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Synthesis, Characterization, and Biological Activity of N′-Trifluoromethanesulfonyl-2-aminopyridine

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ABSTRACT: *The synthesis, characterization and biological activity of N′-trifluoromethanesulfonyl-2-aminopyridine in connection with our studies of trifluoromethanesulfonyl derivatives of the pyridine ring have been achieved. In solution an equilibrium (~ 50:50%) of the amide and imide tautomeric forms was observed, while in the solid state only the imide form was present. Biological tests on the compound showed no effect either upon the growth of Escherichia coli or on Staphylococcus aureus in the agar diffusion tests; however, the growth of Enterococcus faecalis was effectively inhibited.* © 2000 John Wiley & Sons, Inc. Heteroatom Chem 11:308–312, 2000

INTRODUCTION

Although the sulfa drugs have been largely displaced by antibiotics from their original application in systemic disease treatment, they provide a principal treatment of urinary-tract disease for which they are not only cheaper than antibiotics, but may also actually be considered superior by some physicians. In addition they have some applications in the treatment of the fungus-related nocardiosis and in the prophylaxis of rheumatic fever under certain circumstances.

In the course of our work [1] on nucleophilic reactions of 1-trifluoromethanesulfonylpyridinium trifluoromethansulfonate, we detected the formation of the title compound as a by-product. Because the products of that reaction showed significant antimicrobial activity and because of the close structural relationship with proved sulfa drugs (e.g., sulfapyridine), we decided to synthesize and test the biological activity of the *N′*-trifluoromethanesulfonyl-2-aminopyridine.

RESULTS AND DISCUSSION

On the original detection of the title compound as a by-product, its mechanism of formation from pyridine remains uncertain; thus, in the present work, the synthesis was achieved by a modification of the

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method reported by Comins and Dehghani [2] from 2-aminopyridine (Figure 1).

Structure Determination

Practical separation of the product was achieved by column chromatography on silica gel. The presence of the triflyl group was firmly established by its infrared absorptions, and in the mass spectrum, we can find peaks associated with the loss of CF_3, CF_3SO_2, and CF_3SO_2NH moieties from the molecular ion. The ^1H and ^{13}C NMR spectra contrast by their relative complexity; in both spectra (Table 1), all of the signals appeared duplicated, and taking into account the value of the molecular ion, the only possibility to accommodate these facts is to assume a tautomeric equilibrium between the *amide* and *imide* forms (Scheme 1).

The two sets of overlapped signals in the ^1H NMR spectrum, recorded at room temperature, were resolved by a study at variable temperature in the range $-40°$ to 40°C, and individual assignments were made by comparison with the reported values for 2-aminopyridine and 2-pyridinol, which indicated (>95%) tautomeric forms correspond to the amide and imide forms, respectively. The observed equilibrium (56:44 ±2) was determined by integration of the ^1H NMR spectrum. In order to confirm the structure derived by spectroscopic means, and, to determine the tautomeric form present in the solid state, a single crystal X-ray diffraction structure determination was performed.

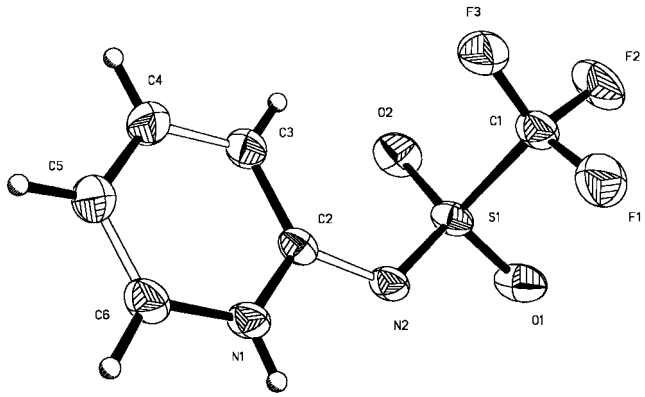


FIGURE 1 ORTEP-type drawing of title compound. Thermal ellipsoids at 30% probability level.

TABLE 1 ^{13}C Data for Tautomeric Forms of the Title Compound (in $CDCl_3$/MeOD)

Atom	*Amide Form*	*Imide Form*
C-1[a]	120.03 (J = 321 Hz)	120.26 (J = 319 Hz)
C-2	154.09	155.77
C-3	113.87	112.30
C-4	134.59	136.51
C-5	118.37	114.99
C-6	143.82	144.32

[a]Quartet.

The bond lengths and angles in the pyridine ring and in the triflamide group (Table 2) as well as in Figure 1 show that, in the crystalline state, the preferred tautomeric form corresponds to the imide form. Three arguments support this conclusion: (1) the crystallographic study clearly shows that the hydrogen atom is bonded to the N1 atom of the pyridine ring; (2) the bond angle C2–N1–C6 [124.0(3)°] is greater than 120°, as found in all compounds in which the N-atom of the pyridine ring is protonated [3]; (3) the bond lengths inside the pyridine ring are different, it being possible to distinguish between single and double bonds. This tautomeric form had been observed in closely related compounds such as sulfapyridine [4] and sulfathiazole [5,6].

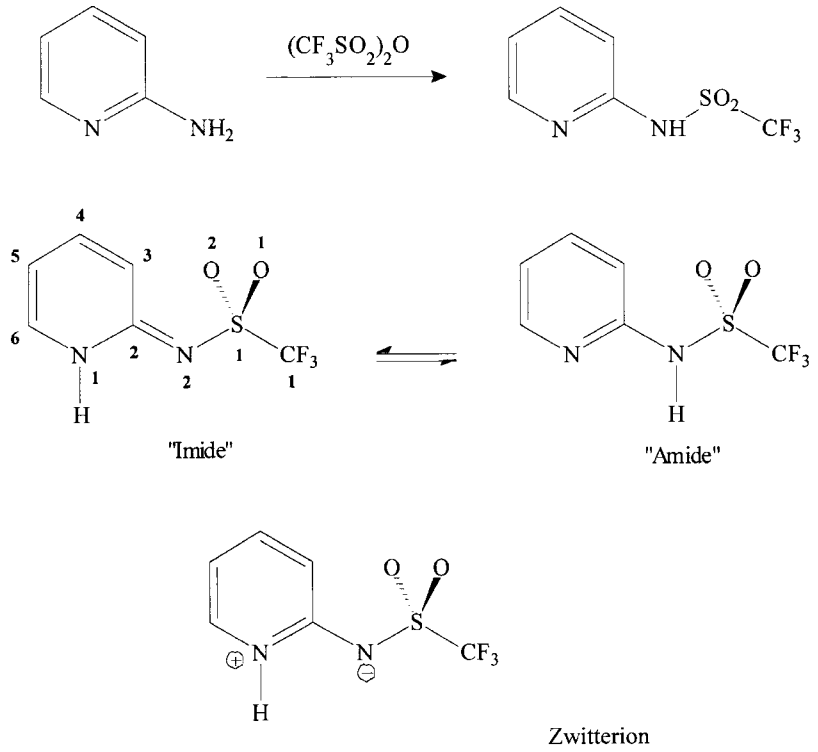
Excluding the trifluoromethyl group, the molecule is essentially planar, and, in the crystal, individual molecules are arranged into centrosymmetric dimers through hydrogen bonds N-H ··· N [H1 ··· N2: 2.17(3) Å, N1 ··· N2: 2.968(4) Å, N-H ··· N: 174(3)°] reinforced by interactions C-H ··· O [H6 ··· O1: 2.41 Å].

The existence of several species in aqueous solutions of the sulfa drugs is relevant to the problem of the relationship between electronic structure and bacteriostatic activity, and, in connection with this, Bell and Robin [7], by correlating the in vitro activity and the pK_a values of a large series of sulfonamides, have assigned to the anion a far greater activity than those of the neutral forms (Scheme 1).

Antimicrobial Activity

N′-trifluoromethanesulfonyl-2-aminopyridine showed no effect upon the growth of either *Escherichia coli* or *Staphylococcus aureus* in the agar diffusion tests; however, the growth of *Enterococcus faecalis* was effectively inhibited. An inhibitory halo of 34 mm around the disk containing 500 μg of N′-trifluoromethanesulfonyl-2-aminopyridine was observed after a 24 hour incubation period, whereas the DMSO vehicle showed no visible effect under identical conditions.

The relatively high dose needed to attain a measurable inhibitory halo could be masked by the low-water solubility of the compound. The specific tox-



SCHEME 1

TABLE 2 Final Atomic Coordinates and Equivalent Temperature Factor

Atom	*x*	*y*	*z*	*Ueq*
S(1)	4357(1)	3310(1)	6926(1)	43(1)
F(1)	906(5)	2407(3)	8850(3)	80(1)
F(2)	4539(5)	1647(3)	9430(3)	84(1)
F(3)	2583(5)	4028(2)	9801(2)	72(1)
O(1)	4707(5)	1879(3)	6116(3)	65(1)
O(2)	6497(4)	3833(3)	7171(3)	63(1)
N(1)	−257(4)	6953(3)	6033(3)	41(1)
N(2)	2260(4)	4547(3)	6288(3)	41(1)
C(1)	3003(6)	2831(4)	8858(3)	51(1)
C(2)	1681(5)	6107(3)	6659(3)	38(1)
C(3)	2786(6)	6929(4)	7572(4)	50(1)
C(4)	1874(7)	8505(4)	7792(4)	58(1)
C(5)	−148(7)	9314(4)	7128(4)	55(1)
C(6)	−1173(6)	8508(4)	6250(4)	50(1)

icity on *Enterococcus faecalis* and the lack of effect upon other bacterial species suggests that its toxicity may be of a very narrow spectrum.

Regrowth inside the inhibitory zone after incubation of 48 hours at 35°C indicates that the compound is exerting a bacteriostatic rather then a bactericidal effect. Further studies are necessary to assess quantitatively this antienterococcal effect and its mechanism of action.

EXPERIMENTAL

The melting point was determined on a Mel-Temp II melting point apparatus and is uncorrected. The IR spectrum was taken on a Nicolet FTIR Magna 750 spectrophotometer and the data are given in cm^{-1}. NMR spectra were measured on Varian Gemini 200 and Unity Plus (200 MHz for ^{1}H and 500 MHz for ^{13}C) spectrometers with tetramethylsilane as an internal standard, and the chemical shifts are given in δ values. The mass spectrum (MS) was taken with a JEOL JMS-SX102A instrument at 70eV, and M^{+} is indicated as *m/z* (%). Column chromatography was performed on silica gel (Merck, 70–230 mesh). The yield is expressed in percent (mol/mol) referred to the quantity of 2-aminopyridine used.

N′-Trifluoromethanesulfonyl-2-aminopyridine (**1**)

A solution of 2-aminopyridine (1.31 g, 14 mmol) in dry CH_2Cl_2 (5 mL) was prepared and dry pyridine (1.2 mL, 15.4 mmol) was added slowly. The solution was cooled at −28°C and trifluoromethanesulfonic anhydride (2.6 mL, 15.4 mmol) was added dropwise to the mixture, which was stirred for 1 hour at −28°C. After this, the reaction mixture was left standing at room temperature for 12 hours. Water

was added, and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed twice with 10 mL portions of cold 10% NaOH, water, and brine. The organic phase was dried over anhydrous Na_2SO_4, filtered through celite and concentrated. Final purification by column chromatography was achieved using a hexane: ethyl acetate (75:25) mixture as eluent to obtain 0.854g (27% yield) of N′-trifluoromethanesulfonyl-2-aminopyridine.

X-ray Crystal Analysis

Single crystals of the title compound were obtained from CH_2Cl_2 solutions by slow evaporation. Crystal data, structure solution, and refinement details are summarized in Table 3. Intensities collected at room temperature (20°C) on a Siemens P4/PC diffractometer were corrected for Lorentz and polarization effects. The structure was determined by direct methods (program SIR92) [8]) and refined by least-squares (program SHELXL97 [9]) using anisotropic temperature factors for non-hydrogen atoms. Ideal positions for H atoms were calculated and included in the structure factor calculations.

The function $\Sigma w(Fo^2 - Fc^2)^2$ was minimized, and, for refinement, the present discrepancy indexes $R = \Sigma||Fo| - Fc||/\Sigma|Fo|$, $wR = [\Sigma(w(Fo^2 - Fc^2)^2)/\Sigma(w(Fo^2)^2]^{1/2}$ and $S = [\Sigma(w(Fo^2 - Fc^2)^2]/(M - N)]^{1/2}$, where M = the number of reflections and N = the number of variables, were used. The final parameters and ORTEP-type drawings of the molecule are given in Table 2 and Figure 1. Anisotropic thermal parameters of non-hydrogen atoms, atomic coordinates, and isotropic thermal parameters of H atoms, bond lengths, and bond angles have been deposited at the Cambridge Crystallographic Data Centre. Any request to the CCDC for this material should quote the full literature citation and the reference number CCDC 140099.

TABLE 3 Crystal Data and Structure Refinements

Crystal dimensions (mm)	0.40 × 0.16 × 0.12
Formula weight	226.18
Crystal system	triclinic
a (Å)	5.625(1)
b (Å)	8.747(2)
c (Å)	8.846(2)
α (°)	87.73(1)
β (°)	81.19(1)
γ (°)	76.63(1)
Cell volume (Å^3)	418.44(15)
Space group	P-1
Formula units	2
D_{calc} (g cm^{-3})	1.795
μ_{calc} (mm^{-1})	0.412
2θ range (deg)	3.0 to 50
Reflns./parameters	1482/148
R, *wR2*	0.0392, 0.0885
S	1.014
Min., max. residuals (eÅ^{-3})	−0.279, 0.252

Biological Assay

By using a 100 mg/mL solution of the title compound in DMSO, agar diffusion tests were performed on Escherichia coli (ATCC 25922), *Staphylococcus aureus* (ATCC 29213), and *Enterococcus faecalis* (ATCC 29212) strains. Liquid cultures were diluted in 0.85% NaCl up to approximately 1 × 10^6 UFC/mL and streaked on the surface of Mueller-Hinton agar plates using a cotton swab. Two paper disks were placed on the inoculated surface, one with 5 μL of the N′-trifluoromethanesulfonyl-2-aminopyridine and the other with 5 μL of DMSO. Plates were incubated for 24 hours at 35°, at the end of which the resulting inhibitory halos were measured.

N′-Trifluoromethanesulfonyl-2-aminopyridine (**1**)

Colorless prismatic crystals from ethyl acetate: acetone (50:50) mixture, m.p. 210–211°C. IR (Nujol): 3392, 3345, 3230 (N-H), 1672 (C=N), 1634, 1504,

TABLE 4 Bond Lengths and Bond Angles for Title Compound

S(1)–O(1)	1.426(2)	C(2)–C(3)	1.401(4)
S(1)–O(2)	1.431(3)	C(3)–C(4)	1.366(5)
S(1)–N(2)	1.564(2)	C(4)–C(5)	1.392(5)
S(1)–C(1)	1.835(3)	C(5)–C(6)	1.342(5)
F(1)–C(1)	1.316(4)	N(1)–H(1)	0.80(3)
F(2)–C(1)	1.324(4)	C(3)–H(3)	0.94(4)
F(3)–C(1)	1.320(4)	C(4)–H(4)	0.94(4)
N(1)–C(6)	1.349(4)	C(5)–H(5)	0.94(4)
N(1)–C(2)	1.350(4)	C(6)–H(6)	0.94(4)
N(2)–C(2)	1.368(4)		
O(1)–S(1)–O(2)	118.34(16)	N(2)–C(2)–C(3)	129.9(3)
O(1)–S(1)–N(2)	107.79(13)	C(4)–C(3)–C(2)	119.7(3)
O(2)–S(1)–N(2)	116.97(15)	C(3)–C(4)–C(5)	121.2(3)
O(1)–S(1)–C(1)	102.93(15)	C(6)–C(5)–C(4)	118.3(3)
O(2)–S(1)–C(1)	103.64(15)	C(5)–C(6)–N(1)	120.2(3)
N(2)–S(1)–C(1)	105.25(14)	C(6)–N(1)–H(1)	119.5(19)
C(6)–N(1)–C(2)	124.0(3)	C(2)–N(1)–H(1)	116.3(19)
C(2)–N(2)–S(1)	123.2(2)	C(4)–C(3)–H(3)	122(2)
F(1)–C(1)–F(3)	108.2(3)	C(2)–C(3)–H(3)	119(2)
F(1)–C(1)–F(2)	107.7(3)	C(3)–C(4)–H(4)	119(2)
F(3)–C(1)–F(2)	107.3(3)	C(5)–C(4)–H(4)	120(2)
F(1)–C(1)–S(1)	111.6(2)	C(6)–C(5)–H(5)	118(2)
F(3)–C(1)–S(1)	111.9(2)	C(4)–C(5)–H(5)	124(2)
F(2)–C(1)–S(1)	109.9(2)	C(5)–C(6)–H(6)	123(2)
N(1)–C(2)–N(2)	113.5(3)	N(1)–C(6)–H(6)	116(2)
N(1)–C(2)–C(3)	116.6(3)		

1464 (aromatic system), 1361, 1160, 1032 (SO_2), 1216 (CF_3), 784 (aromatic *o*-substitution).

^{1}H-RMN ($CDCl_3$/MeOD) *δ:* 6.68 (1H, t, J = 6.7 Hz, C_5-H imide), 6.88 (1H, d, J = 9.0 Hz, C_3-H amide), 6.90 (1H, t, J = 6.8 Hz, C_5-H amide), 7.58, (1H, d, J = 6.6 Hz, C_6-H imide), 7.65 (1H, d, J = 8.6 Hz, C_4-H amide), 7.69 (1H, ddd, J = 7.3, 1.2 Hz, C_3-H imide), 7.81 (1H, d, J = 6.9 Hz, C_4-H imide), 7.84 (1H, dd, 8.6, 1.8 Hz, C_6-H amide).

EM: *m/z*:226 (M^+, 58), 157 (M^+-CF_3, 100), 93 (M^+-SO_2CF_3, 59), 78 (M^+-$NHSO_2CF_3$, 17).

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