure of product **2a** was determined by single crystal X-ray diffraction (Figure 1).[10] Other structures were surmised by analogy.

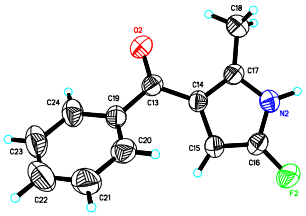


Figure 1 X-ray structure of isolated product

Based on the above results and related reports,[3d-f, 7, 11] we proposed that the mechanism involves the partially ring-opening of *gem*-difluorocyclopropyl ketone and the step-wise cyclization with nitrile (Scheme 2). The protonation of ketone is favourable for partially cleavage of the proximal bond because the resulting carbocation could be stabilized by the fluorines. The nucleophilic attack of the carbocation by acetonitrile followed by intramolecular cyclization constructs the five-membered ring **A**. Dehydrofluorination of intermediate **A** and the following

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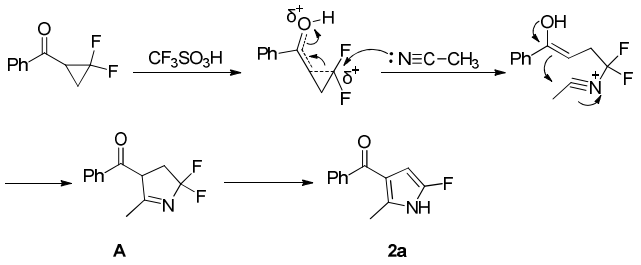
rearrangement affords the final product 2-fluoropyrrole.



Scheme 2 Proposed mechanism

The regioselectivity of ring-cleavage is quite different from that reported by Dolbier and coworkers.[3d-3e] It might be because the strong acid CF_3SO_3H (pKa ~ -14) could lead to the partially ring-cleagave of *gem*-difluorocyclopropyl ketone, while weak acids (pKa of CF_3CO_2H is about -0.25) in Dolbier's cases couldn't. Without the partially ring-cleavage, the nucleophilic reaction would proceed in S_N2-like process.

In conclusion, we have described triflic acid-mediated ring-opening of *gem*-difluorocyclopropyl ketones and the subsequent cyclization with nitriles to give 2-fluoropyrroles. The presence of strong acid favors the cleavage of proximal bond because the two fluorines could stabilize the resulting carbocation. This strategy represents a new method for the synthesis of 2-fluoropyrroles. The study on the ring-opening chemistry of *gem*-difluorocyclopropyl ketone and the applications of this strategy to the synthesis of other important fluorinated compounds are currently underway.

Notes and references

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‡ Electronic Supplementary Information (ESI) available: Experimental procedures, characterization of data for all compounds.

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