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The aza Arndt–Eistert reaction based on *N*-trifluoromethylsulfonylarenecarboximidoyl chlorides

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ABSTRACT

The aza analogues of carboxylic acids chlorides containing the $=NSO_2CF_3$ and $=NSO_2CH_3$ groups instead of oxygen atom were used in the Arndt–Eistert reaction. It was found that *N*-trifluoromethylsulfonyl-(4-fluorophenyl)-carboximidoyl chloride **1** reacts with diazomethane vigorously even at −70 °C with formation of 1-trifluoromethylsulfonylamino-2-(4-fluorophenyl)-2,3-dimorpholine-4-yl-propane **3**, 2-trifluoromethylsulfonylamino-2-(4-fluorobenzyl)-7-oxa-4-azonia-spiro[3.5]nonane **4**, 2-trifluoromethylsulfonylamino-2-(4-fluorobenzyl)-1,3-dimorpholine-4-yl-propane **5** and 1-trifluoromethylsulfonylamino-2-(4-fluorobenzyl)-2,3-dimorpholine-4-yl-propane **6**. Reaction of *N*-methylsulfonylbenzcarboximidoyl chloride **8** with diazomethane proceeds at −15 °C yielding 4-chloro-4-methylsulfonylaminomethyl-3-phenyl-4,5-dihydro-1H-pyrazoline **9**.

1. Introduction

In a course of a systematic research on nucleophilic rearrangements of carbonyl compounds analogues in which the sp^2-hybridized oxygen atom is replaced by a trifluoromethylsulfonylimino group, we previously reported that aza analogues of acid azides, arenehydroxamic acids and carboxamides undergo the aza Curtius [1], Lossen [2] and Hofmann [3] rearrangements. The aza Curtius reaction was shown to proceed under mild conditions yielding the carbodiimides containing the $=NSO_2CF_3$ group [1]. In contrast acid azides with fluorine-free sulfonylimino groups react with sodium azide yielding heterocyclic compounds and no Curtius rearrangement was observed [1]. Trifluoromethylsulfonylimides of arenehydroxamic acids undergo a Lossen-type rearrangement to form *N*-trifluoromethylsulfonyl-*N*′-arylcarbodiimides or *N*-trifluoromethylsulfonyl-*N*′-arylchloroformamidines depending on the reaction conditions [2]. *N*-Trifluoromethylsulfonyl arenecarboxamidines undergo an oxidative aza Hofmann rearrangement under the action of (diacyloxyiodo)arenes to form carbodiimides. All these reactions proceed via nucleophilic migration of a substituent from carbon atom to nitrogen atom (Scheme 1).

Bearing in mind specific effects of the $=NSO_2CF_3$ group in various rearrangements mentioned above, in the present research we have studied the influence of the trifluoromethylsulfonylimino group on the known Wolff rearrangement. In the key step of this process a substituent undergoes C–C migration via carbene intermediate formation. The Wolff rearrangement is the second stage of the Arndt–Eistert reaction, which includes the following stages: (1) reaction of acid chloride with diazomethane in appropriate solvent yielding a stable diazoketone; (2) the Wolff rearrangement of isolated or crude diazoketone in the presence of suitable reagents. With water the corresponding acid is formed, an ester is produced in an alcohol, and an amide results when ammonia or an amine is used. The Wolff rearrangement of diazoketones is triggered by metal catalyst, irradiation or heating [4].

2. Results and discussion

It is well known that the aromatic fluorine atom is a very helpful mark in product identification, therefore we have selected the *N*-trifluoromethylsulfonyl-(4-fluorophenyl)-carboximidoyl chloride **1** [1] as a model compound for our study. Morpholine was chosen

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[1] Crystal structure analysis.
[2] HPLC separation.
[3] Two-dimensional NMR spectra analysis.

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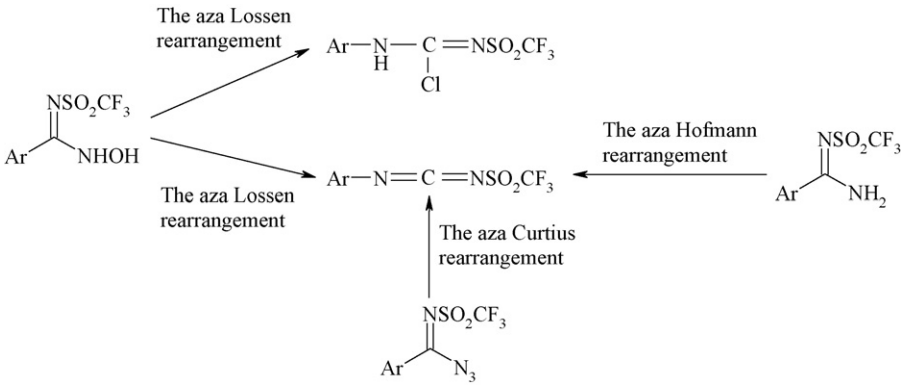


Scheme 1.

as nucleophile and was added to the reaction mixture after the evolution of nitrogen finished. Ether, THF and glyme were used as solvents in this reaction; it is noteworthy to mention that positive results were achieved only in glyme. Besides, for other rearrangements of *N*-trifluoromethylsulfonyl derivatives of carbonyl compounds (the aza Curtius, aza Lossen and aza Hofmann rearrangements) glyme was preferred to other solvents due to its coordinating effect on the compounds of this type [1]. Taking into account these observations we had also preferred glyme for the Arndt–Eistert reaction.

Remarkably, the reaction between *N*-trifluoromethylsulfonyl-(4-fluorophenyl)-carboximidoyl chloride **1** and diazomethane occurs vigorously even at low temperature (−70 °C). The resulting diazoketone was found to be a very unstable compound which underwent further transformations at −70 °C yielding a mixture of four products **3**–**6** in total 5% yield (Scheme 2). Reaction is attended by significant resinification. A product of morpholine addition to *N*-trifluoromethylsulfonyl-4-fluorophenylketenimine **2** does not form.

Probably, there is a partial positive charge on the central carbon atom of the ketenimine **2** induced by the strong electron acceptor—the $=NSO_2CF_3$ group. This may be the reason of its high reactivity and instability.

Phenylazide is known to be an efficient trapping agent for compounds with unstable and highly reactive double bonds [5]. Nevertheless, attempts to use phenylazide instead of morpholine to obtain stable heterocyclic products from keteneimine **2** failed. On the other hand, in this case no resinification has been observed. We supposed that phenylazide can stabilize the partial positive charge in **2** and to verify this assumption the reaction between **1** and diazomethane in the presence of phenylazide using morpholine as a nucleophile was carried out. Similar reactions were performed using lithium chloride [6] for stabilization of the partial positive charge on the central carbon atom of **2**.

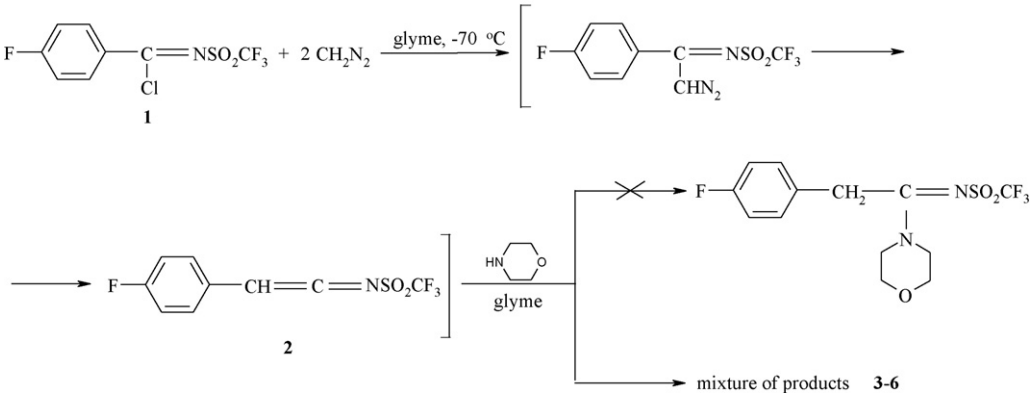
We have found that stabilization of **2** by three equivalents of phenylazide or lithium chloride and usage of three equivalents of diazomethane led to higher overall yield of four products **3**–**6** (40–55%) (Scheme 3).

There is dependence between yields of products **3**–**6** and the reagent (PhN_3 or LiCl) used. These data are summarized in Table 1.

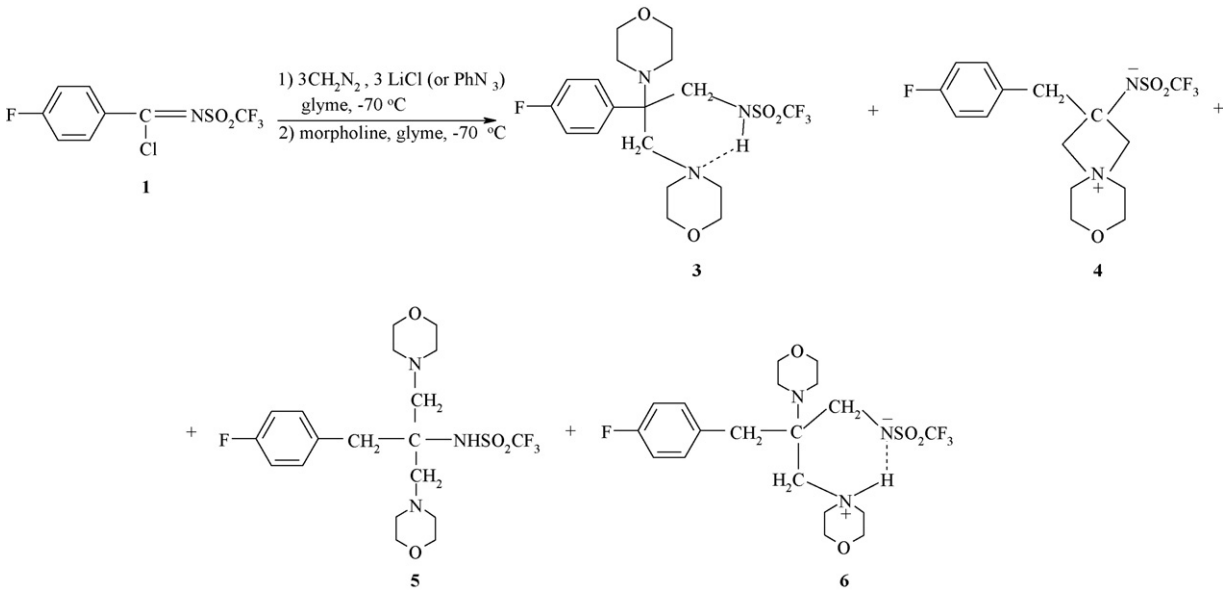
Compounds **3**–**6** were separated by crystallization and HPLC, and their structure was determined by X-ray analysis (Figs. 1–4). Only tarry products were obtained if one equivalent of phenylazide or lithium chloride with three equivalents of diazomethane was used in these conditions. It is interesting that using of two equivalents of diazomethane in the presence of one equivalent of phenylazide or lithium chloride leads to compound **4** only with 5–10% yield.

As a result of X-ray diffraction study it was found, that in the compound **3** there is very strong [7] intramolecular hydrogen bond N(1)–H···N(3) [N(1)–N(3) 2.593(5) Å, N(3)–H 1.80(4)Å, N(1)–H(1) 0.92(4)Å, N(1)HN(3) 144(4)°], which forms 6-membered cycle N(3)C(14)C(7)C(8)N(1)H(1). The N(1) atom has a trigonal-planar bond configuration (sum of the bond angles 358.0(6)°). The atoms N(2) and N(3) have pyramidal bond configuration (sum of the bond angles 336.7(6)° and 333.6(6)°, respectively).

The peculiarity of the compound **4** is the presence of 4-membered cycle C(8)–C(9)–N(2)–C(10), which is almost planar—the average deviation from the least square plane does not exceed 0.012 Å. The bond lengths and angles in this cycle are similar to the corresponding values in picrate 2-hydroxy-7-oxa-4-azoniaspiro[3.5]nonane [8].



Scheme 2.



Scheme 3.

In the molecule of the compound **5** the atom N(3) has a trigonal-planar bond configuration (sum of the bond angles 359.1(4)°). The N(1) and N(2) atoms have pyramidal bond configuration (sum of the bond angles 333.6(5)° and 332.6(5)°, respectively). In the solid state molecules **5** are organized in chains by the intermolecular hydrogen bonds N(3)–H(3)···O(4) with the following parameters: N(3)···O(4) 2.824(2) Å, N(3)–H(3) 0.80(2) Å, H(3)···O(4) 2.04(2) Å, N(3)H(3)O(4) 171(2)° (Fig. 5).

Table 1
Yields of products **3**–**6** depending on the reaction conditions.

Reagent	Yields of products [%]				
	3	**4**	**5**	**6**	Overall
PhN_3	15	10	20	10	55
LiCl	18	8	2	12	40

It was found that the main peculiarity of the compound **6** is the strong [7] intramolecular hydrogen bond N(2)–H···N(3) [N(2)–N(3) 2.650(3) Å, N(3)–H 1.83(3) Å, N(2)–H 0.88(3) Å, N(2)HN(3) 153(3)°], which forms the 6-membered ring N(2)C(9)C(8)C(18)N(3)H(2). The N(1) atom has a pyramidal bond configuration (sum of the bond angles 337.2(5)°).

Substance **3** results from diazoketone transformations without Wolff rearrangement. For its formation we can propose the following scheme (Scheme 4).

Compounds **4**–**6** are formed as a result of the Wolff rearrangement followed by interaction of *N*-trifluoromethylsulfonyl-4-fluorophenylketenimine **2** with diazomethane and morpholine.

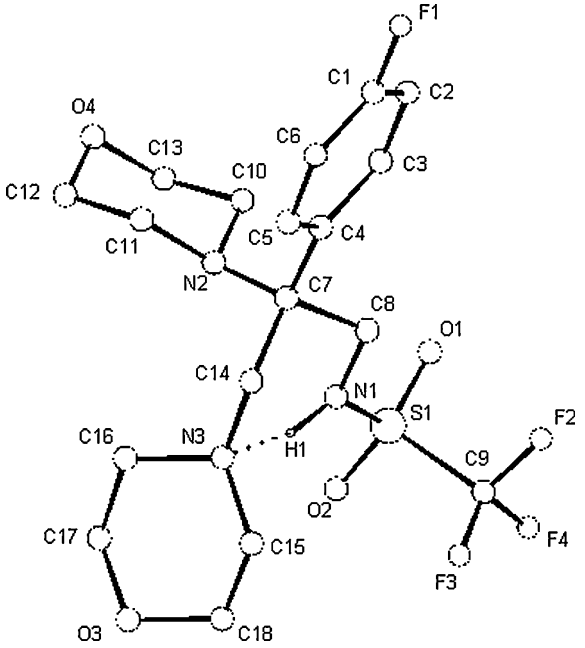


Fig. 1. Molecular structure of compound **3**. Selected bond lengths [Å] and angles [°]: S(1)–N(1) 1.553(2), N(1)–C(8) 1.465(4), C(7)–C(8) 1.551(3), C(7)–C(14) 1.548(4), N(3)–C(14) 1.483(4), N(2)–C(7) 1.491(3), S(1)–C(9) 1.819(4); N(1)S(1)C(9) 106.2(2), S(1)N(1)C(8) 125.0(2), N(2)C(7)C8) 110.0(2), N(2)C(7)C(14) 109.1(2), C(7)C(8)N(1) 109.5(2), C(7)C(14)N(3) 114.9(2), C(8)C(7)C(14) 107.2(2).

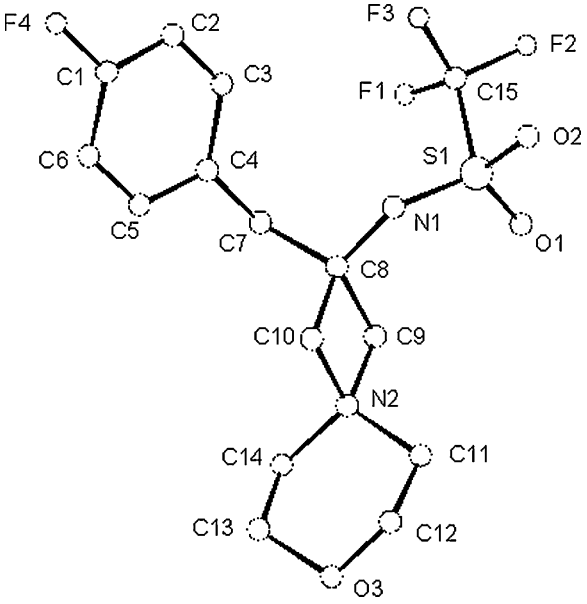


Fig. 2. Molecular structure of compound **4**. Selected bond lengths [Å] and angles [°]: C(7)–C(8) 1.533(3), C(8)–C(9) 1.557(3), N(2)–C(9) 1.517(2), N(2)–C(10) 1.530(2), C(8)–C(10) 1.548(2), N(1)–C(8) 1.453(2), S(1)–N(1) 1.515(1); S(1)N(1)C(8) 126.5(1), C(7)C(8)N(1) 112.3(2), N(1)C(8)C(9) 118.8(2), C(8)C(9)N(2) 91.2(1), C(9)N(2)C(10) 89.9(1), C(8)C(10)N(2) 91.0(1).

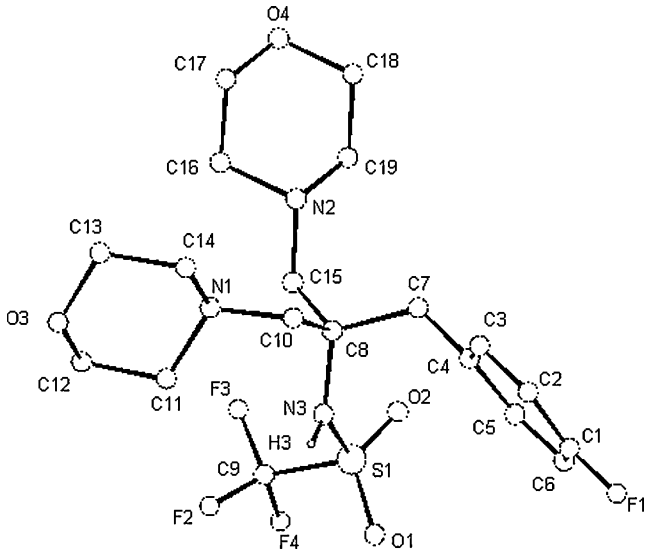


Fig. 3. Molecular structure of compound **5**. Selected bond lengths [Å] and angles [°]: S(1)–N(3) 1.585(2), N(3)–C(8) 1.499(2), C(8)–C(10) 1.550(2), N(1)–C(10) 1.460(3), C(7)–C(8) 1.553(3), C(8)–C(15) 1.531(3), N(2)–C(15) 1.476(2), F(1)–C(1) 1.353(3); S(1)N(3)C(8) 128.7(1), N(3)C(8)C(10) 106.7(1), N(3)C(8)C(15) 109.4(2), C(7)C(8)N(3) 110.7(1), C(8)C(10)N(1) 116.2(2), C(8)C(15)N(2) 112.1(2).

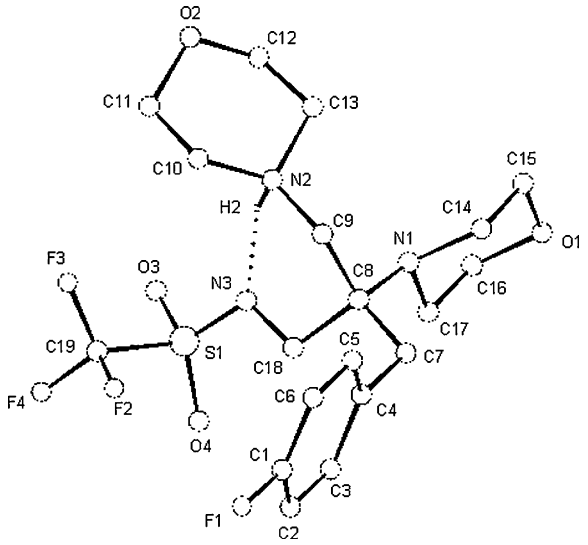


Fig. 4. Molecular structure of compound **6**. Selected bond lengths [Å] and angles [°]: S(1)–N(3) 1.529(2), N(3)–C(18) 1.476(3), C(8)–C(18) 1.538(3), C(7)–C(8) 1.556(3), C(8)–C(9) 1.529(3), N(2)–C(9) 1.508(3), N(1)–C(8) 1.491(3); S(1)N(3)C(18) 118.7(2), C(8)C(18)N(3) 111.2(2), C(7)C(8)C(18) 108.1(2), N(1)C(8)C(9) 108.1(2), C(7)C(8)N(1) 112.5(2), C(8)C(9)N(2) 112.9(2), C(7)C(8)C(9) 108.2(2).

Their formation the most likely proceeds according to Schemes 5 and 6. Probably, the reaction occurs through the formation of intermediate **A**. Interaction of **A** with HCl and then with morpholine yields compounds **4** and **5** (Scheme 5).

Intermediate **A** can also undergo an intramolecular rearrangement via formation of carbenoid transition state. This route leads to formation of product **6** (Scheme 6).

We suppose that hydrogen chloride formed from **1** and diazomethane takes part in further transformations (see Schemes 4–6). Formation of morpholine hydrochloride in quantitative yield observed in these reactions may be the evidence of our assumption.

If **1** was treated with diazomethane in ether solution in the presence of triethylamine (for trapping of hydrogen chloride) and

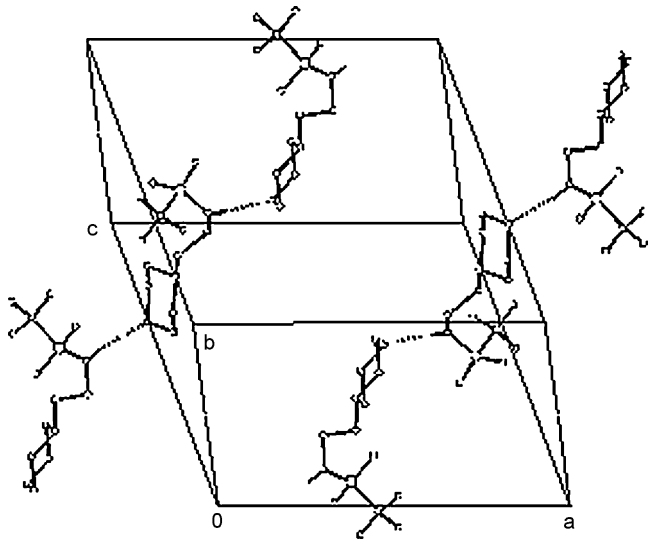
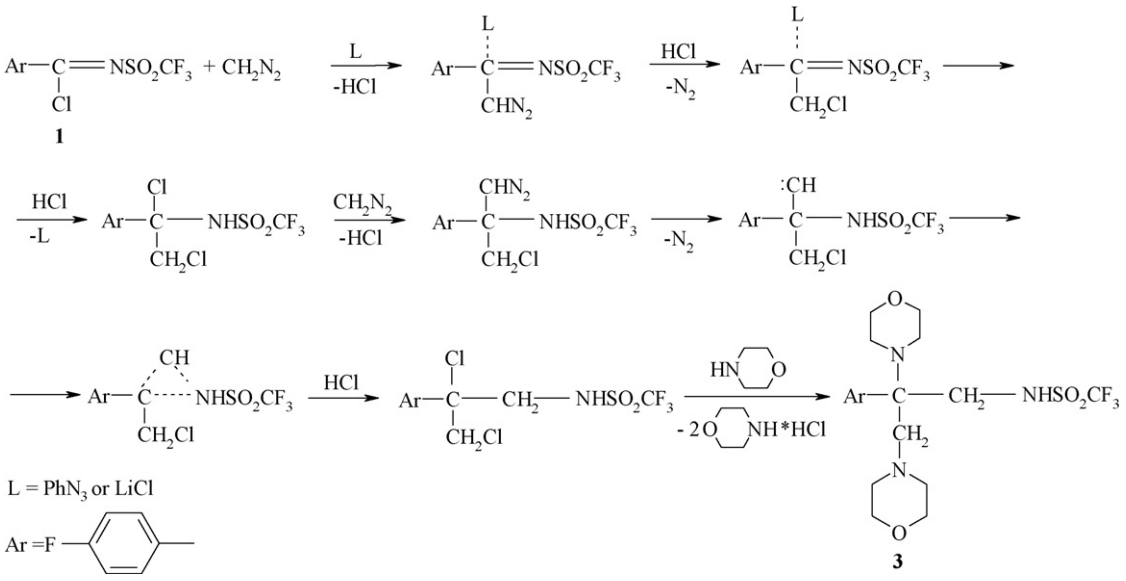


Fig. 5. Fragment of the crystal packing of compound **5**. Substituents not participating in the intermolecular hydrogen bonds are omitted for clarity.

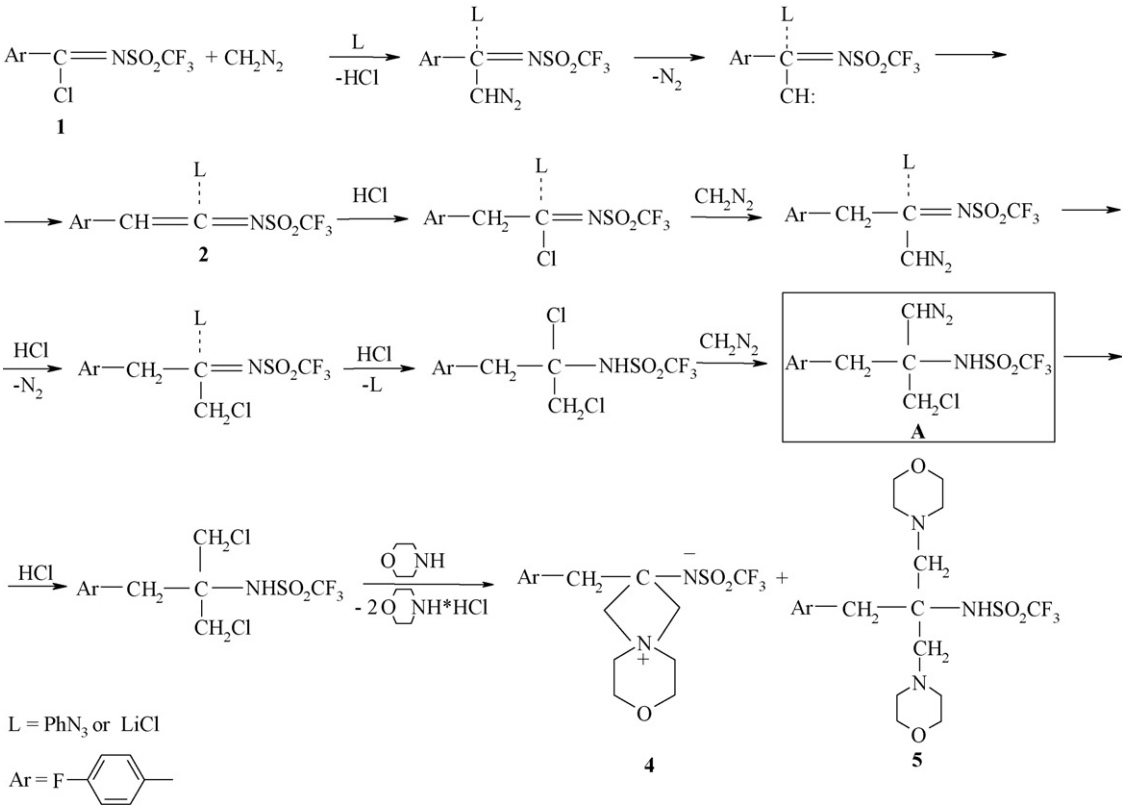
without addition of phenylazide or lithium chloride, the only isolated product was 4-fluorophenacyl chloride in minor amounts. It is likely, that formation of diazoketone takes place, but it reacts with HCl and hydrolysis of trifluoromethylsulfonylimino group occurs during separation.

Trimethylsilyldiazomethane is known to be less reactive than diazomethane (the most probably for steric effects) [9]. There are many examples of the Arndt–Eistert reaction using TMS-diazomethane or its lithium salt [9]. Reaction of acyl chloride with TMS-diazomethane proceeds in the presence of base or without base yielding the corresponding diazoketone or TMS-diazoketone depending on solvent used. In ether or THF TMS-diazoketone is formed. Usage of THF:acetonitrile 1:1 mixture leads to diazoketone. But it was the single example of TMS-diazoketone formation [10]. We carried out reaction of *N*-trifluoromethylsulfonyl-(4-fluorophenyl)-carboximidoyl chloride with TMS-diazomethane in the presence of triethylamine in THF. Reaction proceeds vigorously as well as with diazomethane. The isolated products were 4-fluorophenacyl chloride and trifluoromethanesulfonamide. Attempts to use TMS-diazomethane lithium salt in glyme gave no positive results also. It is likely, that formation of TMS-diazoketone takes place (starting imidoyl chloride disappears from the reaction mixture) but no rearrangement was observed. The only isolated product was *N*-trifluoromethylsulfonyl-(4-fluorophenyl)-imidoyl morpholide **7**.

Faced with these difficulties, we also attempted to carry out the Arndt–Eistert reaction using ethyl diazoacetate instead of diazomethane. In contrast to previous cases reaction of **1** with ethyl diazoacetate proceeds slowly at room temperature. Starting imidoyl chloride disappears from reaction mixture (monitoring by TLC and ^{19}F NMR spectra) after stirring for 24 h. Attempts to isolate diazoketone formed in this reaction were unsuccessful. Heating of the reaction mixture to 60 °C in presence of the excess of morpholine leads to evolution of nitrogen being the result of diazoketone decomposition. However, the only isolated product was **7** and no Wolff rearrangement was observed (Scheme 7). It is likely, that **7** is formed by substitution of diazoacetate residue with morpholine. If diazoketone decomposition was induced by the action of silver oxide or dirhodium tetraacetate only tarry products have been obtained. UV-irradiation of the diazoketone with Hg lamp (PRK-4, 950 W) leads to the compound **7**. In these conditions reactions begin only at 60 °C as well, so we can assume that



Scheme 4.

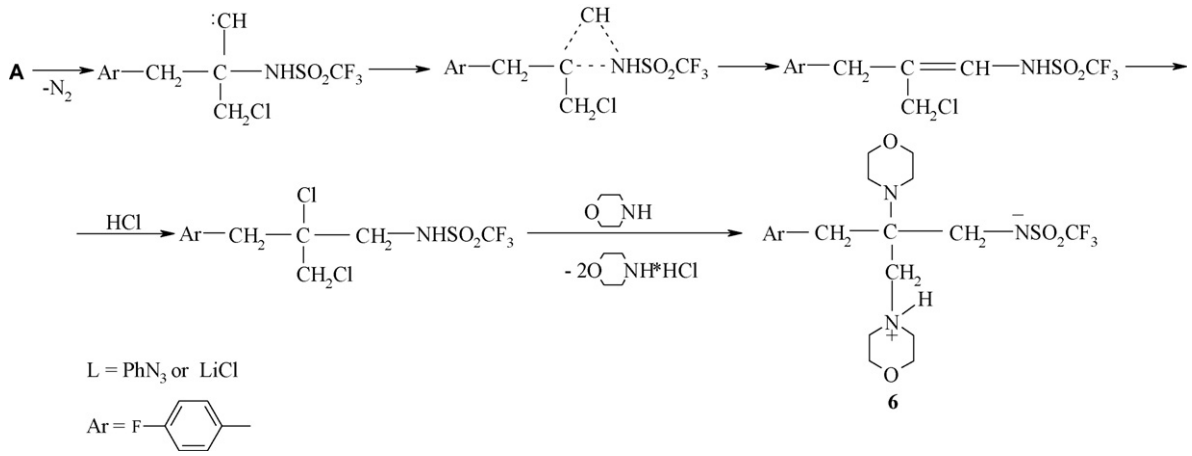


Scheme 5.

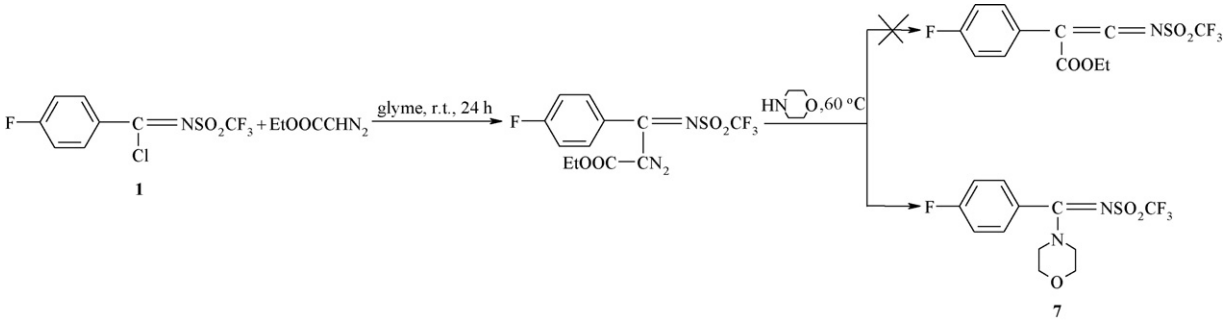
transition metals or irradiation have not the influence on the reaction course.

To compare the reactivity of fluorine-containing imidoyl chlorides to that of analogous fluorine-free ones, we carried out reactions between *N*-methyl- and *N*-phenylsulfonylbenzcarboximidoyl chlorides and diazomethane in the presence of phenylazide or lithium chloride and morpholine. Only tarry products were obtained from *N*-phenylsulfonylbenzcarboximidoyl chloride if phenylazide was used. In the presence of lithium chloride destruction of molecule was observed and benzenesulfonamide was isolated from the reaction mixture in nearly quantitative amount.

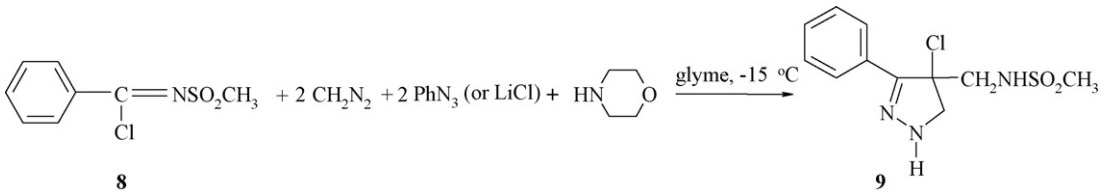
Interaction between *N*-methylsulfonylbenzcarboximidoyl chloride **8** and diazomethane in the presence of phenylazide or lithium chloride and morpholine is more controllable. It was found that reaction proceeds at −15 °C with formation of compound **9** as main product (Scheme 8). This transformation needs only two equivalents of diazomethane and gives better yield of **9** in the presence of lithium chloride (45% by LC–MS of reaction mixture). If morpholine was not added to the reaction mixture, yield of **9**



Scheme 6.



Scheme 7.



Scheme 8.

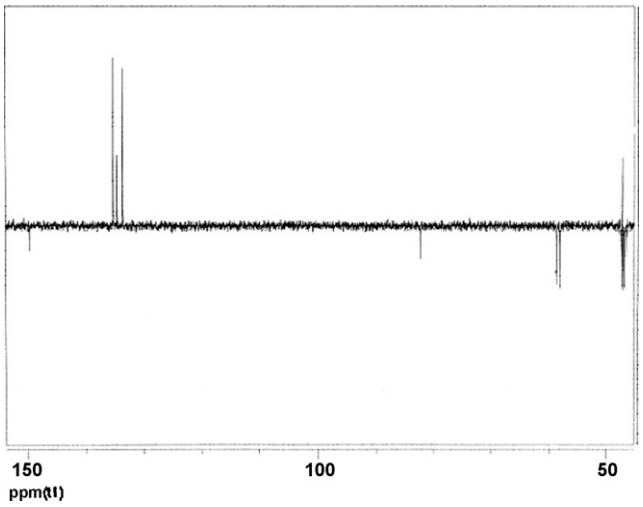


Fig. 6. APT spectrum of compound **9**.

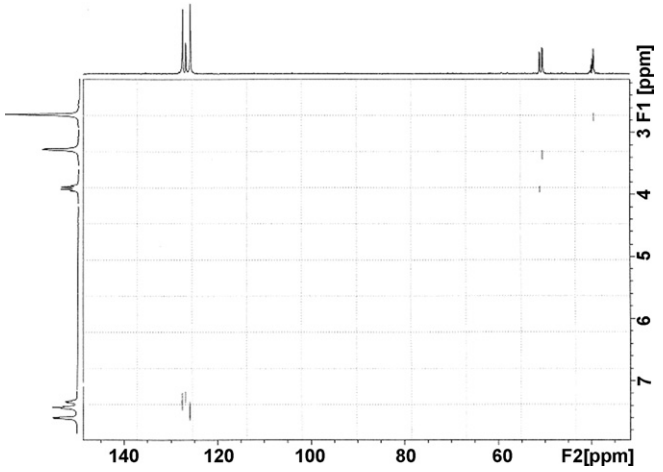


Fig. 7. HMQC spectrum of compound **9**.

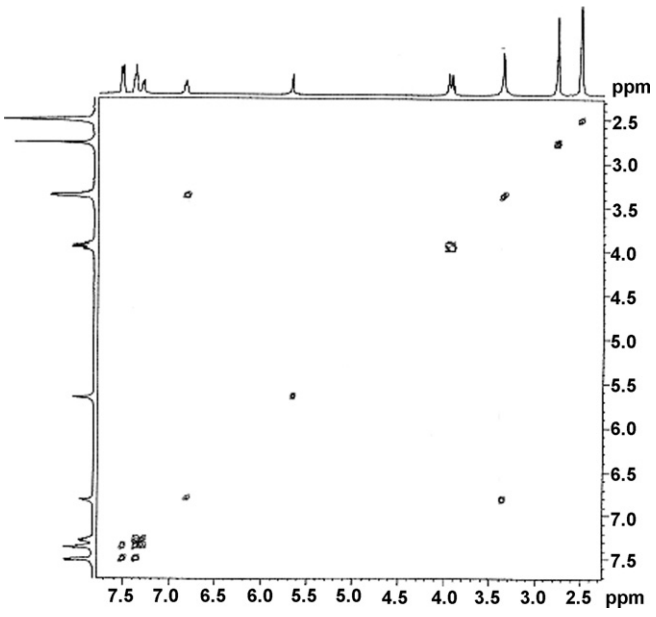


Fig. 8. COSY spectrum of compound **9**.

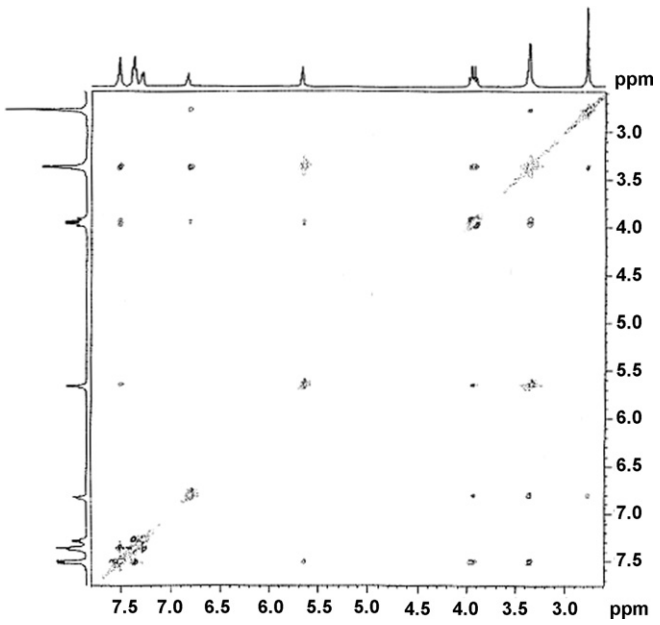
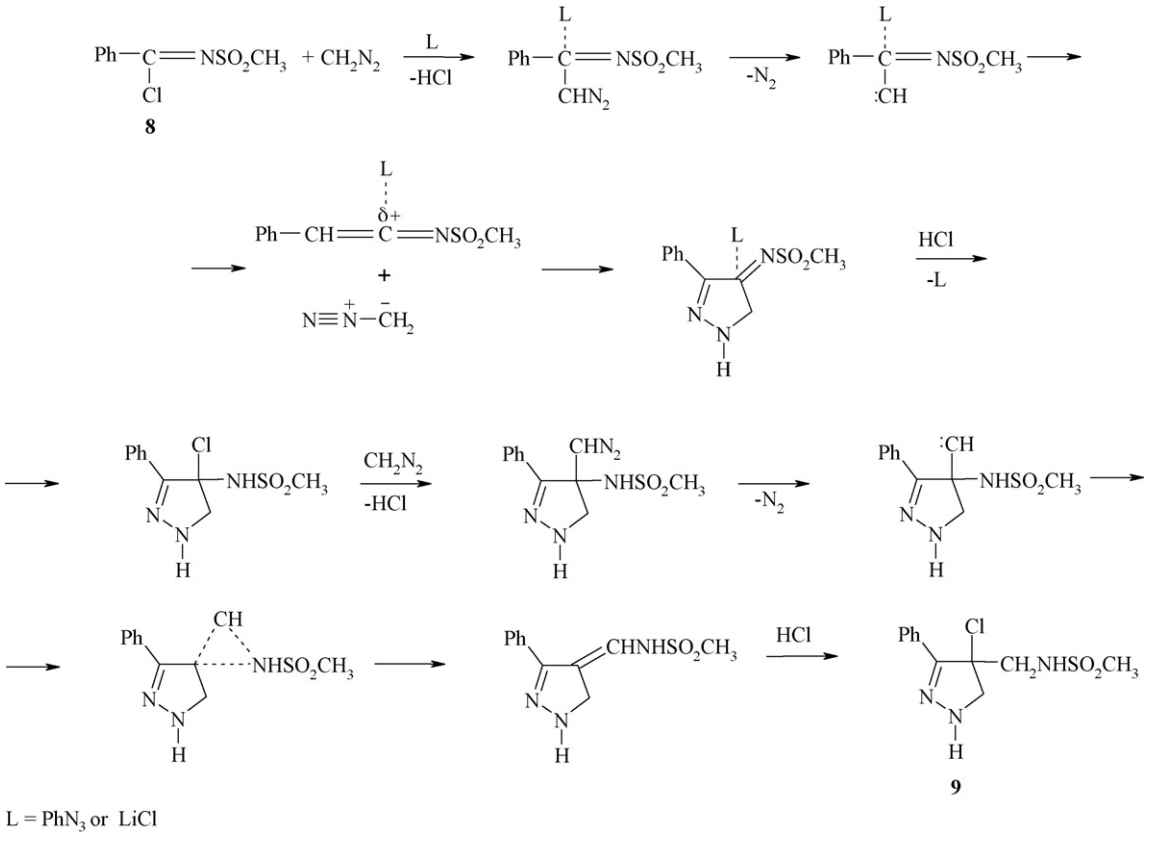


Fig. 9. NOESY spectrum of compound **9**.

decreased. Usage of triethylamine instead of morpholine leads to the analogous results. If penylazide was used, yield of product was only 12–20%.

Unfortunately, all attempts to obtain suitable single crystals of compound **9** failed. We believe that structure of **9** shown in Scheme 8 is the most probable. It agrees with data obtained from IR-spectrum, LC–MS and one- and two-dimensional NMR spectra (^{1}H, ^{13}C, APT, ^{1}H–^{13}C HMQC, COSY and NOESY) (Figs. 6–9). Presence of two molecular ions (M and M + 2) with intensity ratio 3:1 in mass-spectra establishes that this molecule contains one chlorine atom [11]. APT spectrum (Fig. 6) indicates the presence of CH_3, $2CH_2$ and C sites in compound **9** besides benzene ring. ^{1}H NMR and HMQC (Fig. 7) spectra show that there are two different NH-groups in molecule. The single ^{1}H–^{1}H correlation (Fig. 8) shows that more acidic NH-group (evidently, it is $NHSO_2CH_3$ group) is attached directly to one of the methylene sites. Thus, molecule of **9** should



Scheme 9.

contain the $CH_2NHSO_2CH_3$ fragment. The other CH_2 site is isolated. Chemical shift of this group in ^1H NMR spectrum indicates that it is attached to the nitrogen atom. It can be the nitrogen atom of pyrazoline ring. NOESY spectrum shows that $CH_2NHSO_2CH_3$ fragment is located close to the second methylene site and *o*-protons of benzene ring. Such NOE pattern does not contradict to the structure of **9** shown in Scheme 8.

It is likely, that formation of product **9** proceeds according to the following scheme (Scheme 9).

3. Conclusions

The Arndt–Eistert reaction based on *N*-trifluoromethylsulfonyl-(4-fluorophenyl)-carboximidoyl chloride **1** has been studied. It was shown that reaction proceeds vigorously even at low temperatures. It was found that the presence of substances being able to stabilize the positive charge at the central carbon atom of resulting ketenimine is needed. Comparison of the reactivity of imidoyl chlorides containing the $=NSO_2CF_3$ and $=NSO_2CH_3$ groups was made.

4. Experimental

4.1. General

All reactions were carried out under dry argon using flame-dried glassware. Solvents were distilled from appropriate drying agents immediately prior to use. Phenylazide was prepared as described in [12]. Lithium chloride was dried at 200 °C in vacuum (0.03 Torr). Reactions were monitored by thin-layer chromatography (TLC) on precoated silica gel Kieselgel 60 F/UV_{254} plates (Merck); spots were visualized with UV light. Purification of some products was carried out using column chromatography (CC) on silica gel, 70–230 mesh 60A (Aldrich). Purification of most products was performed by preparative HPLC with SHIMADZU instrument equipped with two LS-8A pumps, CBM-20A controller and SPD-20A UV-detector (λ = 215 and 254 nm) using Waters 30 mm × 75 mm silica column (stationary phase—SunFire Prep C18 5 μm with gradient elution by acetonitrile/water (0–100%)). ^{13}C NMR spectra and two-dimensional NMR spectra were recorded on a Bruker AVANCE DRX 500 instrument at 125 and 500.13 MHz, respectively, ^1H and ^{19}F NMR spectra were recorded at 299.5 and 282.2 MHz, respectively, with a Varian VXR-300 spectrometer, and chemical shifts are given in ppm relative to Me_4Si and CCl_3F, respectively, as internal standards. LCMS spectra were registered on "Agilent 1100 Series" instrument with diode-matrix and mass-selective detector "Agilent 1100 LS/MSD SL" (ionization method – chemical ionization at atmospheric pressure; ionization chamber operation conditions – simultaneous scanning of positive and negative ions in the range 80–1000 *m/z*). Melting points were determined in open capillaries and are uncorrected. Elemental analysis was performed in the Analytical Laboratory of the Institute of Organic Chemistry, NAS of Ukraine, Kiev.

4.2. General procedure for the Arndt–Eistert reaction of *N*-trifluoromethylsulfonyl-(4-fluorophenyl)-carboximidoyl chloride 1

Diazomethane solution in glyme (15 mL, 9 mmol) was added dropwise to the stirred mixture of imidoyl chloride **1** (0.87 g, 3 mmol) and PhN_3 (1.1 g, 9 mmol) or LiCl (0.32 g, 9 mmol) in glyme (15 mL) at −70 °C over 30–40 min. The reaction mixture was stirred at −70 °C until nitrogen evolution (200–210 mL) ceased (ca. 30 min). Morpholine (2 mL) was added to the reaction mixture at −70 °C in one portion. After stirring for 24 h at room temperature precipitated morpholine hydrochloride (or its mixture with lithium chloride) was filtered off and anhydrous ether (ca. 30 mL) was added to the filtrate. Solution obtained was left to stand overnight. Precipitate of **4** was filtered off and filtrate was evaporated to dryness *in vacuo*. Residue was crystallized (from methanol/water 1:1) gave the mixture of **3**, **5**, **6**. Compound **6** was separated in pure state by crystallization from ether. HPLC of mixture gave pure compounds **3** (RT = 4.55 min) and **5** (RT = 3.95 min).

4.2.1. 1-Trifluoromethylsulfonylamino-2-(4-fluorophenyl)-2,3-dimorpholine-4-yl-propane 3

m.p. 170–171 °C. ^1H NMR ([D_6]acetone): δ 2.4–3.05 (11H, m, $5CH_2$ + NH), 2.5–2.7 (m, 8H, $4CH_2$), 3.85 (1H, d, CH_2, $^2J_{HH}$ = 12 Hz), 4.12 (1H, d, CH_2, $^2J_{HH}$ = 12 Hz), 7.14–7.20 (2H, m, ArH), 7.53–7.57 (2H, m, ArH); ^{19}F NMR ([D_6]acetone): δ −77.3 (s, 3F, SO_2CF_3), −115.3 (s, 1F, ArF); ^{13}C {^1H} NMR ([D_6]acetone): δ 163.8 (d, $^1J_{CF}$ = 243.8 Hz), 136.2, 130.9 (d, $^3J_{CF}$ = 7.5 Hz), 122.1 (q, $^1J_{CF}$ = 320.0 Hz), 116.6 (d, $^2J_{CF}$ = 21.3 Hz), 68.8, 68.1, 64.5, 63.4, 56.8, 49.0, 48.6. LC–MS (*m/z*): 456.2 $[M]^+$. Anal. calcd for $C_{18}H_{25}F_4N_3O_4S$: C 47.5, H 5.5, N 9.2. Found C 47.7, H 5.3, N 9.3.

4.2.2. 2-Trifluoromethylsulfonylamino-2-(4-fluorobenzyl)-7-oxa-4-azonia-spiro[3.5]nonane 4

m.p. 180–190 °C. ^1H NMR ([D_6]DMSO): δ 3.10 (2H, s, CH_2), 3.45–3.82 (m, 8H, $4CH_2$), 4.28 (2H, d, CH_2, $^2J_{HH}$ = 10 Hz), 4.34 (2H, d, CH_2, $^2J_{HH}$ = 10 Hz), 7.00–7.20 (2H, m, ArH), 7.35–7.52 (2H, m, ArH); ^{19}F NMR ([D_6]DMSO): δ −78.2 (s, 3F, SO_2CF_3), −117.6 (s, 1F, ArF); ^{13}C {^1H} NMR ([D_6]DMSO): δ 161.0 (d, $^1J_{CF}$ = 241.4 Hz), 133.1, 132.0, 125.2 (q, $^1J_{CF}$ = 340.0 Hz), 114.3 (d, $^2J_{CF}$ = 21.0 Hz), 73.6, 61.2, 60.8, 60.1, 59.8, 53.6, 46.2. LC–MS (*m/z*): 383.2 $[M]^+$. Anal. calcd for $C_{15}H_{19}F_4N_2O_3S$: C 47.0, H 5.0, N 7.3. Found C 47.2, H 4.9, N 7.6.

4.2.3. 2-Trifluoromethylsulfonylamino-2-(4-fluorobenzyl)-1,3-dimorpholine-4-yl-propane 5

m.p. 140 °C. ^1H NMR ([D_6]acetone): δ 2.63–2.78 (12H, m, $6CH_2$), 3.1 (1H, br s, NH), 3.26 (2H, s, CH_2), 3.63 (m, 8H, $4CH_2$), 7.03–7.09 (2H, m, ArH), 7.39–7.47 (2H, m, ArH); ^{19}F NMR ([D_6]acetone): δ −78.1 (s, 3F, SO_2CF_3), −116.7 (s, 1F, ArF); ^{13}C {^1H} NMR ([D_6]acetone): δ 163.7 (d, $^1J_{CF}$ = 250.0 Hz), 134.8 (d, $^3J_{CF}$ = 7.5 Hz), 134.0, 121.3 (q, $^1J_{CF}$ = 320.0 Hz), 116.6 (d, $^2J_{CF}$ = 21.2 Hz), 68.3, 68.2, 64.9, 57.4, 42.7. LC–MS (*m/z*): 470.1 $[M]^+$. Anal. calcd for $C_{19}H_{27}F_4N_3O_4S$: C 24.3, H 2.9, N 4.5. Found C 24.6, H 2.5, N 4.6.

4.2.4. 1-Trifluoromethylsulfonylamino-2-(4-fluorobenzyl)-2,3-dimorpholine-4-yl-propane 6

m.p. 185–186 °C. ^1H NMR ([D_6]DMSO): δ 2.59–3.60 (22H, m, $11CH_2$), 7.13–7.25 (4H, m, ArH), 12.72 (1H, br s, NH); ^{19}F NMR ([D_6]DMSO): δ −76.6 (s, 3F, SO_2CF_3), −116.3 (s, 1F, ArF); ^{13}C {^1H} NMR ([D_6]DMSO): δ 160.8 (d, $^1J_{CF}$ = 240.1 Hz), 132.9, 132.1 (d, $^3J_{CF}$ = 7.6 Hz), 122.3 (q, $^1J_{CF}$ = 320.0 Hz), 114.7 (d, $^2J_{CF}$ = 20.6 Hz), 66.4, 65.2, 59.9, 59.2, 53.7, 48.6, 45.2, 34.4. LC–MS (*m/z*): 470.1 $[M]^+$. Anal. calcd for $C_{19}H_{27}F_4N_3O_4S$: C 24.3, H 2.9, N 4.5. Found C 24.1, H 2.3, N 4.1.

4.3. The Arndt–Eistert reaction of *N*-trifluoromethylsulfonyl-(4-fluorophenyl)-carboximidoyl chloride 1 with ethyl diazoacetate

Imidoyl chloride **1** (0.87 g, 3 mmol) in glyme (15 mL) was added dropwise to the stirred solution of ethyl diazoacetate [13] (0.68 g, 6 mmol) in glyme (15 mL) at 0–5 °C over 15 min. The reaction mixture was stirred at room temperature until nitrogen evolution (70 mL) ceased (ca. 24 h). Then morpholine (1 mL) was added in one portion and reaction mixture was heated at 60–65 °C until nitrogen evolution (70 mL) ceased (about 1 h). Solvent was evaporated to dryness *in vacuo*. Column chromatography of residue (eluent ethylacetate/hexane = 1:2) gave 0.3 g (30%) of

Table 2
The main crystallographic parameters of the compounds **3**–**6**.

Cell parameters	Compound			
	3	**4**	**5**	**6**
a [Å]	10.4894(6)	8.4842(4)	13.9124(9)	10.1697(2)
b [Å]	15.9856(8)	10.1822(5)	10.1998(7)	12.3642(3)
c [Å]	12.5397(8)	11.2630(6)	16.6565(10)	17.3192(5)
α [°]	90	65.164(3)	90	90
β [°]	95.504(2)	70.720(4)	110.105(3)	99.562(1)
γ [°]	90	86.073(4)	90	90
V [Å^3]	2093.0(2)	830.7(1)	2219.6(3)	2147.5(1)
Z	4	2	4	4
D [g cm^{-3}]	1.45	1.53	1.40	1.45
Crystal system	Monoclinic	Triclinic	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P-1$	$P2_1/n$	$P2_1/c$
μ [cm^{-1}]	2.20	2.55	2.09	2.16
F(000)	952	396	984	984
Indexes	$12 \geq h \geq -10$ $19 \geq k \geq -15$ $15 \geq l \geq -15$	$10 \geq h \geq -10$ $12 \geq k \geq -12$ $14 \geq l \geq -14$	$17 \geq h \geq -17$ $12 \geq k \geq -11$ $20 \geq l \geq -20$	$12 \geq h \geq -11$ $15 \geq k \geq -13$ $20 \geq l \geq -20$
θ_{max} [°]	26.5	26.5	26.5	26.4
No. of reflections				
Collected	15,289	8,453	33,411	16,466
Independent	4,246	3,396	4,355	4,054
In refinement ($I \geq 3\sigma(I)$)	1,867	2,514	2,238	2,387
R(int)	0.031	0.019	0.050	0.042
No. of refined parameters	275	226	284	284
Obsd./var.	6.79	11.12	7.88	8.40
Final R indices				
R_1(F)	0.035	0.035	0.034	0.035
R_w(F)	0.038	0.038	0.031	0.035
GOF	1.156	1.123	1.158	1.132
Weighting coefficients	0.70 −0.14 0.42 −0.19	0.80 0.45 0.68 0.09 0.19	0.75 0.63 0.61	1.16 -0.07 0.87
Largest peak/hole [e cm^{-3}]	−0.21/0.25	−0.23/0.24	−0.23/0.30	−0.34/0.42
CCDC deposition number	739998	739995	739997	739996

pure **7** (R_f = 0.3). m.p. 155–157 °C. ^{1}H NMR ([D$_6$]DMSO): δ 3.32–3.89 (8H, m, 4CH$_2$), 7.38–7.44 (2H, m, ArH), 7.56–7.61 (2H, m, ArH); ^{19}F NMR ([D$_6$]DMSO): δ −79.2 (s, 3F, SO$_2$CF$_3$), −108.4 (s, 1F, ArF). Anal. calcd for $C_{12}H_{12}F_4N_2O_3S$: C 42.4, H 3.6, N 8.2. Found C 42.5, H 3.4, N 8.3.

4.4. The Arndt–Eistert reaction of *N*-methylsulfonylbenzcarboximidoyl chloride 8

Diazomethane solution in glyme (12 mL, 7 mmol) was added dropwise to the stirred mixture of imidoyl chloride **8** (0.76 g, 3.5 mmol) and PhN$_3$ (0.83 g, 7 mmol) or LiCl (0.3 g, 7 mmol) in glyme (15 mL) at −15 °C over 30–40 min. The reaction mixture was stirred at −15 °C until nitrogen evolution (160 mL) ceased (ca. 2–3 h) and then allowed to warm to 0 °C. Morpholine (2 mL) was added to the reaction mixture at 0 °C in one portion. After stirring for 24 h at room temperature precipitate was filtered off and filtrate was evaporated to dryness *in vacuo*. HPLC of residue gave pure compound **9** (RT = 5.43 min). m.p. 100–105 °C. ^{1}H NMR ([D$_6$]DMSO): δ 2.77 (3H, s, SO$_2$CH$_3$), 3.37 (2H, d, CH$_2$, $^3J_{HH}$ = 5 Hz), 3.95 (2H, m, CH$_2$), 5.67 (1H, s, NH), 6.83 (1H, t, NH, $^3J_{HH}$ = 5 Hz), 7.28–7.38 (3H, m, ArH), 7.52 (2H, d, ArH); ^{13}C {^{1}H} NMR ([D$_6$]DMSO): δ 142.8, 128.3, 127.6, 126.7, 75.5, 51.8, 51.2, 40.1. IR (KBr): ν 3512, 3289 (N–H). LC–MS (m/z): 287.1, 289.1 [M]$^+$.

4.5. X-ray crystallography

All crystallographic measurements were performed at 173 K on a Bruker Smart Apex II diffractometer (Mo Kα). Data were corrected for Lorentz and polarization effects. The SADABS procedure [14] absorption correction was applied. The structures were solved by direct methods and refined by the full-matrix least-squares technique in the anisotropic approximation using the SHELXS97 and SHELXL97 programs [15,16] and CRYSTALS program package [17]. In the refinement the Chebychev weighting scheme [18] was used. All hydrogen atoms were located in the difference Fourier maps and refined with fixed positional and thermal parameters (only hydrogen atoms participating in the hydrogen bonds were refined isotropically).

Full crystallographic details have been deposited at Cambridge Crystallographic Data Centre (CCDC) (Table 2).

References

[1] L.M. Yagupolskii, S.V. Shelyazhenko, I.I. Maletina, V.N. Petrik, E.B. Rusanov, A.N. Chernega, Eur. J. Org. Chem. (2001) 1225–1233.
[2] L.M. Yagupolskii, S.V. Shelyazhenko, I.I. Maletina, L.V. Sokolenko, A.N. Chernega, E.B. Rusanov, I.F. Tsymbal, J. Fluorine Chem. 128 (2007) 515–523.
[3] L.M. Yagupolskii, I.I. Maletina, L.V. Sokolenko, Y.G. Vlasenko, S.A. Buth, J. Fluorine Chem. 129 (2008) 486–492.
[4] W.E. Bachmann, W.S. Struve, The Arndt–Eistert synthesis, in: R. Adams (Ed.), Organic Reactions, vol. 1, J. Wiley and Sons, New York, 1942, pp. 38–62.

[5] L.F. Fieser, M. Fieser, Reagents for Organic Synthesis, vol. 1, J. Wiley and Sons, New York/London/Sydney, 1968, pp. 829–832.
[6] D. Bethell, V. Gold, Carbonium Ions. An Introduction, Academic Press, London/New York, 1967 (Ch. 5).
[7] L.N. Kuleshova, P.M. Zorkii, Acta Crystallogr. Sect. B 37 (1981) 1363–1366.
[8] V.N. Knyazev, O.Y. Borbulevich, O.V. Shishkin, Russ. J. Org. Chem. 36 (2000) 706–711.
[9] J. Podlech, J. Pract. Chem. 340 (1998) 679–682.
[10] A. Wong, C.J. Welch, J.T. Kuethe, E. Vazquez, M. Shaimi, D. Henderson, I.W. Davies, D.L. Hughes, Org. Biomol. Chem. 2 (2004) 168–174.
[11] C.G. Herbert, R.A.W. Johnstone, Mass Spectrometry. Basics, CRC Press, New York, 2003, p. 339.
[12] R.O. Lindsay, C.F.H. Allen, Org. Synth. Coll. 3 (1955) 710.
[13] N.E. Searle, Org. Synth. 36 (1956) 25.
[14] G.M. Sheldrick, SADABS: Program for Scaling and Correction of Area Detector Data, University of Gottingen, Germany, 1996.
[15] G.M. Sheldrick, SHELXS97: Program for the Solution of Crystal Structure, University of Gottingen, Germany, 1997.
[16] G.M. Sheldrick, SHELXL97: Program for the Refinement of Crystal Structures, University of Gottingen, Germany, 1997.
[17] D.J. Watkin, C.K. Prout, J.R. Carruthers, P.W. Betteridge, CRYSTALS Issue 10, Chemical Crystallography Laboratory, University of Oxford, Oxford, 1996.
[18] J.R. Carruthers, D.J. Watkin, Acta Crystallogr. Sect. C 35 (1979) 698–699.