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The Synthesis of Pyrroles with Insecticidal Activity*

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Abstract: The 2-aryl-4-bromo-5-trifluoromethylpyrrole-3-carbonitriles represent a new class of insect control agents. The high insectidical activity observed in this series prompted us to investigate the preparation of regioisomeric arylhalotrifluoromethylpyrrole carbonitriles. The synthesis and biological activity of eight of the twelve possible regioisomers are described and discussed.

1 INTRODUCTION

As part of a program utilizing natural products as templates for the design of new insect control agents, our attention was drawn to the discovery of the insecticidal activity of a fermentation broth derived from a strain of *Streptomyces* spp. Isolation of the active component was accomplished by Carter *et al.* at Lederle Laboratories in 1987.[1] The compound, named dioxapyrrolomycin, was shown to have the structure **1** (Fig. 1).

Early work in this series, centered on preparing less complex analogs of **1** that retained insecticidal activity,[2,3] indicated that the dihalo aryl pyrrole nucleus was necessary for good biological activity. At the same time, it was found that replacement of the nitro substituent by cyano still provided pyrroles with good insecticidal activity.

With these data in hand, work was directed toward replacing one or both of the halogens on the pyrrole nucleus in an effort to enhance the biological profile. One substituent that was of particular interest was the trifluoromethyl (CF_3) group. This group, considered a 'pseudo-halogen', has often been found to impart unique biological activity.[4] This work culminated in an efficient synthesis of the 2-aryl-4-halo-5-trifluoromethylpyrrole-3-carbonitrile nucleus,[5] and yielded compounds which were found to be more active as insecticides than the corresponding 4,5-di-halo compounds.

This report details our effort to prepare eight of the possible twelve regioisomeric aryl halo trifluoromethyl pyrrole carbonitriles, whose general structure is shown in Fig. 2, and presents a comparison of their insecticidal activities.

2 EXPERIMENTAL

2.1 General

All melting points are uncorrected. The [^{1}H]NMR spectra were determined on either a Varian XL300, a Varian Unity 300 or a Varian EM360L spectrometer. [^{19}F] Spectra were obtained on the XL300 or Unity 300 instruments. Microanalyses were performed by Microlit Laboratories (North Caldwell, NJ).

All solvents were stored over 3Å or 4Å molecular sieves or 'THE'® desiccant prior to use.

2.2 Synthesis

The experimental procedures for the synthesis of the target compounds, and some of the intermediates are described below, and reaction pathways are given in Figs 3–9.

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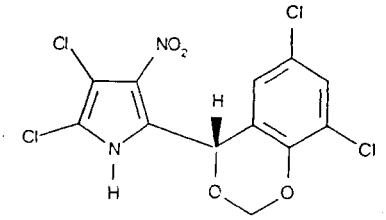

Fig. 1. Structure of dioxapyrrolomycin I.

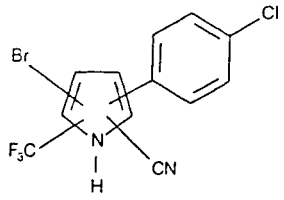

Fig. 2. General structure for the trifluoromethylpyrrolecarbonitriles.

2.2.1 2-(4-Chlorophenyl)-5-trifluoromethylpyrrole-3-carbonitrile (**4**)

To a mixture of 4-(4-chlorophenyl)-2-trifluoromethyl-3-oxazolin-5-one, (**3**; 20·6 g; 0·078 mol) and α-chloroacrylonitrile (6·2 ml, 0·078 mol) in acetonitrile (150 ml) was added triethylamine (8·07 g, 0·080 mol) dropwise, causing the temperature to rise to 50°C. The reaction mixture was then heated at reflux for 10 min, cooled to room temperature and then to 0°C (ice/water bath). The resulting solid was removed by filtration, washed with water and dried to give the product (12·53 g, 59 %); m.p. 238–241°C (dec); [^{1}H]NMR (hexadeuterodimethylsulfoxide) δ 7·30 (s, 1H), 7·64–7·84 (ABq, 4H); [^{19}F]NMR δ-54·5 (s).

2.2.2 4-Bromo-2-(4-chlorophenyl)-5-trifluoromethylpyrrole-3-carbonitrile (**5**)

A mixture of **4**(5·4 g, 0·02 mol) and anhydrous sodium acetate (1·97 g, 0·024 mol) in glacial acetic acid (100 ml) was warmed to 90°C. A solution of bromine (6·4 g, 0·04 mol) in acetic acid (10 ml) was added dropwise and the mixture was heated at reflux for 2 h, cooled to room temperature and poured into water (20 ml). The resulting off-white solid was removed by filtration, washed with water and dried under vacuum at 60°C to give **5** (6·56 g, 94 %); m.p. 247–250°C (dec); [^{1}H]NMR (hexadeuterodimethylsulfoxide) δ 7·5–7·7 (ABq); [^{19}F]NMR δ-54·30 (s).

2.2.3 2-(4-Chlorophenyl)-4-trifluoromethylpyrrole-3-carbonitrile (**7**)

Sodium hydride (0·28 g of 60 % mineral oil dispersion, 0·007 mol) was added to a mixture of dimethoxyethane (15 ml) and dimethyl sulfoxide (5·5 ml). A solution of methyl 4-chloro-*N*-[(phenylsulfonyl)methyl]-thiobenzimidate, (**6**; 1·0 g, 0·0029 mol) and 4,4,4-trifluorocrotononitrile[6] (0·38 g, 0·0037 mol) in dimethoxyethane (20 ml) was added dropwise with stirring and cooling to maintain the temperature below 30°C. The mixture was stirred for 90 min, poured into water (100 ml), acidified with 6M hydrochloric acid, cooled and filtered. The solid was dissolved in ether and the solution was dried with magnesium sulfate. After removal of the solvent under reduced pressure, the residue was stirred in methylene chloride and filtered to obtain **7** as a solid (0·4 g, 51 %); m.p. 225–228°C; [^{1}H]NMR (hexadeuterodimethylsulfoxide) δ 7·6–7·8 (ABq, 4H), 7·7 (s, 1H).

2.2.4 Trimethylsilylmethylisothiocyanate (**8**)[7]

Sodium azide (19·5 g, 0·3 mol) was added to a solution of trimethylsilylmethyl chloride (41·0 ml, 0·3 mol) and 18-crown-6 (4·0 g, 0·015 mol) in acetonitrile (300 ml) and the suspension was heated at reflux for 20 h. The mixture was cooled to −5°C, the solids were removed by filtration and washed with acetonitrile (100 ml) and the combined filtrates were used without further purification. Triphenylphosphine (78·6 g, 0·3 mol) in carbon disulfide (72·1 ml, 1·2 mol) was added rapidly to the acetonitrile solution of (trimethylsilyl)methyl azide prepared above. Nitrogen was evolved, and as the evolution began to subside, the mixture was heated at reflux for 2 h. The solution was cooled to room temperature and the solvent removed under reduced pressure. The resulting semi-solid residue was slurried in warm hexane and filtered. The filtrate was evaporated under reduced pressure. Distillation of the resulting oil gave **8** as a clear liquid, b.p. $_{(0\cdot15\ mm)}$ 52–55°C; [^{1}H]NMR, (deuterochloroform) δ 0·16 (s, 9H), 2·96 (s, 2H).

2.2.5 S-Methyl-N-(trimethylsilyl)methyl-4-chlorobenzenethioimidate (**9**)

A solution of 4-chlorophenylmagnesium bromide in ether (1 M, 200 ml) was added dropwise to tetrahydrofuran (100 ml) at 0°C, causing a precipitate to form. The mixture was allowed to warm to room temperature and a solution of the isothiocyanate, **8**, (21·8, 0·15 mol) in tetrahydrofuran (75 ml) was added dropwise over 40 min. The solution was stirred for a further 2 h at room temperature and warmed at 45°C for additional 2 h. On cooling to 5°C, a solid formed. A solution of methyl iodide (13 ml, 0·2 mol) in tetrahydrofuran (40 ml) was added dropwise over 20 min and the reaction mixture was allowed to reach ambient temperature and was then stirred for 16 h. The resulting thick suspension was cooled to 5°C and filtered. The solid was washed with tetrahydrofuran and the combined filtrate was evaporated under reduced pressure to give a viscous oil. The oil was partitioned between ether and water and the water layer was extracted with fresh ether. The

combined ether extracts were dried with magnesium sulfate and the solvent removed under pressure to leave a yellow oil. Bulb-to-bulb distillation gave a pale yellow oil, **9**; b.p.$_{(0\cdot2\ mm)}$ 90–110°C; [^{1}H]NMR, (deuterochloroform) δ 0·003 & 0·123 (2s, 9H total), 2·07 & 2·38 (2s, 3H total); 3·16 & 3.64 (2s, 2H total); 7·19–7·47 (m, 4H total).

2.2.6 2-(4-Chlorophenyl)-3-trifluoromethylpyrrole (**10**)

Under nitrogen, **9** (5·4 g, 0·02 mol) was added to hexamethylphosphoric triamide (HMPA, 20 ml), followed by 2-bromo-3,3,3-trifluoropropene[8] (11·2 g, 0·06 mol) in HMPA (20 ml). Water (1·1 ml, 0·06 mol) was added in a single portion followed by additional HMPA (5 ml). The resulting clear solution was stirred at room temperature for 30 min and warmed to 45°C after which the temperature was allowed to drop to 30°C and heating was resumed. At 60°C, an exothermic reaction occurred causing the temperature to rise to 75°C. The mixture was allowed to cool to room temperature and was stirred for a further 18 h. HPLC analysis of the reaction mixture indicated partial reaction. Additional **9** (10·8 g, 0·04 mol) was added and the mixture was heated at 110°C for 18 h. After cooling to room temperature, the reaction mixture was poured into ice + water and extracted with ether. The combined extracts were washed with water, dried over magnesium sulfate and the ether removed under reduced pressure to leave a dark amber oil. Chromatography using dichloromethane + ethyl acetate (49 + 1 by volume) gave the product, **10**, as an oil (1·4 g, 29 %) that decomposed when stored at room temperature; [^{1}H]NMR (deuterochloroform) δ 6·6 (1s, 1H), 7·1 (s, 1H), 7·4 (s, 4H).

2.2.7 5-(4-Chlorophenyl)-4-trifluoromethylpyrrole-2-carbonitrile (**11**)

Under nitrogen, **10** (1·8 g, 0·0075 mol) was dissolved in acetonitrile (8 ml) and the solution was cooled to 10°C. A solution of chlorosulfonyl isocyanate (1·0 ml, 0·011 mol) in acetonitrile (4 ml) was added dropwise, causing a slight exotherm. The ice bath was removed and the reaction mixture was stirred at ambient temperature for 3 h. The solution was cooled to 10°C and *N*,*N*-dimethylformamide (1 ml) was added dropwise. After the resulting exotherm had subsided, the solution was allowed to stir at room temperature for 30 min then warmed briefly to 50°C. The reaction mixture was stirred at room temperature for a further 18 h and then poured onto ice/water. The resulting pink solid was removed by filtration, washed with water and air-dried. Recrystallization from 1,2-dichloroethane gave **11** as a white solid (1·5 g, 57 %) m.p. 208–211°C; [^{1}H]NMR (deuteroacetone) δ 7·05 (s, 1H); 7·4–7·8 (m, 4H); [^{19}F]NMR δ-54·20.

2.2.8 2-(4-Chlorophenyl)-4-trifluoromethylpyrrole (**13**)

Under nitrogen, water (1·1 ml, 0·06 mol) was added in a single portion to solution of **9** (4·7 g, 0·02 mol) and 1-phenylsulfonyl-3,3,3-trifluoropropene (**12**) (5·4 g, 0·02 mol) in HMPA (20 ml). The reaction mixture was heated at 100°C for 18 h. After cooling to room temperature, the reaction mixture was poured onto ice + water and extracted with small portions of ether. The combined ether extract was washed repeatedly with water and then with brine. Removal of the solvent followed by chromatography using hexane + ethyl acetate (8 + 1 by volume) gave **13** as a clear oil (1·5 g, 28 %) that discolored on standing at room temperature; [^{1}H]NMR (deuterochloroform) δ 6·5 (m, 1H), 6·7 (m, 1H), 7·3–7·5 (ABq, 4H), 8·9 (br, s, 1H); [^{19}F]NMR δ-60·0.

2.2.9 3-Bromo-5-(4-chlorophenyl)-4-trifluoromethylpyrrole-2-carbonitrile (**14**)

A solution of **11** (1·35 g, 0·005 mol) in tetrahydrofuran (15 ml) under nitrogen, was cooled in an ice/acetone bath. *N*-Bromosuccinimide (NBS; 0·9 g, 0·005 mol) was added in portions. The reaction mixture was stirred cold for 30 min and then warmed to room temperature. After stirring at room temperature for 18 h, additional NBS (0·45 g, 0·0025 mol) was added over 4 h. The mixture was heated briefly at reflux then stirred at ambient temperature for 18 h. The solvent was removed under reduced pressure and the residue poured onto ice/water. The resulting solid was removed by filtration, washed with water and air-dried. Recrystallization from methyl cyclohexane gave **14** as a solid (0·6 g, 34 %); m.p. 85–190°C; [^{1}H]NMR (deuteroacetone) δ 7·6–7·9 (m).

2.2.10 2-(4-Chlorophenyl)-3-trifluoromethyl-1-pyrroline-4-carbonitrile (**16**)

Tetrahydrofuran (20 ml) was cooled to −5°C and **9** (2·7 g, 0·01 mol) and 2-bromo-4,4,4-trifluorocrotononitrile (**15**; 2·0 g, 0·01 mol) were added sequentially. A solution of tetrabutylammonium fluoride (1M in THF, 1 ml, 0·001 mol) was added dropwise over 15 min. The red reaction mixture was stirred at −5°C for 1 h then at ambient temperature for 18 h. The solution was heated briefly to reflux, cooled and filtered, the solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and water. The aqueous phase was extracted twice with ethyl acetate and the combined organic layers were washed with water and brine, dried over magnesium sulfate and the solvent evaporated under reduced pressure. Chromatography using hexane + ethyl acetate (8 + 1 by volume) gave the pyrroline (0·26 g, 10 %); m.p. 171–173°C; [^{1}H]NMR (deuteroacetone) δ 3·7–4·2 (m, 4H), 7·5–7·8 (m, 4H); [^{19}F]NMR δ-69·34 (d).

2.2.11 3-(4-Chlorophenyl)-1,1,1-trifluorohex-5-en-2-one (**18**)

A solution of 3-(4-chlorophenyl)-1,1,1-trifluoro-2-propanone (**17**; 9·5 g, 0·043 mol) in tetrahydrofuran (75 ml) was added dropwise to a 1·5 M solution (30 ml, 0·045 mol) of commercial lithium diisopropylamide in tetrahydrofuran (100 ml) maintained at −78°C. After stirring for 1 h, a solution of allyl iodide (7·6 g, 0·045 mol) in tetrahydrofuran (100 ml) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 2 h and then for a further 20 h at reflux, cooled and the solvent removed under reduced pressure. The residue was partitioned between ethyl acetate and water and the organic layer was washed with brine and dried with magnesium sulfate. Evaporation under reduced pressure gave a brown oil. Flash chromatography using hexane + ethyl acetate (6 + 1 by volume) gave **18** as a light yellow oil (9·8 g, 87 %); [^{1}H]NMR (hexadeuterodimethylsulfoxide) δ 2·46–2·85 (m, 2H), 4·53 (t, 1H), 4·95–5·02 (m, 2H) 5·50–5·69 (m, 1H), 7·29–7·46 (AB, 4H); [^{19}F]NMR δ −70·94.

2.2.12 3-(4-Chlorophenyl)-2-trifluoromethylpyrrole (**20**)

A solution of **18** (10·0 g, 0·039 mol) in methanol + methylene chloride (1 + 1 by volume, 300 ml) was cooled to −78°C and ozone was bubbled through the reaction mixture *via* a gas dispersion tube until the blue color persisted, after which nitrogen was passed into the reaction mixture until the color was discharged. Dimethylsulfide (5 ml) was then added dropwise and the mixture was allowed to warm to room temperature and stirred for 18 h. The solvent was removed under reduced pressure and the residue was partitioned between ether and water. The organic layer was washed sequentially with water and brine and the solvent was removed under reduced pressure to leave the keto aldehyde **19** (10·0 g) as a pale yellow oil. The oil was dissolved in acetic acid (70 ml) containing ammonium acetate (4 g, 0·05 mol) and the mixture was heated at 45–50°C for 3 h. After cooling to room temperature, the mixture was partitioned between ether and water and the aqueous phase extracted with additional ether. The combined organic layer was washed with saturated sodium hydrogen carbonate until neutral, then with brine, dried over magnesium sulfate and the solvent removed under reduced pressure. Purification of the residue by flash chromatography using hexane + ethyl acetate (5 + 1 by volume) gave **20** as a light red oil (4·2 g, 45 %); [^{1}H]NMR (hexadeuterodimethylsulfoxide) δ 6·36 (br s, 1H), 7·07 (t, 1H) 7·44 (ABq, 4H).

2.2.13 4-(4-Chlorophenyl)-5-trifluoromethylpyrrole-3-carbonitrile (**22**)

Potassium *tert*-butoxide (2·46 g, 0·022 mol) was added in portions to a solution of 3-(4-chlorophenyl)-1,1,1-trifluoro-2-propanone oxime (**21**; 4·25 g, 0·02 mol) in tetrahydrofuran (20 ml). The temperature was maintained at 25–30°C with occasional cooling. The resulting solution was stirred for 15 min and then added dropwise to a solution of β-chloroacrylonitrile (1·75 g, 0·02 mol) in tetrahydrofuran (15 ml) at 10–15°C, over 30 min. The cooling bath was removed and the reaction was stirred for 1 h, then diluted with water, acidified with dilute hydrochloric acid and extracted with ether. The ether extracts were washed with water and brine and dried with sodium sulfate. Evaporation of the solvent under reduced pressure left an oil which was dissolved in methylene chloride, filtered through a bed of silica gel and the filter pad washed with ethyl acetate + methylene chloride (1 + 1 by volume). The combined filtrates were evaporated and the resulting semi-solid was crystallized from methylene chloride–hexane to give the product as a yellow solid (2·1 g, 39 %); m.p. 162·5–164·0°C; [^{1}H]NMR (hexadeuterodimethylsulfoxide) δ 7·40–7·58 (q, 4H) 8·02 (s, 1H); [^{19}F]NMR δ −51·24.

*2.2.14 Ethyl 2-cyano-*N*-[2-(4-chlorobenzoyl)-1-trifluoromethyl]glycinate* (**24**)

Ethyl 2-cyanoglycinate[17] (5·0 g, 0·039 mol) and 1-(4-chlorophenyl)-4,4,4-trifluoro-1,3-butanedione (**23**; 8·0 g, 0·32 mol) in benzene (60 ml) were heated at reflux for 90 min. Water was removed with a Dean & Stark trap. The mixture was cooled to room temperature and the volume concentrated to about one-half, causing a precipitate to form. The product, **24**, was collected by filtration and washed with ether + light petroleum distillate (35 g, 25 %); m.p. 151–155°C; [^{1}H]NMR (hexadeuterodimethylsulfoxide) δ 1·1–1·4 (m, 3H), 3·4–3·7 (q, 2H), 3·9–4·1 (2s, 1H), 7·5–8·3 (m, 4H); [^{19}F]NMR δ −70·99 & −72·71.

2.2.15 3-(4-Chlorophenyl)-5-trifluoromethylpyrrole-2-carbonitrile (**25**)

A solution of **24** (3·0 g, 0·008 mol) in trifluoroacetic acid (70 ml) was heated at reflux for 2 h. The reaction mixture was cooled to room temperature and poured onto ice. The resulting solid was collected by filtration and washed with water and light petroleum distillate. Flash chromatography using hexane + ethyl acetate (5 + 1 by volume) gave the product, **25**, as a white solid (0·9 g, 42 %); m.p. 206–210°C; [^{1}H]NMR (hexadeuterodimethylsulfoxide) δ 7·23 (s, 1H) 7·5–7·9 (ABq, 4H); [^{19}F]NMR δ −52·48.

3 RESULTS AND DISCUSSION

3.1 Synthetic methods

For ease of comparison, the discussion is limited to the 4-chlorophenyl group as the aryl group and bromine as the halogen substituent.

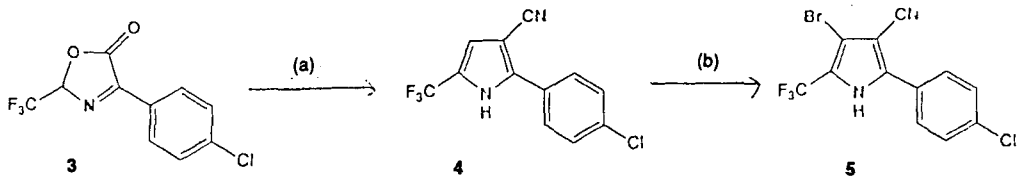

Fig. 3. (a) α-chloroacrylonitrile, $(C_2H_5)_3N$, (b) Br_2, NaOAc, acetic acid.

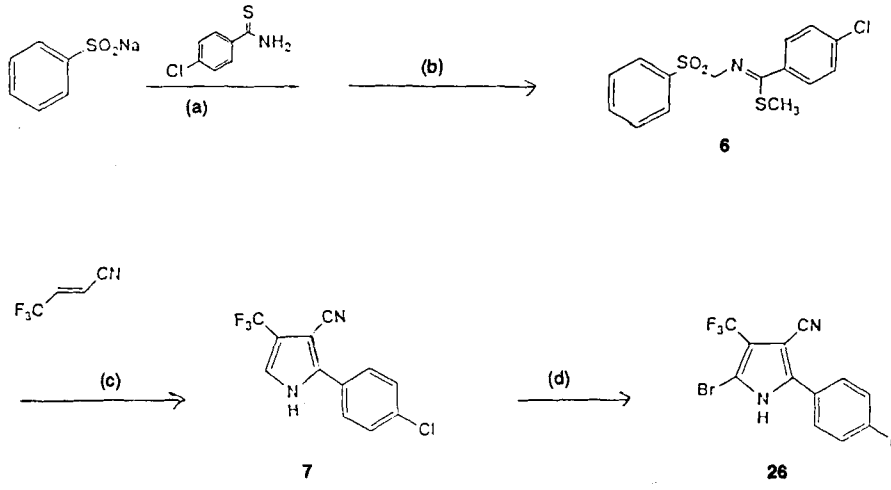

Fig. 4. (a) $(CH_2O)_n$, HCO_2H, H_2O; (b) $(CH_3)_3O^+ BF_4^-$, Proton Sponge®, methylene chloride; (c) NaH, dimethoxyethane, dimethyl sulfoxide; (d) Br_2, NaOAc, acetic acid.

While direct introduction of a trifluoromethyl group onto the pyrrole nucleus has previously been achieved, the examples have generally involved non-deactivated rings.[9,10] Therefore, because of the structural requirements of the regioisomers reported in this work, we developed novel synthetic routes to each member.

The synthesis of 4-bromo-2-(4-chlorophenyl)-5-trifluoromethylpyrrole-3-carbonitrile (**5**) is shown in Fig. 3.[5]

Treatment of 4-chlorophenylglycine with excess trifluoroacetic anhydride in refluxing toluene gave the oxazolinone **3**. Base-induced cycloaddition of **3** with α-chloroacrylonitrile gave 2-(4-chlorophenyl)-5-trifluoromethylpyrrole-3-carbonitrile, **4**, in excellent yield. This reaction was found to be regiospecific (no 4-cyano isomer was detected). Compound **4** was brominated using bromine and sodium acetate in warm acetic acid to give **5** in 80 % yield.

The synthesis of 5-bromo-2-(4-chlorophenyl)-4-trifluoromethylpyrrole-3-carbonitrile (**26**) was accomplished utilizing a variation of the desulfonylative cycloaddition chemistry developed by van Leusen and co-workers[6,11] (Fig. 4).

The synthon bearing the aryl group on one of the dipole carbons (**6**) was prepared by condensation of sodium benzenesulfinate with 4-chlorothiobenzamide in the presence of paraformaldehyde to give a thioamide; methylation on sulfur then gave the desired thioimidate **6** as a mixture of isomers.

The thioimidate **6** underwent smooth cycloaddition with 4,4,4-trifluorocrotononitrile in the presence of sodium hydride to give the pyrrole **7** in 51 % yield. Bromination at the 5-position then gave **26** in 93 % yield.

The preparation of isomers **14**, **27**, **28** involved a modification of the desilylative cycloaddition method for generating dipole partners developed by Achiwa *et al.*[12] and expanded upon by Tsuge *et al.*[7] The key intermediate, thioimidate **9**, was prepared using a modification of the procedure of Tsuge, *et al.*,[7] as shown in Fig. 5. The synthesis of **14**, **27** and **28** is shown in Fig. 6.

For the synthesis of **27**, the olefin of choice was 1-phenylsulfonyl-3,3,3-trifluoropropene **12**. This was prepared by condensation of the anion of methyl phenyl sulfone with ethyl trifluoroacetate to give the ketone, which was reduced with sodium borohydride in aqueous ethanol to the alcohol. Dehydration with methanesulfonyl chloride and triethylamine gave the olefin **12**.

Cycloaddition of the olefin **12** with the previously prepared silyl thioimidate **9** in HMPA containing two to three equivalents of water gave 2-(4-chlorophenyl)-4-trifluoromethylpyrrole (**13**). A nitrile group was introduced into the 2-position of the pyrrole using chlorosulfonyl isocyanate (CSI) and *N*,*N*-dimethylformamide (DMF),[13] and bromination then gave **27**.

Reaction of **9** with 2-bromo-3,3,3-trifluoropropene[8] in HMPA containing two to three equivalents of water gave 2-(4-chlorophenyl)-3-trifluoromethylpyrrole (**10**) in 29 % yield. Bromination gave the pyrrole **14**.

Finally, previous work from our laboratory had demonstrated that 2-bromo-4,4,4-trifluorocrotononitrile,

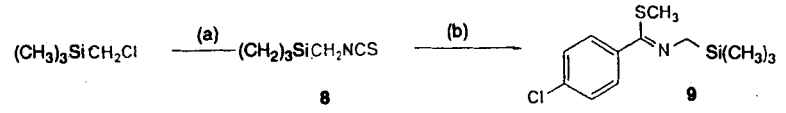

Fig. 5. (a) (1) NaN_3, 18-crown-6, (2) CS_2, $(C_6H_5)_3P$; (b) (1) 4-Cl-C_6H_4-CH_2MgBr, ether, hexane, (2) CH_3I, O°C.

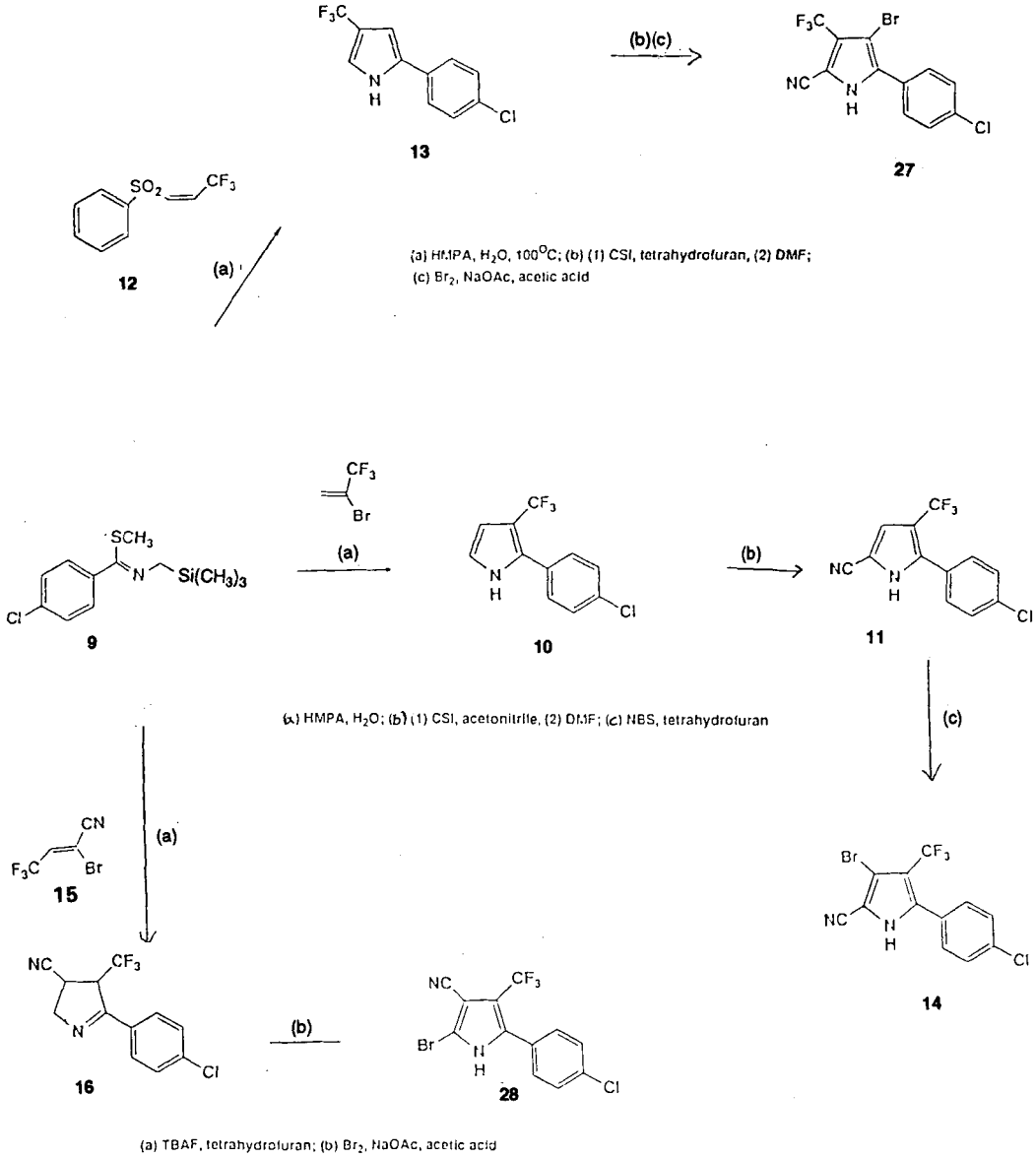

Fig. 6.

15, was an excellent partner for cycloaddition reactions.[5,14] This dipolarophile was used in the preparation of the 2-bromo-5-(4-chlorophenyl)-4-trifluoromethylpyrrole-3-carbonitrile isomer, **28**.

Cycloaddition of **15** with the thioimidate **9** using tetrabutylammonium fluoride (TBAF) and desilylation to generate the azadipole gave 2-(4-chlorophenyl)-3-trifluoromethyl-1-pyrroline-4-carbonitrile, **16**. This product could arise from the oxidative coupling of the methylsulfide by-product with concomitant reduction of the putative pyrrole to **16**. Bromination using the conditions described previously gave the desired isomer **28** in 27% yield.

The synthesis of 3-bromo-4-(4-chlorophenyl)-5-trifluoromethylpyrrole-2-carbonitrile (**29**) was accomplished using classical Paal–Knorr chemistry.[15] The synthesis began as shown in Fig. 7, with the condensation of the Grignard reagent derived from 4-chlorobenzylchloride with ethyl trifluoroacetate to give, after hydrolysis, the trifluoromethyl ketone **17**. Treatment of **17** with lithium diisopropylamide followed by allyl iodide gave **18** in 87% yield. Ozonolysis gave the unstable

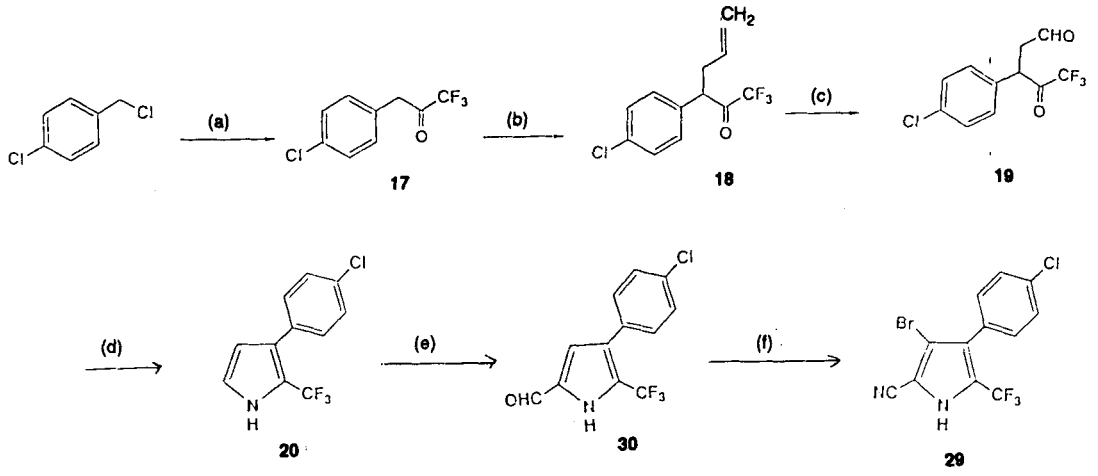

Fig. 7. (a) Mg, ether, (2) $CF_3CO_2C_2H_5$, (3) H_3O^+; (b) (1) LDA, tetrahydrofuran, (2) allyl iodide; (c) (1) O_3, methanol, methylene chloride, 0°C, (2) $(CH_3)_2S$; (d) NH_4OAc, acetic acid; (e) (1) $POCl_3$, DMF, (f) (1) H_2NOSO_3H, ethanol, water; (2) NBS, tetrahydrofuran.

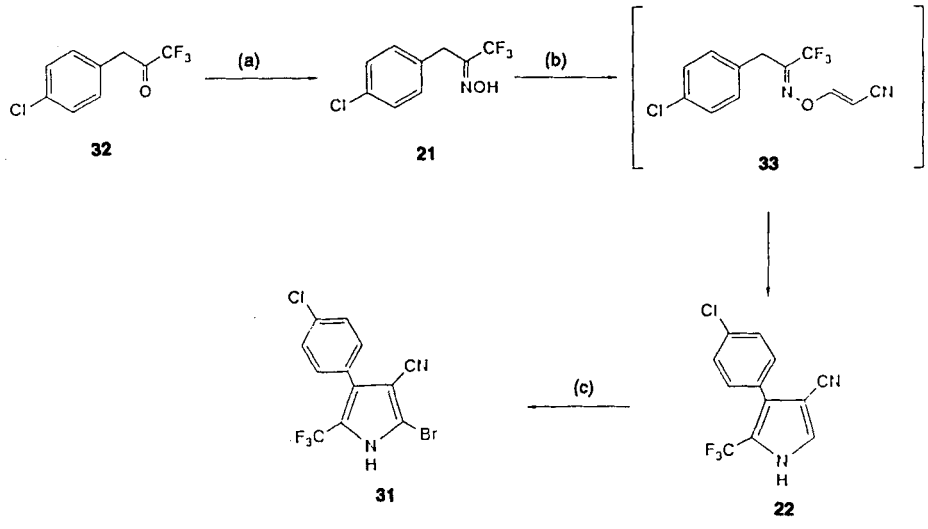

Fig. 8. (a) $NH_2OH \cdot HCl$, NaOAc, ethanol, water; (b) 2-chloroacrylonitrile, $(CH_3)_3COK$, tetrahydrofuran; (c) NBS, tetrahydrofuran.

keto-aldehyde **19**, which was cyclized directly using ammonium acetate to give the pyrrole **20** in 45 % yield from the ketone **17**.

Attempts to cyanate **20** directly using the conditions described earlier (i.e. chlorosulfonylisocyanate/DMF) resulted in a complex mixture of products. Therefore milder conditions were developed for the introduction of the nitrile group. The pyrrole **20** under Vilsmeier conditions gave the aldehyde **30** exclusively (53 %). Treatment of **30** with hydroxylamine *O*-sulfonic acid then gave the 2-cyanopyrrole in excellent yield; this was brominated using NBS to give **29** in 75 % isolated yield.

The rearrangement of *O*-vinyl oximes, as reported by Sheradsky[16] represents a potentially useful route to highly substituted pyrroles. This chemistry was utilized in the preparation of 2-bromo-4-(4-chlorophenyl)-5-trifluoromethylpyrrole-3-carbonitrile (**31**), Fig. 8.

The oxime **21** was prepared from the ketone **32** and hydroxylamine hydrochloride. Reaction of **21** with β-chloroacrylonitrile in the presence of potassium *tert*-butoxide gave the pyrrole, **22**, directly in 39 % yield from the putative intermediate *O*-vinyl oxime. The final product, **31**, was prepared in 75 % yield by bromination of **22** with NBS.

The Knorr pyrrole synthesis was the basis for the preparation of 4-bromo-3-(4-chlorophenyl)-5-trifluoromethylpyrrole-2-carbonitrile, **34**, (Fig. 9). Condensation of the β-diketone **23** (derived from the corresponding acetophenone and ethyl trifluoroacetate) with ethyl cyanoglycinate[17] gave the keto enamine **24** as a mixture of *E* and *Z* isomers (as shown by [^{19}F] and [^{1}H]NMR). Trifluoroacetic acid-promoted cyclization of **24** gave the cyano pyrrole **25** exclusively. Bromination using *N*-bromosuccinimide then gave the pyrrole isomer **34** in 25 % yield.

3.2 Biological activity

The compounds were screened against third-instar southern armyworms *Spodoptera eridania* (Cramer) and

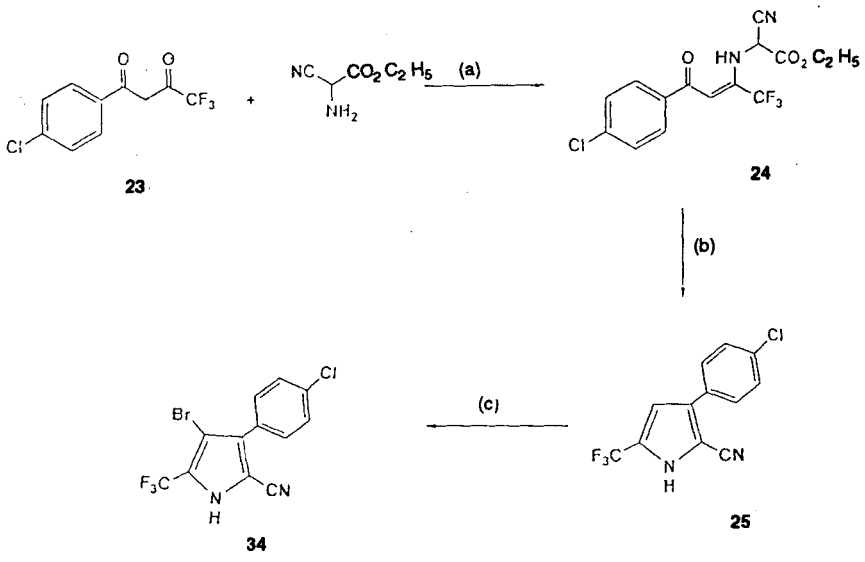

Fig. 9. (a) benzene, △; (b) CF_3CO_2H, △; (c) NBS, tetrahydrofuran.

TABLE 1
Percentage Mortality with Candidate Compounds

Compound No.[a,b]	*Southern armyworm* Spodoptera eridania *3rd-Instar*	*Tobacco budworm* Helicoverpa virescens *3rd-Instar*
5	100	100
26	100	0
14	0	0
27	100	0
28	0	0
29	0	0
34	100	0
31	0	0

[a] For structural formulae see Figs 3–9.
[b] Compounds were used at 10 mg litre^{-1}.

third-instar tobacco budworms *Helicoverpa virescens* (F) using a standard leaf dip bioassay with technical material. Results are presented as percent mortality determined at the specified dose, in Table I. As can be seen none of the isomers was as active as the lead compound **5**.

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