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A FACILE SYNTHESIS OF 5-AMINO-3-TRIFLUOROMETHYL-4-METHOXYCARBONYLISOXAZOLE

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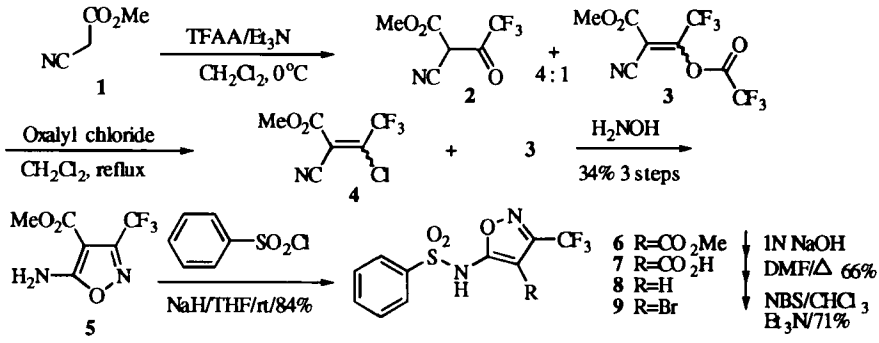
ABSTRACT: The title compound was synthesized in 3 steps from readily available cyanoacetate and TFAA. The ester group allowed access to other functionalized isoxazole derivatives.

During work on the synthesis of endothelin receptor antagonists,[1] we needed to study the structure-activity relationships of N-(3-trifluoromethyl-5-isoxazolyl)benzene sulfonamides. The sulfonamides were synthesized by coupling benzenesulfonyl chlorides with the requisite aminoisoxazoles under standard conditions. There are a variety of ways of synthesizing aminoisoxazoles.[2-6] The synthetic method that has been successfully applied to a series of 5-amino-3-trifluoroisoxazoles with an alkyl substituent at the 4-position involved the deprotonation of a nitrile with LDA followed by acylation with methyl



trifluoroacetate, and reaction of the resulting cyano trifluoroacetone with hydroxylamine.[3] However, when we set out to make the 4-methoxycarbonyl compound **5** using these procedures we did not obtain the desired product in acceptable yields. Deprotonating the cyano acetate **1** at low temperature followed by the addition of methyl trifluoroacetate gave predominantly uncharacterized mixture of by-products.

A successful synthesis began with treating the cyano acetate **1** with trifuoroacetic anhydride (TFAA) in the presence of triethylamine in dichloromethane at 0°C to give a mixture of the desired trifluoro ketone **2** and the corresponding vinyl trifluoroacetate **3**. This mixture was directly treated with oxalyl chloride to provide the corresponding vinyl chloride **4** with the vinyl trifluoroacetate **3** being carried over unchanged. This mixture of **3** and **4** was again not separated or purified but reacted directly with hydroxylamine under alkaline conditions to give the desired aminoisoxazole **5** after recrystallization from methanol/water in 34% yield based on **1**. This amino isoxazole was then coupled with benzene sulfonyl chloride in THF using NaH to give sulfonamide **6**. Alkaline

hydrolysis of **6** afforded acid **7**, which upon thermal decarboxylation and bromination with NBS produced sulfonamides **8** and **9** respectively. In summary, we devised a facile method of accessing 5-amino-4-methoxycarbonyl-3-trifluoromethylisoxazole which is otherwise difficult to obtain. The ester group at the 4-position serves as a handle for further elaborations, therefore making a variety of functionalized isoxazoles accessible.

Experimental Section

General. Melting points were determined in capillary tubes with a Mel-Temp II apparatus and are uncorrected. Proton NMR (^{1}H NMR) spectra were recorded on a GE QE-300 Plus spectrometer at 300 MHz. Chemical shifts were reported in parts per million as δ units relative to tetramethylsilane or residual solvent as internal standard. IR spectra were recorded on a Mattson GL-2020 Fourier transform infrared spectrophotometer. High-resolution mass spectra were recorded with fast atom bombardment (FAB) ionization by the University of Minnesota Mass Spectrometry Service Laboratory (Minneapolis, MN). Elemental analyses were performed by Desert Analytics (Tucson, AZ) and were within 0.4% of theoretical values unless otherwise indicated. Anhydrous solvents were obtained from Aldrich Chemical Co. (Milwaukee, WI) in Sure-Seal bottles. Unless otherwise stated, reagents and chemicals were of the highest grade from commercial sources and were used without further purification. Flash chromatography was performed on silica gel 60 (230-400 mesh, E. Merck). Thin layer chromatography was performed with E. Merck silica gel 60 F-254 plates (0.25 mm) and visualized with UV light, phosphomollybdic acid, or iodine vapor.

Analytical HPLC was performed on Vydac C18 column (4.6 × 250 mm), preparative HPLC on Dynamax-60A (83-241-c) with acetonitrle:water gradients containing 0.1% trifluoroacetic acid. The detection wave length was 254 nm.

5-Amino-3-trifluoromethyl-4-methoxycarbonylisoxazole (5): Methyl cyanoacetate (5.62 g, 56.7 mmol) and TFAA (14.3 g, 68.0 mmol) were sequentially added to dichloromethane (100 ml). Triethylamine (14.3 g, 141.8 mmol) was added dropwise at 0°C. The reaction was allowed to warm to room temperature and stirred for 1 h. A standard workup gave a 4:1 mixtureof **2** and **3**. To a solution of this oily residue in dichloromethane was added oxalyl chloride (36 g, 284 mmol). Once the bubbling ceased, a few drops of pyridine was added and the mixture was brought to reflux for 4 h. The mixture was allowed to cool to room temperature and poured into water and then worked up. To a mixture of the resulting oil and hydroxylamine hydrochloride (3.94 g, 56.7 mmol) in water (20 mL) was added 10% NaOH to adjust the pH to ~8. The mixture was stirred for 20 min when yellow crystals settled out. A standard workup followed by a recystallization from methanol/water gave **5**. ^{1}H NMR (300 MHz, $CDCl_3$): **2**: δ 3.99 (s, 3H), 3.18 (q, 1H). **5**, a yellow solid: 6.28 (br s, 2H), 3.85 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 173.1, 162.5, 153.1 (q, *J*=157.9 Hz), 119.3 (q, *J*=1089.5 Hz), 85.5, 53.5. Four derivatives of **5** were fully characterized as shown below.

N-(3-Trifluromethyl-4-methoxycarbonyl-5-isoxazolyl)-benzenesulfonamide (6): Compound **6** was synthesized using the standard NaH/THF procedure as a white solid, mp 100-101°C; ^{1}H NMR (300 MHz,

$CDCl_3$): δ 9.54 (br s, 1H), 8.12 (dd, 2H), 7.70 (tt, 1H), 7.61 (m, 2H), 3.90 (s, 3H); HRMS (FAB) calcd for $C_{12}H_9F_3N_2O_5S$ $(M+H)^+$: 351.0263, found: 351.0282; anal. calcd for $C_{12}H_9F_3N_2O_5S$: C, 41.15; H, 2.59; N, 8.00; S, 9.15; found: C, 41.23; H, 2.61; N, 8.04; S, 9.21.

N-(3-Trifluromethyl-4-carboxyl-5-isoxazolyl)-benzenesulfonamide (7): Compound **7** was obtained by hydrolyzing **6** in 1 N NaOH as a white solid, mp 175-190°C (decarboxylation); ^1H NMR (300 MHz, DMSO-d_6): δ 8.10 (dd, 2H), 7.70 (tt, 1H), 7.60 (m, 2H); HRMS (FAB) calcd for $C_{11}H_7F_3N_2O_5S$ $(M+H)^+$: 337.0106, found:337.0107; anal. calcd for $C_{11}H_7F_3N_2O_5S$: C, 39.29; H, 2.10; N, 8.33; S, 9.54; found: C, 39.32; H, 2.01; N, 8.30; S, 9.27; IR (KBr pellet): 3267, 1703 cm^{-1}.

N-(3-Trifluromethyl -5-isoxazolyl)-benzenesulfonamide (8): Compound **8** was synthesized by refluxing **7** in DMF for 8 h as an off-white needles, mp 101-102°C; ^1H NMR (300 MHz, $CDCl_3$): δ 7.92 (dd, 2H), 7.70 (tt, 1H), 7.60 (m, 2H), 6.26 (s, 1H); HRMS (FAB) calcd for $C_{10}H_7F_3N_2O_3S$ $(M+H)^+$: 293.0204, found: 293.0206; anal. calcd for $C_{10}H_7F_3N_2O_3S$: C, 41.10; H, 2.41; N, 9.59; S, 10.97; found: C, 41.19; H, 2.40; N, 9.54; S, 10.89.

N-(4-Bromo-3-Trifluromethyl-5-isoxazolyl)-benzenesulfonamide (9): Compound **9** was synthesized from **8** using the literature method[1b] as an off-white solid, mp 104-105°C; ^1H NMR (300 MHz, $CDCl_3$): δ 8.01 (dd, 2H), 7.70 (tt, 1H), 7.60 (m, 2H); HRMS (FAB) calcd for $C_{10}H_6BrF_3N_2O_3S$ $(M+H)^+$: 370.9313, found: 370.9337; anal. calcd for $C_{10}H_6BrF_3N_2O_3S$: C, 32.36; H, 1.63; N, 7.55; S, 8.64; found: C, 32.55; H, 1.52; N, 7.33; S, 8.63.

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