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Simple methods for the preparation of *N*-triflyl guanidines and the structure of compounds with the $CF_3SO_2N{=}C{-}N$ fragment

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ABSTRACT

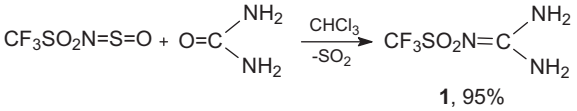
Two novel and simple approaches to *N*-triflyl guanidines are elaborated. Owing to very strong conjugation the formally double C=N bond of $TfN{=}C(NHR)_2$ is longer than the formally single N–C bonds. Energetic effect of the triflyl group on the conjugation in the N–C=N moiety is estimated to be ≥150 kcal/mol.

1. Introduction

The guanidine functionality is an important group responsible for biological activity of many natural substances. *N*-triflyl guanidines $TfN{=}C(NHR)_2$ ($Tf{=}CF_3SO_2$) represent a novel class of functionalized guanidines, which, on the one hand, are biologically active themselves [1], and, on the other hand, are efficient reagents for guanidinylation of amines [2,3] due to high nucleofugality of the triflyl group. Note, that in a later work of Powell et al. [4] these reactions are referred to as *guanylation* reactions, which involve the attachment of a guanyl group $-C(=NH)NR_2$ to nitrogen atom, as distinct from *guanidinylation* reactions of alkyl halides, alcohols, etc., which involve the attachment of a guanidino moiety $-NH(C{=}NH)NR_2$ to the carbon atom. In the pioneering works of Goodman [2,3], *N*-triflyl guanidines with Boc and CBz protecting groups $TfN{=}C(NHPG)_2$ were synthesized by the reaction of the properly diprotected guanidines with triflic anhydride. Later on, the same group of researchers published the synthesis of the Alloc (allyloxycarbonyl) protected guanidines using the same approach and utilizing them for solid-phase synthesis of the resin-bound guanidines [5]. A brief overview of the synthesis and application of diprotected *N*-triflyl guanidines was given recently [6]. Unprotected *N*-triflyl guanidines were obtained by Yagupolsky et al. by amination of *N*-bis(methylthio)methylenetrifluoromethanesulfonylamide $TfN{=}C(SMe)_2$ [7] or *N*-phenyl-*N*′-(trifluoromethylsulfonyl)carbodiimide $TfN{=}C{=}NPh$ [8] or *N*-trifluoromethylsulfonyl-*N*′-arenechloroformamidines $TfN{=}C(Cl)NHAr$ [9,10]. Recently, a one-pot method for preparation of different *N*-sulfonylguanidines [11] was extended to *N*-triflyl derivatives and a series of unprotected *N*-triflyl guanidines $TfN{=}C(NHAr)NRR'$ was synthesized by the reaction of aryl isothiocyanates ArNCS with triflamide $TfNH_2$ followed by treatment with amines RR′NH [1].

2. Results and discussion

Here we present two new approaches to *N*-triflyl guanidines which allow to obtain the target products in close to quantitative yields. The first one is the reaction of *N*-sulfinyltrifluoromethanesulfonamide $CF_3SO_2N{=}S{=}O$ with the carbonyl group of urea as exemplified by reaction (1) resulting in *N*-triflyl guanidine (Scheme 1.).



Scheme 1. Synthesis of *N*-triflyl guanidine (first approach).

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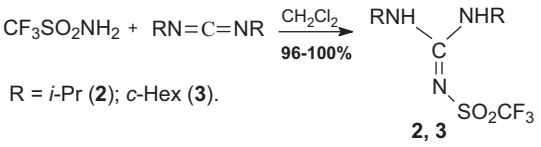


Scheme 2. Synthesis of *N*-triflyl guanidines (second approach).

The second method is the addition of trifluoromethanesulfonamide to the system of cumulated bonds N=C=N, realized on the examples of its reaction with *N*,*N*′-dipropylcarbodiimide and *N*,*N*′-dicyclohexylcarbodiimide (Scheme 2):

Scheme 2 is the first example of the reaction of sulfonamides with carbodiimides. Both reactions proceed under mild conditions in close to quantitative yields.

Strange as it might be, while the reactions in Scheme 2 proceed at room temperature, the reaction of trifluoromethanesulfonamide with *N*,*N*′-diphenylcarbodiimide does not occur even upon prolonged reaction time (25 °C, 50 h) or reflux in THF.

The structure of compounds **1**–**3** was proved by NMR and IR spectroscopy (see Supporting Information). The alternative tautomeric structure of *N*-guanyltriflamide $CF_3SO_2NHC(NH_2)$=NH was ruled out by the following reasons. First, tautomers **1**–**3** are more stable due to direct polar conjugation of the amino groups with the C=N bond bearing a strong acceptor substituent at the imine nitrogen. The absence of tautomers with the $-NHSO_2CF_3$ residue was shown for a number of related structures [2,9,10] both in crystal and in solution. Second, the IR spectra of diluted solutions of **1** in CCl_4 and CH_2Cl_2 have only two ν(NH) bands at 3479 and 3366 cm^{-1}; for a less symmetrical *N*-guanyltriflamide there should have been at least four bands [$\nu_{as}(NH_2)$, $\nu_s(NH_2)$, ν(NH), ν(=NH)]. Finally, calculations at the MP2/6-311G(d,p) level predict even the most stable conformer of *N*-guanyltriflamide to be 12.6 kcal/mol higher in energy than *N*-triflyl guanidine, which is too large to be overcome by any solvent effect, the more so that the calculated polarity of *N*-triflyl guanidine (μ = 7.92 D) is much larger than that of *N*-guanyltriflamide (μ = 4.32 D).

For compound **3**, a single crystal suitable for diffraction experiments was grown and X-ray analysis proved the presence of the intramolecular hydrogen bond. The perspective view of **3** is shown in Fig. 1, and the selected bond lengths and angles (except for those in the cyclohexyl fragments) are listed in Table 1. The hydrogen bond parameters are given in Table 2.

The most interesting structural feature is a longer C–N distance for the formally double C2–N2 bond relative to the formally single C2–N1 and C2–N3 bonds. This is definitely indicative of a very strong conjugation of the N1 and N3 lone pairs with the C=NTf moiety.

We have compiled all available structural data for *N*-triflyl guanidines and closely related compounds; the bond distances in the fragment –NH–C=NTf are given in Table 3.

As follows from the data of Table 3, there is only one clear-cut instance of a "normally" shorter C=NTf bond as compared to the C–N bonds (No. 2), which is realized in the molecule, in which the conjugation of the lone pairs of the N1 and N2 atoms with the *t*-Boc group diminishes their conjugation with the azomethine C=NTf group. In the absence (No. 1, 3–5) or for a less strong competitive conjugation (No. 6, 7) the formally double C=NTf bond is always longer than the formally single C–N bond.

Another indication of specific interactions in *N*-triflyl guanidines comes from the analysis of the crystal packing of phenylhydroxamic acid trifluoromethanesulfonylimide TfN=C(Ph)NHOH [9]. In spite of a low basicity of the sulfonamide oxygen atoms, the molecules in the crystal are bound by N–H···O=S and O–H···O=S intermolecular hydrogen bonds, the azomethine nitrogen atom not being involved in the hydrogen

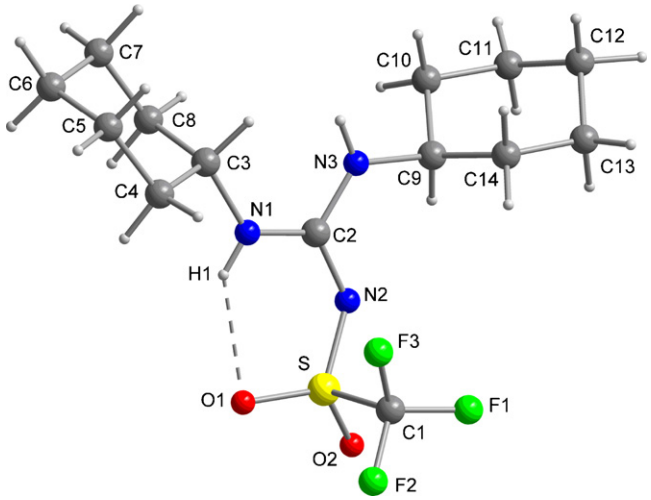


Fig. 1. Molecular structure of **3**.

bond formation. This is indicative not only of a strong conjugation of the amino group with the C=N bond but also of a significant shift of the electron density from the N–C=N fragment to the triflyl group.

To estimate the effect of the triflyl group quantitatively, we performed NBO analysis for guanidine **4**, 1,3-dicyclohexylguanidine **5** and molecule **3** using the MP2/6-311G(d,p) optimized geometry [13]. The energy of the $(n_{N1} + n_{N3}) \rightarrow \pi^*_{C=N2}$ interaction is 219.40, 35.8, and 28.6 kcal/mol for compounds **3**, **4** and **5**, respectively. Even if to add the values for the $(n_{N1} + n_{N3}) \rightarrow \sigma^*_{C=N2}$ interaction (which is absent for molecule **3**), the corresponding values are 219.40, 64.8, and 70.7 kcal/mol, that is, the effect of the triflyl group amounts to ~150 kcal/mol. Correspondingly, the calculated difference between the lengths of the C–N1(3) and C=N2 bonds is 0.10–0.12 Å in molecules **4** and **5**, but drastically drops to 0.01 Å in molecule **3**.

The results of calculations also allowed us to explain the aforementioned inertness of *N*,*N*′-diphenylcarbodiimide in the reaction with trifluoromethanesulfonamide. *N*,*N*′-Dialkyl- and *N*,*N*′-diphenylcarbodiimides have practically the same geometry of the C–N=C=N–C fragment and the charges on the N=C=N

Table 1
Selected bond lengths, bond angles and dihedral angles in molecule **3**.

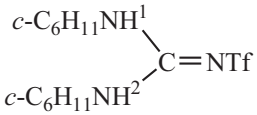
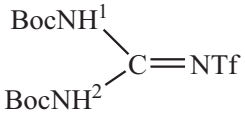
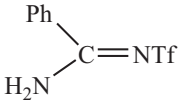
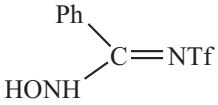
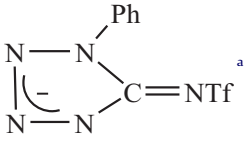
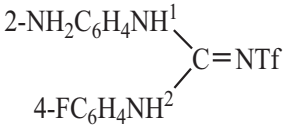
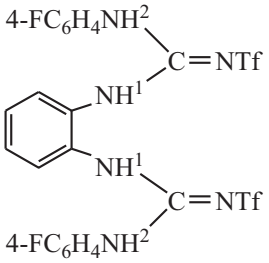
Bond	Length (Å)	Angle	Degrees
C1–F1	1.314(2)	C1–S–O1	103.19(9)
C1–F2	1.317(3)	C1–S–O2	104.70(9)
C1–F3	1.327(3)	O1–S–O2	117.23(7)
C1–S	1.825(2)	S–N2–C2	123.59(12)
C2–N1	1.329(2)	N2–C2–N1	123.80(15)
C2–N2	1.358(2)	N2–C2–N3	115.83(15)
C2–N3	1.325(2)	N1–C2–N3	120.35(15)
N2–S	1.548(1)	N2–C2–N3–C9	−2.3(3)
S–O1	1.436(1)	N2–C2–N1–C3	176.60(16)
S–O2	1.430(1)	O1–S–N2–C2	29.69(17)
C1–S1	1.825(2)	O2–S–N2–C2	165.94(13)
N1–C3	1.466(2)	S–N2–C2–N1	−18.3(2)
N3–C9	1.464(2)	S–N2–C2–N3	163.68(13)

Table 2
Hydrogen bond geometry in **3**.

D–H···A	D–H	H···A	D···A	D–H···A
N3–H3···O2[a]	0.83(2)	2.26(2)	2.974(2)	143.8(19)
N1–H1···O1	0.79(2)	21.14(2)	2.795(2)	141(2)

[a] Symmetry code: $y - 0.25$, $0.75 - x$, $z - 0.25$.

Table 3
C–N bond lengths (Å) in the molecules containing the –NH–C=NTf moiety (NH^1 refers to the NH group forming the N–H···O=S hydrogen bond).

No.	Molecule	C–NTf	$C–N^1$	$C–N^2$	Ref.
1		1.358(2)	1.329(2)	1.325(2)	This work
2		1.310	1.374	1.344	[3]
3		1.341	1.302		[10]
4		1.315	1.307		[9]
5		1.351	1.335	1.330	[8]
6		1.341	1.337	1.342	[12]
7		1.334 1.344	1.347 1.335	1.334 1.340	[12]

[a] Morpholinium cation as a counterion.

atoms but principally differ in the structure of the high-lying occupied molecular orbitals. For *N*,*N*′-dialkylcarbodiimides the HOMO is localized mainly on the *p*-orbitals of the nitrogen atoms, whereas for *N*,*N*′-diphenylcarbodiimide the similarly localized MO is only fifth in energy, the HOMO being localized mainly on the aromatic carbon atoms.

3. Conclusions

Two new one-step synthetic approaches to *N*-triflyl guanidines are elaborated. Addition of trifluoromethanesulfonamide to *N*,*N*′-dialkylcarbodiimides or condensation of *N*-sulfinyltrifluoromethanesulfonamide with urea allow to prepare *N*-triflyl guanidines under mild conditions in yields close to quantitative. Strong conjugation of the amino groups with the azomethine bond results in a longer formally double C=N bond as compared to the formally single N–C bonds.

4. Experimental

4.1. General

Melting points are uncorrected. IR spectra were taken on a Bruker Vertex 70 spectrophotometer in KBr. ^1H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker DPX 400 spectrometer at working frequencies 400 (^1H), 100 (^{13}C), and 376 (^{19}F) MHz; ^1H and ^{13}C NMR chemical shifts are reported in parts per million downfield to TMS, and ^{19}F NMR in parts per million downfield to $CFCl_3$.

X-ray structure determination of **3**. The crystal was embedded in perfluoropolyalkylether oil and mounted on a glass fibre. Intensity data were collected at 210 K using a STOE Imaging Plate Diffraction System IPDS-2 with graphite monochromatized $Mo_{K\alpha}$ radiation ($\lambda = 0.71073^\circ$) at 50 kV and 40 mA (180 frames, $\Delta\omega = 1^\circ$, 2 min exposure time per frame). The data were corrected for Lorentz, polarization and extinction effects [15]. No absorption correction was applied. The structure was solved with direct methods using SHELXS-97 and refined with full-matrix least-squares on F^2 using the program SHELXL-97 [16,17]. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were located from the difference Fourier map and allowed to refine without constraints.

All solvents were dried and purified before use according to standard procedures. Urea was twice crystallized from ethanol and dried in vacuum. Commercial diisopropylcarbodiimide of 99% purity (Aldrich) and dicyclohexylcarbodiimide of 99% purity (Alfa Aesar) were used. Trifluoromethanesulfonamide [18] and *N*-sulfinyltrifluoromethanesulfonamide [19] were synthesized by the known procedures.

4.2. Synthesis

2-(Trifluoromethylsulfonyl)guanidine 1. To the solution of *N*-sulfinyltrifluoromethanesulfonamide (0.51 g, 2.6 mmol) in chloroform (5 mL) urea (0.15 g, 2.6 mmol) was added at vigorous stirring. The mixture was refluxed for 40 min, then kept overnight. The precipitate was filtered off, washed with chloroform and dried in vacuum to get 1 0.47 g (95%) of product **1** as white crystals with m.p. 158 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ = 6.77 (s, 1H, NH), 8.82 ppm (br.s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6), δ = 119.56 q (CF_3, J 320.8 Hz), 155.47 ppm (C=N); ^{19}F NMR (376 MHz, DMSO-d_6), δ = −79.34. Anal. calcd. for $C_2H_4F_3N_3O_2S$: C, 12.57; H, 2.11; F, 29.82; N, 21.98; S, 16.78; found: C, 12.91; H, 2.42; F, 29.74; N, 21.99; S, 16.11.

1,3-Diisopropyl-2-(trifluoromethylsulfonyl)guanidine 2. To the solution of 0.18 g (1.4 mmol) of diisopropylcarbodiimide in 2 mL of methylene chloride 0.21 g (1.4 mmol) of *N*-triflamide was added at vigorous stirring, stirred for 6 h, kept overnight, evaporated in vacuum to get 0.37 g (96%) of product **2** as white crystals with m.p. 149–150 °C. IR, ν, cm^{-1}: 3358, 2989, 1606, 1584, 1402, 1370, 1298, 1219, 1206, 1190, 1162, 1146, 1094, 969, 801, 653, 623, 599. ^{1}H NMR ($CDCl_3$), δ, ppm: 7.00 br.s (1H, NH), 5.46 br.s (1H, NH), 4.76 br.s (1H, NCH), 3.71 br.s (1H, NCH), 1.23 d (12H, CH_3, J 6.0 Hz). ^{13}C NMR ($CDCl_3$), δ, ppm: 154.57 (C=NTf), 120.42 q (CF_3, J 322.5 Hz), 44.25 (CH′), 22.44 (CH_3). ^{19}F NMR ($CDCl_3$), δ, ppm: −79.61. Found, %: C, 35.01; H, 6.01; F, 20.99; N, 15.34; S, 11.26. $C_8H_{16}F_3N_3O_2S$. Calcd., %: C, 34.90; H, 5.86; F, 20.70; N, 15.26; S, 11.65.

1,3-Dicyclohexyl-2-(trifluoromethylsulfonyl)guanidine 3. To the solution of 0.29 g (1.4 mmol) of dicyclohexylcarbodiimide in 1 mL of methylene chloride 0.21 g (1.4 mmol) of *N*-triflamide was added at vigorous stirring, stirred for 6 h, kept overnight, evaporated in vacuum to get 0.49 g (100%) of product **3** as white crystals with m.p. 160 °C. IR, ν, cm^{-1}: 3364, 3348, 2939, 2860, 1595, 1360, 1304, 1212, 1175, 1114, 1058, 975, 649, 599. ^{1}H NMR ($CDCl_3$), δ, ppm: 7.20 br.s (1H, NH), 4.73 br.s (1H, NH), 3.87 br.s (1H, NCH), 3.25 br.s (1H, NCH), 1.93 m (4H, CH_2), 1.74 m (4H, CH_2), 1.62 m (2H, CH_2), 1.46–1.10 m (10H, CH_2). ^{13}C NMR ($CDCl_3$), δ, ppm: 154.41 (C=NTf), 120.36 q (CF_3, J 322.0 Hz), 50.66 (C^1, $C^{1'}$), 32.56 br. ($C^{2,6,2',6'}$), 25.16 ($C^{4,4'}$), 24.26 br. ($C^{3,5,3',5'}$). ^{19}F NMR ($CDCl_3$), δ, ppm: −79.75. Found, %: C, 47.57; H, 6.73; F, 17.97; N, 11.58; S, 9.68. $C_{14}H_{24}F_3N_3O_2S$. Calcd., %: C, 47.31; H, 6.81; F, 16.04; N, 11.82; S, 9.02.

Crystal data: $C_{14}H_{24}F_3N_3O_2S$, M_r = 355.42 g mol^{-1}, crystal dimensions 0.60 mm × 0.40 mm × 0.20 mm, tetragonal, space group $I4_1/a$, a = 19.7439(6), b = 19.7439(6), c = 18.1092(6) Å, V = 7059.4(4) Å^3, Z = 16, ρ_{calcd} = 1.338 g cm^{-1}; T = 210 K; $2\Theta_{max}$ = 50.00°, 22,552 reflections measured, 3113 unique (R_{int} = 0.0247), R = 0.0370, wR = 0.0981 ($I > 2\sigma(I)$). For details of the data collection and the structure solution and refinement see Supplementary data. CCDC 850199 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jfluchem.2011.12.004.

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