Valentine Nenajdenko
Editor

Fluorine in Heterocyclic Chemistry Volume 1

5-Membered Heterocycles and Macrocycles

Springer

Editor
Valentine Nenajdenko
Department of Chemistry
Moscow State University
Moscow, Russia

Volume 1: ISBN 978-3-319-04345-6 ISBN 978-3-319-04346-3 (eBook)
Volume 2: ISBN 978-3-319-04434-7 ISBN 978-3-319-04435-4 (eBook)
Set ISBN 978-3-319-06036-1
DOI 10.1007/978-3-319-04346-3
DOI 10.1007/978-3-319-04435-4
Springer Cham Heidelberg New York Dordrecht London

Library of Congress Control Number: 2014942653

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Fluorinated Indolizines

Eugene V. Babaev

Contents

Abstract The chapter is devoted to the synthesis and application of indolizines bearing fluorine atoms, perfluorinated alkyl (aryl) groups, and $COCF_3$ fragments.

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

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V. Nenajdenko (ed.), *Fluorine in Heterocyclic Chemistry Volume 1: 5-Membered Heterocycles and Macrocycles*, DOI 10.1007/978-3-319-04346-3_4,

1 Introduction

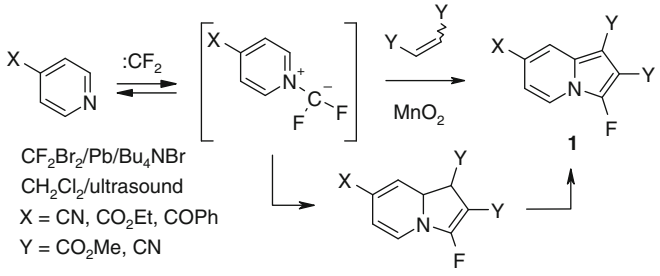
Fluorinated heterocycles have received increasing attention due to their important biological properties. Considerable efforts have been paid to the exploitation of new synthetic routes to these fluorinated compounds. Indolizine is an important fundamental ring system in view of its similarity to indole. 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 substituents 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

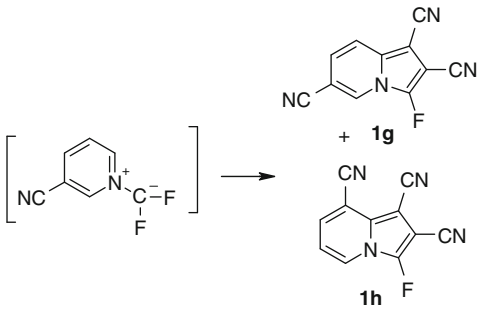
Although the position 3 in the indolizine ring is the most reactive toward electrophilic attack, no direct fluorination of indolizines have been reported. Instead, in the recent work [2] 1,3-dipolar cycloaddition was studied to difluoro-substituted pyridinium ylides.



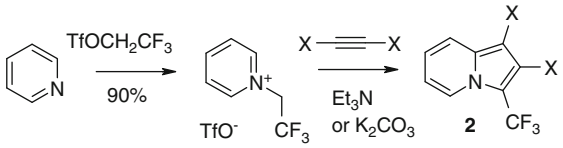
Pyridine	Dipolarophile	Yield (%)
4-COPh	CO_2Me	18 (**1a**)
4-COPh	CN	31 (**1b**)
4-CO_2Et	CO_2Me	23 (**1c**)
4-CO_2Et	CN	28 (**1d**)
4-CN	CO_2Me	48 (**1e**)
4-CN	CN	43 (**1f**)
3-CN	CO_2Me	16 (**1g:1h**) (1:1)

Difluoromethylides were prepared from 4-cyano, 4-benzoyl- and 4-ethoxycarbonyl-substituted pyridines under difluorocarbene generation conditions (ultrasound, CF_2Br_2/Pb/Bu_4NBr) 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 where 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:

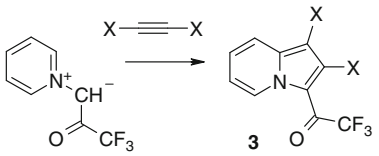


The reaction of N-CH_2CF_3 pyridinium salt with dimethyl acetylenedicarboxylate or perfluorobut-2-yne in the presence of base (Et_3N or K_2CO_3) [3] has provided first formation of indolizines **2** with CF_3-group in position 3.

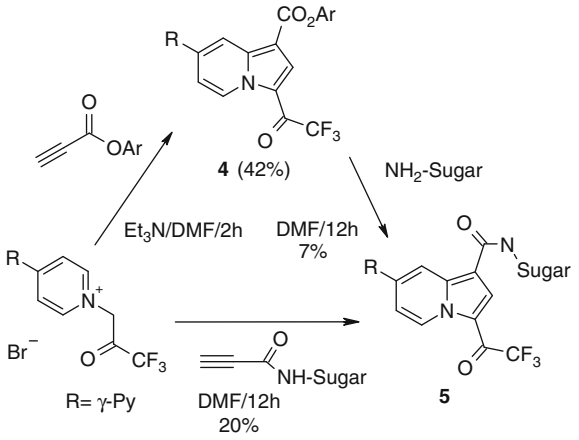


X = CO_2Me (11%); CF_3 (12%)

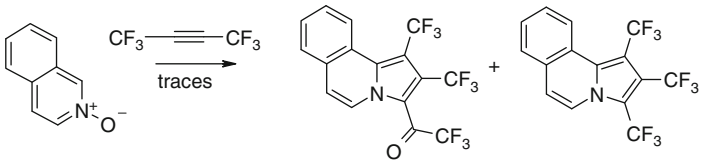
Similarly, the reaction of ylide formed from N-CH_2COCF_3 pyridinium salt and dimethyl acetylenedicarboxylate or perfluorobut-2-yne gave rise to 3-$COCF_3$-indolizines **3** [4].



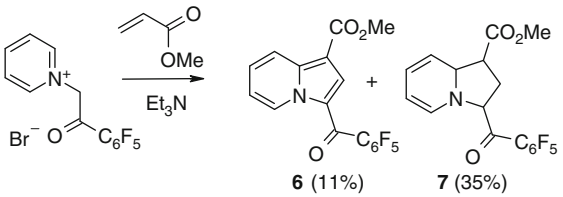
The same methodology was applied to N-CH_2COF_3 γ,γ'-bipyridinium salt leading to intermediate indolizine **4** or final aminosugar **5** with 3-$COCF_3$ group [5].



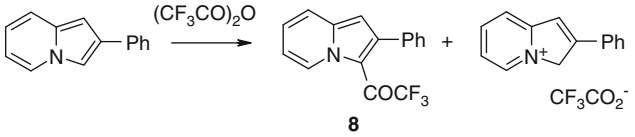
It should be mentioned that isoquinoline 2-oxide reacted with perfluorobut-2-yne similarly forming (among other products) 1,2,3-tris(trifluoromethyl)- and 1,2-bis(trifluoromethy1)-3-trifluoroacethylpyrrolo[2,1-a]isoquinoline [6].



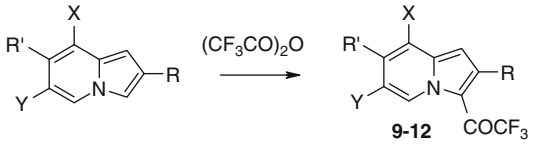
Finally, 3-COC_6F_5 indolizine **6** was obtained together with more saturated product **7** by cycloaddition of the corresponding ylide and methyl acrylate [7].



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 indolizinium cation formed by protonation of starting material [8].

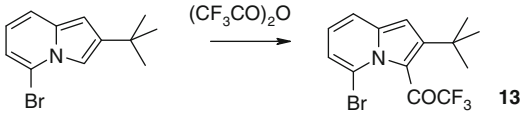


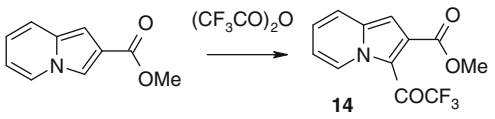
Nitroindolizines having 6- and 8-nitro group in the same reaction led to trifluoroacetyl derivatives **9–12** in quantitative yield [9]. It was shown that their basicity is decreased.



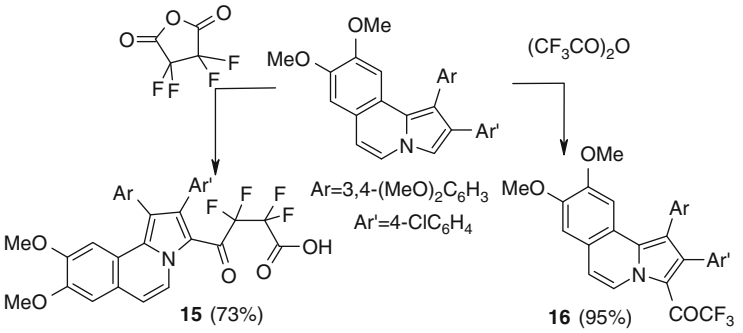
Indolizine		Yield (%)
9	3-$COCF_3$-6-NO_2-2-Ph-7-Me	97
10	3-$COCF_3$-6-NO_2-2-Me	96
11	3-$COCF_3$-8-NO_2-2-Me	100
12	3-$COCF_3$-8-NO_2-2-Ph	100

5-Bromoindolizine underwent trifluoroacetylation selectively at position 3 leading to compound **13**; the yield was 83 % [10]. 2-Carbomethoxyindolizine is transformed to 3-$COCF_3$ derivative **14** in 85 % yield [11].

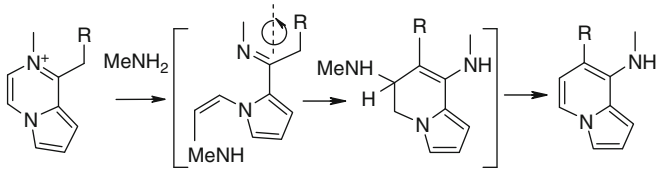




There is only one example of trifluoroacylation in the series of benzoindolizines. 3-Perfluoroacyl derivatives **15** and **16** were obtained in high yield [12] using trifluoroacetic and perfluorosuccinic anhydride as acylating agents.

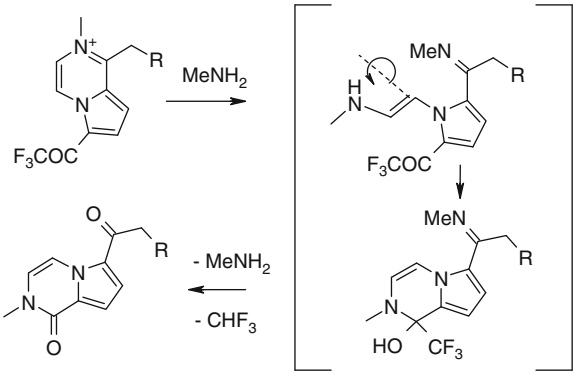


Pyrrolo[1,2-a]pyrazinum (7-azaindolizinium) cations may underwent ring opening and transformation of the pyrazinium fragment under the action of $MeNH_2$. The rearrangement is known as Kost-Sagitullin (enamine) rearrangement.

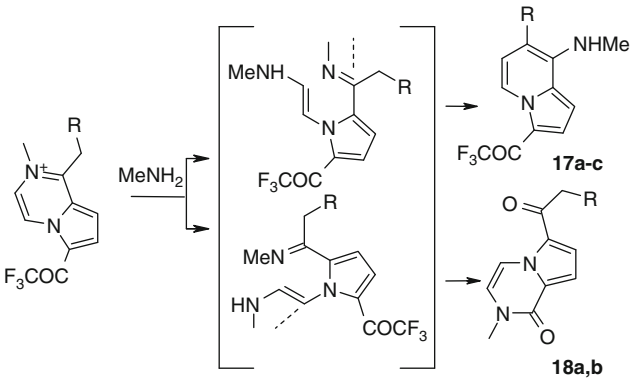


On the other hand, 7-azaindolizinium cations with $COCF_3$ group may be involved in haloformic recyclization leading to oxo-derivatives of pyrrolo[1,2-a]pyrazines.

Here the NHMe-amino group was originated from the reagent.

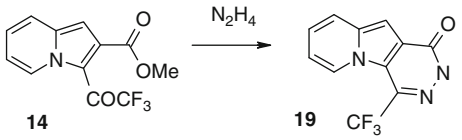


At lower temperature the product **17** of enamine rearrangement to pyridine ring predominated, whereas at higher temperature (and in water solution) the ring transformation occurred with haloformic reaction to form **18** [13].

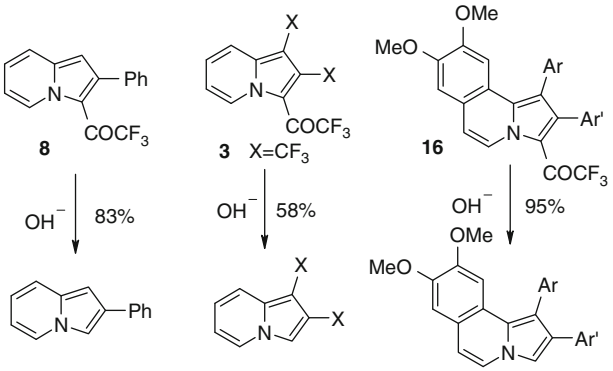


		17:18	
№	R	30 °C	170 °C
a	Et	10:39	45:6
b	n-Pr	15:50	44:10
c	$PhCH_2$	60:0	70:0

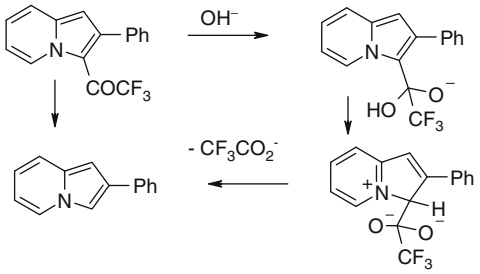
Electrophilic nature of 3-$COCF_3$ group is displayed by the reaction of indolizine **14** with hydrazine forming pyridazinone derivative **19** in the yield 79 % [11].



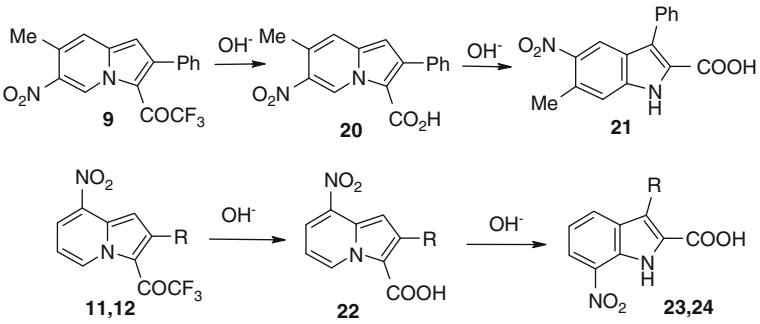
3-Trifuoroacetyl indolizines underwent removal of 3-$COCF_3$ group in good yield by the reaction with cold alkali [9, 4, 12].



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].

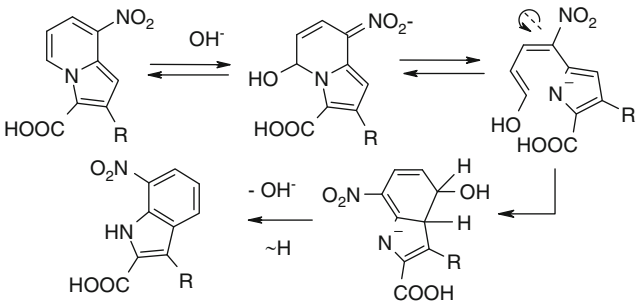


Particularly, this statement was confirmed by reaction of trifluoroacetyl derivatives of 6- and 8-nitroindolizines with alkali. Being less basic these compounds underwent haloformic reaction to form nitroindolizine-2-carboxilic acids. The reaction, however, did not stop at this point and finalized with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



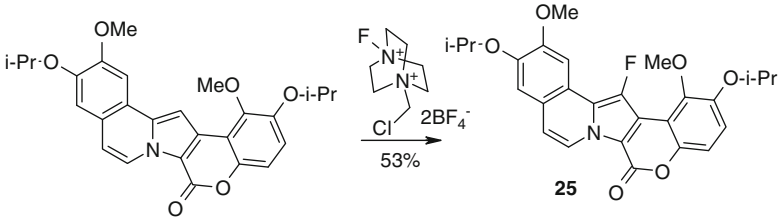
Indolizine	Indole (acid)	Yield of indole (acid), %
9	**21** (**20**)	98 (67)
11	**23** (**22**)	72 (42)
12	**24**	80

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:

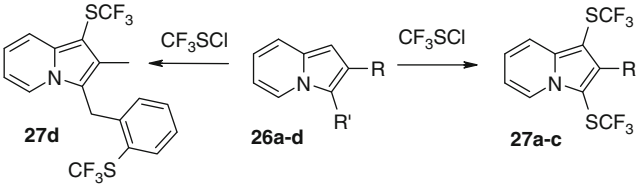


2.2 *Indolizines with Substituent at Position 1*

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.

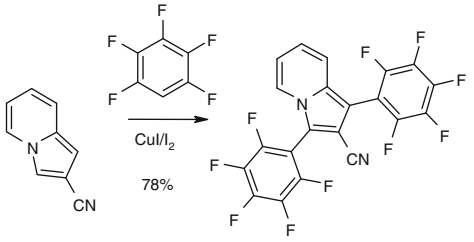


Another example of direct incorporation of perfluorinated substituent at the position 1 is the insertion of CF_3S group using CF_3SCl as electrophile [16]. Reaction proceeded at positions 1 and 3 even in the case of deactivated 3-COMe indolizine quantitatively. In the case of 3-benzylindolizine substitution at C-1 is accompanied by insertion of electrophile in the benzyl fragment as well.

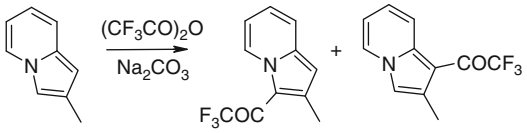


26a	R=R'=H	**27a**
26b	R=H, R'=Me	**27b**
26c	R=Me, R'=Ac	**27c**
26d	R=Me, R'=$PhCH_2$	**27d**

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.

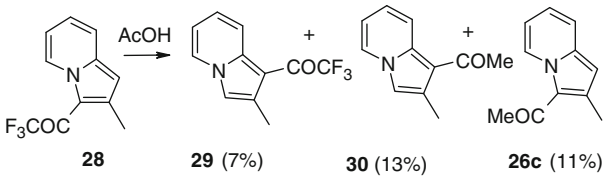


Investigation of the direction of trifluoroacetylation of 2-methylindolizine has shown minor amounts of the 1-substituted isomer formed in addition to the "usual" product of substitution in the 3 position [18].

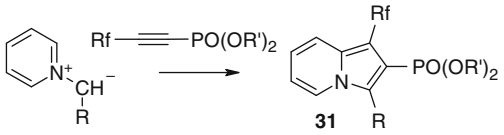


28 (93%) **29** (3.5%)

Furthermore, 1-$COCF_3$ isomer is formed when 3-$COCF_3$ indolizine was heated in CH_3COOH (together with 1- and 3-acetylindolizines) [14]. The reaction mechanism seemed to be intramolecular.



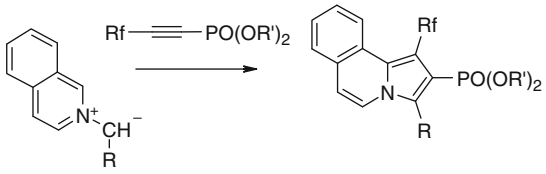
28 **29** (7%) **30** (13%) **26c** (11%)



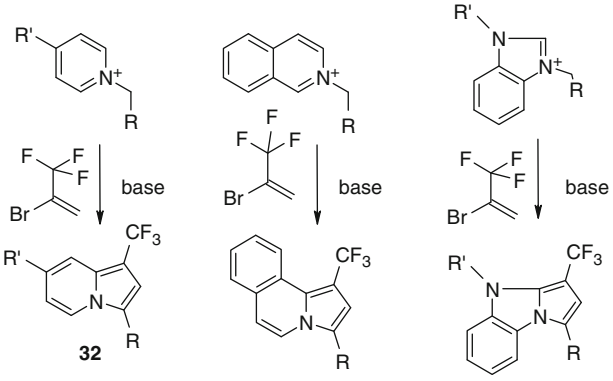
31

Compound	Rf	R'	R	Yield (%)
31a	CF_3	Et	CN	74
31b	CF_3	Pr	CN	70
31c	C_2F_5	Et	CN	73
31d	C_2F_5	Pr	CN	49
31e	CF_3	Et	CO_2Et	47
31f	CF_3	Pr	CO_2Et	51
31g	C_2F_5	Et	CO_2Et	51
1 h	CF_3	Et	COPh	77
31i	C_2F_5	Et	COPh	65
31j	C_3F_7	Et	COPh	70

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 phosphonate in 49–77 % yields. Similar reaction was proposed to obtain pyrrolo[1,2-a]isoquinolinyl phosphonates in 48–78 % yields [20].

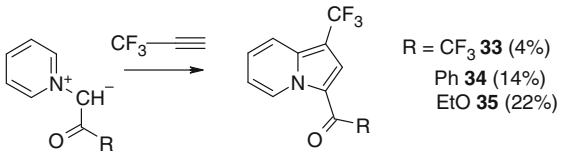


In the reaction of 2-bromo-3,3,3-trifluoropropene with pyridinium ylides cycloaddition occurred readily leading to 1-CF_3 derivatives of indolizines [21]. Similar reaction took place in the cases of pyridazinium and isoquinolinium ylides.

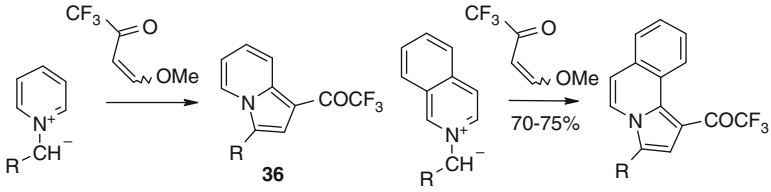


R	R'	Yield (%)	R	R'	Yield (%)
COPh	H	40	COPh	Me	49
COMe	H	24	COMe	Me	27
CO_2Et	H	35			

The reaction of 3-$COCF_3$ pyridinium ylide with 1,1,1-trifluoropropyne proceeded similarly giving 1-CF_3 indolizine in low yield [4]. Similarly behaved other pyridinium ylides with benzoyl and ester groups [22].



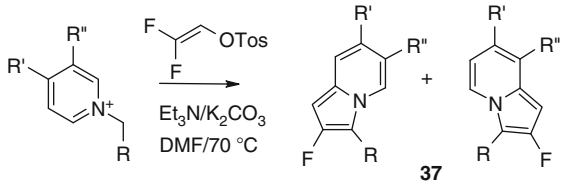
Pyridinium ylides reacted with 4-ethoxy-1,1,1-trifluorobut-3-en-2-one to give the corresponding 1-trifluoroacetyl-substituted indolizines [23]. Isoquinolinium ylides behaved similarly.



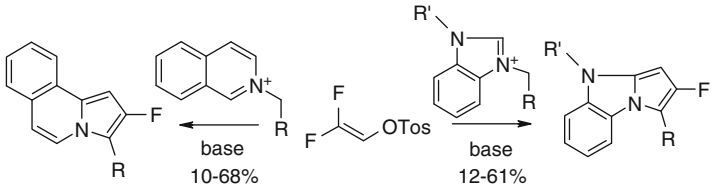
R	Yield (%)
COPh	76 %
CN	74 %
CO_2Et	R=CO_2Et/Me

2.3 *Indolizines with Substituent at Position 2*

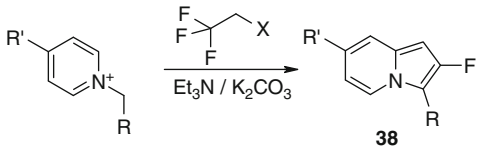
2-Fluoroindolizines are easily available via cycloaddition of fluorinated vinyl tosylates and pyridinium ylides [24]. Using β-substituted pyridinium ylides both isomers (6 and 8) were formed with clear predominance of 8-isomers. One product with 3-CO_2Et group was recently patented as the intermediate [25]. The reaction also proceeded with isoquinolinium and benzimidazolium ylides.



R R' R"	Yield (%)	R R' R"	Yield (%)
COPh H H	34	CO_2Et H COPh	8 (1:1.5)
COPh CH_3 H	23	CN H H	59
COPh H CH_3	37 (1:2)	CN CH_3 H	33
COPh H Br	27 (1:1.5)	CN H CH_3	67 (1:10)
CO_2Et H Br	40 (1:6)	CN H Br	58 (1:1.7)



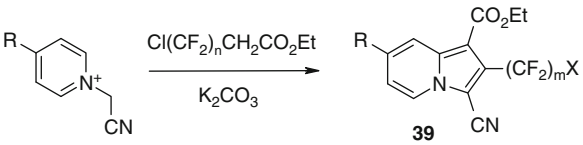
Further modification of the strategy was proposed; 1-chloro-2,2,2-trifluoroethane (bp 6 °C) or 1,1,1,2-tetrafluoroethane (bp –27 °C) gave the corresponding 2-fluoroindolizines **38** via 1,3-dipolar cycloaddition at 80–100 °C in DMSO at atmospheric pressure in normal glassware [26]. The reaction started with the elimination of HF from CF_3CH_2X and can be applied to isoquinolinium ylides.



38

X	R, R'	Yield of 38	X	R, R'	Yield of 38
Cl	COPh, H	45	F	COPh, H	37
Cl	COPh, Me	67	F	CO_2Et, H	47
Cl	CO_2Et, H	82	F	CO_2Et, Me	28
Cl	CO_2Et, Me	76			

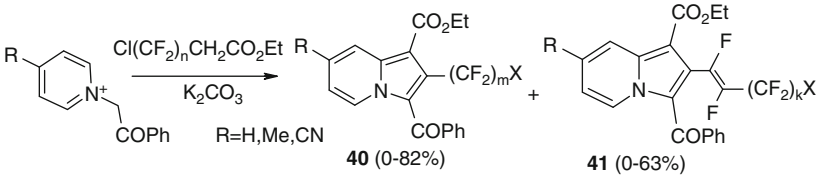
In the presence of base, 2,2-dihydropolyfluoroalkanoates of the type $R_FCF_2CH_2CO_2Et$ reacted with N-(cyanomethyl)pyridinium ylides to give the corresponding indolizine derivatives carrying both a fluoroalkyl and a cyano group [27].



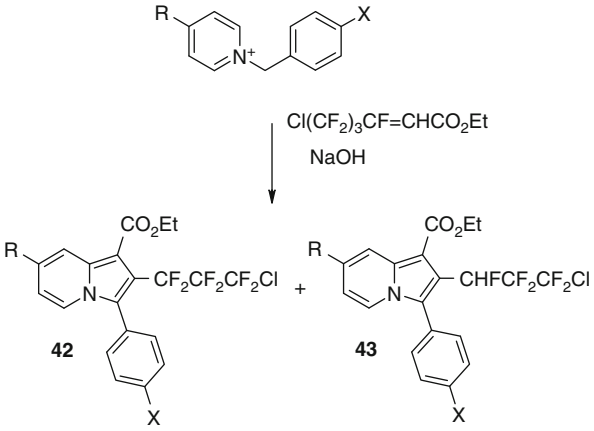
39

R	n	m	X	Yield	R	n	m	X	Yield
H	2	1	H	76	Me	2	1	H	90
H	4	3	Cl	70	Me	4	3	Cl	83
H	6	5	Cl	61	Me	6	5	Cl	88
H	8	7	Cl	52					

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.

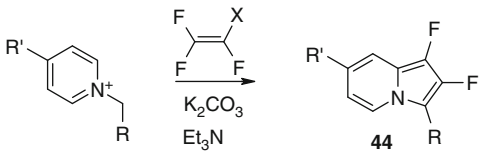


N-Benzylpyridinium ylides (generated in situ from the N-benzylpyridinium bromide and alkali) reacted with ethyl 3-fluoro-3-fluoroalkyl acrylates to give one or two fluoroalkylated indolizine derivatives through 1,3-dipolar cycloaddition followed by an oxidative aromatization or 1,3-H-shift aromatization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



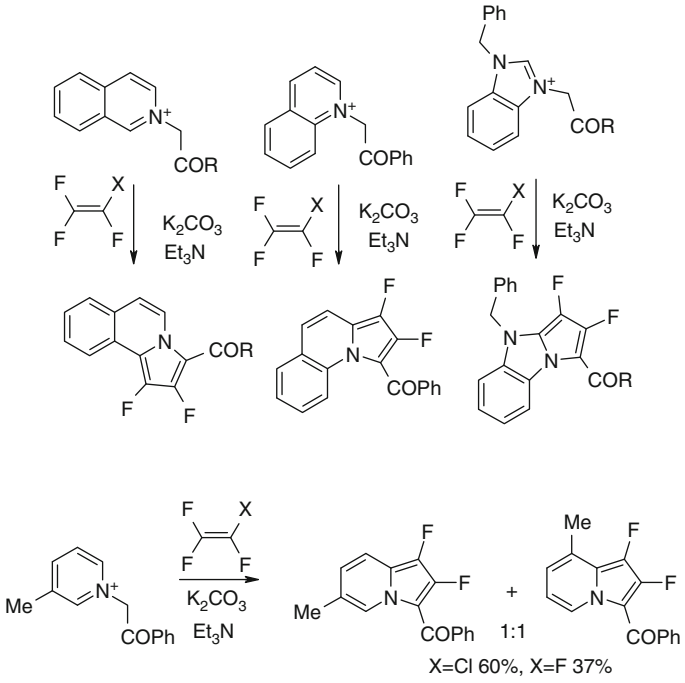
Pyridinium salt	Products and yield (%)	
R=H, X=H	**42a** (18)	**43a** (14)
R=H, X=OMe	**42b** (31)	**43b** (18)
R=H, X=NO_2	**42c** (31)	**43c** (29)
R=CO_2Et, X=H	**42d** (35)	**43d** (8)
R=Me, X=NO	**42e** (5)	–
R=CO_2Et, X=NO_2	**42f** (33)	–

In the presence of K_2CO_3 and Et_3N, pyridinium N-ylides, generated in situ from their halides, reacted with gaseous fluoroalkenes CF_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 tetrafluoroethene in an autoclave [30].

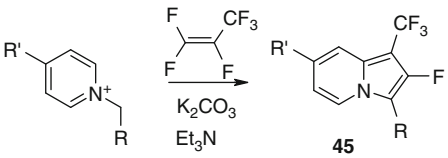


Alkene/X	Ylide, R,R'	Yield
Cl	COPh, H	66
Cl	COPh, Me	64
Cl	CO_2Et, H	37
Br	COPh, H	57
Br	COPh, Me	77
Br	CO_2Et, H	75
F	COPh, Me	32

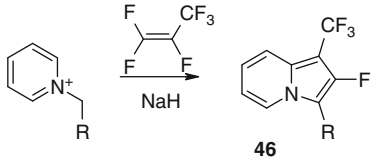
The reaction proceeded also with quinolinium, isoquinolinium and benzimidazolium ylides. In the reaction of ylide obtained from β-picoline the mixture of 6- and 8-isomers was formed.



Similar reaction took place for hexafluoropropene to form 1-CF_3 indolizines. The result was similar to the early one by Banks with $NCH_2CO_2Bu^t$ [31], [32], NCH_2COCF_3 [4] and NCH_2COR [22] pyridinium salts.



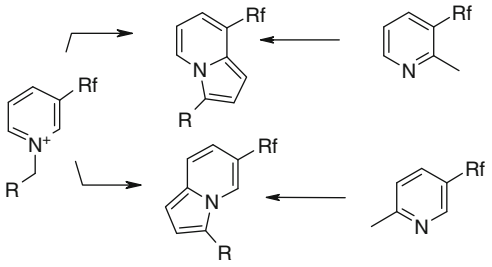
R, R'	Yield of **45** (%)	R	Yield of **46** (%)
COPh, H	62	CO_2Bu^t	37
COPh, Me	71	$COCF_3$	10
CO_2Et, H	57	COPh	12
CO_2Et, Me	53	CO_2Et	13



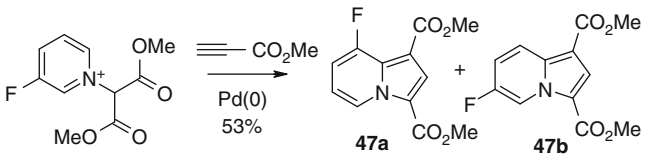
3 Synthesis of Indolizines with Substituent in Pyridine Ring

3.1 Indolizines with Substituent at Position 6 and 8

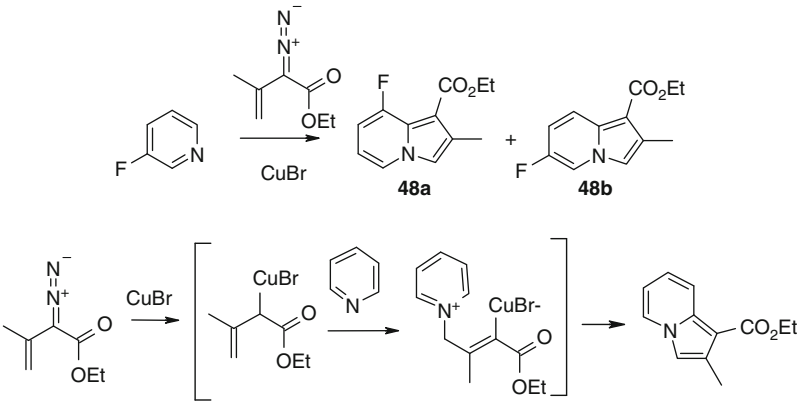
It is difficult to obtain pure isomers containing fluoro (or perfluorinated group) at 6- or 8-position. Since the substituents cannot be inserted directly into the pyridine fragment of indolizine ring, they should already exist in the precursors of the corresponding indolizines. However, this caused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



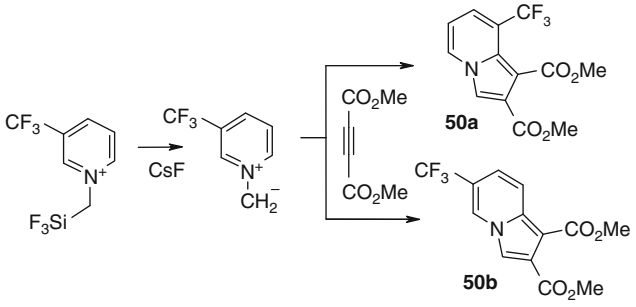
For example, reaction between 3-fluorosubstituted pyridinium N-bis-(methoxycarbonyl)methylide and methyl propiolate [33] proceeded in the yield 53 % giving predominant formation of 8-isomer (**47a:47b** = 65:35). CNDO2 calculations showed that the site selectivity can be rationalized by dipole-dipole interactions.



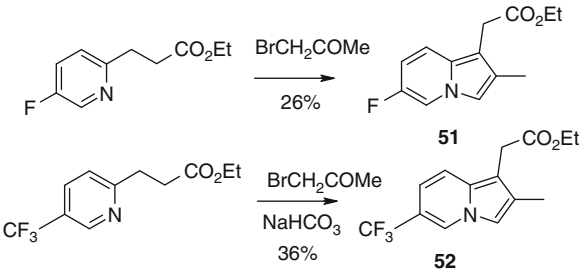
Another example was the copper(I)-catalyzed cycloaddition of ethyl isopropenyldiazoacetate to 3-F-pyridine [34]; reaction took place in the yield 60 % with clear predominance of 8-isomer (**48a:48b** = 3:1). The process represents the first successful example of metal-catalyzed cyclization of a π-deficient heterocyclic system with alkenyldiazo compounds.



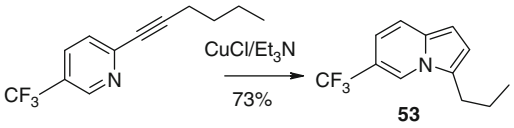
More one example is connected with generation of unsubstituted ylides [35]. As facile precursors for non stabilized pyridinium methylides N-(trimethylsilylmethyl) pyridinium triflates were synthesized. Cesium fluoride induced desilylation of the precursors liberated the nonstabilized pyridinium methylides 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.



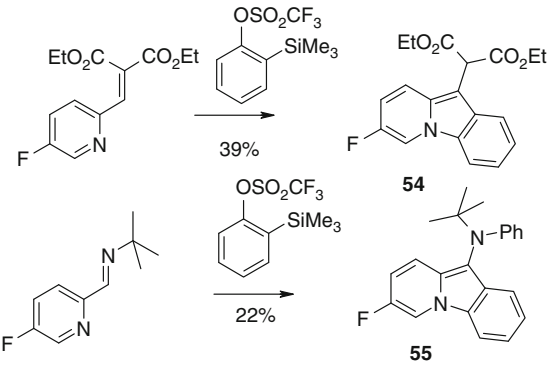
In the patent literature there were two examples of preparation of indolizyl-1-acetic acid according to Chichibabin methodology: the first one – 6-fluoroindilinzine **51** [36] and the second one – 6-CF_3-derivative [37].



Successful cycloisomerization of acyclic alkynyl imines to pyrroles 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].

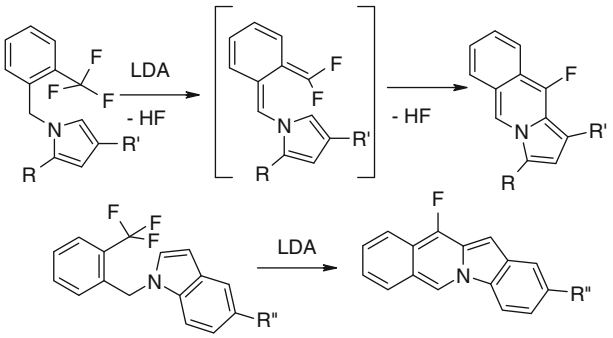


2-(Pyridin-2-yl-methylene)malonates and arynes reacted to produce pyrido[1,2-a]indoles which in some cases (**54**, **55**) correspond to 6-fluoroderivatives of benzoindolizines [39].



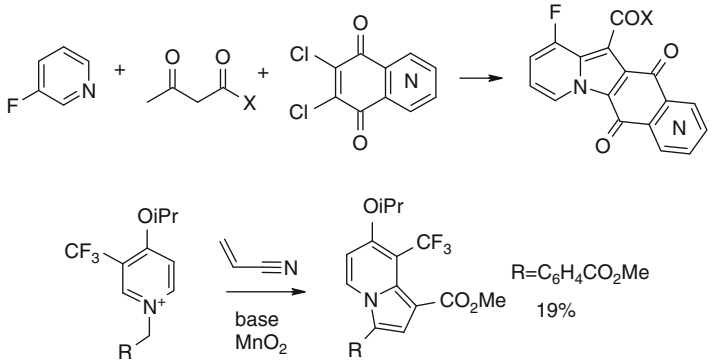
A base-promoted conversion of ortho-trifluoromethyl benzyl derivatives of NH-heterocycles into a respective fluorinated isoquinolines (38–57 % isolated yields) was reported [40]. The reaction is general for the benzylated derivatives of the electron-rich NH heterocycles, particularly indoles. The outcome of the reaction

could be explained by an intermediate formation of a highly reactive quinone methylide species.

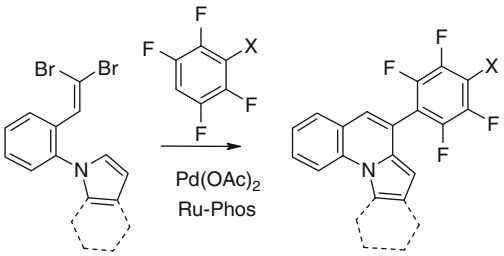


R	R'	R"	Yield, %	R	R'	R"	Yield, %
H	H	–	38	–	–	H	44
Me	H	–	39	–	–	Cl	52
Me	Me	–	48	–	–	OMe	43

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-CF_3-pyridinium ylide is claimed to result in 8-CF_3-derivative of indolizine [25].



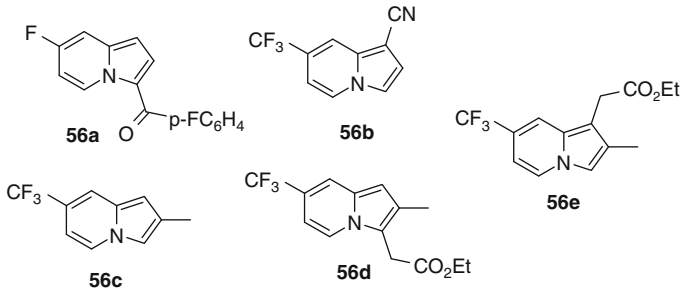
A novel and efficient preparation of 4-polyfluoroaryl substituted pyrrolo[1,2-a] quinolines via a palladium-catalyzed reaction of 1-[2-(2,2-dibromo-ethenyl) phenyl]-1H-pyrrole with polyfluorinated arenes was described [44]. The reaction is also applicable to obtain indoloquinolines with the same substitution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



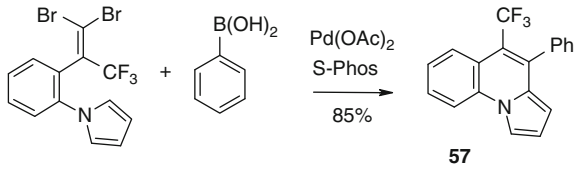
X	Yield, %	X	Yield, %
F	90	Me	68
MeO	80	CF_3	82

3.2 *Indolizines with Substituent at Position 7*

7-F or 7-CF_3 indolizines can be found only in the patent literature, namely compounds **56a** [45], **56b** [25], **56c**, **56d** [46] and **56e** [37].

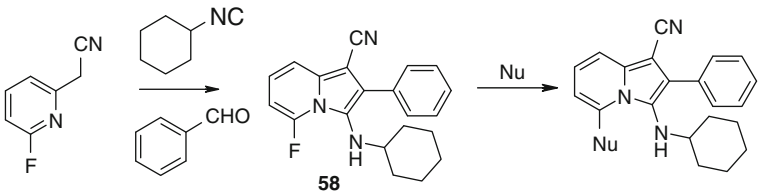


A water-accelerated palladium-catalyzed reaction of gem-dibromoolefins with a boronic acid via a tandem Suzuki-Miyaura coupling and direct arylation was reported [47]. One of the products, **57**, corresponded to 7-CF_3 derivative of benzoindolizine.



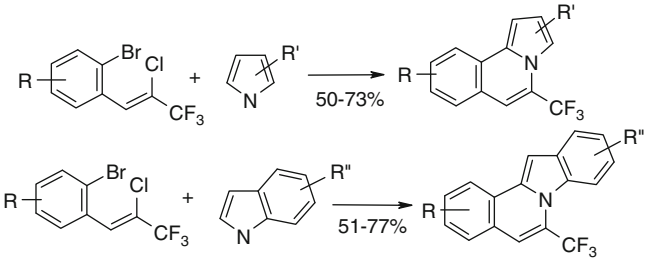
3.3 *Indolizines with Substituent at Position 5*

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-subsituted derivatives.



Indolizine (Nu)	Yield, %	Indolizine (Nu)	Yield, %
F (**58**)	65	$O(CH_2)_3NMe_2$	17
SCH_2CO_2Me	98	1-Morpholinyl	61
SCH_2CO_2H	95	$NH(CH_2)_2NMe_2$	48
SMe	49		

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].



A variety of CF_3-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).

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