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Synthesis of Indolizines from Pyridinium Salts and Ethyl Bromodifluoroacetate

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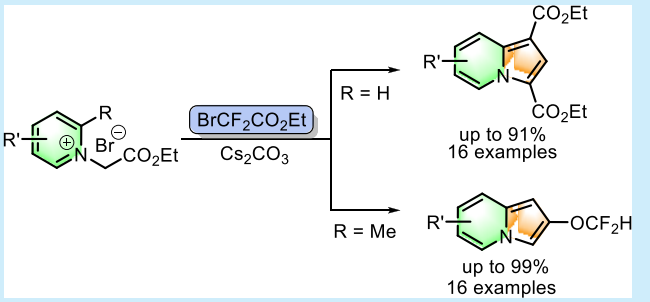
ABSTRACT: Here we present a novel annulation of pyridinium salts with $BrCF_2CO_2Et$ to access the indolizine derivatives with high efficiency. The α substitution of pyridine plays a key role in determining the reaction pathways. Various types of indolizines can be conveniently accessed from easily available pyridinium salts under mild and simple reaction conditions.

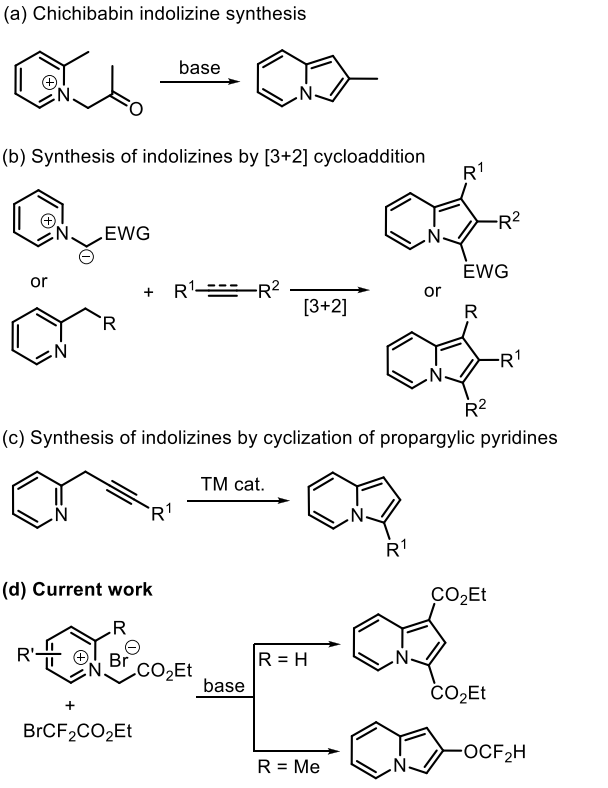


N-Heterocycles are ubiquitous structural motifs in natural products and synthetic pharmaceuticals.[1] Among them, indolizine is an important *N*-fused skeleton which possesses a pyridine-type six-membered ring condensed with a pyrrole-type five-membered ring. The indolizine derivatives are widely spread in many bioactive and pharmaceutical compounds that display remarkable biological activities.[2] Generally, indolizines can be accessed by the following methods: (1) Chichibabin indolizine synthesis, which involves a base-mediated cyclization of 1-(2-oxoalkyl)-2-methylpyridinium salts for the synthesis of 2-substituted indolizines (Scheme 1a);[3] (2) intermolecular cyclization which involves [3 + 2] cycloadditions of pyridiniums or C2-substituted pyridines with various unsaturated substrates such as alkynes, alkenes, and allenes (Scheme 1b);[4] (3) intramolecular cyclization that features transition metal catalyzed cycloisomerization reactions of propargylic pyridines (Scheme 1c).[5] Although there are many efficient and useful methods for synthesis of indolizines, there are still some unsolved issues. For example, 2-alkyloxy indolizines have only been sporadically reported with low yields.[3b,c] Therefore, development of novel and convenient synthetic strategies toward various biologically active indolizines derivatives is still in great demand.

Fluorine-containing organic compounds have received widespread attention in recent years due to their specific bioactivity and good biocompatibility compared with their nonfluorinated analogues.[6] Fluorine-containing indolizines have been reported with fluorine in fluoroalkyl motifs or directly docked on aromatic rings.[7] However, 2-difluoromethoxy indolizines have never been reported in previous literature.

Commercially available ethyl halodifluoroacetate (XCF_2CO_2Et) has been widely used as a difluoroalkylating reagent to synthesize various fluorinated compounds in

Scheme 1. Synthesis of Indolizines Starting from Pyridines



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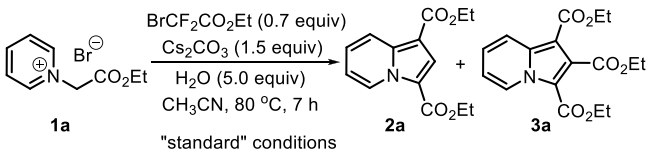
medicinal chemistry.[8] Generally, XCF_2CO_2Et can serve as a precursor to the ethyl difluoroacetate radical[9] and difluorocarbene[10] species. In addition, XCF_2CO_2Et can also serve as a novel C1 source, the application of which has been explored by the Song group since 2018.[11] Our group has been devoted to development of various types of tandem reactions initiated by difluoromethylation with $BrCF_2CO_2Et$ and its derivatives.[12] Herein, we disclose a novel reaction of $BrCF_2CO_2Et$ with various *N*-pyridinium salts leading to a series of indolizines. Depending on the substitution mode of pyridine at α-position, highly regioselective 1,3-diester substituted indolizines (when α-position is unsubstituted) or indolizines with a 2-difluoroalkoxy group (when α-position is substituted by methyl group) can be obtained (Scheme 1d).

We initially treated 1-(2-ethoxy-2-oxoethyl)pyridin-1-ium bromide (**1a**) with $BrCF_2CO_2Et$ in the presence of Cs_2CO_3 and water in acetonitrile (CH_3CN) at 80 °C for 7 h (Table 1, entry 1). To our delight, **2a** was obtained with a 94% yield. Water is essential to the reaction since in the absence of water a low yield of **2a** resulted together with **3a** as byproduct (Table 1, entry 2). Then, various reaction parameters were screened for reaction optimization with **1a** and $BrCF_2CO_2Et$ as substrates, and the results were summarized in Table 1. Other solvents such as tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), toluene (Tol), and dimethyl sulfoxide (DMSO) were also tested, but no better results resulted (entries 3−6). Afterward, various bases had been evaluated with CH_3CN as solvent in the presence of 5.0 equiv of water. NaOH and K_3PO_4 led to lower yields in this reaction (entries 7−8). When K_2CO_3 was used as a base, product **2a** was obtained with 90% yield, which is similar to that of Cs_2CO_3 (entry 9). When organic base tetramethylethylenediamine (TMEDA) was used, no reaction occurred (entry 10). When the reaction time was shortened to 5 h, the yield decreased to 90%, and when the reaction time was extended to 16 h, the yield was 95% with trace byproduct **3a** (see Table S1 in the Supporting Information (SI) for details of reaction conditions optimization). Based on the above screening results, the following reaction parameters were chosen as the optimized conditions: Cs_2CO_3 as a base and CH_3CN as solvent with 5.0 equiv of H_2O at 80 °C for 7 h.

With the optimized conditions in hand, the reaction compatibility toward various substitutions on the pyridine ring was explored, and the results were summarized in Scheme 2. Although the model substrate **1a** gave a high isolated yield of 91%, the yields drastically decreased to 55% and 44% when 1-(2-ethoxy-2-oxoethyl)-4-methylpyridin-1-ium bromide (**1b**) and 1-(2-ethoxy-2-oxoethyl)-3,5-dimethylpyridin-1-ium bromide (**1d**) were used as substrates. When the pyridine ring was substituted at the C3-position, **2c** was obtained with a yield of 83%, which indicates that the C2-position is more reactive. When the C3-position was substituted with other groups such as amino, amide, and alkoxy groups, moderate to good yields resulted for **2e**−**2k** (49−78%) with excellent regioselectivities. When the pyridine was halogenated at the C3-position, the reaction still occurred at the C2-position to afford the corresponding products (**2l**−**2m**, 49−52% yields) with excellent regioselectivities. When the C3-position was

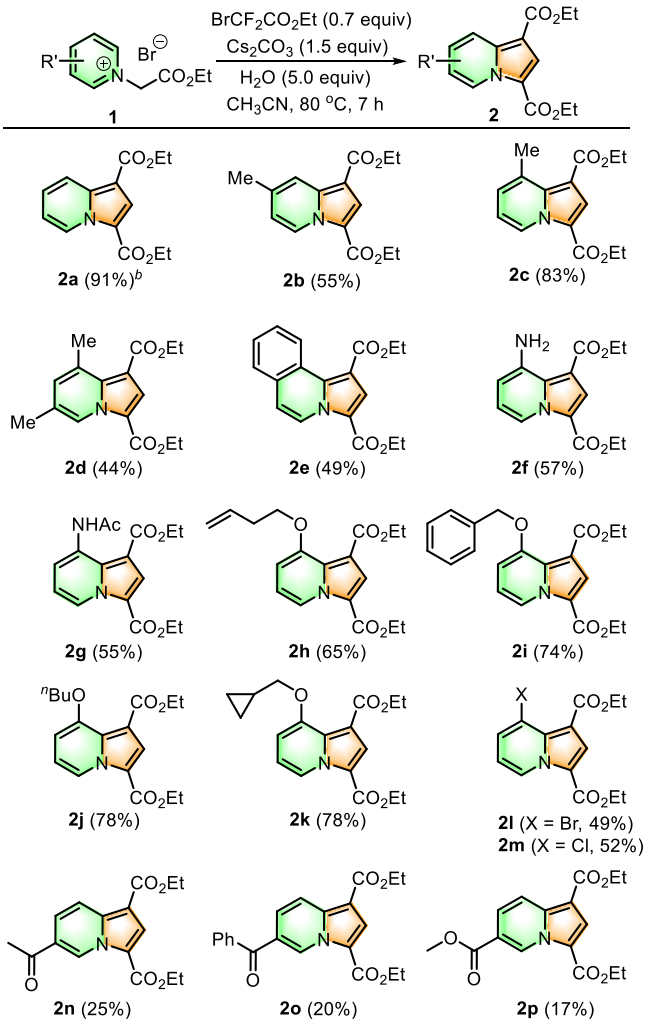
Table 1. Optimization of Reaction Conditions[a]



entry	variation from the "standard" conditions	**2a** (%)	**3a** (%)
1	none	94 (91)	0
2	without H_2O	16	10
3	THF, instead of CH_3CN	10	1
4	CH_2Cl_2, instead of CH_3CN	1	4
5	Tol, instead of CH_3CN	0	0
6	DMSO, instead of CH_3CN	10	8
7	NaOH, instead of Cs_2CO_3	4	0
8	K_3PO_4, instead of Cs_2CO_3	12	4
9	K_2CO_3, instead of Cs_2CO_3	90 (87)	0
10	TMEDA, instead of Cs_2CO_3	0	0

[a]Reaction conditions: **1a** (0.5 mmol), $BrCF_2CO_2Et$ (0.7 equiv), base (1.5 equiv), H_2O (5.0 equiv) in solvent (2.0 mL) for 7 h under argon atmosphere. Yields were determined by GC analysis with mesitylene as an internal standard. The numbers in parentheses are isolated yields.

Scheme 2. Scope with Various Pyridinium Salts[a]



[a]Reaction conditions: Unless otherwise noted, all reactions were performed with **1** (1.0 mmol), $BrCF_2CO_2Et$ (0.7 equiv), H_2O (5.0 equiv), Cs_2CO_3 (1.5 equiv) in CH_3CN (4 mL) at 80 °C under Ar for 7 h. Isolated yields. [b]90% yield in a 5.0 mmol scale.

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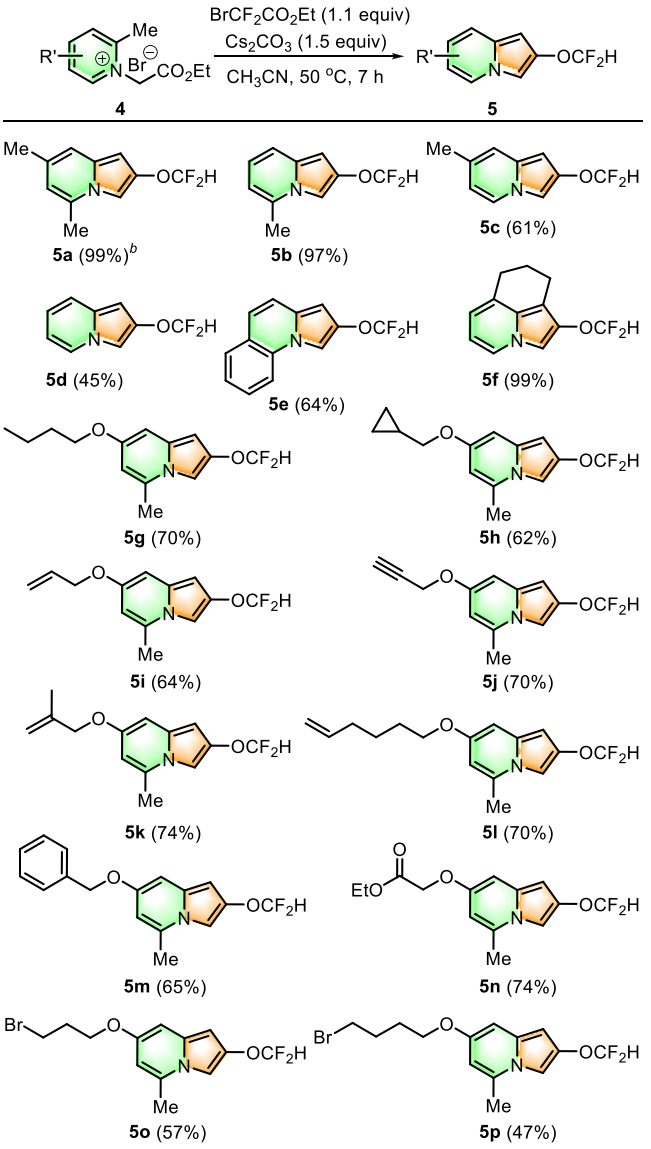
substituted by an electron-withdrawing group (e.g., *m*-COMe, *m*-COPh, *m*-CO_2Me), the reaction selectively occurred at the C6-position with a low yield (**2n**−**2p**, 17−25%). Substrates with other electron-withdrawing groups on the pyridine ring (e.g., *m*-$CONH_2$, CONHBn, *m*-CHO, *m*-F, *p*-CN) or other substituents on nitrogen (e.g., *N*-cyanomethyl salt, *N*-2-oxo-2-phenylethyl salt) have also been subjected to the current conditions; however, the reactions are messy and no desired products can be isolated. A detailed discussion on regioselectivity of *m*-substituted pyridinium salts and reaction of more substrates is included in the SI (see Schemes S1−S3).

When we used the collidine-derived salt (**4a**) instead of **1a**, the product **5a** was obtained in 70% isolated yield. The reaction conditions were optimized, and the yield can be improved to 99% in the absence of water at 50 °C (see Table S2 in the Supporting Information for details of reaction conditions optimization). Next, the substrate scope of this reaction was explored, and the results were summarized in Scheme 3. First, the effect of the methyl position on pyridine was investigated. When the methyl groups were present at both C2- and C6-positions of pyridiniums, the yields were excellent (**5a**, 99% and **5b**, 97%). However, when there was no methyl group at the C6-position of pyridiniums, the yields decreased to moderate levels (**5c**, 61% and **5d**, 45%). Quinolinium salts were also investigated, and 1-(2-ethoxy-2-oxoethyl)-2-methylquinolin-1-ium bromide (**4e**) and 1-(2-ethoxy-2-oxoethyl)-5,6,7,8-tetrahydroquinolin-1-ium bromide (**4f**) under these reaction conditions led to the desired products **5e** and **5f** in 64% and 99% yield, respectively. Therefore, the substitutions on the C2- and C6-positions of pyridinium salts were beneficial to this reaction. A series of pyridinium salts substituted with methyl groups at both C2- and C6-positions were prepared (**4g**−**4p**) and subjected to the optimized conditions. Gratifyingly, different ether substitutions (such as alkyl, propargyl, allyl, benzyl, and ester groups) on the C4-position of 2,6-dimethylpyridinium salts could be well tolerated with the target products being obtained in moderate yields ranging from 62% to 74% (**5g**−**5n**). However, when the bromine atom was attached to the alkyloxy group, the yields slightly decreased to 47−57% (**5o**−**5p**). When 2-(2-methoxy-2-oxoethyl)-1-methylisoquinolin-2-ium bromide was subjected to the same conditions, the desired product 2-(difluoromethoxy)pyrrolo-[2,1-*a*]isoquinoline was obtained together with ester group substituted byproducts (see Scheme S4 in the Supporting Information for the reaction details).

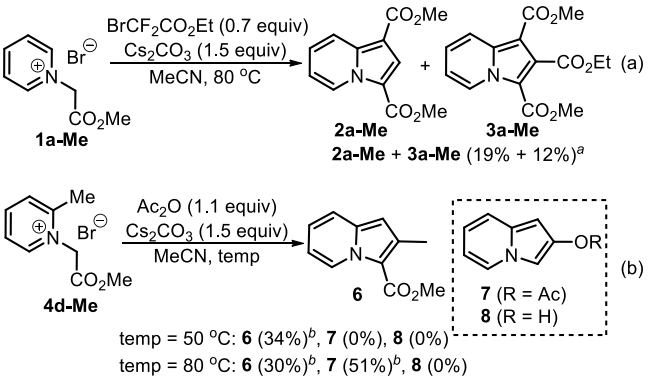
To clarify the reaction mechanism of these transformations, a series of control experiments were carried out. For the reaction of **1a**, three additional carbons were installed, which might come from another molecule of pyridinium salt, or $BrCF_2CO_2Et$, or both. When we treated compound **1a** under the optimized conditions in the absence of $BrCF_2CO_2Et$, no **2a** resulted. This implied that $BrCF_2CO_2Et$ was essential to formation of **2a**, and at least one carbon was derived from $BrCF_2CO_2Et$. In order to prove the origin of the esters in product **2a**, **1a**-Me with methyl ester was synthesized and subjected to the optimized conditions except in the absence of water (Scheme 4a). Two products were obtained with the yield of **2a-Me** being 19% and the yield of **3a-Me** being 12%. The ethyl ester of indolizine at C2 implies that the C2 originates from $BrCF_2CO_2Et$ while the other two methyl esters originate from pyridinium salt **1a-Me**. Besides, GC analysis of the reaction indicates that pyridine was formed, which suggested that the reaction involved the participation of another

Scheme 3. Scope with Various 2-Methylpyridinium Salts[a]



[a]Reaction conditions: Unless otherwise noted, all reactions were performed with **4** (1.0 mmol), $BrCF_2CO_2Et$ (1.1 equiv), Cs_2CO_3 (1.5 equiv) in CH_3CN (4 mL) at 50 °C under Ar for 7 h. Isolated yields. [b]92% yield in a 4.0 mmol scale.

Scheme 4. Control Experiments for Mechanistic Studies



[a]Yield and ratio were determined by GC analysis with mesitylene as an internal standard. [b]Isolated yields.

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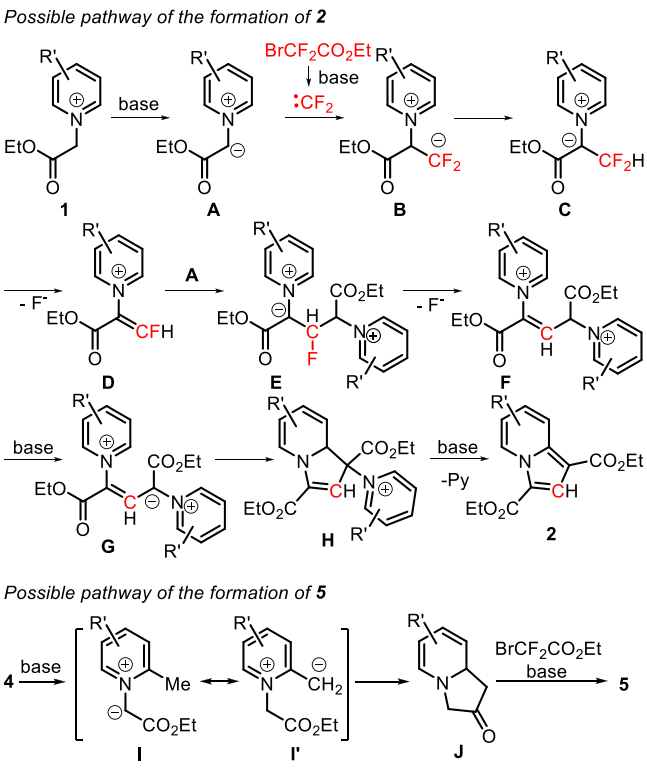
molecule of pyridinium salt **1a** with the release of a pyridine molecule. For a detailed discussion, see Scheme S5 in the Supporting Information.

For compounds **4** with α-substitution, the α-deprotonation become preferred. It is possible that compound **4** can undergo base catalyzed intramolecular cyclization to afford **8**, which can capture difluorocarbene from $BrCF_2CO_2Et$ to afford **5**. However, when **4d** was treated under the optimized conditions in the absence of $BrCF_2CO_2Et$, no **8** was afforded. Considering the lability of **8** reported in the literature,[3a] we attempted to capture **8** with acetic anhydride. However, we only got **6** with 34% yield instead of the Chichibabin-like cyclization product **7**. When the reaction temperature rose to 80 °C, both compounds **6** and **7** can be isolated in 30% and 51% yields, respectively. With $BrCF_2PO(OEt)_2$ as the CF_2 carbene precursor instead of $BrCF_2CO_2Et$, Chichibabin-like cyclization product **5a** can be isolated in 45% yield, which is lower than that of $BrCF_2CO_2Et$. Then carbene trap experiments were attempted, which indicated that difluoromethyl carbene is involved in the process of generating compounds **2a** and **5a** (for a detailed discussion, see Schemes S7 and S8 in the Supporting Information).

Based on the above experimental observations and previous reports,[3,13] a plausible reaction mechanism for the synthesis of indolizines was proposed in Scheme 5. First, in the presence of

Scheme 5. Proposed Reaction Mechanism



Cs_2CO_3, the pyridinium salt would be deprotonated to afford ylide **A** which could capture the difluorocarbene to afford **B**. Then intermediate **B** will undergo proton exchange and elimination of F^- to afford **D**, which would undergo nucleophilic addition by another molecule of **A**. Elimination of F^- followed by deprotonation results in **G**, which would undergo intramolecular nucleophilic addition to furnish intermediate **H**. Finally, removal of a molecule of pyridine in the presence of base will lead to diester **2**. In the absence of water, **3a** can be afforded which indicates that the reaction might proceed through other pathways.

When R is CH_3, the anion **I'** resulted which undergoes intramolecular cyclization to result in intermediate **J**. Then tautomerization of **J** followed by capture of difluorocarbene would result in **5** as a stable product. The formation of **6** in Scheme 4b can be explained by the reaction of **I'** with acetic anhydride. A detailed mechanism for formation of **6** and other possible mechanisms for **3** and **5** are included in Scheme S9 in the Supporting Information.

The role of water remains unclear in the above transformations. As shown in Scheme 2, water can improve the regioselectivity toward the diester **2**. However, for the formation of 2-difluoroalkoxy indolizines **5**, the reaction proceeds more smoothly without water. This duality is due to the different reaction mechanisms involved. For selective synthesis of **2**, the water might serve as a proton mediator that promotes the proton transfer from **B** to **C**, thus improving the regioselectivity and yield of **2**. When D_2O was used instead of H_2O, deuterated product **2a-D** can be obtained (see Scheme S6 in the Supporting Information for details). For the formation of **5**, the key step is intramolecular cyclization of highly active and moisture-sensitive **I'** to form intermediate **J**. Therefore, the anhydrous condition is more favorable under this situation.

In summary, we have developed an efficient method for synthesis of indolizines by the annulation of pyridinium salts with $BrCF_2CO_2Et$ as a key reagent. Through the regulation of the α substitution of pyridine, highly regioselective 1,3-disubstituted indolizines and C2-difluoromethoxylation indolizines derivatives can be afforded, thus enriching the indolizine compound library. The current transformations not only provide a new synthetic strategy toward biologically active indolizine derivatives but also enrich the chemistry of $BrCF_2CO_2Et$ as a versatile precursor. Further studies to elucidate the mechanistic details of the transformation and apply it to the synthesis of bioactive compounds is in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03540.

Experimental procedures, spectral and analytical data, copies of ^1H, ^{19}F, and ^{13}C NMR spectra for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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