Journal of Fluorine Chemistry 129 (2008) 486–492

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

N-Perfluoroalkylsulfonylimido derivatives of arenecarboxylic acid amides and their oxidative aza Hofmann rearrangement

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ARTICLE INFO

Article history:
Received 26 December 2007
Received in revised form 4 March 2008
Accepted 5 March 2008
Available online 13 March 2008

Keywords:
Amidines
Rearrangements
X-ray structure
Carbodiimides

ABSTRACT

The analogues of carboxamides in which the sp^2-hybridized oxygen atom is replaced by more electron-withdrawing groups, $=NSO_2CF_3$ and $=NSO_2C_4F_9$, have been synthesized. The resulting *N*-perfluoroalkylsulfonyl arenecarboxamidines $ArC(=NSO_2R_f)NH_2$ ($R_f = CF_3$, C_4F_9) undergo an oxidative Hofmann-type rearrangement to the corresponding carbodiimides $ArN=C=NSO_2R_f$ under the action of (diacyloxyiodo)arenes. Rearrangement of related compounds $ArC(=NSO_2R)NH_2$ (R = CH_3, Ph) containing fluorine-free substituents at the sulfonyl group also occurs in similar conditions. It was found that the reactivity of amidines rises with the increasing electron-withdrawing ability of the substituent R.

1. Introduction

Nucleophilic rearrangements of carboxylic acid derivatives via migration of a substituent with its electron pair from carbon atom to nitrogen atom (rearrangements of azides (Curtius), hydroxamic acids (Lossen), amides (Hofmann)) are widely used in organic chemistry for synthesis of isocyanates and amines [1].

As reported by us previously, substitution of a sp^2-hybridized oxygen atom in various compounds by the $=NSO_2CF_3$ group (a stronger electron acceptor) leads to significant changes in their properties, in particular, increased reactivity [2] and acidity [3,4] as well as a deepening of colour [5].

We carried out systematic research on nucleophilic rearrangements of carboxylic acid derivatives in which the carbonyl oxygen atom is replaced by a trifluoromethylsulfonylimido group. Such substitution in acid azides enables the Curtius rearrangement to occur under very mild conditions affording carbodiimides [6]. Aza analogues of hydroxamic acids containing the $=NSO_2CF_3$ group instead of the carbonyl oxygen atom undergo a Lossen-type rearrangement to carbodiimides or *N*-trifluoromethylsulfonyl-*N*′-arenechloroformamidines, depending on the reaction conditions [7].

These results encouraged us to explore the ability of arenecarboxylic acid amidines (aza analogues of amides) to undergo the Hofmann rearrangement.

2. Results and discussion

2.1. Synthesis of N-substituted amidines

N-Trifluoromethylsulfonyl arenecarboximidoyl chlorides **1a–e** were converted to hitherto unknown *N*-trifluoromethylsulfonyl arenecarboxamidines **2a–e** by reaction with gaseous ammonia in ether solution (Scheme 1).

N-Methylsulfonylbenzamidine **3**, *N*-phenylsulfonylbenzamidine **4**, and *N*-nonafluorobutylsulfonyl-4-fluorobenzamidine **5** were prepared in the same manner (Scheme 2).

2.2. Structure of N-trifluoromethylsulfonyl arenecarboxamidines

Amidines **2a–e** may exist in two tautomeric forms, **A** and **B** (Scheme 3).

In the result of X-ray determination of amidine **2a** we have established that compounds **2a–e** have the structure **A** in the solid state. There is an interesting feature in the formation of the N(1)–H···O(2) intramolecular hydrogen bond (N···O 2.806 (2), O···H 2.20 (2) (Å), N(1)HO(2) 131.2 (19)°). The perspective view of molecule **2a** and selected geometrical parameters are given in Fig. 1. The analysis of ^{19}F NMR spectra of the compounds with rigid $C=NSO_2CF_3$ and $C–NHSO_2CF_3$ groups has confirmed that a signal of

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[1] Crystal structure analysis.

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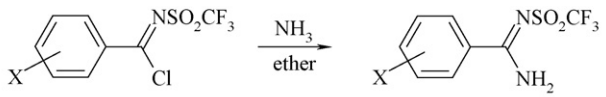
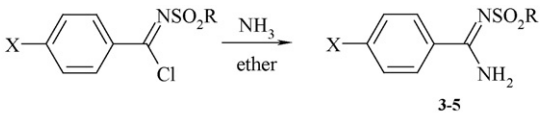
doi:10.1016/j.jfluchem.2008.03.001



1a-e **2a-e**

Product	2a	2b	2c	2d	2e
X	H	4-OCH_3	4-F	4-CF_3	3-CF_3
Yield (%)	88	83	86	84	72

Scheme 1.



3-5

Product	3	4	5
X	H	H	F
R	CH_3	Ph	C_4F_9
Yield (%)	70	66	78

Scheme 2.

the $=NSO_2CF_3$ group is in the range −78 to −80 ppm, and that of $NHSO_2CF_3$ group at −75 to −77 ppm [6,7]. In the ^{19}F NMR spectra of the compounds **2a–e** signals at −79 to −80 ppm are observed, which correspond to structure **A** in solution.

The IR spectrum of compound **2a** dissolved in methylene chloride shows two medium-intensity bands at 3481 and 3344 cm^{-1} arising from the vibrations ν_{as} (N–H) and ν_s (N–H), respectively. Another weak band at 3253 cm^{-1} is assigned to the H-bonded N–H group. As the intensity of either free or H-bonded N–H group vibrations is practically insensitive to dilution, one can assume the intramolecular character of the H-bond in this compound. Presumably, hydrogen atom of N–H group is bonded with oxygen atom of the sulfonyl group.

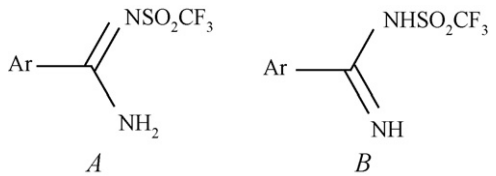
2.3. The oxidative aza Hofmann rearrangement of N-substituted amidines

The classical Hofmann rearrangement of primary carboxamides occurs under the action of alkaline solutions of sodium hypochlorite or hypobromite [8]. The reaction of compounds **2a–e** with sodium hypobromite leads to nearly complete recovery of starting amidines, whereas treatment with sodium hypochlorite results in a mixture of unidentified products.

Attempts to obtain *N*-chloro or *N*-bromo-*N′*–trifluoromethylsulfonyl-4-fluorobenzamidines under anhydrous conditions were unsuccessful. The sodium or silver salts of *N*-trifluoromethylsulfonyl-4-fluorobenzamidine **2c** in acetonitrile or glyme, if treated with bromine, are converted into the *N*-bromo derivative which decomposes to starting materials even in the dark at 20 °C. Chlorination of the same salts with sulfuryl chloride in carbon tetrachloride or with *tert*-butyl hypochlorite in glyme does not proceed in the cold, whereas heating results in a mixture of products among which *N,N*-dichloro-*N′*–trifluoromethylsulfonyl-4-fluorobenzamidine predominates. Treatment of the amidine **2c** sodium salt with chlorine solution in glyme in the cold leads to analogous results. Amidine **2c** is unreactive both to sulfuryl chloride and to *tert*-butyl hypochlorite even on heating.

The Hofmann rearrangement of carboxamides is known to proceed under the action of oxidants as, for instance, lead tetraacetate, (diacetoxyiodo)benzene, and [bis(trifluoroacetoxy) iodo]benzene [9,10]. We carried out this reaction with compound **2c** under anhydrous conditions in the presence of organic bases (pyridine and di-*iso*-propylethylamine (DIEA), as in Ref. [9]) using 4-[bis(trifluoroacetoxy)iodo]toluene as an oxidant (Scheme 4). The resulting carbodiimide **6c** was isolated and characterized as its morpholine derivative **7c**.

Carbodiimides containing a trifluoromethylsulfonylimino group are very sensitive to strong acids and bases. The rearrangement is



Scheme 3.

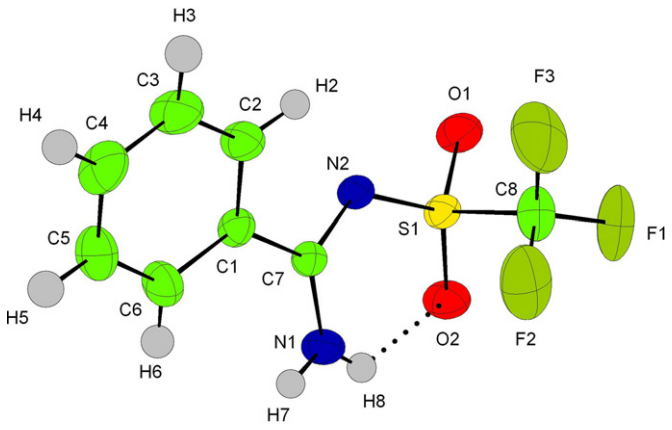
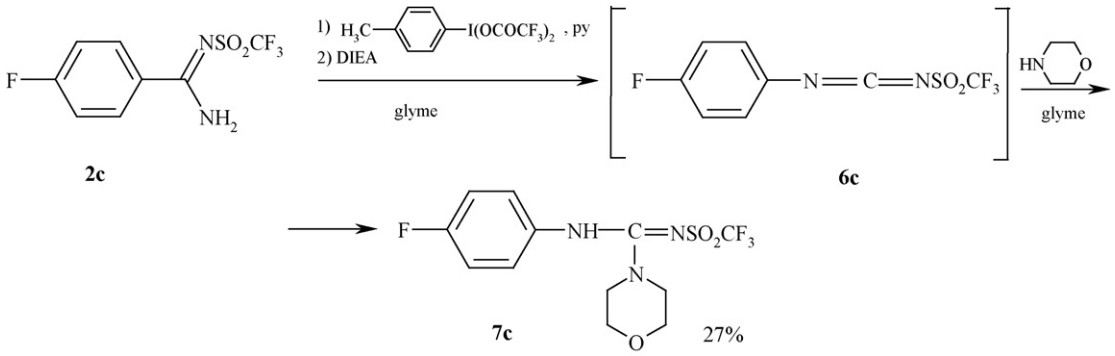
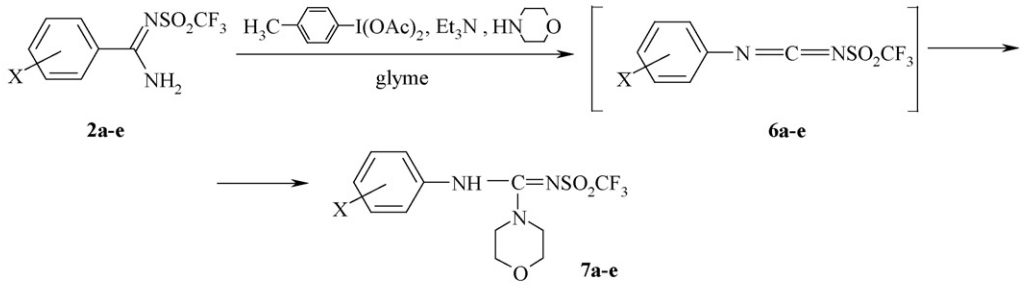


Fig. 1. Molecular structure of **2a**. Selected bond lengths (Å) and angles (°) for **2a**: C(8)–S(1) 1.829(2), O(1)–S(1) 1.4229(14), O(2)–S(1) 1.4279(14), N(2)–S(1) 1.5823(15), C(7)–N(2) 1.341(2), C(7)–N(1) 1.302(2), C(1)–C(7) 1.481(3); O(2)S(1)C(8) 104.28(11), O(1)S(1)C(8) 104.83(10), N(2)S(1)C(8) 102.67(9), O(2)S(1)N(2) 116.50(8), O(1)S(1)N(2) 108.82(8), C(7)N(2)S(1) 123.07(13), N(1)C(7)N(2) 125.97(17), F(2)C(8)S(1) 110.39(16), F(1)C(8)S(1) 110.66(16), F(3)C(8)S(1) 111.65(17), N(2)C(7)C(1) 115.53(16).



Scheme 4.



Substrate	**2a**	**2b**	**2c**[a]	**2d**	**2e**
Product	**7a**	**7b**	**7c**	**7d**	**7e**
X	H	4-OCH_3	4-F	4-CF_3	3-CF_3
Time (h)	0.5	0.5	1	9	3
Temperature (°C)	85	25	85	45	45
Yield (%)	75	80	65	17	17

[a]The reaction proceeds at room temperature within 72 h with the same yield of product **7***c*.

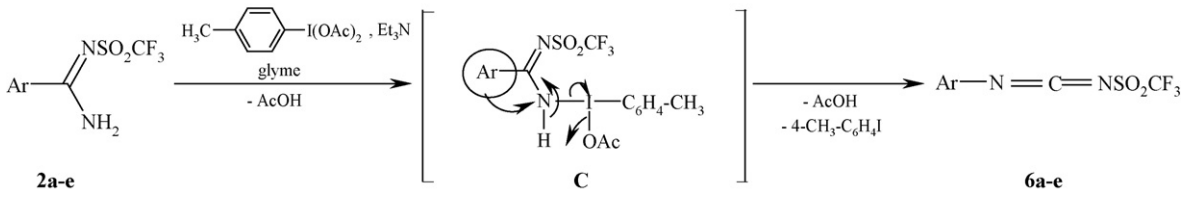
Scheme 5.

conducted with excess of strong base, DIEA, and the reaction products include trifluoroacetic acid. Both substances could lead to polymerization of carbodiimide **6c**, which may be the cause of a low yield of product **7c**.

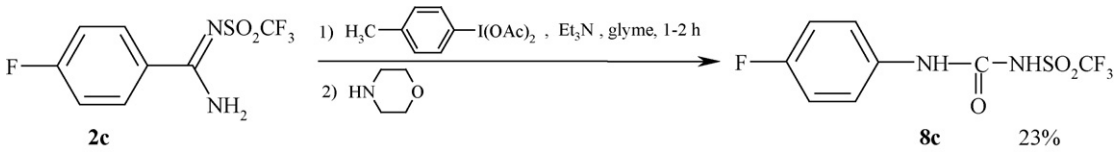
When treated with 4-(diacetoxyiodo)toluene amidines **2a–e** rearrange in higher yields. Typically, a mixture of appropriate amidine **2**, triethylamine, and morpholine in glyme was added to a suspension of 4-(diacetoxyiodo)toluene in glyme at 0 °C (Scheme 5). The time and temperature required for the reaction completion were varied according to the substituent on the benzene ring.

The data of Scheme 5 demonstrate that the Hofmann-type rearrangement of compounds **2a–e** occurs the more readily, the stronger electron-donating ability of a substituent on the benzene ring is. The reaction with amidines **2d**,**e** bearing electron-withdrawing groups on the ring provides very low yields of products **7d**,**e** mixed with the morpholinium salt of trifluoromethanesulfonamide. Attempts to isolate the pure product from the mixture either chromatographically or by crystallization were unsuccessful.

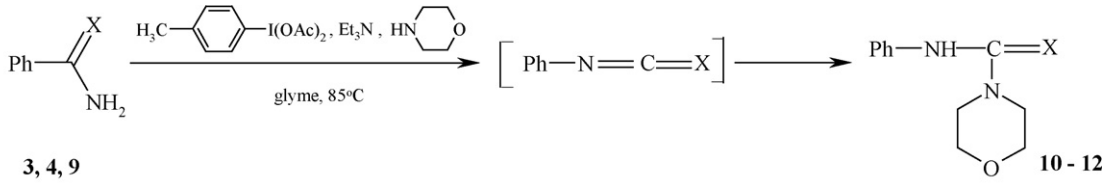
As assumed by analogy with carboxamides [10], formation of carbodiimides **6a–e** proceeds by the following mechanism (Scheme 6).



Scheme 6.



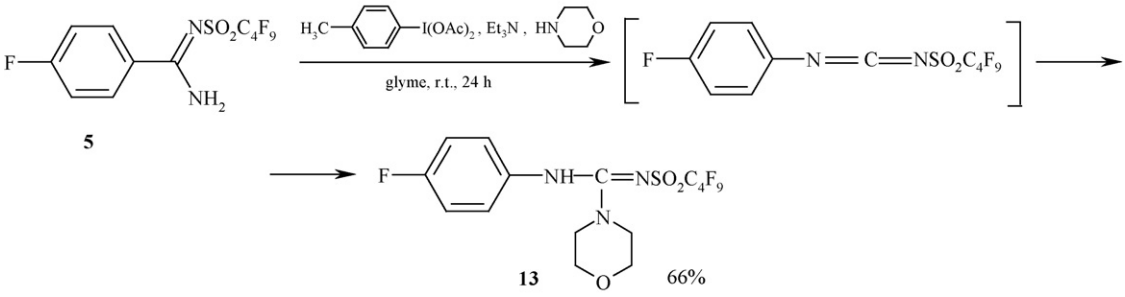
Scheme 7.



X = O (**9**, **10**), NSO_2CH_3 (**3**, **11**), NSO_2Ph (**4**, **12**)

Substrate	**9**	**3**	**4**	**2c**
Product	**10**	**11**	**12**	**7c**
X	O	NSO_2CH_3	NSO_2Ph	NSO_2CF_3
Time (h)	5	4	2.5	0.5
Yield (%)	50	43	55	65

Scheme 8.



Scheme 9.

We propose the initial formation of an intermediate **C**, that loses iodotoluene and undergoes aryl group migration from carbon atom to nitrogen atom to give the carbodiimide **6**.

If morpholine is added to the reaction mixture not at the same time as the amidine but 1–2 h later, the urea **8c** is obtained (Scheme 7):

It is likely that acetic acid released in the reaction is added to the carbodiimide and the resulting adduct is hydrolyzed giving urea **8c** (conversions of this kind were described previously [11]).

To compare the reactivity of fluorine-containing arenecarboxamidines **2** to that of analogous fluorine-free amides and amidines, we carried out the rearrangement with benzamide **9**, *N*-methylsulfonylbenzamidine **3**, and *N*-phenylsulfonylbenzamidine **4** under the same conditions (Scheme 8).

It is evident (Scheme 8) that in going from benzamide to its aza analogues containing the $=NSO_2CH_3$, $=NSO_2Ph$, and $=NSO_2CF_3$ groups, the reaction time decreases as the electron-withdrawing ability of the group rises, i.e., the reactivity of the compounds under study increases in the order **9** < **3** < **4** < **2c**.

Compound **5** contains the somewhat stronger electron-withdrawing $=NSO_2C_4F_9$ group (in comparison with the $=NSO_2CF_3$ group in compound **2c**). As a result, amidine **5** undergoes the Hofmann-type rearrangement (Scheme 9) much more readily; the reaction is complete within 24 h at room temperature (cf. to 72 h necessary for amidine **2c** to rearrange under the same conditions).

3. Conclusions

The aza analogues of arenecarboxamides containing the $=NSO_2CF_3$ and $=NSO_2C_4F_9$ groups instead of the carbonyl oxygen atom have been synthesized. The conditions which allow compounds of this kind to undergo an oxidative Hofmann-type rearrangement have been found. It has been shown that the reaction substantially depends on the nature of the substituents on the benzene ring. It is facilitated by electron-donating and hindered by electron-withdrawing groups. To compare the reactivity of arenecarboxamides and their various aza analogues,

the same rearrangement under similar conditions with benzamide and benzamidines containing the $=NSO_2CH_3$ and $=NSO_2Ph$ groups have also been realized. As found, the Hofmann-type rearrangement of compounds $PhC(=X)NH_2$ proceeds the more readily, the stronger the electron-withdrawing ability of the substituent **X** is.

4. Experimental

4.1. General

Moisture-sensitive reactions were carried out under dry argon using flame-dried glassware. All chemicals were of reagent grade or were purified by standard methods before use. Solvents were distilled from appropriate drying agents immediately prior to use. Some 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 most products was performed by column chromatography (CC) on Silica gel, 70–230 mesh 60A (Aldrich). ^{13}C NMR spectra were recorded on a Bruker DRX 500 instrument at 125 MHz, ^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. IR spectra were recorded with a Vertex 70 (Bruker) instrument (KBr tablets or solutions in CH_2Cl_2). 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.

The preparations of *N*-methylsulfonyl benzcarboximidoyl chloride [12] *N*-phenylsulfonyl benzcarboximidoyl chloride [13], *N*-trifluoromethylsulfonyl arenecarboximidoyl chlorides **1a–c** [6,14], and *N*-nonafluorobutylsulfonyl-4-fluorobenzcarboximidoyl chloride [6] were described previously. Compounds **1d**,**e** were synthesized from the corresponding *N*-trifluoromethylsulfonyl benzamides according to the literature procedure [6]. Characterization data of these compounds and starting *N*-trifluoromethylsulfonyl benzamides are listed below.

4.2. *N*-Trifluoromethylsulfonyl arenecarboximidoyl chlorides (**1d,e**) and the corresponding *N*-trifluoromethylsulfonyl benzamides

4.2.1. *N*-Trifluoromethylsulfonyl-4-trifluoromethylbenzcarboximidoyl chloride (**1d**)

4.2.1.1.N-Trifluoromethylsulfonyl-4-trifluoromethylbenzamide. m.p. 175–176 °C (from benzene). ^1H NMR ([D_6]acetone): δ 4.41–5.31 (1H, w s, NH), 7.96–8.28 (4H, dd, ArH); ^{19}F NMR ([D_6]acetone): δ −63.3 (s, 3F, CF_3), −76.2 (s, 3F, SO_2CF_3). Anal. calcd for $C_9H_5F_6NO_3S$: C 33.7, H 1.6, N 4.4. Found C 33.8, H 1.5, N 4.5.

4.2.1.2.N-Trifluoromethylsulfonyl-4-trifluoromethylbenzcarboximidoyl chloride. b.p. 110 °C/0.05 Torr. m.p. 74–75 °C. ^{19}F NMR ($CHCl_3$): δ −63.9 (s, 3F, CF_3), −78.7 (s, 3F, SO_2CF_3). Anal. calcd for $C_9H_4ClF_6NO_2S$: Cl 10.4. Found Cl 10.5.

4.2.2. *N*-Trifluoromethylsulfonyl-3-trifluoromethylbenzcarboximidoyl chloride (**1e**)

4.2.2.1.N-Trifluoromethylsulfonyl-3-trifluoromethylbenzamide. m.p. 148–149 °C (from benzene); Ref. [15] 148–149.5 °C. ^1H NMR ([D_6]acetone): δ 7.63–7.68 (1H, m, ArH), 7.82–8.00 (2H, m, ArH), 8.15–8.18 (1H, m, ArH), 9.17–9.31 (1H, w s, NH); ^{19}F NMR ([D_6]acetone): δ −61.4 (s, 3F, CF_3), −77.9 (s, 3F, SO_2CF_3). Anal. calcd for $C_9H_5F_6NO_3S$: C 33.7, H 1.6, N 4.4. Found C 33.9, H 1.5, N 4.3.

4.2.2.2.N-Trifluoromethylsulfonyl-3-trifluoromethylbenzcarboximidoyl chloride. b.p. 135 °C/0.03 Torr. m.p. 62–64 °C. ^{19}F NMR ($CHCl_3$): δ −61.7 (s, 3F, CF_3), −78.9 (s, 3F, SO_2CF_3). Anal. calcd for $C_9H_4ClF_6NO_2S$: Cl 10.4. Found Cl 10.5.

4.3. General procedure for the synthesis of amidines (**2–5**)

Through a solution of the corresponding carboximidoyl chloride (13 mmol) in anhydrous ether (50 mL), a slow stream of anhydrous gaseous ammonia was bubbled at −15 °C over 20 min. The precipitated ammonium chloride was filtered off, the filtrate was concentrated to dryness, and the residue was purified by crystallization (from ether/hexane or ethylacetate/hexane) affording pure amidines **2–5**.

4.3.1. *N*-Trifluoromethylsulfonylbenzamidine (**2a**)

m.p. 125–127 °C (ether/hexane). ^1H NMR ([D_6]acetone): δ 7.58–7.77 (3H, m, ArH), 8.07–8.09 (2H, m, ArH), 8.60–9.20 (2H, w s, NH_2); ^{19}F NMR ([D_6]acetone): δ −79.1 (s, 3F, SO_2CF_3); ^{13}C {^1H} NMR (125 MHz, [D_6]DMSO): δ 166.1, 133.4, 131.8, 128.7, 128.3, 119.6 (q, $^1J_{CF}$ = 320 Hz); IR (KBr): ν 3444, 3326, 3259 (N–H), 1631 (C=N). Anal. calcd for $C_8H_7F_3N_2O_2S$: C 38.1, H 2.8, N 11.1. Found C 37.9, H 2.8, N 11.0.

4.3.2. *N*-Trifluoromethylsulfonyl-4-methoxybenzamidine (**2b**)

m.p. 125–126 °C (ether/hexane). ^1H NMR ([D_6]acetone): δ 3.94 (3H, s, OCH_3), 7.10–8.11 (4H, dd, ArH), 8.50–8.70 (1H, w s, NH), 9.00–9.20 (1H, w s, NH); ^{19}F NMR ([D_6]acetone): δ −79.2 (s, 3F, SO_2CF_3); ^{13}C {^1H} NMR (125 MHz, [D_6]DMSO): δ 165.1, 163.6, 130.6, 123.3, 119.7 (q, $^1J_{CF}$ = 325 Hz), 114.1, 55.5; IR (KBr): ν 3429, 3342, 3254 (N–H), 1636 (C=N). Anal. calcd for $C_9H_9F_3N_2O_3S$: C 38.3, H 3.2, N 9.9. Found C 38.2, H 3.3, N 9.8.

4.3.3. *N*-Trifluoromethylsulfonyl-4-fluorobenzamidine (**2c**)

m.p. 103–106 °C (ether/hexane). ^1H NMR ([D_6]acetone): δ 7.36–7.42 (2H, m, ArH), 8.15–8.20 (2H, m, ArH), 8.40–9.40 (2H, w s, NH_2); ^{19}F NMR ([D_6]acetone): δ −79.9 (s, 3F, SO_2CF_3), −105.4 (s, 1F, ArF); ^{13}C {^1H} NMR (125 MHz, [D_6]DMSO): δ 165.2 (d, $^1J_{CF}$ = 250 Hz), 164.9, 131.2 (d, $^3J_{CF}$ = 9 Hz), 128.2, 119.6 (q, $^1J_{CF}$ = 316 Hz), 115.8 (d, $^2J_{CF}$ = 22 Hz); IR (KBr): ν 3412, 3342, 3272 (N–H), 1663, 1524 (C=N). Anal. calcd for $C_8H_6F_4N_2O_2S$: C 35.6, H 2.2, N 10.4. Found C 35.5, H 2.3, N 10.3.

4.3.4. *N*-Trifluoromethylsulfonyl-4-trifluoromethylbenzamidine (**2d**)

m.p. 114–115 °C (ether/hexane). ^1H NMR ([D_6]acetone): δ 7.95–8.29 (4H, dd, ArH), 8.80–9.60 (2H, w s, NH_2); ^{19}F NMR ([D_6]acetone): δ −62.7 (s, 3F, CF_3), −79.2 (s, 3F, SO_2CF_3); ^{13}C {^1H} NMR (125 MHz, [D_6]DMSO): δ 164.9, 136.3, 132.6 (q, $^2J_{CF}$ = 32 Hz), 129.1, 125.5 (q, $^3J_{CF}$ = 4 Hz), 123.6 (q, $^1J_{CF}$ = 263 Hz), 119.6 (q, $^1J_{CF}$ = 313 Hz); IR (KBr): ν 3400, 3337, 3263 (N–H), 1655, 1529 (C=N). Anal. calcd for $C_9H_6F_6N_2O_2S$: C 33.8, H 1.9, N 8.8. Found C 33.7, H 1.9, N 8.7.

4.3.5. *N*-Trifluoromethylsulfonyl-3-trifluoromethylbenzamidine (**2e**)

m.p. 93–94 °C (ether/hexane). ^1H NMR ([D_6]acetone): δ 7.82–7.91 (1H, m, ArH), 8.08–8.10 (1H, m, ArH), 8.36–8.39 (2H, m, ArH), 8.80–9.09 (1H, w s, NH), 9.41–9.71 (1H, w s, NH); ^{19}F NMR ([D_6]acetone): δ −61.7 (s, 3F, CF_3), −78.5 (s, 3F, SO_2CF_3); ^{13}C {^1H} NMR (125 MHz, [D_6]DMSO): δ 164.4, 133.4, 132.2, 129.9, 129.5, 124.8, 123.6 (q, $^1J_{CF}$ = 250 Hz), 119.6 (q, $^1J_{CF}$ = 321 Hz). Anal. calcd for $C_9H_6F_6N_2O_2S$: C 33.8, H 1.9, N 8.8. Found C 33.7, H 2.0, N 8.8.

4.3.6. *N*-Methylsulfonylbenzamidine (**3**)

m.p. 118–120 °C (ethylacetate/hexane); Ref. [16] 122–123 °C. ^1H NMR ([D_6]acetone): δ 3.02 (3H, s, SO_2CH_3), 7.51–7.67 (3H, m, ArH), 7.98–8.00 (2H, m, ArH), 8.12–8.36 (2H, w s, NH_2); ^{13}C {^1H}

NMR (125 MHz, [D_6]DMSO): δ 162.3, 133.4, 132.2, 128.4, 127.8, 41.4.

4.3.7. N-Phenylsulfonylbenzamidine (4)

m.p. 148–150 °C (ethylacetate/hexane); Ref. [13] 149–151 °C. ^{1}H NMR ([D_6]acetone): δ 7.48–7.64 (6H, m, ArH), 7.96–8.04 (4H, m, ArH), 8.20–8.60 (2H, w s, NH_2); ^{13}C {^{1}H} NMR (125 MHz, [D_6]DMSO): δ 162.7, 142.4, 133.1, 132.4, 132.1, 128.9, 128.4, 127.8, 126.0.

4.3.8. N-Nonafluorobutylsulfonyl-4-fluorobenzamidine (5)

m.p. 86–87 °C (ether/hexane). ^{1}H NMR ([D_6]acetone): δ 7.37–7.43 (2H, m, ArH), 8.18–8.22 (2H, m, ArH), 8.77–9.02 (1H, w s, NH), 9.22–9.50 (1H, w s, NH); ^{19}F NMR ([D_6]acetone): δ −80.0 (s, 3F, $SO_2(CF_2)_3\underline{CF_3}$), −104.6 (s, 1F, ArF), −113.1 (s, 2F, $SO_2(\underline{CF_2})_3CF_3$), −120.0 (s, 2F, $SO_2(\underline{CF_2})_3CF_3$), −125.0 (s, 2F, $SO_2(\underline{CF_2})_3CF_3$); ^{13}C {^{1}H} NMR (125 MHz, [D_6]DMSO): δ 165.3 (d, $^1J_{CF}$ = 250 Hz), 164.8, 131.3 (d, $^3J_{CF}$ = 9 Hz), 128.1, 115.8 (d, $^2J_{CF}$ = 22.5 Hz), 120.3–107.8 (m, C_4F_9); IR (KBr): ν 3401, 3338, 3261 (N–H), 1659, 1519 (C=N). Anal. calcd for $C_{11}H_6F_{10}N_2O_2S$: C 31.4, H 1.4, N 6.7. Found C 31.6, H 1.3, N 6.5.

4.4. Salts of N-trifluoromethylsulfonyl-4-fluorobenzamidine (2c)

4.4.1. Sodium salt of N-trifluoromethylsulfonyl-4-fluorobenzamidine

A solution of amidine **2c** (4 mmol) in ether (20 mL) was added dropwise to a stirred suspension of sodium hydride (4 mmol) in ether. The reaction mixture was heated under reflux until the evolution of hydrogen ceased. The ether was evaporated in vacuo (0.03 Torr) to give 1.28 g (a quantitative yield) of *N*-trifluoromethylsulfonyl-4-fluorobenzamidine sodium salt. ^{1}H NMR ([D_6]DMSO): δ 7.11–7.17 (2H, m, ArH), 8.01–8.06 (2H, m, ArH); ^{19}F NMR ([D_6]DMSO): δ −77.6 (s, 3F, SO_2CF_3), −112.7 (s, 1F, ArF).

4.4.2. Silver salt of N-trifluoromethylsulfonyl-4-fluorobenzamidine

Amidime **2c** (4 mmol), dry silver oxide (2 mmol), and anhydrous acetonitrile (50 mL) were heated under reflux for 48 h. Unchanged silver oxide was filtered off and acetonitrile was evaporated in vacuo (0.05 Torr) to give 1.48 g (98%) of a grey solid. ^{19}F NMR (CH_3CN): δ −78.6 (s, 3F, SO_2CF_3), −103.6 (s, 1F, ArF).

4.5. The aza Hofmann rearrangement of compound (2c) with 4-[bis(trifluoroacetoxy)iodo]toluene

A solution of freshly prepared 4-[bis(trifluoroacetoxy)iodo]toluene [17] (3 mmol) in anhydrous glyme (10 mL) was added dropwise to a stirred solution of amidine **2c** (2 mmol) and pyridine (4 mmol) in glyme (10 mL) at 0 °C in 15 min. After 5 min, DIEA (8 mmol) and morpholine (6 mmol) were added to the reaction mixture at 0 °C. After stirring for 24 h at room temperature, the solution was concentrated to dryness in vacuo (10 Torr). Column chromatography (eluent hexane/ethylacetate 2:1) and following crystallization (from ether/hexane) gave 0.18 g (27%) of pure **7c**. m.p. 144–146 °C; Ref. [6] 142–144 °C. ^{1}H NMR ([D_6]acetone): δ 3.60 (4H, t, $2CH_2$), 3.73 (4H, t, $2CH_2$), 7.14–7.32 (4H, m, ArH), 8.80–9.00 (1H, w s, NH); ^{19}F NMR ([D_6]acetone): δ −79.2 (s, 3F, SO_2CF_3), −117.2 (s, 1F, ArF); ^{13}C {^{1}H} NMR (125 MHz, [D_6]DMSO): δ 159.4 (d, $^1J_{CF}$ = 241 Hz), 154.7, 134.8, 125.2 (d, $^3J_{CF}$ = 7.5 Hz), 119.5 (q, $^1J_{CF}$ = 321 Hz), 115.4 (d, $^2J_{CF}$ = 22.5 Hz), 65.5, 47.3.

4.6. The aza Hofmann rearrangement of compounds (2–5, 9) with 4-(diacetoxyiodo)toluene

A mixture of corresponding amidine **2–5** (2 mmol) or benzamide **9** (2 mmol) with triethylamine (6 mmol) and morpholine (4 mmol) in glyme was added dropwise to a stirred suspension of 4-(diacetoxyiodo)toluene [18] (3 mmol) in glyme at 0 °C over 15 min. The reaction mixture was stirred at the appropriate temperature during the time necessary for the rearrangement (Schemes 5 and 8). Column chromatography (eluent hexane/ethylacetate 2:1 for compounds **7a**, **7c–e**, **12**, **13** and hexane/ethylacetate 1:1 for compounds **7b**, **11**, **10**) and following crystallization (from ether/hexane) gave pure products **7a–e**, **10–13**. For compound **10**, repeated column chromatography (eluent chloroform) before crystallization was applied.

4.6.1. 4-[N-Phenyl-N′-trifluoromethylsulfonylamidino]morpholine (7a)

m.p. 115–116 °C; Ref. [6] 112–114 °C. ^{1}H NMR ([D_6]acetone): δ 3.59 (4H, t, $2CH_2$), 3.72 (4H, t, $2CH_2$), 7.21–7.25 (3H, m, ArH), 7.40–7.45 (2H, m, ArH), 8.87 (1H, s, NH); ^{19}F NMR ([D_6]acetone): δ −79.1 (s, 3F, SO_2CF_3); ^{13}C {^{1}H} NMR (125 MHz, [D_6]DMSO): δ 154.5, 138.6, 128.9, 124.7, 122.3, 119.6 (q, $^1J_{CF}$ = 320 Hz), 65.4, 47.3.

4.6.2. 4-[N-(4-Methoxyphenyl)-N′-trifluoromethylsulfonylamidino]morpholine (7b)

m.p. 140–142 °C; Ref. [7] 142–144 °C. ^{1}H NMR ([D_6]acetone): δ 3.56 (4H, t, $2CH_2$), 3.68 (4H, t, $2CH_2$), 3.83 (3H, s, OCH_3), 6.96–7.20 (4H, dd, ArH), 8.73 (1H, s, NH); ^{19}F NMR ([D_6]acetone): δ −79.1 (s, 3F, SO_2CF_3); ^{13}C {^{1}H} NMR (125 MHz, [D_6]DMSO): δ 156.8, 154.8, 131.1, 124.8, 119.6 (q, $^1J_{CF}$ = 320 Hz), 114.0, 65.5, 55.1, 47.2.

4.6.3. 4-[N-(4-Trifluoromethylphenyl)-N′-trifluoromethylsulfonylamidino]morpholine (7d)

It was obtained as a 2:1 mixture with the morpholinium salt of trifluoromethanesulfonamide.

^{1}H NMR ([D_6]acetone): δ 3.69–3.86 (8H, m, $4CH_2$), 7.42–7.75 (4H, dd, ArH), 9.10 (1H, s, NH); ^{19}F NMR ([D_6]acetone): δ −61.6 (s, 3F, CF_3), −79.2 (s, 3F, SO_2CF_3).

4.6.4. 4-[N-(3-Trifluoromethylphenyl)-N′-trifluoromethylsulfonylamidino]morpholine (7e)

It was obtained as a 1:1 mixture with the morpholinium salt of trifluoromethanesulfonamide.

^{1}H NMR ([D_6]acetone): δ 3.72–3.83 (8H, m, $4CH_2$), 7.54–7.68 (4H, m, ArH), 9.00–9.14 (1H, w s, NH); ^{19}F NMR ([D_6]acetone): δ −61.5 (s, 3F, CF_3), −78.5 (s, 3F, SO_2CF_3).

4.6.5. Morpholino-4-carbanilide (10)

m.p. 156–158 °C; Ref. [19] 161.5–162 °C. ^{1}H NMR ([D_6]DMSO): δ 3.43 (4H, t, $2CH_2$), 3.61 (4H, t, $2CH_2$), 6.92–6.94 (1H, m, ArH), 7.21–7.26 (2H, m, ArH), 7.46 (2H, d, ArH), 8.54 (1H, s, NH).

4.6.6. 4-[N-Phenyl-N′-methylsulfonylamidino]morpholine (11)

m.p. 123–125 °C. ^{1}H NMR ([D_6]acetone): δ 2.90 (3H, s, SO_2CH_3), 3.40 (4H, t, $2CH_2$), 3.61 (4H, t, $2CH_2$), 7.14–7.24 (3H, m, ArH), 7.39–7.44 (2H, m, ArH), 8.52–8.62 (1H, w s, NH); ^{13}C {^{1}H} NMR (125 MHz, [D_6]DMSO): δ 154.4, 139.5, 129.3, 123.8, 120.4, 65.3, 46.9, 42.4. Anal. calcd for $C_{12}H_{17}N_3O_3S$: C 50.9, H 6.1, N 14.8. Found C 50.9, H 6.0, N 14.9.

4.6.7. 4-[N-Phenyl-N′-phenylsulfonylamidino]morpholine (12)

m.p. 109–110 °C. ^{1}H NMR ([D_6]acetone): δ 3.37 (4H, t, $2CH_2$), 3.58 (4H, t, $2CH_2$), 6.97–7.85 (10H, m, ArH), 8.68 (1H, s, NH); ^{13}C {^{1}H} NMR (125 MHz, [D_6]DMSO): δ 154.3, 143.7, 139.0, 131.4, 129.1, 128.7, 125.6, 123.8, 120.3, 65.3, 47.0. Anal. calcd for $C_{17}H_{19}N_3O_3S$: C 59.1, H 5.5, N 12.2. Found C 59.2, H 5.5, N 12.1.

4.6.8. 4-[N-(4-Fluorophenyl)-N′-nonafluorobutylsulfonylamidino]morpholine (13)

Light-yellow oil; Ref. [6] m.p. 127–129 °C. ^{1}H NMR ([D_6]acetone): δ 3.62 (4H, m, $2CH_2$), 3.73 (4H, m, $2CH_2$), 7.17–7.33 (4H, m,

ArH), 8.90 (1H, s, NH); ^{19}F NMR ([D$_6$]acetone): δ −80.5 (s, 3F, $SO_2(CF_2)_3\underline{CF_3}$), −112.9 (s, 2F, $SO_2(\underline{CF_2})_3CF_3$), −117.0 (s, 1F, ArF), −120.4 (s, 2F, $SO_2(\underline{CF_2})_3CF_3$), −125.4 (s, 2F, $SO_2(\underline{CF_2})_3CF_3$); ^{13}C {^{1}H} NMR (125 MHz, [D$_6$]DMSO): δ 159.3 (d, $^1J_{CF}$ = 240 Hz), 154.5, 134.8, 125.0 (d, $^3J_{CF}$ = 9 Hz), 115.5 (d, $^2J_{CF}$ = 22.5 Hz), 118.0–108.0 (m, C_4F_9), 65.4, 47.2. Anal. calcd for $C_{15}H_{13}F_{10}N_3O_3S$: C 35.7, H 2.6, N 8.3, S 6.4. Found C 35.9, H 2.5, N 8.2, S 6.4.

4.7. The aza Hofmann rearrangement leading to N-(4-fluorophenyl)-N′-trifluoromethylsulfonylurea (8c)

A mixture of amidine **2c** (2 mmol) with triethylamine (6 mmol) in glyme (10 mL) was added dropwise to a stirred suspension of 4-(diacetoxyiodo)toluene (3 mmol) in glyme (15 mL) at 0 °C over 15 min. After stirring for 1–2 h at room temperature, morpholine (4 mmol) was added to the reaction mixture in one portion. The reaction mixture was stirred for 24 h at room temperature. Column chromatography (eluent ethylacetate) and following crystallization (from ether/hexane) gave pure product **8c**. m.p. 136–140; Ref. [7] 136–140 °C. ^{1}H NMR ([D$_6$]DMSO): δ 6.90–7.10 (2H, m, ArH), 7.40–7.60 (2H, m, ArH), 8.92 (1H, s, NH); ^{19}F NMR ([D$_6$]DMSO): δ −76.0 (s, 3F, SO_2CF_3), −122.7 (s, 1F, ArF); ^{13}C {^{1}H} NMR (125 MHz, [D$_6$]DMSO): δ 157.4, 156.9 (d, $^1J_{CF}$ = 271 Hz), 137.6, 121.0 (q, $^1J_{CF}$ = 329 Hz), 119.4 (d, $^3J_{CF}$ = 3.5 Hz), 114.6 (d, $^2J_{CF}$ = 24 Hz).

4.8. X-ray crystallography

All crystallographic measurements were performed at room temperature on a Bruker Smart Apex II diffractometer operating in the ω and φ scans mode. The cell parameters were obtained from the least-squares treatment of 2150 reflections in the θ range of 2.95–26.74°. The intensity data were collected within the range of $2.95 \leq \theta \leq 26.00°$ ($-6 < h < 6$, $-11 < k < 11$, $-11 < l < 12$) using Mo Kα radiation (λ = 0.71078 Å). The intensities of 5568 reflections were collected (1980 unique reflections, R_{int} = 0.02). Data were corrected for Lorentz and polarization effects. The SADABS procedure [20] absorption correction (the ratio of minimum to maximum apparent transmission is 0.713887) was applied.

4.8.1. Structure solution and refinement

The structure was solved by direct methods and refined by the full-matrix least-squares technique in the anisotropic approximation for non-hydrogen atoms using the SHELXS97 and SHELXL97 programs [21,22]. Hydrogen atoms were located in the difference Fourier maps and refined isotropically. In the refinement 1980 reflections (1662 reflections with $I \geq 2\sigma(I)$) were used. Convergence was obtained at R1 = 0.0347 and wR2 = 0.0815, GOF = 1.047 (173 parameters; observed/variable ratio 9.61; the largest and minimal peaks in the final difference map 0.25 and −0.28 e/Å^3, weighting scheme is as follows: $\omega = 1/[\sigma^2(Fo^2) + (0.0358P)^2 + 0.2173P]$, where $P = (Fo^2 + 2Fc^2)/3$). Full crystallographic details have been deposited at Cambridge Crystallographic Data Centre (CCDC). Any request to the CCDC for these materials should quote the full literature citation and reference number CCDC 669739.

4.8.2. Crystal data for 2a

$C_8H_7F_3N_2O_2S$, M = 252.22, triclinic, space group P i (N 2), a = 5.5343(9), b = 9.4529(16), c = 10.3516(17) Å, α = 84.387(2), β = 76.624(2)° γ = 75.366(2), V = 509.32(15) Å^3, Z = 2, d_c = 1.645 g cm^{-3}, μ = 0.348 mm^{-1}, F(0 0 0) = 256, crystal size ca. 0.42 mm × 0.37 mm × 0.3 mm.

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