Fluorine in Heterocyclic Chemistry
Volume 1

5-Membered Heterocycles and Macrocycles
Fluorinated Indolizines

Eugene V. Babaev

Contents
1 Introduction ................................................................................................................ 158
2 Synthesis of Indolizines with Substituent in Pyrrole Fragment ...................................... 158
   2.1 Indolizines with Substituent at Position 3 ................................................................. 158
   2.2 Indolizines with Substituent at Position 1 ................................................................. 165
   2.3 Indolizines with Substituent at Position 2 ................................................................. 168
3 Synthesis of Indolizines with Substituent in Pyridine Ring .............................................. 172
   3.1 Indolizines with Substituent at Position 6 and 8 ....................................................... 172
   3.2 Indolizines with Substituent at Position 7 ................................................................. 176
   3.3 Indolizines with Substituent at Position 5 ................................................................. 177
4 Conclusion .................................................................................................................. 177
References .................................................................................................................... 178

Abstract The chapter is devoted to the synthesis and application of indolizines bearing fluorine atoms, perfluorinated alkyl (aryl) groups, and COF$_3$ fragments.

Keywords Indolizine • Fluorine • Trifluoromethyl group • Synthesis • Fluorinated heterocycles

E.V. Babaev (✉)
Department of Chemistry, Moscow State University,
Leninskie Gory, Moscow 119992, Russian Federation
Moscow Institute of Physics and Technology,
Institutskii per. 9, 141700 Dolgoprudny, Moscow Region, Russia
e-mail: babaev@org.chem.msu.ru
1 Introduction

Fluorinated heterocycles have received increasing attention due to their important biological properties. Considerable efforts have been paid to the exploitation of new synthetic routes to these fluorinated compounds. Indolizine is an important fundamental ring system in view of its similarity to indole. This heterocycle occurs commonly as a fully reduced form in natural products. Owing to the increasing importance of fluorine containing heterocycles in biology, pharmacology, and industrial application, synthesis of fluorine-containing indolizines became of considerable interest. In spite of existence of numerous reviews on the chemistry of indolizines [1] no attention have been paid to its fluorinated derivatives. In fact, this area is relatively young (the first research paper on this topic appeared 30 years ago). In spite of many efforts, up to now no indolizines with perfluorinated groups appeared on the market.

The review is organized in the following way. First, indolizines with substitutents at pyrrole fragment are covered. This includes indolizines substituted at positions 3 and 1 (since these positions are most easily substituted), and then 2-substituted derivatives. Then, indolizines substituted at pyridine ring are covered: structures with 6(8)-perfluorinated groups are reviewed, and finally, 7- and 5-derivatives are discussed. Major attention is paid to indolizines; benzo-derivatives are also included.

2 Synthesis of Indolizines with Substituent in Pyrrole Fragment

2.1 Indolizines with Substituent at Position 3

Although the position 3 in the indolizine ring is the most reactive toward electrophilic attack, no direct fluorination of indolizines have been reported. Instead, in the recent work [2] 1,3-dipolar cycloaddition was studied to difluoro-substituted pyridinium ylides.

\[
\begin{align*}
\text{CF}_2\text{Br}_2/\text{Pb}/\text{Bu}_2\text{NBr} & \quad \text{CF}_2,\text{Br}_2/\text{Pb}/\text{Bu}_2\text{NBr} \\
\text{CH}_2\text{Cl}_2/\text{ultrasound} & \quad \text{MnO}_2 \\
\text{X} = \text{CN, CO}_2\text{Et, COPh} & \quad \text{Y} = \text{CO}_2\text{Me, CN} \\
\end{align*}
\]
Difluoromethylides were prepared from 4-cyano, 4-benzoyl- and 4-ethoxycarbonyl-substituted pyridines under difluorocarbene generation conditions (ultrasound, CF$_2$Br$_2$/Pb/Bu$_4$NBr) and trapped with dimethyl maleate or fumaronitrile. 3-Fluoroindolizines were isolated as final products of the reaction which involves dehydrofluorination of the primary cycloadducts followed by dehydrogenation by active MnO$_2$.

These ylides were shown to dissociate to carbene and pyridine with low activation barrier. The equilibrium constant of the reaction increases with increasing electron-withdrawing ability of substituents in the pyridine ring. There was no reaction with unsubstituted pyridine or picolinic acid nitrile. In the reaction of nicotinic acid nitrile with the fumaronitrile a mixture of the regioisomeric products was formed:

The reaction of N-CH$_2$CF$_3$ pyridinium salt with dimethyl acetylenedicarboxylate or perfluorobut-2-yne in the presence of base (Et$_3$N or K$_2$CO$_3$) [3] has provided first formation of indolizines 2 with CF$_3$-group in position 3.
Similarly, the reaction of ylide formed from \(N-\text{CH}_2\text{COCF}_3\) pyridinium salt and dimethyl acetylenedicarboxylate or perfluorobut-2-yne gave rise to \(3\text{-COF}_3\)-indolizines 3 [4].

\[
\begin{align*}
\text{X} & \equiv \text{X} \\
\text{N}^+ & \text{CH}^- \\
\text{O} & \text{COF}_3 \\
\text{3} & \text{O} \equiv \text{CF}_3 \\
\text{X} & = \text{CO}_2\text{Me} \ (70\%) \\
\text{X} & = \text{CF}_3 \ (20\%)
\end{align*}
\]

The same methodology was applied to \(N-\text{CH}_2\text{COF}_3\) \(\gamma,\gamma'\)-bipyridinium salt leading to intermediate indolizine 4 or final aminosugar 5 with \(3\text{-COF}_3\) group [5].

\[
\begin{align*}
\text{R} & \equiv \text{Ar} \\
\text{O} & \text{CO}_2\text{Ar} \\
\text{4} & (42\%) \\
\text{R} & \equiv \gamma\text{-Py} \\
\text{Br}^- & \equiv \text{CF}_3 \\
\text{Et}_3\text{N}/\text{DMF}/2\text{h} & \equiv \text{DMF}/12\text{h} \\
7\% & 20\%
\end{align*}
\]

It should be mentioned that isoquinoline 2-oxide reacted with perfluorobut-2-yne similarly forming (among other products) 1,2,3-tris(trifluoromethyl)- and 1,2-bis(trifluoromethyl)-3-trifluoroacethylpyrrolo[2,1-a]isoquinoline [6].

\[
\begin{align*}
\text{N}^+ & \equiv \text{O} \\
\text{Et}_3\text{N} & \equiv \text{DMF}/12\text{h} \\
\text{traces} & \equiv 5\%
\end{align*}
\]

Finally, \(3\text{-COC}_6\text{F}_5\) indolizine 6 was obtained together with more saturated product 7 by cycloaddition of the corresponding ylide and methyl acrylate [7].
Meanwhile, it is much easier to prepare indolizines with perfluoroacyl substituent at position 3 by perfluoroacylation reaction. The reaction yields are strongly depended on the basicity of the parent indolizine: thus 2-phenylindolizine underwent trifluoroacetylation to form 8 in 36%; the rest (60% after regeneration) was indolizinum cation formed by protonation of starting material [8].

Nitroindolizines having 6- and 8-nitro group in the same reaction led to trifluoroacetyl derivatives 9–12 in quantitative yield [9]. It was shown that their basicity is decreased.

<table>
<thead>
<tr>
<th>Indolizine</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>3-COCF₃, 6-NO₂, 2-Ph, 7-Me</td>
</tr>
<tr>
<td>10</td>
<td>3-COCF₃, 6-NO₂, 2-Me</td>
</tr>
<tr>
<td>11</td>
<td>3-COCF₃, 8-NO₂, 2-Me</td>
</tr>
<tr>
<td>12</td>
<td>3-COCF₃, 8-NO₂, 2-Ph</td>
</tr>
</tbody>
</table>

5-Bromoindolizine underwent trifluoroacetylation selectively at position 3 leading to compound 13; the yield was 83% [10]. 2-Carbomethoxyindolizine is transformed to 3-COCF₃ derivative 14 in 85% yield [11].
There is only one example of trifluoroacylation in the series of benzoindolizines. 3-Perfluoroacetyl derivatives 15 and 16 were obtained in high yield [12] using trifluoroacetic and perfluorosuccinic anhydride as acylating agents.

Pyrrolo[1,2-a]pyrazinum (7-azaindolizinium) cations may undergo ring opening and transformation of the pyrazinium fragment under the action of MeNH₂. The rearrangement is known as Kost-Sagitullin (enamine) rearrangement.

On the other hand, 7-azaindolizinium cations with COCF₃ group may be involved in haloformic recyclization leading to oxo-derivatives of pyrrolo[1,2-a]pyrazines. Here the NHMe-amino group was originated from the reagent.
At lower temperature the product 17 of enamine rearrangement to pyridine ring predominated, whereas at higher temperature (and in water solution) the ring transformation occurred with haloformic reaction to form 18 [13].

![Chemical structure](image)

<table>
<thead>
<tr>
<th>№</th>
<th>R</th>
<th>30 °C</th>
<th>170 °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Et</td>
<td>10:39</td>
<td>45:6</td>
</tr>
<tr>
<td>b</td>
<td>n-Pr</td>
<td>15:50</td>
<td>44:10</td>
</tr>
<tr>
<td>c</td>
<td>PhCH₂</td>
<td>60:0</td>
<td>70:0</td>
</tr>
</tbody>
</table>

Electrophilic nature of 3-COCF₃ group is displayed by the reaction of indolizine 14 with hydrazine forming pyridazinone derivative 19 in the yield 79 % [11].

![Chemical structure](image)

3-Trifluoroacetyl indolizines underwent removal of 3-COCF₃ group in good yield by the reaction with cold alkali [9, 4, 12].
It should be mentioned that similar pyrroles, indoles and azulenes bearing COCF$_3$ group all reacted with alkali with haloformic removal of CHCF$_3$; the “strange” behavior of 3-COCF$_3$ indolizines was explained by their higher basicity and possibility of substitution of trifluoroacetate ion by ipso-protonation [14].

![Chemical structure](image)

Particularly, this statement was confirmed by reaction of trifluoroacetyl derivatives of 6- and 8-nitroindolizines with alkali. Being less basic these compounds underwent haloformic reaction to form nitroindolizine-2-carboxylic acids. The reaction, however, did not stop at this point and finalized with transformation of pyridine ring (of indolizines) to benzene ring of indoles [9].

![Chemical reactions](image)

<table>
<thead>
<tr>
<th>Indolizine</th>
<th>Indole (acid)</th>
<th>Yield of indole (acid), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>21 (20)</td>
<td>98 (67)</td>
</tr>
<tr>
<td>11</td>
<td>23 (22)</td>
<td>72 (42)</td>
</tr>
<tr>
<td>12</td>
<td>24</td>
<td>80</td>
</tr>
</tbody>
</table>

It should be mentioned that conversion of indolizines to indole 2-carboxylic acids proceeded in higher yields and in milder conditions (0 °C) than for indolizines without COCF$_3$ group. The overall mechanism is of the ANRORC type:
2.2 Indolizines with Substituent at Position 1

Position 1 of the indolizine ring is the second one (after position 3) that can be attacked by electrophiles. However, there are no examples of direct fluorination of indolizine ring at position 1. Among the benzoindolizines there is such an example [15] where the desired F-containing scaffold 25 was obtained by use of Selectfluor.

Another example of direct incorporation of perfluorinated substituent at the position 1 is the insertion of CF₃S group using CF₃SCl as electrophile [16]. Reaction proceeded at positions 1 and 3 even in the case of deactivated 3-COMe indolizine quantitatively. In the case of 3-benzylindolizine substitution at C-1 is accompanied by insertion of electrophile in the benzyl fragment as well.

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>26a</td>
<td>R=R'=H</td>
<td>27a</td>
</tr>
<tr>
<td>26b</td>
<td>R=H, R'=Me</td>
<td>27b</td>
</tr>
<tr>
<td>26c</td>
<td>R=Me, R'=Ac</td>
<td>27c</td>
</tr>
<tr>
<td>26d</td>
<td>R=Me, R'=PhCH₂</td>
<td>27d</td>
</tr>
</tbody>
</table>
As it was shown recently [17], perfluorophenyl group can be inserted at position 1 and 3 under the cross-coupling conditions. This regioselective reaction took place with pyridine, potassium phosphate, copper (I) iodide, 1,10-phenanthroline and iodine in 1,4-dioxane at 120–130 °C during 74 h.

Investigation of the direction of trifluoroacetylation of 2-methylindolizine has shown minor amounts of the 1-substituted isomer formed in addition to the “usual” product of substitution in the 3 position [18].

Furthermore, 1-COCF₃ isomer is formed when 3-COCF₃ indolizine was heated in CH₃COOH (together with 1- and 3-acetylindolizines) [14]. The reaction mechanism seemed to be intramolecular.
In addition to direct insertion of perfluorinated group at position 1, there are plenty of methods how to introduce such a group via cycloaddition reaction. Thus, convenient method to perfluoroalkylated indolizinyl-phosphonates 31 was reported [19]. The reaction proceeded regioselectively via the 1,3-cycloaddition of pyridinium N-ylide and perfluoroalkynyl phosphate in 49–77 % yields. Similar reaction was proposed to obtain pyrrolo[1,2-a]isoquinolinyl phosphonates in 48–78 % yields [20].

In the reaction of 2-bromo-3,3,3-trifluoropropene with pyridinium ylides cycloaddition occurred readily leading to 1-CF₃ derivatives of indolizines [21]. Similar reaction took place in the cases of pyridazinium and isoquinolinium ylides.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Rf</th>
<th>R’</th>
<th>R</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>31a</td>
<td>CF₃</td>
<td>Et</td>
<td>CN</td>
<td>74</td>
</tr>
<tr>
<td>31b</td>
<td>CF₃</td>
<td>Pr</td>
<td>CN</td>
<td>70</td>
</tr>
<tr>
<td>31c</td>
<td>C₂F₅</td>
<td>Et</td>
<td>CN</td>
<td>73</td>
</tr>
<tr>
<td>31d</td>
<td>C₂F₅</td>
<td>Pr</td>
<td>CN</td>
<td>49</td>
</tr>
<tr>
<td>31e</td>
<td>CF₃</td>
<td>Et</td>
<td>CO₂Et</td>
<td>47</td>
</tr>
<tr>
<td>31f</td>
<td>CF₃</td>
<td>Pr</td>
<td>CO₂Et</td>
<td>51</td>
</tr>
<tr>
<td>31g</td>
<td>C₂F₅</td>
<td>Et</td>
<td>CO₂Et</td>
<td>51</td>
</tr>
<tr>
<td>1h</td>
<td>CF₃</td>
<td>Et</td>
<td>COPh</td>
<td>77</td>
</tr>
<tr>
<td>31i</td>
<td>C₂F₅</td>
<td>Et</td>
<td>COPh</td>
<td>65</td>
</tr>
<tr>
<td>31j</td>
<td>C₃F₇</td>
<td>Et</td>
<td>COPh</td>
<td>70</td>
</tr>
</tbody>
</table>

Fluorinated Indolizines
<table>
<thead>
<tr>
<th>R</th>
<th>R’</th>
<th>Yield (%)</th>
<th>R</th>
<th>R’</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPh</td>
<td>H</td>
<td>40</td>
<td>COPh</td>
<td>Me</td>
<td>49</td>
</tr>
<tr>
<td>COMe</td>
<td>H</td>
<td>24</td>
<td>COMe</td>
<td>Me</td>
<td>27</td>
</tr>
<tr>
<td>CO₂Et</td>
<td>H</td>
<td>35</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The reaction of 3-COCF₃ pyridinium ylide with 1,1,1-trifluoropropyne proceeded similarly giving 1-CF₃ indolizine in low yield [4]. Similarly behaved other pyridinium ylides with benzoyl and ester groups [22].

![Reaction Scheme](image)

Pyridinium ylides reacted with 4-ethoxy-1,1,1-trifluorobut-3-en-2-one to give the corresponding 1-trifluoroacetyl-substituted indolizines [23]. Isoquinolinium ylides behaved similarly.

![Reaction Scheme](image)

<table>
<thead>
<tr>
<th>R</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPh</td>
<td>76 %</td>
</tr>
<tr>
<td>CN</td>
<td>74 %</td>
</tr>
<tr>
<td>CO₂Et</td>
<td>R=CO₂Et/Me</td>
</tr>
</tbody>
</table>

### 2.3 Indolizines with Substituent at Position 2

2-Fluoroidolizines are easily available via cycloaddition of fluorinated vinyl tosylates and pyridinium ylides [24]. Using β-substituted pyridinium ylides both isomers (6 and 8) were formed with clear predominance of 8-isomers. One product with 3-CO₂Et group was recently patented as the intermediate [25]. The reaction also proceeded with isoquinolinium and benzimidazolium ylides.

![Reaction Scheme](image)
Further modification of the strategy was proposed; 1-chloro-2,2,2-trifluoroethane (bp 6 °C) or 1,1,1,2-tetrafluoroethane (bp -27 °C) gave the corresponding 2-fluoroindolizines 38 via 1,3-dipolar cycloaddition at 80–100 °C in DMSO at atmospheric pressure in normal glassware [26]. The reaction started with the elimination of HF from CF₃CH₂X and can be applied to isoquinolinium ylides.

In the presence of base, 2,2-dihydroyfluoroalkanoates of the type RₙCF₂CH₂CO₂Et reacted with N-(cyanomethyl)pyridinium ylides to give the corresponding indolizine derivatives carrying both a fluoroalkyl and a cyano group [27].
Ethyl 2,2-dihydropoly(per)fluoroalkanoates reacted with N-phenacylpyridinium ylides in DMF to give poly(per)fluoroalkyl-substituted indolizines 40 and 41 [28]. Origin of the products 41 is explained by the adduct aromatization.

\[
\begin{align*}
&\text{N}R^+\text{COPh} + \text{Cl(CF}_2\text{)}_n\text{CH}_2\text{CO}_2\text{Et} + \text{R=H, Me, CN}
\end{align*}
\]

N-Benzylpyridinium ylides (generated in situ from the N-benzylpyridinium bromide and alkali) reacted with ethyl 3-fluoro-3-fluoroalkyl acrylates to give one or two fluoroalkylated indolizine derivatives through 1,3-dipolar cycloaddition followed by an oxidative aromatization or 1,3-H-shift aromatization process [29].

\[
\begin{align*}
&\text{R=H, X=H} & \text{42a} (18) & \text{43a} (14) \\
&R=H, X=\text{OMe} & \text{42b} (31) & \text{43b} (18) \\
&R=H, X=\text{NO}_2 & \text{42c} (31) & \text{43c} (29) \\
&R=\text{CO}_2\text{Et, X=H} & \text{42d} (35) & \text{43d} (8) \\
&R=\text{Me, X=NO} & \text{42e} (5) & - \\
&R=\text{CO}_2\text{Et, X=NO}_2 & \text{42f} (33) & - \\
\end{align*}
\]

In the presence of K\textsubscript{2}CO\textsubscript{3} and Et\textsubscript{3}N, pyridinium N-ylides, generated in situ from their halides, reacted with gaseous fluoroalkenes CF\textsubscript{2}=CFX (X=Cl, Br) in DMF under atmospheric pressure in normal glassware at 70 °C to give the corresponding 1,2-fluorinated indolizines. Similar results were obtained with tetrafluoroethylene in an autoclave [30].
The reaction proceeded also with quinolinium, isoquinolinium and benzimidazolium ylides. In the reaction of ylide obtained from β-picoline the mixture of 6- and 8-isomers was formed.

<table>
<thead>
<tr>
<th>Alkene/X</th>
<th>Ylide, R,R'</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl</td>
<td>COPh, H</td>
<td>66</td>
</tr>
<tr>
<td>Cl</td>
<td>COPh, Me</td>
<td>64</td>
</tr>
<tr>
<td>Cl</td>
<td>CO₂Et, H</td>
<td>37</td>
</tr>
<tr>
<td>Br</td>
<td>COPh, H</td>
<td>57</td>
</tr>
<tr>
<td>Br</td>
<td>COPh, Me</td>
<td>77</td>
</tr>
<tr>
<td>Br</td>
<td>CO₂Et, H</td>
<td>75</td>
</tr>
<tr>
<td>F</td>
<td>COPh, Me</td>
<td>32</td>
</tr>
</tbody>
</table>

Similar reaction took place for hexafluoropropene to form 1-CF₃ indolizines. The result was similar to the early one by Banks with NCH₂CO₂Bu⁺ [31], [32], NCH₂COCF₃ [4] and NCH₂COR [22] pyridinium salts.
3 Synthesis of Indolizines with Substituent in Pyridine Ring

3.1 Indolizines with Substituent at Position 6 and 8

It is difficult to obtain pure isomers containing fluoro (or perfluorinated group) at 6- or 8-position. Since the substituents cannot be inserted directly into the pyridine fragment of indolizine ring, they should already exist in the precursors of the corresponding indolizines. However, this caused loss of regioselectivity (if β-substituted pyridinium salts were used) or necessity to use poorly available β-substituted α-picolines.

For example, reaction between 3-fluorosubstituted pyridinium N-bis-(methoxy-carbonyl)methylide and methyl propiolate [33] proceeded in the yield 53% giving predominant formation of 8-isomer (47a:47b = 65:35). CNDO2 calculations showed that the site selectivity can be rationalized by dipole-dipole interactions.
Another example was the copper(I)-catalyzed cycloaddition of ethyl isopropenyl diazoacetate to 3-F-pyridine \([34]\); reaction took place in the yield 60 % with clear predominance of 8-isomer \((48a:48b = 3:1)\). The process represents the first successful example of metal-catalyzed cyclization of a \(\pi\)-deficient heterocyclic system with alkenyldiazo compounds.

More one example is connected with generation of unsubstituted ylides \([35]\). As facile precursors for non stabilized pyridinium methylides \(N\)-(trimethylsilylmethyl) pyridinium triflates were synthesized. Cesium fluoride induced desilylation of the precursors liberated the nonstabilized pyridinium methylides which were trapped as the cycloadducts to dimethyl acetylenedicarboxylate. Trapping of 3-CF$_3$-pyridinium ylide gave the mixture of isomers \((50a:50b = 1:5)\) in 53 % overall yield.
In the patent literature there were two examples of preparation of indolizyl-1-acetic acid according to Chichibabin methodology: the first one – 6-fluoroindilinzine $^{51}$ [36] and the second one – 6-CF$_3$-derivative [37].

Successful cycloisomerization of acyclic alkynyl imines to pyroles caused an attempt to the cycloisomerization of the cyclic alkynyl imines; thus 2-alkynyl pyridine with CF$_3$-group gave a product of cyclization, indolizine $^{53}$ [38].

2-(Pyridin-2-yl-methylene)malonates and arynes reacted to produce pyrido[1,2-a]indoles which in some cases ($^{54, 55}$) correspond to 6-fluoroderivatives of benzo-indolizines [39].

A base-promoted conversion of ortho-trifluoromethyl benzyl derivatives of NH-heterocycles into a respective fluorinated isoquinolines (38–57 % isolated yields) was reported [40]. The reaction is general for the benzylated derivatives of the electron-rich NH heterocycles, particularly indoles. The outcome of the reaction
could be explained by an intermediate formation of a highly reactive quinone methylide species.

\[
\begin{array}{cccc}
R & R' & R'' & \text{Yield, \%} \\
H & H & - & 38 \\
Me & H & - & 39 \\
Me & Me & - & 48 \\
\end{array}
\]

\[
\begin{array}{cccc}
R & R' & R'' & \text{Yield, \%} \\
H & - & - & H & 44 \\
- & - & Cl & 52 \\
- & - & OMe & 43 \\
\end{array}
\]

In several cases the reported structures of 8-fluoro indolizine were in fact mixtures; however, no analysis of traces of the 6-fluoro isomer was performed. Thus, to the product of reaction of 3-fluoropyridine, CH-acid and active quinone compound the structure of 8-F-indolizine was assigned [41, 42, 43]. Similarly, cycloaddition to β-CF₃-pyridinium ylide is claimed to result in 8-CF₃-derivative of indolizine [25].

A novel and efficient preparation of 4-polyfluoroaryl substituted pyrrolo[1,2-a]quinolines via a palladium-catalyzed reaction of 1-[2-(2,2-dibromo-ethenyl)phenyl]-1H-pyrrole with polyfluorinated arenes was described [44]. The reaction is also applicable to obtain indoloquinolines with the same substitution pattern.
3.2 Indolizines with Substituent at Position 7

7-F or 7-CF₃ indolizines can be found only in the patent literature, namely compounds 56a [45], 56b [25], 56c, 56d [46] and 56e [37].

A water-accelerated palladium-catalyzed reaction of gem-dibromoolefins with a boronic acid via a tandem Suzuki-Miyaura coupling and direct arylation was reported [47]. One of the products, 57, corresponded to 7-CF₃ derivative of benzoindolizine.
3.3 Indolizines with Substituent at Position 5

The only reaction which allowed introducing fluorine atom at position 5 of indolizine ring was the Ugi-type reaction [48]. The resulting 5-fluoroinolizine 58 was sensitive to nucleophiles giving rise to mini-library of 5-substituted derivatives.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Indolizine (Nu)</th>
<th>Yield, %</th>
<th>Indolizine (Nu)</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>F (58)</td>
<td>65</td>
<td>O(CH₂)₂NMe₂</td>
<td>17</td>
</tr>
<tr>
<td>SCH₂CO₂Me</td>
<td>98</td>
<td>1-Morpholinyl</td>
<td>61</td>
</tr>
<tr>
<td>SCH₂CO₂H</td>
<td>95</td>
<td>NH(CH₂)₂NMe₂</td>
<td>48</td>
</tr>
<tr>
<td>SMe</td>
<td>49</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Finally, a palladium- and copper-catalyzed tandem N-H/C-H bond functionalization reaction of ortho-(2-chlorovinyl)bromobenzenes with indoles and pyrroles has been developed [49].

![Chemical structure](image)

A variety of CF₃-containing indolo- and pyrrolo[2,1-a]isoquinolines were prepared in moderate to good yields via the cyclization of 1-bromo-2-(2-chloro-3,3,3-trifluoroprop-1-enyl)benzenes with indoles and pyrroles.

4 Conclusion

Fluorinated indolizines remained relatively rare class of compounds. In contrast to indolizines substituted at pyrrole fragment the structures having a perfluoro-substituent in the pyridine ring are less available. This is caused by the fact that 3
and 1 substituted indolizines are easily available by direct insertion of fluorine containing group. It should be mentioned that 1-, 2- and 3-substituted indolizines could be easily obtained by 1,3-dipolar cycloaddition reactions, whereas there is lack of general methods to the structures substituted in pyridine ring.

Acknowledgments  This work was funded by RFBR (grant 12-03-00644-a).

References


