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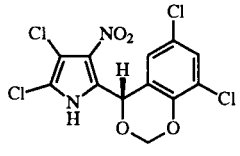
Received December 5, 1994

A general method for the preparation of 2-aryl-3-trifluoromethylsulfonylpyrroles **2** has been developed. Procedures for the construction of the key enamine intermediates **9** and their cyclizations to pyrroles are reported.

J. Heterocyclic Chem., **32**, 871 (1995).

As part of a synthesis program directed toward the investigation of the insecticidal activity associated with pyrroles based on dioxapyrrolomycin **1** [2,3], we required an efficient method for the construction of a series of 2-aryl-3-trifluoromethylsulfonylpyrroles **2**. A synthetic approach permitting variation of substituents on the aryl ring was desired.

Reported syntheses of pyrroles with a trifluoromethylsulfonyl substituent have primarily involved the reaction of a preconstructed pyrrole nucleus with trifluoromethylsulfonyl chloride to afford trifluoromethylthiopyrroles, followed by oxidation to the corresponding trifluoromethylsulfonylpyrroles [4]. Utilization of such an approach toward the targeted pyrroles **2** would involve preparation of 2-arylpyrroles appropriately substituted with positional blocking/directing groups on the 5- and/or 4-positions in order to achieve the desired regiochemistry. These blocking groups would then have to be removed at a latter stage. It was felt that a lengthy synthetic scheme such as this would not be amenable to analog synthesis. A more direct route toward the pyrroles **2** in which the pyrrole nucleus is constructed from acyclic precursors containing the trifluoromethylsulfonyl functionality was considered to be a more suitable approach.



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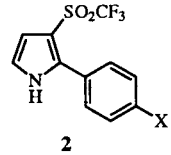
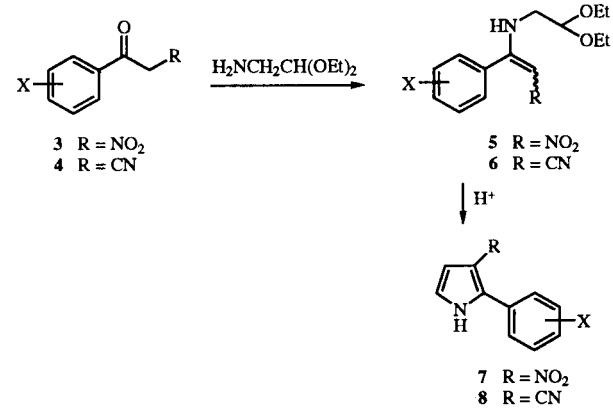


2

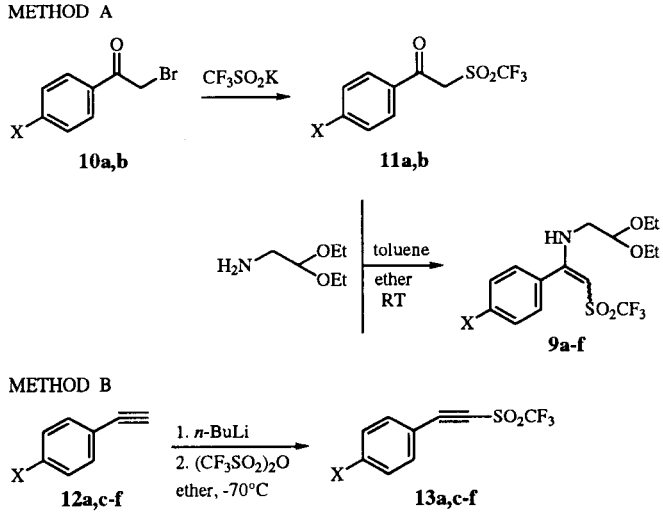
Employing a reaction scheme analogous to that reported for the synthesis of 2-methylthiopyrroles additionally substituted at the 3-position with aroyl, acyl or nitro groups [5], co-workers from our labs have developed an efficient synthesis of 2-aryl-3-nitropyrroles and 2-aryl-3-cyanopyrroles (Scheme 1) [6]. This methodology involves the condensation of α–nitroacetophenones **3** and α-cyanoacetophenones **4** with aminoacetaldehyde diethyl acetal to afford enamines **5** and **6** respectively as mixtures of *E* and *Z* isomers. Upon treatment with trifluoroacetic acid or concentrated hydrochloric acid, these enamines readily cyclized to afford 2-aryl-3-nitropyrroles **7** and 2-aryl-3-cyanopyrroles **8**. It was reasoned that if the analogous trifluoromethylsulfonyl enamine intermediates could be constructed, the desired 2-aryl-3-trifluoromethylsulfonylpyrroles **2** would be accessible *via* a similar cyclization.

Scheme 1



As shown in Scheme 2, two general methods have been developed for the preparation of the key enamine intermediates **9**. These methods are exemplified by the synthesis of the enamine intermediate **9a**, which was prepared *via* both

Scheme 2



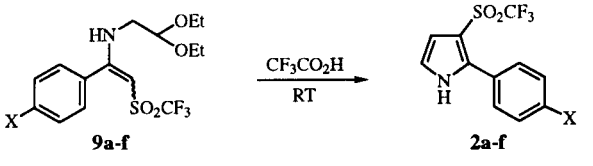
a: X = Cl, **b**: X = OCH_3, **c**: X = Br, **d**: X = $C(CH_3)_3$ **e**: X = CH_3, **f**: X = H

methods. In Method A, potassium trifluoromethanesulfinate [7] was reacted with 4-chlorophenacyl bromide **10a** in refluxing acetonitrile for 2 days to afford the α-trifluoromethylsulfonylacetophenone **11a** in 55% yield. Use of dimethylacetamide as a solvent for nucleophilic displacement by trifluoromethanesulfinate anion [8] gave similar yields at lower temperatures (50°) and shorter reaction times (16 hours). Reaction of **11a** with aminoacetaldehyde diethyl acetal in refluxing toluene afforded the crude enamine **9a** as a mixture (8:2) of isomers by ^{1}H nmr analysis. The configurations of these isomers (*E* and *Z*) were not assigned.

As an alternative approach to the enamine **9a** (Method B), it was found that 4-chlorophenyl(trifluoromethylsulfonyl)acetylene **13a** reacted readily with aminoacetaldehyde diethyl acetal in a Michael fashion at room temperature in ether to give the enamine as a 85:15 mixture of isomers. Either method afforded the same major configurational isomer. Several preparations of aryl(trifluoromethylsulfonyl)acetylenes **13** by the addition of triflic anhydride to metaloarylacetylenes have been reported [9-11].

After isolation, the crude enamines **9** [12] formed by either Method A or Method B were cyclized with trifluoroacetic acid at room temperature to afford the 2-aryl-3-trifluoromethylsulfonylpyrroles **2** (Scheme 3). As shown, the best yields of pyrroles were obtained for examples **2a,f** when the corresponding enamines **9a,f** were prepared *via* Method B from purified aryl(trifluoromethylsulfonyl)acetylenes **13a,f**. However the isolated purified yields of these acetylenes were low due to their thermal lability [9-11]. For pyrrole **2a**, the yield over the two steps from

Scheme 3



9a-f **2a-f**

		Overall yield of **2** (%)
a:	X = Cl	**a:** 45 [a], 46 [b], 93 [c]
b:	X = OCH_3	**b:** 14 [a]
c:	X = Br	**c:** 52 [b]
d:	X = $C(CH_3)_3$	**d:** 24 [b]
e:	X = CH_3	**e:** 34 [b]
f:	X = H	**f:** 67 [c]

[a] Overall yield from the α-trifluoromethylsulfonylacetophenone intermediates **11** from which the enamines **9** were prepared using Method A. [b] Overall yield from the arylacetylene intermediates **12** from which the enamines **9** were prepared using Method B. The aryl(trifluoromethylsulfonyl)acetylene intermediates **13** were not purified. [c] Overall yield from purified aryl(trifluoromethylsulfonyl)acetylenes **13** from which the enamines **9** were prepared using Method B.

purified **13a** was 93%, while the isolated purified yield of **13a** was only 35% from **12a** resulting in an overall yield of only 33%. When **2a** was prepared from **12a** without purification of intermediate **13a**, the overall yield was 46%. Consequently the pyrroles **2c-e** were prepared from the corresponding arylacetylenes **12c-e** without purification of the intermediate aryl(trifluoromethylsulfonyl)acetylenes **13c-e.**

EXPERIMENTAL

Melting points were determined using a Thomas Hoover apparatus and are uncorrected. The ^{1}H nmr and ^{19}F nmr spectra were determined on Varian Unity 300 or XL 300 Spectrometers at 300 MHz and 282 MHz respectively. The ^{1}H nmr chemical shifts were measured in ppm using deuterated solvents as internal standards and ^{19}F nmr shifts were measured in ppm using fluorotrichloromethane as an external standard. Infrared spectra were taken on a Perkin Elmer 1420 spectrometer. Microanalyses were performed by Microlit Laboratories, Caldwell, NJ.

Preparation of α-Trifluoromethylsulfonylacetophenones **11a-b** from Phenacyl Bromides **10a-b.**

4'-Chloro-2-[(trifluoromethyl)sulfonyl]acetophenone (**11a**).

A stirred solution of 4-chlorophenacyl bromide **10a** (23.73 g, 0.102 mole), potassium trifluoromethanesulfinate (17.5 g, 0.102 mole) and potassium iodide (0.84 g, 0.0051 mole) in 225 ml of acetonitrile was heated at reflux. After 2 days the reaction was concentrated *in vacuo,* water was added and the mixture extracted with ethyl acetate. The organic layer was separated, washed with brine, dried over magnesium sulfate and concentrated *in vacuo* to afford a yellow solid. Recrystallization from ethyl acetate-hexanes gave **11a** as a white solid, 10.4 g (35%). Concentration of the mother liquor followed by flash chromatography of the residue on silica gel (elution with 1:10 ethyl acetate-hexanes) afforded an additional 5.6 g (20%) of **11a**. The total yield of **11a** was 16.0 g (55%), mp 120-121°; ^{1}H nmr (deuteriochloroform): δ 4.82 (s, 2, CH_2), 7.52-7.94 (2d, 4, aryl); ^{19}F nmr (deuteriochloroform): δ -77.30 (s, SO_2CF_3); ir (thin film): 3058, 2941, 1692, 1587 cm^{-1}.

Anal. Calcd. for $C_9H_6ClF_3O_3S$: C, 37.71; H, 2.11. Found: C, 37.84; H, 2.09.

4'-Methoxy-2-[(trifluoromethyl)sulfonyl]acetophenone (**11b**).

A stirred solution of 4-methoxyphenacyl bromide **10b** (1.5 g, 0.0065 mole) and potassium trifluoromethanesulfinate (1.35 g, 0.0079 mole) in 15 ml of dimethylacetamide was heated at 50°. After 20 hours the reaction was cooled to room temperature, diluted with ether, washed with water, brine dried over magnesium sulfate and concentrated *in vacuo* to afford a yellow-brown solid. Flash chromatography on silica gel (elution with 1:4 ethyl acetate-hexanes) yielded **11b** a yellow solid, 0.92 g (50%). Analytically pure material was obtained by recrystallization from methanol, mp 91-93°; ^{1}H nmr (deuteriochloroform): δ 3.90 (s, 3, OCH_3), 4.79 (s, 2, CH_2), 7.0 and 7.94 (2d, 4, aryl); ^{19}F nmr (deuteriochloroform): δ -77.48 (s, SO_2CF_3); ir (nujol): 1660, 1590 cm^{-1}.

Anal. Calcd. for $C_{10}H_9F_3O_4S$: C, 42.56; H, 3.21. Found: C, 42.43; H, 3.15.

Preparation of Pyrroles **2a-b**. Conversion of **11a-b** to **9a-b** (Method A) and Subsequent Cyclization to Pyrroles **2a-b**.

2-(*p*-Chlorophenyl)-3-[(trifluoromethyl)sulfonyl]pyrrole (**2a**).

A solution of **11a** (15.9 g, 0.056 mole) and aminoacetaldehyde diethyl acetal (7.39 g, 0.056 mole) in 160 ml of toluene was heated at reflux with removal of water. After 20 hours the reaction was concentrated *in vacuo* to afford crude **9a** as a dark residue consisting of a 85:15 mixture of configurational isomers as determined by ^{1}H nmr analysis; ^{1}H nmr (deuteriochloroform): δ 1.28 (t, 6, methyl protons of the two ethoxy groups), 3.09 (major isomer) and 3.25 (minor isomer) (2t, 4, methylene protons of the ethyleneacetal), 3.4-3.6 (m, 4, methylene protons of the two ethoxy groups), 4.33 (major isomer) and 4.65 (minor isomer) (2t, 1, methine proton of the acetal carbon), 4.43 (major isomer) and 4.85 (minor isomer) (2s, 1, enamine β proton), 7.0-7.4 (m, 4, aryl). The crude **9a** was cooled with an ice-water bath and treated with trifluoroacetic acid (75 ml). After 10 minutes the cooling bath was removed and stirring continued for an additional 3 hours at room temperature. The reaction mixture was concentrated *in vacuo* to afford a dark residue. Flash chromatography on silica gel (elution with 1:2 ethyl acetate-hexanes) yielded 7.75 g (45%) of **2a** as a waxy solid. Recrystallization from 1,2-dichloroethane-hexanes afforded analytically pure **2a** as beige crystals, mp 92-95°; ^{1}H nmr (DMSO-d_6): δ 6.71 (d, 1, 4-H), 7.23 (d, 1, 5-H), 7.54 (s, 4, aryl); ^{19}F nmr (DMSO-d_6): δ -79.35 (s, SO_2CF_3); ir (thin film): 3355, 1538, 1426, 1350 cm^{-1}.

Anal. Calcd. for $C_{11}H_7ClF_3NO_2S$: C, 42.66; H, 2.28; N, 4.52. Found: C, 42.96; H, 2.07; N, 4.38.

2-(*p*-Methoxyphenyl)-3-[(trifluoromethyl)sulfonyl]pyrrole (**2b**).

Compound **2b** was prepared following a procedure similar to the preparation of **2a** but using **11b** (6.0 g, 0.021 mole). Flash chromatography on silica gel (elution with 3:7 ethyl acetate-heptane) gave **2b** as yellow crystals, 0.88 g (14%), mp 138-140°; ^{1}H nmr (DMSO-d_6): δ 6.64 (d, 1, 4-H), 7.12 (d, 1, 5-H), 7.0 and 7.45 (2d, 4, aryl); ^{19}F nmr (DMSO-d_6): δ -76.16 (s, SO_2CF_3); ir (nujol): 3390, 1492, 1170 cm^{-1}.

Anal. Calcd. for $C_{12}H_{10}F_3NO_3S$: C, 47.21; H, 3.30; N, 4.59; S, 10.50. Found: C, 47.12; H, 2.97; N, 4.43; S, 10.56.

Preparation of Aryl(trifluoromethylsulfonyl)acetylenes **13a,f** from Arylacetylenes **12a,f.**

p-Chlorophenyl(trifluoromethylsulfonyl)acetylene (**13a**).

To a stirred solution of *n*-BuLi (29.3 ml of a 2.5 *M* solution in hexanes, 0.073 mole) in 200 ml of ether cooled to -78° was added a solution of *p*-chlorophenylacetylene **12a** (10.0 g, 0.073 mole) in 100 ml of ether dropwise over a period of 45 minutes. After stirring for 1 hour at -78°, this solution was cannulated over a period of 20 minutes into a solution of triflic anhydride (20.66 g, 0.073 mole) in 300 ml of ether cooled to -78°. After stirring for 45 minutes at -78° and an additional 1 hour at room temperature, the reaction mixture was washed with water, brine, dried over magnesium sulfate and concentrated *in vacuo* to afford 17.3 g of a dark syrup. Flash chromatography on silica gel (elution with 1:100 ether-hexanes) yielded **13a** as a yellow solid, 6.9 g (35%), mp 37-45°; ^{1}H nmr (deuteriochloroform): δ 7.47 and 7.63 (2d, 4, aryl); ^{19}F nmr (deuteriochloroform): δ -77.92 (s, SO_2CF_3). This material was stored under nitrogen at -10° to avoid decomposition.

Phenyl(trifluoromethylsulfonyl)acetylene (**13f**).

Compound **13f** was prepared following a procedure similar to the preparation of **13a**, but using **12f** (6.13 g, 0.060 mole). Flash chromatography on silica gel (elution with hexanes then 5:95 ether-hexanes) gave **13f** as a yellow solid, 2.50 g (18%), mp 26-30° (lit mp 31° [10]).

Preparation of Pyrroles **2a,f**. Conversion of Purified **13a,f** to Enamines **9a,f** (Method B) and Subsequent Cyclization to Pyrroles **2a,f**.

2-(Phenyl)-3-[(trifluoromethyl)sulfonyl]pyrrole (**2f**).

A solution of phenyl(trifluoromethylsulfonyl)acetylene **13f** (2.43 g, 0.0104 mole) and aminoacetaldehyde diethyl acetal (1.38 g, 0.0104 mole) in 25 ml of ether was stirred overnight at room temperature. The reaction mixture was concentrated *in vacuo* to afford crude **9f** as a red syrup. This crude product was cooled with an ice-water bath and treated with trifluoroacetic acid (15 ml). After stirring 10 minutes the cooling bath was removed and stirring continued overnight at room temperature. The reaction mixture was concentrated *in vacuo* to afford a dark residue. Flash chromatography on silica gel (elution with 1:4 ethyl acetate-hexanes) yielded **2f** as a tan solid, 1.65 g (67%), mp 116-118°; ^{1}H nmr (DMSO-d_6): δ 6.80 (d, 1, 4-H), 7.17 (d, 1, 5-H), 7.4-7.55 (4, aryl); ^{19}F nmr (DMSO-d_6): δ -76.17 (s, SO_2CF_3); ir (nujol): 3300, 1610, 1560 cm^{-1}.

Anal. Calcd. for $C_{11}H_8F_3NO_2S$: C, 48.00; H, 2.93; N, 5.09; S, 11.65. Found: C, 47.83; H, 2.91; N, 5.11; S, 11.88.

2-(*p*-Chlorophenyl)-3-[(trifluoromethyl)sulfonyl]pyrrole (**2a**).

Compound **2a** was prepared following a procedure similar to the preparation of **2f** but using **13a** (2.92 g, 0.0109 mole). Flash chromatography on silica gel (elution with 1:2 ethyl acetate-hexanes) gave **2a** as a tan solid, 3.13 g (93%), identical to **2a** prepared above.

Preparation of Pyrroles **2c-e**. Conversion of **12c-e** to **13c-e, 13c-e** to Enamines **9c-e** (Method B) and Subsequent Cyclization to Pyrroles **2c-e**.

2-(*p*-Bromophenyl)-3-[(trifluoromethyl)sulfonyl]pyrrole (**2c**).

To a stirred solution of *n*-BuLi (8.84 ml of a 2.5 *M* solution in hexanes, 0.0221 mole) in 100 ml of ether cooled to -78° was added a solution of *p*-bromophenylacetylene **12c** (4.0 g, 0.0221 mole) in 50 ml of ether. After stirring for 1 hour at -78°, this solution was cannulated over a period of 10 minutes into a solution of triflic anhydride (6.23 g, 0.0221 mole) in 100 ml of ether cooled to -78°. After stirring for 1 hour at -78° and an additional 1 hour at room temperature, the reaction mixture was washed with water, brine, dried over magnesium sulfate and concentrated *in vacuo* to give crude **13c** as a dark residue; ^{1}H nmr (deuteriochloroform): δ 7.49 and 7.55 (2d, 4, aryl); ^{19}F nmr (deuteriochloroform): δ -80.61 (s, SO_2CF_3). The crude **13c** was dissolved in ether (50 ml), cooled with an ice-water bath and treated with aminoacetaldehyde diethyl acetal (2.70 g, 0.0203 mole). After stirring overnight at room temperature the reaction was concentrated *in vacuo* to afford crude **9c**. This material was cooled with an ice-water bath and treated with trifluoroacetic acid (20 ml). After 10 minutes the cooling bath was removed and stirring continued for an additional 5 hours at room temperature. The mixture was concentrated *in vacuo* to afford a dark residue. Flash chromatography on silica gel (elution with 3:7 ethyl acetate-hexanes) yielded **2c** as a tan solid,

4.10 g (52%), mp 87-89°; ^{1}H nmr (deuteriochloroform): δ 6.64 (t, 1, 4-H), 6.85 (t, 1, 5-H), 7.31 and 7.46 (2d, 4, aryl); ^{19}F nmr (deuteriochloroform): δ -80.70; ir (nujol): 3390, 1592, 1212, 1176, 1125 cm^{-1}.

Anal. Calcd. for $C_{11}H_7BrF_3NO_2S$: C, 37.31; H, 1.99; N, 3.96; S, 9.05. Found: C, 37.55; H, 1.64; N, 3.79; S, 8.95.

2-(*p*-*t*-Butylphenyl)-3-[(trifluoromethyl)sulfonyl]pyrrole (**2d**).

Compound **2d** was prepared following a procedure similar to the preparation of **2c**, but using **12d** (7.0 g, 0.044 mole). Flash chromatography on silica gel (elution with 3:7 ethyl acetate-hexanes) gave **2d** as a tan solid, 3.6 g (24%), mp 116-118°; ^{1}H nmr (deuteriochloroform): δ 1.29 (s, 9, *t*-butyl), 6.67 (t, 1, 4-H), 6.80 (t, 1, 5-H), 7.36-7.43 (4, aryl), 9.05 (bs, 1, NH); ^{19}F nmr (deuteriochloroform): δ -80.71 (s, SO_2CF_3); ir (nujol): 3390, 1350, 1225, 1110 cm^{-1}.

Anal. Calcd. for $C_{15}H_{16}F_3NO_2S$: C, 54.37; H, 4.87; N, 4.23; S, 9.68. Found: C, 54.37; H, 4.88; N, 4.04; S, 9.98.

2-(*p*-Methylphenyl)-3-[(trifluoromethyl)sulfonyl]pyrrole (**2e**).

Compound **2e** was prepared following a procedure similar to the preparation of **2c**, but using **12e** (10.3 g, 0.0887 mole). Flash chromatography on silica gel (elution with 3:7 ethyl acetate-hexanes) gave **2e** as a tan solid, 8.80 g (34%), mp 101-103°; ^{1}H nmr (deuteriochloroform): δ 2.33 (s, 3, CH_3), 6.66 (t, 1, 4-H), 6.80 (t, 1, 5-H), 7.15 and 7.34 (2d, 4, aryl), 9.1 (bs, 1, NH); ^{19}F nmr (deuteriochloroform): δ -80.75 (s, SO_2CF_3).

Anal. Calcd. for $C_{12}H_{10}F_3NO_2S$: C, 49.83; H, 3.48; N, 4.84; S, 11.08. Found: C, 49.71; H, 3.29; N, 4.67; S, 11.26.

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[12] Attempts to purify the crude enamine syrups **9** *via* flash chromatography were unsuccessful.