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Regioselective reactions of β-aminovinyl trifluoromethyl ketones with tosyl isocyanate

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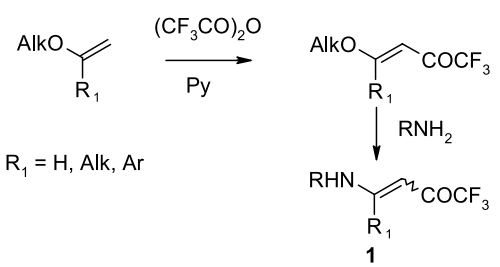
Abstract—The NH- and α-CH-insertion reactions of tosyl isocyanate with *N*-monosubstituted and *N*,*N*-disubstituted trifluoromethyl-containing enaminones have been studied. The regioselectivity of *N*-tosylcarbomoylation of *N*-monosubstituted β-aminovinyl trifluoromethyl ketones depends on the structure of enaminones, the reaction temperature, the nature of solvent and catalyst. The *Z* configuration of fluorinated vinylogous sulphonylurea **3e** was deduced from X-ray analysis. The reaction of *N*,*N*-disubstituted enaminone **5a** with tosyl isocyanate gave the product mixture of electrophilic attack on either the α-CH- or the oxygen atom of $COCF_3$ group—vinylog of sulfonylurea **6a** and tosylamide **7a**, correspondingly.

1. Introduction

Enaminones are widely used building blocks for the synthesis of various organic compounds[1] especially for natural bioactive substances and their analogs.[2] Fluorine-containing enaminones are also very attractive synthons with high potential for the synthesis of fluorinated analogs of natural products, which have received considerable interest in recent years.[3,4] One of the most effective methods used to synthesize the fluoroalkyl-containing enaminone, is the amination reaction of accessible β-alkoxyvinyl polyfluoroalkyl ketones[5] (Scheme 1), which are useful and convenient building blocks for the synthesis of various fluoroalkyl-containing compounds—dyes, heterocycles, drugs, as protective reagent in peptide synthesis.[6] In many cases the fluorinated enaminones, β-aminovinyl polyfluoroalkyl ketones, are intermediately formed. The physicochemical properties of the β-aminovinyl polyfluoroalkyl ketones strongly differ from the ones of non-fluorinated parent enaminones, because of a change of acyl group with a more electron withdrawing polyfluoroacyl group, which polarizes the C=C double bond more and results in significant changes in reactivity and conformation behavior of enaminones.[7–9]



Scheme 1.

The electrophilic reactions of non-fluorinated enaminones are frequently used for the synthesis of various bioactive compounds,[1,2] however, only a few reports are available on the reactions of fluorinated enaminones with electrophiles. Thus, the electrophilic reactions of isocyanates with non-fluorinated *N*-monoalkyl- and *N*,*N*-dialkyl-enaminones usually give products of *N*-tosylcarbomoylation at the α-position of the C=C double bond, that have been used for synthesis of various heterocycles[10] and perspective drugs with hypoglycemic activity.[11] Recently in a short communication[12] we showed that *N*-monosubstituted β-aminovinyl trifluoromethyl ketones (in four examples) reacted with TosNCO not only at the α-carbon atom of the carbon–carbon double bond, that is usually for non-fluorinated enaminones, but also at the nitrogen atom, and mixtures of the two products—vinylogous sulphonylureas and ureas were obtained in high yield. The regioselectivity of the N-tosylcarbomoylation reaction was found to be sensitive to reaction conditions and the structure of the enaminones.

In this article we describe both the synthesis of new fluorinated substances, analogs of hypoglycemic agents, and the detailed study of regioselectivity of the reaction between *N*-monosubstituted and *N*,*N*-disubstituted β-aminovinyl trifluoromethyl ketones with TosNCO. We describe here also the N-tosylcarbomoylation reaction of the parent non-fluorinated enaminone.

Keywords: enaminones; *N*-tosylcarbomoylation; polyfluoroalkyl ketones.

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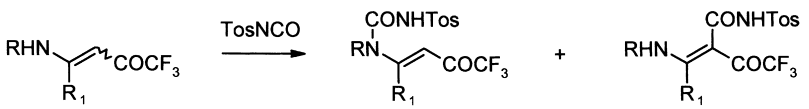


1 **2** **3**

1-3	a	b	c	d	e	f	g	h	i	j
R	H	Me	Et	*n*-Pr	*n*-Bu	*i*-Pr	*t*-Bu	CH_2Ph	Me	Me
R_1	H	H	H	H	H	H	H	H	Me	Ph

Scheme 2.

2. Results and discussion

A number of trifluoromethyl-containing enaminones **1** with various substituents such as hydrogen, alkyl or aryl groups at nitrogen and carbon atoms at the β-position were taken to establish regioselectivity of electrophilic *N*-tosylcarbomoylation. The starting compounds were synthesized in high yield from available β-alkoxyvinyl polyfluoroalkyl ketones[13,14] by amination reaction (Scheme 1) using various amines that gave us the possibility to vary both steric character of *N*-alkyl groups and the electronic influence of *N*-aryl substituents.

Earlier[12] we reported that the reaction of TosNCO with *N*-*tert*-butyl enaminone **1g** gave only product **3g** instead of a mixture of products **2e** and **3e** which was obtained from *N*-*n*-butyl enaminone **1e**. In this work we have particularly studied the effects of steric hindrance caused by a *N*-substituent on the regioselectivity of the reaction of TosNCO with enaminones **1a–h** (Scheme 2). We have found that gradual increase of the steric hindrance on the nitrogen caused by the *N*-alkyl group results in decreased availability of NH group of enaminones **1** for electrophilic attack by TosNCO. As a result of which, in the reaction mixture we observed an increase and a decrease in quantity for ureas **2** and vinylogous sulphonylureas **3**, respectively. And, this follows in the order H<Me<Et~*n*-Pr~*n*-Bu≪Bn~*i*-Pr~*t*-Bu (Table 1). This fact is in a good accordance with known steric characteristics of the *N*-substituents in enaminones **1a–h**. It is noteworthy that the volumes of *i*-Pr, *t*-Bu and Bn groups are quite enough for preventing the electrophilic attack of tosyl isocyanate on NH group of enaminones **1f–h**, and, in practice, we obtained only compounds **3f–h** in high yields.

Introduction of methyl or phenyl group in the β-position of C=C double bond of *N*-methylenaminone **1b** resulted in the same effect as the introduction of *i*-Pr group to nitrogen atom caused. By ^{19}F NMR spectra of the reaction mixtures we have found only several percentage content of the products **2i,j**, that can also be satisfactorily explained by the growth of steric hindrance around to the nitrogen atom of enaminones **1i,j**.

Table 1. Yields and ratio of products **2a–h** and **3a–h**

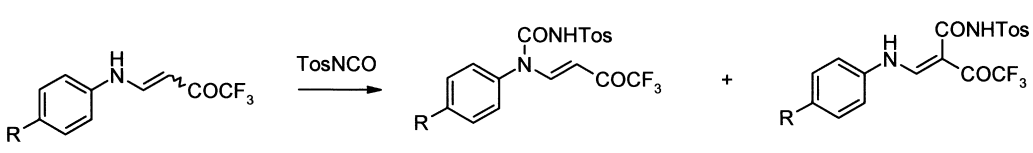
1–3	R	Combined yield of **2** and **3** (%)	Ratio[a] of **2/3** (conversion, %)	
			$CHCl_3$	CH_3CN
a	H	55[b]	30/70 (100)[c]	45/55 (100)[c]
b	Me	87	20/80 (97)	25/75 (100)
c	Et	91	10/90 (95)	15/85 (100)
d	*n*-Pr	92	8/92 (93)	13/88 (100)
e	*n*-Bu	90	7/93 (94)	13/88 (100)
f	*i*-Pr	89	~1/99 (95)	~1/99 (100)
g	*t*-Bu	85[d]	0/100 (>99)	0/100 (100)
h	Bn	95	~2/98 (95)	~2/98 (100)
i	Me	88[d]	0/100 (90)	~1/99 (95)
j	Me	90[d]	0/100 (80)	~1/99 (90)

[a] Ratios were determined by ^{19}F NMR analysis of reaction mixture at 20–25°C after 1 h.
[b] Yield of **3a** after crystallisation.
[c] The reaction time was 24 h.
[d] Yield of **3g,i,j**.

Table 2. Yields and ratio of products **2k–o** and **3k–o**

1–3	R	Combined yield of **2** and **3** (%)	Ratio of **2/3** in CH_3CN (conversion, %)[a]
k	4-Me_2N	93	35/65 (100)
l	4-MeO	95	60/40 (90)
m	4-Me	94	80/20 (85)
n	H	92	80/20 (80)
o	4-Cl	93	85/15 (75)

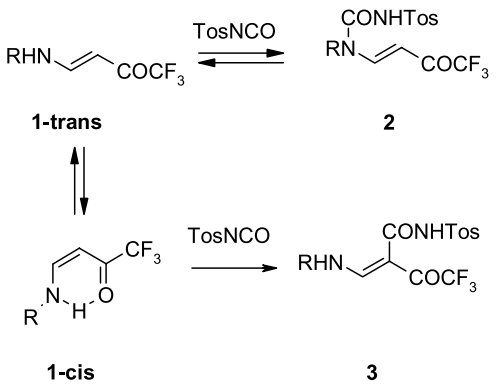
[a] The reaction time is 1 h.



1 **2** **3**

1-3	k	l	m	n	o
R	Me_2N	MeO	Me	H	Cl

Scheme 3.



Scheme 4.

The influence of electronic effects on a ratio of products **2** and **3** in the reaction between enaminones **1** and TosNCO has been studied in the series of *N*-aryl-containing enaminones **1k–o** by the variation of the nature of substituents in the *para*-position of benzene ring (Scheme 3). In the case of *N*-arylenaminones **1k–o** we used acetonitrile as solvent in the reaction with TosNCO due to slow reaction in chloroform, in contrast with *N*-alkyl-enaminones **1b–h**. The enaminones **1k–o** react with TosNCO at room temperature, and the mixture of ureas **2k–o** and vinylogous sulphonylureas **3k–o** was formed in high yields (Table 2). In the order of decreasing electron donating capacity of *para*-substituents we observed a decrease of reaction rate and an increase in the quantity of ureas **2k–o** in the reaction mixture. This can be explained by effective conjugation between the substituent in the *para*-position of the benzene ring and the α-position of the enaminone. Earlier we described that good correlation exists between σ-constants of substituents at the benzene ring and NMR chemical shifts of $\delta_{H\alpha}$ and $\delta_{C\alpha}$ for *N*-arylenaminones such as **1k–o**.[15] It is worth mentioning that the *N*-aryl-enaminones with strong electron withdrawing substituents such as ethoxycarbonyl- and nitro-groups do not react with TosNCO at all.

The regioselectivity of *N*-tosylcarbomoylation of *N*-mono-alkyl(aryl)-β-aminovinyl trifluoromethyl ketones **1b–o** depends on several factors. As we have shown previously,[12] the reaction temperature changes the ratio of products **2** and **3**, that was demonstrated on an example of the reaction between *N*-methylenaminone **1b** and TosNCO at various temperatures from −20 to 60°C. Below 0°C we obtained practically sole product **3b**, while at elevated temperature the mixture of products **2b** and **3b** was formed. It looks like that urea **2b** are thermodynamically controlled product and vinylogous ureas **3** are kinetically controlled product. But when urea **2b** was heated at 110°C in toluene for 4 h, the corresponding ^{19}F NMR spectrum detected only signals of the enaminone **1b** and vinylogous urea **3b**, that is in contrary to the above mentioned temperature dependence of the reaction between *N*-methylenaminone **1b** and TosNCO. However, we obtained additional evidence of instability for ureas **2** in a solution. Earlier[12] we reported that the increase of solvent polarity did not change the ratio of products **2** and **3**, but it essentially accelerated the reaction between enaminones **1** and TosNCO. Thus a change of solvent from toluene to DMF not only accelerated the reaction: from 95% conversion for 5 h to 100% for 10 min, but also changed the ratio of products **2b** and **3b** from 10/90 to 35/65, correspondingly. Moreover, the quantity of urea **2b** in the reaction mixture in DMF was only 7% after 5 days at room temperature. It should be mentioned, that *N*-aryl-containing ureas **2k–o** are more stable compounds than *N*-alkyl derivatives. Above-mentioned facts can be explained only if the products **2** and **3** are formed by different ways as shown in Scheme 4.

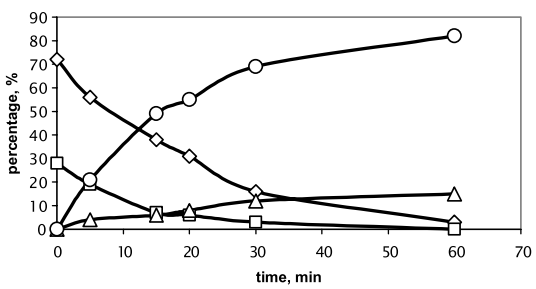
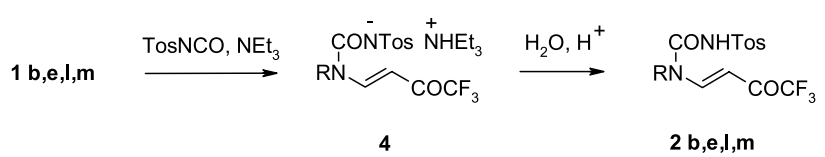


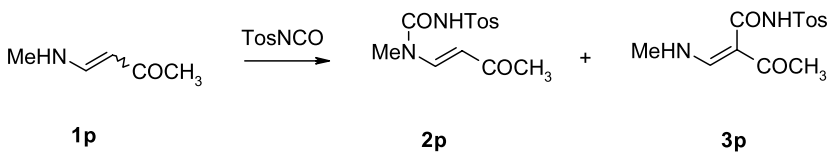
Figure 1. ^{19}F NMR monitoring data of the reaction between enaminone **1b** and TosNCO in CD_3CN at 20°C: (◆)—*cis*-**1b** (−77.2 ppm); (□)—*trans*-**1b** (−77.6 ppm); (△)—**2b** (−78.3 ppm); (○)—**3b** (−68.4 ppm).

It is known that in solution *N*-monosubstituted trifluoro-methyl-containing enaminones **1** exist as a mixture of *cis*- and *trans*-isomers,[8,9] which obviously have different reactivity toward to TosNCO. Thus, the α-position of double C=C bond of the *cis*-isomer is more sensitive to electrophilic attack than nitrogen or oxygen atoms, which participated in intramolecular hydrogen bond formation, whereas in the *trans*-isomer the nitrogen atom is most preferable to electrophilic attack. The effect of different solvents' polarity on the yield of ureas **2** has firmly been established by increase in *trans*-enaminone **1** content of its *cis–trans* isomer mixture in highly polar solvents (e.g. for enaminone **1b** from 1% in CCl_4 up to 75% in DMSO[8]). And, our assumption too, could successfully correlate with the above stated experimental facts.

We have studied the dynamics of percentage changes of *cis*- and *trans*-isomers of enaminone **1b** and the products **2b** and **3b** formed in the reaction with TosNCO in acetonitrile at 22°C by ^{19}F NMR spectroscopy. It was founded that the ratio of *cis*/*trans* isomers is not changed until the conversion goes up to 90% for 1 h (Fig. 1), because of the rate of *cis–trans* equilibrium of enaminones **1** is much faster than the reaction rates of *cis*- and *trans*-isomers with TosNCO. Thus, the temperature dependence of regioselectivity of the



Scheme 5.



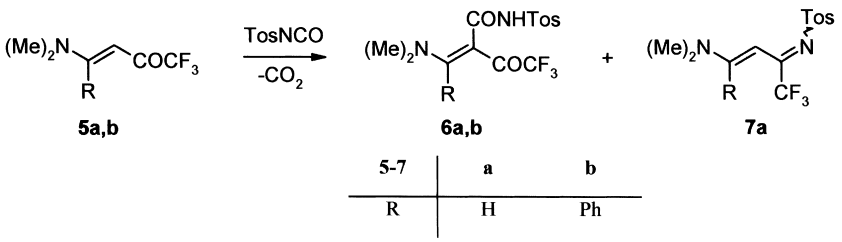
Scheme 6.

reaction of enaminones **1** with TosNCO can be explained only by a significant decrease of the reactivity of the *trans*-isomer of enaminones **1** at low temperature in comparison with the *cis*-isomer.

The effects of catalysts were also studied previously.[12] Nucleophilic catalysts (such as Py, NEt_3) caused a significant increase in the yields of urea because of negative charged nitrogen atom after deprotonation by base is much more sensitive toward electrophilic attack with TosNCO. Use of an equimolar quantity of NEt_3 gave the triethylamine salt of ureas **4** in quantitative yield (Scheme 5). However, enaminone **1g** does not give urea **2g** even in the presence of large excess of NEt_3—we observed only slow formation of vinylogous sulphonylureas **3g**. Pure ureas **2b**,**e** were obtained in moderate yields from triethylamine salts by acidic workup due to their low stability in acid hydrolysis conditions that is usual for fluorinated enaminones **1**.[16] *N*-Aryl-containing ureas **2l**,**m** are more stable compounds in these conditions and their yields are higher.

4-Methylamino-3-buten-2-one—non-fluorinated enaminone **1p**, which contains CH_3 group instead of CF_3 in enaminone **1b**, also reacts with TosNCO in $CHCl_3$, and products **2p** and **3p** are formed in ratio 18/82 (Scheme 6) by ^1H NMR analysis of the reaction mixture. However, urea **2p** is much more unstable, than CF_3-containing urea **2b**, and we have not isolated it in pure state from the reaction mixture both without and with triethylamine catalysis. In the last case, we have obtained only a mixture of unidentified products.

The *N*,*N*-dialkylenaminones can not form urea like **2** in the reaction with TosNCO, because of the lack of a hydrogen atom on the amino group, and should give only vinylogous sulphonylureas like **3**. However, under reaction of *N*,*N*-dimethylenaminone **5a** with TosNCO a gas evolution was observed and the mixture of two products was formed in high yield: vinylogous sulphonylurea **6a** as a result of electrophilic attack on α-carbon atom of C=C double bond and *N*-tosylazadiene **7a** as a result of electrophilic attack on



Scheme 7.

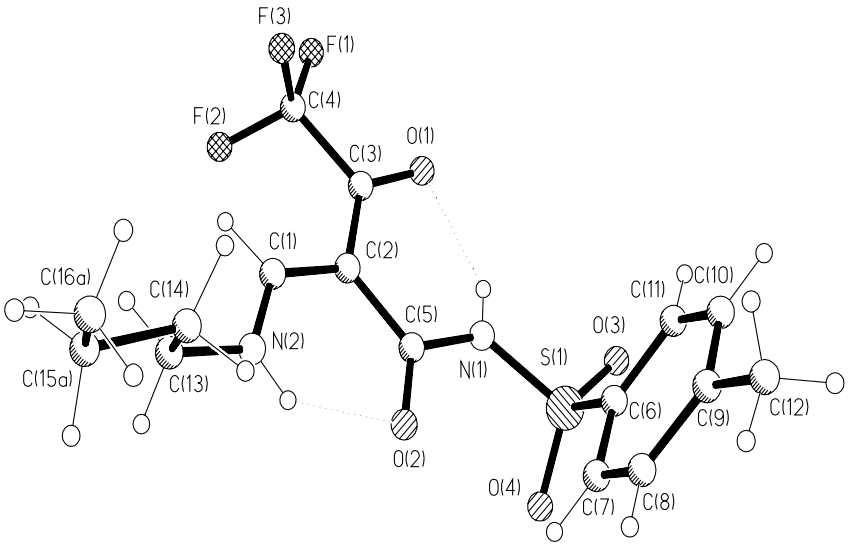


Figure 2. An ORTEP view of vinylogous sulphonylureas **3e**. Selected bond lengths (Å) and torsion angles (°): S(1)–O(3) 1.424(2), S(1)–O(4) 1.415(2), S(1)–N(1) 1.648(3), S(1)–C(6) 1.756(3), O(1)–C(3) 1.225(4), O(2)–C(5) 1.231(4), N(1)–C(5) 1.370(4), N(2)–C(1) 1.302(4), C(1)–C(2) 1.391(5), C(2)–C(3) 1.434(5), C(2)–C(5) 1.461(4), S(1)–N(1)–C(5)–O(2) −5.4(5), O(1)–C(3)–C(2)–C(1) 173.4(4), N(1)–C(5)–C(2)–C(1) −176.3(3), N(1)–C(5)–C(2)–C(3) 1.0(5), N(2)–C(1)–C(2)–C(3) −177.7(3), C(2)–C(1)–N(2)–C(13) 175.5(3).

oxygen atom of carbonyl group with following elimination of CO_2 (Scheme 7). In chloroform solution the percentage of the product **7a** was about 30%, without solvent the quantity increased up to 60%, by ^{19}F NMR data of crude reaction mixture.

But under reaction of β-phenyl-*N*,*N*-dimethylenaminone **5b** with TosNCO we observed only a negligible quantity of corresponding product **7b** in the reaction mixture in various conditions. Like compounds **3**, compounds **6a**,**b** were obtained by crystallization of the reaction mixture, and its properties are very similar excluding only the lack of NH signal in ^1H NMR and IR spectra. *N*-Tosylazadiene **7a** was purified by column chromatography. The vinyl protons in ^1H NMR spectra of **7a** are wide and unresolved which prevents the determination of the correct configuration of C=C double bond and can be explained by fast *syn*–*anti* isomerization of *N*-tosylimino group.

Satisfactory analytical data (^1H and ^{19}F NMR spectra and elemental analyses) were obtained for all compounds. The double bond of the products **2a**–**p** has the *E*-configuration: $^3J_{HH}$~14 Hz, a common feature for *N*,*N*-disubstituted enaminones.[8,9] The urea structure of compounds **2b**–**e**, **k**–**p** was also confirmed by disappearance in the ^1H NMR spectra of magnetic interactions between the NH-proton and the β-olefinic proton and the α-protons of the *N*-alkyl group (for ureas **2b**–**e**). Trifluoromethyl group signals of ureas **2a**–**e**,**k**–**o** in ^{19}F NMR spectra are slightly shifted upfield at ~1 ppm (about −77.0 ppm) relative to the starting enaminones (about −76.1 ppm). On the contrary, the chemical shifts of the trifluoromethyl groups of compounds **3a**–**o** are strongly shifted downfield at ~9 ppm (about −67.2 ppm). In ^1H NMR spectra of vinylogous sulphonylureas **3b**–**p** two downfield signals of NH-protons are observed; one of them has a coupling interaction with the β-vinyl proton, if it exists, and another one is a singlet. Sometimes a weak coupling interaction ($^5J_{HF}$~0.5 Hz) between the β-vinyl proton and the fluorine atoms of the CF_3-group in ^1H NMR spectra of compounds **3a**–**o** was observed. This fact allows us to assume that the vinylogous sulphonylureas **3a**–**p** exist in the *Z*-configuration, which is stabilized by two intramolecular hydrogen bonds N–H···O=C, whereas the *E*-isomer contains only one such bond. X-Ray analysis of compound **3e** confirmed *Z*-configuration of C=C double bond (Fig. 2). The S(1)N(1)C(5)O(2)C(2)C(3)O(1)C(1)N(2) bonds system is planar within 0.09 Å. The $n_{N(1)}-\pi_{C(5)=O(2)}$, $n_{N(2)}-\pi_{C(1)=C(2)}$, $\pi_{O(1)=C(3)}-\pi_{C(1)=C(2)}$ and $\pi_{O(2)=C(5)}-\pi_{C(1)=C(2)}$ conjugation leads to the noticeable shortening of N(1)–C(5), N(2)–C(1), C(2)–C(3) and C(2)–C(5) single bonds and to the elongation of C(3)=O(1), C(5)=O(2) and C(1)=C(2) double bonds.[17] As interesting peculiarity of the molecular structure of **3e** one should note is the extremely strong N–H···O intramolecular bonds 'assisted by resonance'.[18] The main geometrical parameters of these H-bonds: N(1)···O(1) 2.607(4) Å, N(1)H(N1)O(1) 142(3)° N(2)···O(2) 2.615(4) Å, N(2)H(N2)O(2) 130(3)°.

In summary, we have studied the NH- and α-CH-insertion reaction of TosNCO into *N*-mono and *N*,*N*-disubstituted fluorinated enaminones **1** and **5** which is sensitive to reaction conditions: temperature, solvents and catalysts, and affords the highly functionalized trifluoromethyl-containing sulphonylureas **2** and vinylogous sulphonylureas **3** and **6**. These fluorinated substances can be utilized as practical building blocks for effective synthesis of bioactive fluorinated compounds.

3. Experimental

3.1. General

^1H and ^{19}F NMR spectra were recorded on Varian VXR instrument at 300 and 282.2 MHz using TMS and CCl_3F as internal standards respectively. Melting points are uncorrected. Column chromatography was performed on silica gel 60 (Merck) with mixture of chloroform and ethyl acetate. Starting enaminones **1a**–**p**, and **5a**–**b** were prepared according to literature procedures.[5,15] Where necessary, solvents and reagents were dried and purified according to recommended procedures.[19] Synthesis and properties of compounds **2b** and **3b**,**e**,**g**,**n** were reported earlier.[12]

3.2. General procedures for the synthesis of the vinylogous sulphonylureas 3a–p

Tosyl isocyanate (0.51 g, 2.6 mmol) was added dropwise to a solution of **1a**–**j**,**p** (2.9 mmol) in anhydrous chloroform (5–6 mL) or acetonitrile (5–6 mL) (for **1k**–**o**) with stirring at room temperature. After 24 h for **1a**–**j**,**p** and 48 h for **1k**–**o** the solvent was evaporated in vacuo and the residue was washed with hexane (30 mL). The crude products were purified by crystallization from ethanol.

3.2.1. (*Z*)-1,1,1-Trifluoro-3-tosylcarbamoyl-4-aminobut-3-en-2-one 3a. 0.48 g, 55%. White crystals, mp 205–207°C. [Found: C, 42.90; H, 3.38; N, 8.40. $C_{12}H_{11}F_3N_2O_4S$ requires C, 42.86; H, 3.30; N, 8.33%]; ν_{max} (KBr) 3700–2800 (br), 1664, 1613, 1440, 1380, 1340 cm^{-1}; δ_H (300 MHz C_3D_6O) 11.67 (1H, s, CON*H*SO_2), 10.36 and 9.08 (2×1H, 2×br s, NH_2), 8.34 (1H, ddq, *J*=15.7, 9.6, 1.0 Hz, *H*C=), 7.97 and 7.44 (2×2H, 2×d, *J*=8.3 Hz, C_6H_4Me), 2.44 (3H, s, C_6H_4*Me*); δ_F (300 MHz, $CDCl_3$) −67.56 (br d, CF_3).

3.2.2. (*Z*)-1,1,1-Trifluoro-3-tosylcarbamoyl-4-(*N*-ethylamino)but-3-en-2-one 3c. 0.70 g, 74%. White crystals, mp 104–106°C. [Found: C, 46.25; H, 4.30; N, 7.78. $C_{14}H_{15}F_3N_2O_4S$ requires C, 46.15; H, 4.15; N, 7.69%]; ν_{max} ($CHCl_3$) 3500–2800 (br), 1667, 1649, 1608, 1443, 1396, 1352 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 11.76 (1H, s, CON*H*SO_2), 10.96 (1H, br s, N*H*Et), 7.95 and 7.33 (2×2H, 2×d, *J*=7.8 Hz, C_6H_4Me), 7.87 (1H, d, *J*=13.9 Hz, *H*C=), 3.49 (2H, dq, J_1~J_2~7.0 Hz, NCH_2CH_3), 2.44 (3H, s, C_6H_4*Me*), 1.33 (3H, t, *J*=7.2 Hz, NCH_2CH_3); δ_F (300 MHz, $CDCl_3$) −67.17 (s, CF_3).

3.2.3. (*Z*)-1,1,1-Trifluoro-3-tosylcarbamoyl-4-(*N*-propylamino)but-3-en-2-one 3d. 0.75 g, 76%. White crystals, mp 102–104°C. [Found: C, 47.78; H, 4.65; N, 7.53. $C_{15}H_{17}F_3N_2O_4S$ requires C, 47.62; H, 4.53; N, 7.40%]; ν_{max} ($CHCl_3$) 3500–2800 (br), 1667, 1648, 1608, 1444, 1397, 1356 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 11.77 (1H, s, CON*H*SO_2), 10.94 (1H, br s, N*H*Pr), 7.96 and 7.33 (2×2H,

2×d, J=8.2 Hz, C_6H_4Me), 7.84 (1H, d, J=13.9 Hz, HC═), 3.39 (2H, dt, $J_1{\sim}J_2{\sim}$7.0 Hz, NCH_2), 2.44 (3H, s, C_6H_4Me), 1.68 (2H, tq, $J_1{\sim}J_2{\sim}$7.3 Hz, NCH_2CH_2), 0.97 (3H, t, J=7.3 Hz, CH_2CH_3); δ_F (300 MHz, $CDCl_3$) −67.29 (s, CF_3).

3.2.4. (*Z*)-1,1,1-Trifluoro-3-tosylcarbamoyl-4-(*N*-isopropylamino)but-3-en-2-one 3f. 0.90 g, 92%. White crystals, mp 114–116°C. [Found: C, 47.80; H, 4.63; N, 7.55. $C_{14}H_{15}F_3N_2O_4S$ requires C, 47.62; H, 4.53; N, 7.40%]; ν_{max} ($CHCl_3$) 3500–2800 (br), 1666, 1649, 1606, 1442, 1400, 1358 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 11.78 (1H, s, CONHSO$_2$), 10.93 (1H, br s, NHPr-*i*), 7.97 and 7.34 (2×2H, 2×d, J=8.2 Hz, C_6H_4Me), 7.90 (1H, d, J=14.1 Hz, HC═), 3.68 (1H, d sept, $J_1{\sim}J_2{\sim}$6.6 Hz, CHMe$_2$), 2.44 (3H, s, C_6H_4Me), 1.34 (6H, d, J=6.6 Hz, CHMe_2); δ_F (300 MHz, $CDCl_3$) −67.27 (s, CF_3).

3.2.5. (*Z*)-1,1,1-Trifluoro-3-tosylcarbamoyl-4-(*N*-benzylamino)but-3-en-2-one 3h. 1.00 g, 90%. White crystals, mp 131–132°C. [Found: C, 53.65; H, 4.11; N, 6.69. $C_{19}H_{17}F_3N_2O_4S$ requires C, 53.52; H, 4.02; N, 6.57%]; ν_{max} ($CHCl_3$) 3500–2800 (br), 1651, 1608, 1446, 1392, 1356 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 11.70 (1H, s, CONHSO$_2$), 11.17 (1H, br s, NHBn), 7.95 and 7.32 (2×2H, 2×d, J=8.2 Hz, C_6H_4Me), 7.89 (1H, d, J=14.0 Hz, HC═), 7.40 and 7.22 (3H, 2H, 2×m, Ph), 4.56 (2H, d, J=5.6 Hz, CH_2Ph), 2.43 (3H, s, C_6H_4Me); δ_F (300 MHz, $CDCl_3$) −67.24 (s, CF_3).

3.2.6. (*Z*)-1,1,1-Trifluoro-3-tosylcarbamoyl-4-(4-dimethylaminoanilino)but-3-en-2-one 3k. 0.92 g, 78%. Yellow crystals, mp 169–171°C. [Found: C, 52.82; H, 4.49; N, 9.30. $C_{20}H_{20}F_3N_3O_4S$ requires C, 52.74; H, 4.43; N, 9.23%]; ν_{max} (KBr) 3500–2700 (br), 1650, 1600, 1530, 1430, 1363 cm^{-1}; δ_H (300 MHz C_3D_6O) 12.54 (1H, br d, J=14.0 Hz, NHC_6H_4), 11.85 (1H, s, CONHSO$_2$), 8.32 (1H, dq, J=14.0, 0.8 Hz, HC═), 8.00 and 7.46 (2×2H, 2×d, J=8.3 Hz, C_6H_4Me), 7.32 and 6.80 (2×2H, 2×d, J=9.1 Hz, NC_6H_4), 2.99 (6H, s, $C_6H_4NMe_2$), 2.44 (3H, s, C_6H_4Me); δ_F (300 MHz, C_3D_6O) −68.12 (br d, CF_3).

3.2.7. (*Z*)-1,1,1-Trifluoro-3-tosylcarbamoyl-4-(4-methoxyanilino)but-3-en-2-one 3l. 0.86 g, 75%. Pale yellow crystals, mp 150–152°C. [Found: C, 51.62; H, 3.93; N, 6.39. $C_{19}H_{17}F_3N_2O_5S$ requires C, 51.58; H, 3.87; N, 6.33%]; ν_{max} ($CHCl_3$) 3400–2800 (br), 1656, 1615, 1519, 1442, 1383, 1360, 1305 cm^{-1}; δ_H (300 MHz, C_3D_6O) 12.53 (1H, br d, $J{\sim}$13.8 Hz, NHC_6H_4), 11.76 (1H, s, CONHSO$_2$), 8.39 (1H, dq, J=13.8, 0.8 Hz, HC═), 8.00 and 7.36 (2×2H, 2×d, J=8.2 Hz, C_6H_4Me), 7.24 and 7.06 (2×2H, 2×d, J=8.5 Hz, NC_6H_4), 3.84 (3H, s, C_6H_4OMe), 2.44 (3H, s, C_6H_4Me); δ_F (300 MHz, CD_3CN) −68.23 (s, CF_3).

3.2.8. (*Z*)-1,1,1-Trifluoro-3-tosylcarbamoyl-4-(4-methylanilino)but-3-en-2-one 3m. 0.84 g, 76%. Pale yellow crystals, mp 182–185°C. [Found: C, 53.57; H, 4.10; N, 6.64. $C_{19}H_{17}F_3N_2O_4S$ requires C, 53.52; H, 4.02; N, 6.57%]; ν_{max} ($CHCl_3$) 3500–2800 (br), 1656, 1608, 1586, 1443, 1380, 1360 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 12.61 (1H, br d, J=13.6 Hz, NHC_6H_4), 11.71 (1H, s, CONHSO$_2$), 8.33 (1H, d, J=13.6 Hz, HC═), 8.00 and 7.36 (2×2H, 2×d, J=8.1 Hz, C_6H_4Me), 7.24 and 7.06 (2×2H, 2×d, J=8.3 Hz, NC_6H_4), 2.44 (3H, s, C_6H_4Me), 2.37 (3H, s, NC_6H_4Me); δ_F (300 MHz, CD_3CN) −68.29 (s, CF_3).

3.2.9. (*Z*)-1,1,1-Trifluoro-3-tosylcarbamoyl-4-(4-chloroanilino)but-3-en-2-one 3o. 0.85 g, 73%. White crystals, mp 172–174°C. [Found: C, 48.45; H, 3.21; N, 6.35. $C_{18}H_{14}ClF_3N_2O_4S$ requires C, 48.38; H, 3.16; N, 6.27%]; ν_{max} (KBr) 3600–2800 (br), 1663, 1611, 1596, 1580, 1496, 1440, 1425, 1374, 1356 cm^{-1}; δ_H (300 MHz, C_3D_6O) 12.54 (1H, br d, $J{\sim}$13.6 Hz, NHC_6H_4), 11.65 (1H, s, CONHSO$_2$), 8.49 (1H, d, J=13.6 Hz, HC═), 8.00 and 7.47 (2×2H, 2×d, J=8.2 Hz, C_6H_4Me), 7.56 (4H, m, NC_6H_4Cl), 2.45 (3H, s, C_6H_4Me); δ_F (300 MHz, C_3D_6O) −68.32 (s, CF_3).

3.2.10. (*Z*)-1,1,1-Trifluoro-3-tosylcarbamoyl-4-(4-methylamino)-4-methylbut-3-en-2-one 3i. 0.83 g, 88%. White crystals, mp 152–154°C. [Found: C, 46.20; H, 4.22; N, 7.76. $C_{14}H_{15}F_3N_2O_4S$ requires C, 46.15; H, 4.15; N, 7.69%]; ν_{max} (KBr) 3600–2600 (br), 1661, 1614, 1588, 1452, 1352, 1310 cm^{-1}; δ_H (300 MHz C_3D_6O) 11.69 (1H, br s, CONHSO$_2$), 10.79 (1H, br s, NHMe), 7.93 and 7.45 (2×2H, 2×d, J=8.4 Hz, C_6H_4Me), 3.18 (3H, d, J=5.1 Hz, NHMe), 2.45 (3H, s, C_6H_4Me), 2.05 (3H, s, MeC═); δ_F (300 MHz C_3D_6O) −71.40 (br s, CF_3).

3.2.11. (*Z*)-1,1,1-Trifluoro-3-tosylcarbamoyl-4-(4-methylamino)-4-phenylbut-3-en-2-one 3j. 1.00 g, 90%. White crystals, mp 165–167°C. [Found: C, 53.58; H, 4.08; N, 6.64. $C_{19}H_{17}F_3N_2O_4S$ requires C, 53.52; H, 4.02; N, 6.57%]; ν_{max} (KBr) 3600–2700 (br), 1670, 1596, 1452, 1419, 1356, 1300 cm^{-1}; δ_H (300 MHz, C_3D_6O) 11.68 (1H, br s, CONHSO$_2$) 10.42 (1H, br s, NHMe), 7.56 (2H, d, J=8.4 Hz, two of the C_6H_4Me), 7.49–7.22 (7H, m, two of the C_6H_4Me and Ph), 2.88 (3H, d, J=5.2 Hz, NHMe), 2.45 (3H, s, C_6H_4Me); δ_F (300 MHz, C_3D_6O) −67.97 (s, CF_3).

3.2.12. (*Z*)-3-Tosylcarbamoyl-4-(4-methylamino)but-3-en-2-one 3p. 0.68 g, 77%. White crystals, mp 188–191°C. [Found: C, 52.75; H, 5.50; N, 9.51. $C_{13}H_{16}N_2O_4S$ requires C, 52.69; H, 5.44; N, 9.45%]; ν_{max} (KBr) 3600–2600 (br), 1660, 1632, 1595, 1439, 1399, 1372, 1345 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 12.79 (1H, s, CONHSO$_2$), 10.19 (1H, br d, J=13.6 Hz, NHMe), 7.95 and 7.30 (2×2H, 2×d, J=8.1 Hz, C_6H_4Me), 7.76 (1H, d, J=13.6 Hz, HC═), 3.15 (3H, d, J=5.1 Hz, NHMe), 2.42 (3H, s, C_6H_4Me), 2.26 (3H, s, MeCO).

3.3. General procedures for the synthesis of the ureas 2e,l,m

Tosyl isocyanate (0.51 g, 2.6 mmol) was added dropwise to a mixture of **1e**,**l**,**m** (2.9 mmol) and Et_3N (0.44 g, 4.3 mmol) in anhydrous chloroform (5 mL) with stirring at −10°C The reaction mixture was left for 24 h at room temperature and then washed with 5% aqueous solution of citric acid (3×20 mL). The chloroform layer was separated, dried ($MgSO_4$) and concentrated. The crude product **2e** was obtained in 50% yield and 90% purity. Products **2l**,**m** were obtained in high yields and 100% purity.

3.3.1. (*E*)-4-(*N*-Butyl-*N*-tosylamino)-1,1,1-trifluorobut-3-en-2-one 2e. 0.51 g, 50%. Yellow solid, mp 70–73°C. [Found: C, 49.03; H, 4.94; N, 7.21. $C_{16}H_{19}F_3N_2O_4S$

requires C, 48.98; H, 4.88; N, 7.14%]; ν_{max} ($CHCl_3$) 3500–2600 (br), 1720, 1587, 1440, 1428, 1347 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.44 (1H, d, J=13.6 Hz, NC*H*=), 7.93 and 7.33 (2×2H, 2×d, J=8.1 Hz, C_6H_4Me), 7.33 (1H, s, CON*H*SO_2), 5.76 (1H, d, J=13.6 Hz, COC*H*=), 3.58 (2H, t, J=7.6 Hz, NCH_2), 2.44 (3H, s, C_6H_4*Me*), 1.53 (2H, m, NCH_2CH_2), 1.30 (2H, m, CH_2CH_3), 0.90 (3H, t, J=7.3 Hz, CH_2CH_3); δ_F (300 MHz, $CDCl_3$) −77.29 (s, CF_3).

3.3.2. (*E*)-4-(*N*-4-Methoxyanilino-*N*-tosylamino)-1,1,1-trifluorobut-3-en-2-one 2l. 0.90 g, 78%. Yellow crystals, mp 121–123°C. [Found: C, 51.62; H, 3.92; N, 6.39. $C_{19}H_{17}F_3N_2O_5S$ requires C, 51.58; H, 3.87; N, 6.33%]; ν_{max} ($CHCl_3$) 3600–2800 (br), 1735, 1600, 1515, 1420, 1348 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.71 (1H, d, J=14.0 Hz, NC*H*=), 7.90 and 7.38 (2×2H, 2×d, J=8.2 Hz, C_6H_4Me), 7.46 (1H, s, CON*H*SO_2), 7.08 (4H, m, C_6H_4OMe), 5.17 (1H, d, J=4.0 Hz, COC*H*=), 3.87 (3H, s, O*Me*), 2.47 (3H, s, C_6H_4*Me*); δ_F (300 MHz, CD_3CN) −78.10 (s, CF_3).

3.3.3. (*E*)-4-(*N*-4-Methylanilino-*N*-tosylamino)-1,1,1-trifluorobut-3-en-2-one 2m. 0.83 g, 75%. Pale yellow crystals, mp 119–121°C. [Found: C, 53.59; H, 4.10; N, 6.63. $C_{19}H_{17}F_3N_2O_4S$ requires C, 53.52; H, 4.02; N, 6.57%]; ν_{max} ($CHCl_3$) 3500–2800 (br), 1731, 1593, 1512, 1416, 1360, 1342 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.72 (1H, d, J=14.0 Hz, NC*H*=), 7.91 and 7.07 (2×2H, 2×d, J=8.2 Hz, C_6H_4Me), 7.39 (4H, m, NC_6H_4Me), 7.34 (1H, s, CON*H*SO_2), 5.16 (1H, d, J=14.0 Hz, COC*H*=), 2.48 (3H, s, NC_6H_4*Me*), 2.46 (3H, s, C_6H_4*Me*); δ_F (300 MHz, CD_3CN) −78.22 (s, CF_3).

3.4. General procedures for the synthesis of the vinylogous sulphonylureas 6a,b

Tosyl isocyanate (0.51 g, 2.6 mmol) was added dropwise to a solution of **5a**,**b** (2.9 mmol) in anhydrous chloroform (3 mL) with stirring at room temperature. After 24 h the solvent was evaporated in vacuo and the residue was washed with hexane (30 mL). The crude products were purified by crystallization from ethanol.

3.4.1. (*Z*)-1,1,1-Trifluoro-3-tosylcarbamoyl-4-(*N*,*N*-dimethylamino)but-3-en-2-one 6a. 0.52 g, 55%. Pale yellow crystals, mp 109–111°C. [Found: C, 46.20; H, 4.22; N, 7.76. $C_{14}H_{15}F_3N_2O_4S$ requires C, 46.15; H, 4.15; N, 7.69%]; ν_{max} ($CHCl_3$) 3600–2600 (br), 1677, 1640, 1588, 1420, 1349 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 11.29 (1H, br s, CON*H*SO_2) 7.95 and 7.31 (2×2H, 2×d, J=8.3 Hz, C_6H_4Me), 7.82 (1H, s, *H*C=), 3.43 and 3.08 (2×3H, 2×s, NMe_2), 2.41 (3H, s, C_6H_4*Me*); δ_F (300 MHz, $CDCl_3$) −68.85 (s, CF_3).

3.4.2. (*Z*)-1,1,1-Trifluoro-3-tosylcarbamoyl-4-(*N*,*N*-dimethylamino)phenylbut-3-en-2-one 6b. 0.59 g, 52%. Pale yellow crystals, mp 125–127°C. [Found: C, 54.61; H, 4.40; N, 6.40. $C_{20}H_{19}F_3N_2O_4S$ requires C, 54.54; H, 4.35; N, 6.36%]; ν_{max} ($CHCl_3$) 3600–2600 (br), 1654, 1600, 1562, 1429, 1408, 1388, 1364, 1344 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 12.40 (1H, s, CON*H*SO_2) 7.99 and 7.32 (2×2H, 2×d, J=8.0 Hz, C_6H_4Me), 7.64–7.36 (5H, m, Ph), 3.45 (6H, s, NMe_2), 2.44 (3H, s, C_6H_4*Me*); δ_F (300 MHz, $CDCl_3$) −69.10 (s, CF_3).

3.4.3. *N*-[(*E*,2*E*)-3-(Dimethylamino)-1-(trifluoromethyl)-2-propylidene]-4-methyl-benzenesulfonamide 7a. Tosyl isocyanate (1.2 g, 6.0 mmol) was added dropwise to **5a** (1.0 g, 6.0 mmol) at room temperature. After 48 h the resulting oil was purified by flash chromatography (20% ethyl acetate/$CHCl_3$) to give the title compound **7a** (0.98 g, 51%) as a yellow solid, mp 133–136°C. [Found: C, 47.14; H, 4.38; N, 9.23. $C_{12}H_{13}F_3N_2O_2S$ requires C, 47.06; H, 4.28; N, 9.15%]; R_f (20% ethyl acetate/$CHCl_3$) 0.63; ν_{max} ($CHCl_3$) 3600–2600 (br), 1626, 1548, 1480, 1412, 1356, 1282 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.86 and 7.28 (2×2H, 2×d, J=8.3 Hz, C_6H_4Me), 7.70 (1H, br s, NC*H*=), 5.93 (1H, br s, N=CC*H*=), 3.28 and 3.06 (2×3H, 2×s, NMe_2), 2.41 (3H, s, C_6H_4*Me*).

3.5. X-Ray crystal structure analysis of 3e

Suitable crystals were obtained from ethanol. Crystal data: $C_{16}H_{19}F_3N_2O_4S$, M=392.39, monoclinic, a=10.3796(8), b=17.110(2), c=10.829(1) Å, β=100.36(1), V=1891.7(3) $Å^3$, space group $P2_1/n$, Z=4, D_c=1.38 g cm^{-3}, μ=2.00 mm^{-1}, $F(000)$=816, crystal dimensions 0.35×0.38×0.44 mm. The intensities of 2973 reflections were measured on a Enraf-Nonius CAD4 diffractometer (Cu K_α-radiation, T=293 K, $4<\theta<60°$, 2804 unique reflections). The structure was solved by direct methods[20] and refined on F^2 by full-matrix least-squares techniques[21] in anisotropic approximation (2618 reflection with $I>2\sigma(I)$, 266 variables, observations/variables=9.8, weighting scheme $w^{-1}=\sigma^2(F_o^2)+(0.0957P)^2+0.5116P$, where $P=(F_o^2+2F_c^2)/3$). Atoms H(1), H(1N) and H(2N) were located in the difference Fourier maps and refined isotropically. All remaining hydrogen atoms were placed geometrically and included in the final refinement with the fixed positional and thermal parameters. Convergence was obtained at $R(F)$=0.054, $R_w(F^2)$=0.148, GOF=1.054, $\Delta\rho$(min/max)=−0.32/0.25 e $Å^{-3}$. Atomic coordinates and further crystallographic details have been deposited at the Cambridge Crystallographic Data Centre, deposition number 196140, and copies of this data can be obtained in application to CCDC, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK.

References

1. Kukländer, U. Enamines as Synthones. In *The Chemistry of Enamines*; Rappaport, Z., Ed.; Wiley: New York, 1994; pp 523–636.
2. Michael, J. P.; de Konig, C. B.; Gravestock, D.; Hosken, G. D.; Howard, A. S.; Jungmann, C. M.; Krause, R. W. M.; Parsons, A. S.; Pelly, S. C.; Stanbury, T. V. *Pure Appl. Chem.* **1999**, *71*, 979.
3. *Organofluorine Compounds in Medicinal Chemistry and Biochemical Applications*; Filler, R., Kobayashi, Y., Yagupolskii, L. M., Eds.; Elsevier: Amsterdam, 1993.
4. *Fluorine in Bioorganic Chemistry*; Welch, J. T., Eswarakrishnan, S., Eds.; Wiley: New York, 1991.
5. Gerus, I. I.; Gorbunova, M. G.; Vdovenko, S. I.; Yagupolskii, Y. L.; Kukhar, V. P. *Zh. Org. Khim.* **1990**, *26*, 1877.
6. Gerus, I. I.; Gorbunova, M. G.; Kukhar, V. P. *J. Fluorine Chem.* **1994**, *69*, 195.

7. Vdovenko, S. I.; Gerus, I. I.; Gorbunova, M. G. *J. Fluorine Chem.* **1997**, *82*, 167.
8. Vdovenko, S. I.; Gerus, I. I.; Gorbunova, M. G. *J. Chem. Soc. Perkin Trans. 2* **1993**, 559.
9. Wojcik, J.; Domalewski, W.; Kamienska-Trela, K.; Stefaniak, L.; Vdovenko, S. I.; Gerus, I. I.; Gorbunova, M. G. *Magn. Reson. Chem.* **1993**, *31*, 808.
10. Tsuge, O.; Inaba, A. *Bull. Chem. Soc. Jpn* **1973**, *46*, 286. Tsuge, O.; Inaba, A. *Bull. Chem. Soc. Jpn* **1976**, *49*, 2828.
11. Viswanathan, N.; Ravindranath, K. R.; Talwalkar, P. K. *Indian J. Chem.* **1979**, *B17*, 478.
12. Gerus, I. I.; Lyutenko, N. V.; Kacharov, A. D.; Kukhar, V. P. *Tetrahedron Lett.* **2000**, *41*, 10141.
13. Hojo, M.; Masuda, R.; Kokuryo, Y.; Shioda, H.; Matsuo, S. *Chem. Lett.* **1976**, 499.
14. Hojo, M.; Masuda, R.; Sakaguchi, S.; Takagawa, H. *Synthesis* **1986**, 1016.
15. Lyutenko, N. V.; Gerus, I. I.; Vdovenko, S. I.; Bzhezovsky, V. M.; Iksanova, S. V.; Kudryavcev, A. A. *Proc. Acad. Sci. Ukraine* **2002**, 141.
16. Gorbunova, M. G.; Gerus, I. I.; Galushko, S. V.; Kukhar, V. P. *Synthesis* **1991**, 207.
17. Allen, F. H.; Kennard, O.; Watson, D.; Brammer, L.; Orpen, A. G.; Taylor, R. *J. Chem. Soc. Perkin Trans. 2* **1987**, 1.
18. Bertolasi, V.; Gilli, P.; Ferretti, V.; Gilli, G. *Acta Crystallogr.* **1995**, *B51*, 1004.
19. Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; 3rd ed., Pergamon: Oxford, 1998.
20. Sheldrick, G. M. *SHELXS-86. Program for the Solution of Crystal Structures*; University of Gottingen: Gottingen, Germany, 1986.
21. Sheldrick, G. M. *SHELXL-93. Program for the Refinement of Crystal Structures*; University of Gottingen: Gottingen, Germany, 1993.