JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY

*J. Agric. Food Chem.* **2007,** *55,* 7517−7526 **7517**

# Structure−Activity Relationship Development of Dihaloaryl Triazole Compounds as Insecticides and Acaricides. 1. Phenyl Thiophen-2-yl Triazoles

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An extended lipophilic system that incorporated some key elements of first-generation 2,6-dihaloaryl actives, such as **1**, demonstrated desirable efficacy against chewing insects as well as sap-feeding insects. These four-ring systems, based on **2**, were accessed primarily via Suzuki couplings of halothiophene derivatives with appropriately substituted boronic acids. In particular, phenylthiophene systems that incorporated haloxyether groups, such as those in **3**, **4**, and **5**, had the broadest spectrum of activity across chewing and sap-feeding insect pests. Expansion of this structure−activity relationship to include compounds with differing substitution patterns on the thiophene-C-ring and aryl-D-rings was undertaken. The synthesis and insecticidal activity of 3-aryl-5-(thiophen-2-yl)-1-methyl-1*H*-[1,2,4]triazoles will be described.

**KEYWORDS: Insecticides; 2,6-dihaloaryl triazoles; C-ring thiophenes; 2-substitution**

## INTRODUCTION

In recent years, there have been a number of patent applications related to 2,6-dihaloarylheterocycles (*1*−*9*). The key feature of these molecules is a 2,6-dihalogenated aryl A-ring attached to a central nitrogen-containing B-ring heterocycle (**Figure 1**). Early work at Dow AgroSciences (DAS) was initiated because of the interesting growth regulatory activity exhibited by an Ihara/Kumiai material, **6** (*7*, *8*). The unknown mode of action (MOA) and clean toxicity profile made this class of compounds worthy of pursual for potential leads. Progress toward this goal resulted in the discovery of **7**, a highly efficacious compound with activity against aphids (*10*), containing a C-ring thiophene rather than a C-ring pyridine. Subsequent work provided a number of proprietary leads (*11*, *12*), the best of which was **1** (*13*−*15*). Compound **1** has aphid and mite control comparable to that of **7** with commercial levels of whitefly control.

Work since then has focused on developing a lead that has a spectrum complementary to that of compound **1**. To find a

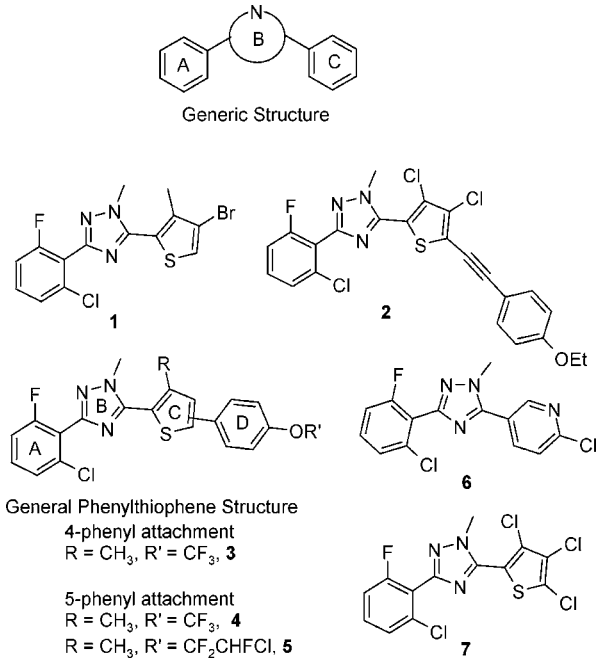


**Figure 1.** Series of 2,6-dihaloaryl heterocycles.

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10.1021/jf071498s CCC: $37.00 
Published on Web 08/14/2007

second-generation 2,6-dihalo active, compounds exhibiting lepidopteran−aphid (chewing and sap-feeding insect pests, respectively) coactivity were sought. In the structure−activity relationship (SAR) development around **1**, compounds with extended lipophilicity (*16*), such as alkyne **2**, were synthesized, and it was discovered that these compounds retained sap-feeding insect pest activity while also exhibiting lepidopteran activity. Thus, it was determined that the extended lipophilicity provided the lepidopteran activity in the thiophene series. Removal of the photolytically unstable alkynyl moiety and direct attachment of the phenyl D-ring to the thiophene C-ring at either the 4- or 5-position of the thiophene resulted in compounds that retained both chewing and sap-feeding insect pest activity. SAR development demonstrated that ring systems with similar lipophilicity, such as **3**, an early testing candidate, **4**, and a field testing candidate, **5**, had broad-spectrum chewing and sap-feeding insect pest activity (*17*).

Expansion of this area to include compounds with various substitutions on the C-ring thiophene, as well as on the D-ring (alkyl, alkenyl, aryl), was undertaken. The synthesis and insecticidal activity of these phenylthiophenes will be described.

## MATERIALS AND METHODS

**Synthesis.** All nonaqueous reactions were carried out under a nitrogen atmosphere. Reaction solvents were purchased from Aldrich (Sure/Seal) and used as is. Unless otherwise noted, all reagents and solvents were used as received. Melting points were recorded on a Thomas Hoover Melting Point apparatus using the appropriate partial immersion thermometer. Elemental analyses were conducted by Midwest Microlab, Indianapolis, IN. Reactions were monitored by thin-layer chromatography (TLC) on 250 $\mu$m precoated Analtech Uniplate plates, with visualization by ultraviolet light. Flash or gravity column chromatography was performed on 230−400 mesh silica gel 60 from EM Science, Darmstadt, Germany, using ACS grade solvents. Reversed-phase high-performance liquid chromatography (RP-HPLC) was conducted on a Gilson Liquid Handler 215 with HPLC grade acetonitrile and water (both with 0.1% acetic acid). Mass spectral data were obtained by electron ionization on a Hewlett-Packard Series 1100 mass selective detector, a Hewlett-Packard 5890 series II with a Hewlett-Packard 5890A mass spectrometer, or a Hewlett-Packard 6890 series GC system with a 5973 mass selective detector. High-resolution mass spectral (HRMS) data were acquired on a Thermo Finnigan LTQ-FT mass spectrometer (S/N 06120F). NMR spectra were obtained in $CDCl_3$ and DMSO-$d_6$, used as purchased, and were recorded on a Varian Gemini (300 MHz) spectrometer (unless otherwise stated), referenced to an internal standard of tetramethylsilane (TMS $^1$H: $\delta$ 0.00). $^1$H−$^1$H couplings are assumed to be first order, and peak multiplicity is reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or b (broad).

**3-(2-Chloro-6-fluorophenyl)-5-(3-chlorothiophen-2-yl)-1-methyl-1*H*-[1,2,4]triazole (9a).** To a suspension of 3-chlorothiophene-2-carboxylic acid (**8**, R1 = Cl; 5.02 g, 30.8 mmol) in 1,2-dichloroethane (DCE, 250 mL) were added thionyl chloride (2.5 mL, 34.1 mmol) and *N*,*N*-dimethylformamide (DMF, 5 drops from a Pasteur pipet). After refluxing under $N_2$ for 5 h, the reaction mixture was cooled to 25 °C and concentrated under reduced pressure. The residue was dissolved in DCE (250 mL) and added to 2-chloro-6-fluorothiobenzimidic acid methyl ester hydrogen bromide (8.80 g, 30.9 mmol) at 25 °C. To the suspension was added dry pyridine (5.5 mL, 68 mmol). The reaction mixture was stirred for 16 h and then was washed with $H_2O$ (250 mL), saturated aqueous $NaHCO_3$ (250 mL), and saturated aqueous NaCl (250 mL). The organic layer was dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure to give an orange-brown solid (9.36 g, 87% yield): mp 118−121 °C; $^1$H NMR ($CDCl_3$), $\delta$ 7.50 (d, $J$ = 5.1 Hz, 1H), 7.34−7.28 (m, 1H), 7.18 (d, $J$ = 8.0 Hz, 1H), 7.04−6.98 (m, 2H), 2.65 (s, 3H); EIMS, *m*/*z* 312 ([M − Cl]$^+$). Anal. Calcd for $C_{13}H_8Cl_2FNOS_2$: C, 44.84; H, 2.32; N, 4.02; S, 18.41. Found: C, 44.83; H, 2.34; N, 3.92; S, 18.39. Methylhydrazine (6.0 mL, 112 mmol) was added via syringe to a solution of 3-chlorothiophene-2-carboxylic acid (2-chloro-6-fluorophenyl)methylsulfanylmethyleneamide (9.36 g, 27.5 mmol) in toluene (250 mL). The reaction mixture was stirred at 25 °C for 60 h. The reaction mixture was concentrated under reduced pressure, and then $CH_2Cl_2$ was added until most of the material was dissolved. The remaining solid was collected via suction filtration. The filtrate was concentrated and triturated with an ether/hexanes mixture to give a burnt orange-brown solid (5.23 g, 57% yield): mp 82−87 °C; $^1$H NMR ($CDCl_3$), $\delta$ 7.56 (d, $J$ = 5.4 Hz, 1H), 7.47−7.29 (m, 2H), 7.13−7.05 (m, 2H), 4.03 (s, 3H); EIMS, *m*/*z* 327 ([M − H]$^+$). Anal. Calcd for $C_{13}H_8Cl_2FN_3S$: C, 47.58; H, 2.46; N, 12.80; S, 9.77. Found: C, 47.29; H, 2.38; N, 12.63; S, 9.95.

The following compounds were prepared according to the procedure below:

**5-(5-Bromo-3-chlorothiophen-2-yl)-3-(2-chloro-6-fluorophenyl)-1-methyl-1*H*-[1,2,4]triazole (10a).** 3-(2-Chloro-6-fluorophenyl)-5-(3-chlorothiophen-2-yl)-1-methyl-1*H*-[1,2,4]triazole (**9**, Y, R1 = Cl; 5.75 g, 17.5 mmol) was taken up in glacial HOAc (70 mL). To this were added NaOAc (5.40 g, 65.8 mmol) and bromine (1.4 mL, 27.1 mmol). The reaction mixture was stirred at 75 °C for 16 h. TLC (30% EtOAc/hexanes) showed incomplete reaction. Thus, more NaOAc (10.7 g, 130 mmol) and bromine (2.8 mL, 54.3 mmol) were added. The mixture was stirred at 75 °C for 21 h and then was cooled to 25 °C. The reaction mixture was quenched with cold (0 °C) saturated aqueous $NaHCO_3$ (500 mL). The aqueous layer was extracted with $Et_2O$ (3 × 150 mL). The combined organic extracts were washed with $H_2O$ (200 mL) and saturated aqueous NaCl (200 mL), dried ($MgSO_4$), filtered, and concentrated. The quench and extraction procedures were repeated due to the presence of acetic acid. The extractions were done until the organic layer was pH >7. Column chromatography (20−30% $Et_2O$/hexanes) gave three compounds, the second of which was the desired product, an off-white solid (3.67 g, 51% yield): mp 125−128 °C; $^1$H NMR ($CDCl_3$), $\delta$ 7.39−7.30 (m, 2H), 7.15−7.09 (m, 2H), 4.05 (s, 3H); EIMS, *m*/*z* 407 ([M + H]$^+$). Anal. Calcd for $C_{13}H_7BrCl_2FN_3S$: C, 38.36; H, 1.73; N, 10.32; S, 7.88. Found: C, 38.13; H, 1.83; N, 10.36; S, 8.07.

**5-(5-Bromo-3-chlorothiophen-2-yl)-3-(2,6-difluorophenyl)-1-methyl-1*H*-[1,2,4]triazole (10b).** The product was isolated as a white solid (51% yield): mp 134−137 °C; $^1$H NMR ($CDCl_3$), $\delta$ 7.43−7.33 (m, 1H), 7.08 (s, 1H), 7.06−6.98 (m, 2H), 4.02 (s, 3H); EIMS, *m*/*z* 391 ([M + H]$^+$). Anal. Calcd for $C_{13}H_7BrClF_2N_3S$: C, 39.97; H, 1.81; N, 10.76; S, 8.21. Found: C, 39.74; H, 1.82; N, 10.54; S, 8.27.

The following is an example of lithium−halogen exchange, followed by treatment with an electrophile (iodomethane):

**5-(4-Bromo-3,5-dimethylthiophen-2-yl)-3-(2-chloro-6-fluorophenyl)-1-methyl-1*H*-[1,2,4]triazole (11a).** *n*-Butyllithium (0.7 g, 10.8 mmol) was added dropwise to a solution of 3-(2-chloro-6-fluorophenyl)-5-(4,5-dibromo-3-methylthiophen-2-yl)-1-methyl-1*H*-[1,2,4]triazole (**11**, Y = Cl, R4 = Br; 5 g, 10.8 mmol) in THF (70 mL) at −70 °C and stirred for 1 h. Iodomethane (1.6 g, 11.29 mmol) was added to the reaction mixture, and the reaction mixture was allowed to warm to 25 °C. After the addition of saturated aqueous $NH_4Cl$ (10 mL), the organic layer was separated, washed with $H_2O$ and saturated aqueous NaCl (20 mL), dried ($Na_2SO_4$), filtered, and concentrated. Column chromatography (10% EtOAc/hexanes) afforded the product as a yellow oil (2.0 g, 47% yield): $^1$H NMR ($CDCl_3$), $\delta$ 7.38−7.28 (m, 2H), 7.13−7.07 (m, 1H), 3.99 (s, 3H), 2.48 (s, 3H), 2.32 (s, 3H); EIMS, *m*/*z* 400 ([M]$^+$). Anal. Calcd for $C_{15}H_{12}ClBrFN_3S$: C, 44.96; H, 3.02; N, 10.49. Found: C, 44.94; H, 3.01; N, 10.29.

**General Procedure for the Preparation of 3, 4, 12, and 13.** Pd($PPh_3$)$_2Cl_2$ (10 mol %) was added to a suspension of the 1,2,4-triazole (0.49 mmol), the boronic acid (1.01 equiv), $Na_2CO_3$ (1.5 equiv), and (*o*-tolyl)$_3$P (0.10 equiv) in $CH_3CN/H_2O$ (10:1, 4 mL). The mixture was stirred at reflux under $N_2$ for 20 h and at 25 °C for 24 h. The reaction mixture was quenched with 1 N HCl (50 mL) and extracted with $Et_2O$ (3 × 50 mL). The combined organic extracts were washed with saturated aqueous NaCl (50 mL), dried ($MgSO_4$), filtered, and concentrated. Column chromatography, eluting with acetone/, ether/, or ethyl acetate/hexane mixtures, provided the product. Preparative information and mass spectral and proton NMR, as well as microana-

**Table 1.** Preparative Information and Mass Spectral and Proton NMR Data for Compounds **3**, **4**, **12a**–**o**, and **13a**–**h**[a]

| compd | Y | R1 | R2 | R3 | R4 | yield (%) | mp (°C) | MS[b] (*m*/*z*) | $^1$H NMR data ($CDCl_3$) |
|---|---|---|---|---|---|---|---|---|---|
| **3** | Cl | $CH_3$ | 4-$OCF_3$ | H | H | 69 | 108–109 | 467 ($[M]^+$) | 7.29–7.11 (m, 7H), 6.96 (m, 1H), 3.92 (s, 3H), 2.16 (s, 3H) |
| **4** | Cl | $CH_3$ | 4-$OCF_3$ | H | H | 72 | 96–97 | 467 ($[M]^+$) | 7.62 (d, 2H), 7.38–7.21 (m, 5H), 7.07 (m, 1H), 4.05 (s, 3H), 2.41 (s, 3H) |
| **12a** | Cl | Cl | 4-$OCF_3$ | H | H | 62 | 120–123 | 487 ($[M]^+$) | 7.62 (ddd, $J$ = 2.1, 2.9, 8.7 Hz, 2H), 7.40–7.26 (m, 5H), 7.15–7.08 (m, 1H), 4.08 (s, 3H) |
| **12b** | Cl | Cl | 4-$CF_3$ | H | H | 60 | 133–136 | 471 ($[M]^+$) | 7.70 (s, 4H), 7.38–7.30 (m, 3H), 7.15–7.09 (m, 1H), 4.09 (s, 3H) |
| **12c** | Cl | Cl | 4-$CH_3$ | H | H | 69 | 111–115 | 417 ($[M]^+$) | 7.49 (d, $J$ = 8.0 Hz, 2H), 7.46–7.23 (m, 5H), 7.14–7.08 (m, 1H), 4.09 (s, 3H) |
| **12d** | Cl | Cl | 4-OEt | H | H | 66 | 126–128 | 419 ($[M - Et]^+$) | 7.50 (dd, $J$ = 8.7, 2.0 Hz, 2H), 7.39–7.29 (m, 2H), 7.15 (s, 1H), 7.14–7.08 (m, 1H), 6.96–6.92 (m, 1H), 4.11 (m, 5H), 1.44 (t, $J$ = 7.1 Hz, 3H) |
| **12e** | Cl | Cl | 4-Br | H | H | 44 | 126–128 | 483 ($[M]^+$) | 7.57 (d, $J$ = 8.4 Hz, 2H), 7.46 (d, $J$ = 8.4 Hz, 2H), 7.37–7.29 (m, 2H), 7.26 (s, 1H and $CDCl_3$), 7.14–7.08 (m, 1H), 4.08 (s, 3H) |
| **12f** | Cl | Cl | 4-$SCH_3$ | H | H | 66 | 125–126 | 449 ($[M]^+$) | 7.50 (d, $J$ = 8.7 Hz, 2H), 7.40–7.23 (m, 5H), 7.14–7.08 (m, 1H), 4.08 (s, 3H), 2.52 (s, 3H) |
| **12g** | Cl | $CH_3$ | 4-$CF_3$ | H | H | 70 | 85–86 | 451 ($[M]^+$) | 7.72 (q, $J$ = 8.3 Hz, 4H), 7.41–7.25 (m, 3H), 7.10 (m, 1H), 4.12 (s, 3H), 2.43 (s, 3H) |
| **12h** | Cl | $CH_3$ | 3-Cl | 4-F | H | 58 | 121–122 | 436 ($[M]^+$) | 7.55 (d, 2H), 7.31 (m, 1H), 7.22–6.95 (m, 5H), 3.95 (s, 3H), 2.25 (s, 3H) |
| **12i** | Cl | $CH_3$ | 3-OEt | H | H | 73 | 84–87 | 428 ($[M]^+$) | 7.20–7.18 (m, 2H), 7.15–7.07 (m, 2H), 6.89–6.85 (m, 1H), 4.12–4.05 (m, 5H), 2.42 (s, 3H), 1.44 (t, $J$ = 6.96 Hz, 3H) |
| **12j** | Cl | $CH_3$ | 4-OEt | H | $CH_3$ | 31 | 147–148 | 441 ($[M]^+$) | 7.40–7.34 (m, 2H), 7.33–7.28 (m, 2H), 7.13–6.99 (m, 1H), 6.95–6.78 (m, 2H), 4.12–4.05 (m, 5H), 2.31 (s, 3H), 2.20 (s, 3H), 1.45 (t, $J$ = 7.0 Hz, 3H) |
| **12k** | Cl | $CH_3$ | 4-$OCF_3$ | H | $CH_3$ | 47 | 109–112 | 481 ($[M]^+$) | 7.51–7.47 (m, 2H), 7.39–7.28 (m, 4H), 7.14–7.08 (m, 1H), 4.05 (s, 3H), 2.32 (s, 3H), 2.24 (s, 3H) |
| **12l** | F | Cl | 4-$OCF_3$ | H | H | 65 | 105–107 | 471 ($[M]^+$) | 7.63–7.59 (m, 2H), 7.41–7.36 (m, 1H), 7.30–7.25 (m, 3H), 7.06–7.00 (m, 2H), 4.07 (s, 3H) |
| **12m** | F | Cl | 4-$CH_3$ | H | H | 69 | 139–141 | 401 ($[M]^+$) | 7.47 (m, 2H), 7.41–7.35 (m, 1H), 7.26–7.22 (m, 3H), 7.05–7.02 (m, 2H), 4.07 (s, 3H), 2.39 (s, 3H) |
| **12n** | F | Cl | 4-OEt | H | H | 64 | 120–123 | 432 ($[M + H]^+$) | 7.50 (d, $J$ = 8.7 Hz, 2H), 7.38 (m, 1H), 7.15 (s, 1H), 7.05–6.99 (m, 2H), 6.94 (d, $J$ = 8.7 Hz, 2H), 4.06 (m, 5H), 1.44 (t, $J$ = 6.9 Hz, 3H) |
| **12o** | F | Cl | 4-$CF_3$ | H | H | 63 | 156–162 | 455 ($[M]^+$) | 7.70 (s, 4H), 7.42–7.35 (m, 2H), 7.03 (t, $J$ = 8.05 Hz, 2H), 4.08 (s, 3H) |
| **13a** | Cl | $CH_3$ | 4-OEt | H | H | 80 | 124–127 | 427 ($[M + H]^+$) | 7.39–7.30 (m, 5H), 7.13–6.98 (m, 1H), 6.96 (d, $J$ = 8.4 Hz, 2H), 4.06 (s, 3H), 2.31 (s, 3H), 1.45 (t, $J$ = 7.0 Hz, 3H) |
| **13b** | Cl | $CH_3$ | 4-$CF_3$ | H | H | 66 | 102–103 | 467 ($[M]^+$) | 7.71 (d, $J$ = 8.0 Hz, 2H), 7.53 (d, $J$ = 8.0 Hz, 2H), 7.49 (s, 1H), 7.38–7.31 (m, 2H), 7.10 (dd, $J$ = 7.3 Hz, 1H), 4.08 (s, 3H), 2.34 (s, 3H) |
| **13c** | Cl | $CH_3$ | 4-*i*-Pr | H | H | 53 | 109–111 | 425 ($[M + H]^+$) | 7.38–7.28 (m, 7H), 7.14–7.08 (m, 1H), 4.06 (s, 3H), 2.96 (m, 1H), 2.33 (s, 3H) 1.30 (d, $J$ = 6.6 Hz, 6H) |
| **13d** | Cl | $CH_3$ | 4-OEt | H | $CH_3$ | 35 | 140–143 | 322 ($[M]^+$) | 7.38–7.28 (m, 2H), 7.13–7.07 (m, 2H), 4.00 (s, 3H), 2.27 (s, 3H), 2.22 (s, 3H) |
| **13e** | Cl | $CH_3$ | 4-$CF_3$ | H | $CH_3$ | 27 | oil | 466 ($[M]^+$) | 7.70 (d, $J$ = 8.1 Hz, 2H), 7.38–7.24 (m, 6H), 7.13–7.07 (m, 1H), 4.06 (s, 3H), 2.36 (s, 3H), 2.14 (s, 3H) |
| **13f** | Cl | $CH_3$ | 4-$OCF_3$ | H | $CH_3$ | 26 | 93–95 | 482 ($[M]^+$) | 7.38–7.24 (m, 6H), 7.13–7.07 (m, 1H), 4.06 (s, 3H), 2.36 (s, 3H), 2.14 (s, 3H) |
| **13g** | Cl | $CH_3$ | 4-*i*-Pr | H | $CH_3$ | 19 | 154–155 | 432 ($[M]^+$) | 7.43 (d, $J$ = 8.4 Hz, 2H), 7.41–7.28 (m, 2H), 7.17 (d, $J$ = 8.0 Hz, 2H), 7.13–7.06 (m, 1H), 4.05 (s, 3H), 2.35 (s, 3H), 2.13 (s, 3H) |
| **13h** | Cl | $CH_3$ | 4-Cl | H | $CH_3$ | 25 | 85–89 | 440 ($[M]^+$) | 7.37–7.28 (m, 4H) 7.18–7.13 (m, 2H), 7.13–7.06 (m, 1H), 4.05 (s, 3H), 3.01–2.92 (m, 1H), 2.36 (s, 3H), 2.15 (s, 3H), 2.13 (d, $J$ = 7.0 Hz, 7H) |

[a] See **Figure 4** for structures. [b] Electron-impact ionization.

lytical and HRMS, data for compounds **3**, **4**, **12a**−**o**, and **13a**−**h** can be found in **Tables 1** and **2**, respectively.

**4,5-Dibromo-3-chlorothiophene-2-carboxylic Acid (14).** Catalytic DMF (5 drops) was added to a mixture of 3-chlorothiophene-2-carboxylic acid (**8**, R1 = Cl; 5.0 g, 30.8 mmol) and thionyl chloride (2.4 mL, 32.9 mmol) in DCE (250 mL). The reaction mixture was stirred at reflux under $N_2$ for 4.5 h and then was cooled to 25 °C. Absolute EtOH (25 mL, 430 mmol) was added, and the reaction mixture was stirred at 25 °C for 16 h. The mixture was washed with saturated aqueous $NaHCO_3$ (200 mL), $H_2O$ (200 mL), and saturated aqueous NaCl (200 mL), dried ($MgSO_4$), filtered, and concentrated. Column chromatography (5% $Et_2O$/hexanes) provided the product (3.99 g, 68% yield) as a light yellow oil: $^1$H NMR ($CDCl_3$), $\delta$ 7.46 (d, $J$ = 5.1 Hz, 1H), 7.01 (d, $J$ = 5.1 Hz, 1H), 4.36 (q, $J$ = 7.2 Hz, 2H), 1.38 (t, $J$ = 7.1 Hz, 3H); EIMS, *m*/*z* 190 ($[M]^+$). Ethyl 3-chlorothiophene-2-carboxylate (3.96 g, 20.7 mmol) in a suspension of NaOAc (12.7 g, 154 mmol) and glacial HOAc (35 mL) was treated with bromine (9.6 mL, 186 mmol). The reaction mixture was stirred at 75 °C under $N_2$ for 136 h and then at 25 °C for 144 h. The reaction mixture was poured onto ice-cold saturated aqueous $NaHCO_3$ and aqueous $NaHSO_3$. The mixture was stirred with $Et_2O$ (100 mL) for 30 min. Extraction with $Et_2O$ (3 × 150 mL) gave an organic layer that was washed with $H_2O$ (150 mL) and saturated aqueous NaCl (150 mL), dried ($MgSO_4$), and concentrated to give the product as a white solid (5.83 g, 80% yield): mp 58−63 °C; $^1$H NMR ($CDCl_3$), $\delta$ 4.37 (q, $J$ = 7.1 Hz, 2H), 1.38 (t, $J$ = 7.1 Hz, 3H); EIMS, *m*/*z* 347 ($[M]^+$). Ethyl 4,5-dibromo-3-chlorothiophene-2-carboxylate (5.52 g, 15.8 mmol) and lithium hydroxide (0.716 g, 31.7 mmol) were taken up in mixture of THF (30 mL) and water (30 mL). The reaction mixture was stirred at 25 °C for 32 h. The aqueous layer was made acidic by the dropwise addition of concentrated HCl and extracted with $Et_2O$ (3 × 50 mL). The combined organic extracts were dried ($Na_2SO_4$), filtered, and concentrated to give the product as a white solid (4.38 g, 86% yield) that was used without purification: $^1$H NMR ($CDCl_3$ and DMSO-$d_6$), $\delta$ 4.15 (bs, 1H); MS, *m*/*z* 320 ($[M]^+$).

**3-(2-Chloro-6-fluorophenyl)-5-(4,5-dibromo-3-chlorothiophen-2-yl)-1-methyl-1*H*-[1,2,4]triazole (15).** 4,5-Dibromo-3-chlorothiophene-2-carboxylic acid (**14**, 2.05 g, 6.42 mmol) was taken up in DCE (60 mL) to which were added thionyl chloride (0.49 mL, 6.71 mmol) and catalytic DMF (5 drops). The mixture was stirred at reflux under $N_2$ for 6 h. More thionyl chloride (0.49 mL) was added, and the mixture was stirred at 25 °C for 16 h. The mixture was concentrated to a tan solid that was dissolved in DCE (60 mL), to which were added 2-chloro-6-fluoro-thiobenzimidic acid methyl ester methyl sulfate (2.02 g, 6.42 mmol) and pyridine (1.2 mL, 14.8 mmol). The reaction mixture was stirred at 25 °C for 48 h. The organic layer was washed with $H_2O$ (75 mL), 1 N HCl (75 mL), saturated aqueous $NaHCO_3$ (75 mL), and saturated aqueous NaCl (75 mL), dried ($MgSO_4$), filtered, and concentrated to give the product (2.40 g, 73% yield) as a burnt orange solid: mp 111−118 °C; $^1$H NMR ($CDCl_3$), $\delta$ 7.32 (ddd, $J$ = 5.8, 8.0,

**Table 2.** Microanalytical and High-Resolution Mass Spectral (HRMS) Data for Compounds in **Table 1**

| compd | molecular formula | % C (theory) | % H (theory) | % N (theory) | % S (theory) | HRMS (theory) |
|---|---|---|---|---|---|---|
| **3** | $C_{21}H_{14}ClF_4N_3OS$ | | | | | 467.0475 (467.0482) |
| **4** | $C_{21}H_{14}ClF_4N_3OS$ | | | | | 467.0476 (467.0482) |
| **12a** | $C_{20}H_{11}Cl_2F_4N_3OS$ | 49.42 (49.20) | 2.38 (2.27) | 8.37 (8.61) | 6.61 (6.57) | |
| **12b** | $C_{20}H_{11}Cl_2F_4N_3S$ | 51.01 (50.86) | 2.36 (2.35) | 8.67 (8.90) | 6.48 (6.79) | |
| **12c** | $C_{20}H_{14}Cl_2FN_3S$ | 57.19 (57.43) | 3.46 (3.37) | 9.64 (10.04) | 7.16 (7.66) | |
| **12d** | $C_{21}H_{16}Cl_2FN_3OS$ | 56.33 (56.26) | 3.62 (3.60) | 9.31 (9.37) | 7.13 (7.15) | |
| **12e** | $C_{19}H_{11}BrCl_2FN_3S$ | 47.32 (47.23) | 2.34 (2.29) | 8.46 (8.70) | 6.68 (6.64) | |
| **12f** | $C_{20}H_{14}Cl_2FN_3S_2$ | 53.17 (53.34) | 3.19 (3.13) | 9.19 (9.33) | 14.28 (14.24) | |
| **12g** | $C_{21}H_{14}ClF_4N_3S$ | | | | | 451.0531 (451.0533) |
| **12h** | $C_{20}H_{13}Cl_2F_2N_3S$ | | | | | 435.0173 (435.0175) |
| **12i** | $C_{22}H_{19}ClFN_3OS$ | | | | | 427.0920 (427.9021) |
| **12j** | $C_{23}H_{21}ClFN_3OS$ | 62.36 (62.51) | 4.67 (4.79) | 9.45 (9.51) | | |
| **12k** | $C_{22}H_{16}ClF_4N_3OS$ | 54.68 (54.83) | 3.39 (3.35) | 8.65 (8.72) | | |
| **12l** | $C_{20}H_{11}ClF_5N_3OS$ | 50.90 (50.91) | 2.44 (2.35) | 8.64 (8.91) | 6.93 (6.80) | |
| **12m** | $C_{20}H_{14}ClF_2N_3S$ | 59.83 (59.78) | 3.61 (3.51) | 10.22 (10.46) | 8.16 (7.98) | |
| **12n** | $C_{21}H_{16}ClF_2N_3OS$ | 58.44 (58.40) | 3.88 (3.73) | 9.48 (9.73) | 7.23 (7.42) | |
| **12o** | $C_{20}H_{11}ClF_5N_3S$ | 52.81 (52.70) | 2.50 (2.43) | 9.13 (9.22) | 7.11 (7.03) | |
| **13a** | $C_{22}H_{19}ClFN_3OS$ | 61.74 (61.75) | 4.53 (4.48) | 9.63 (9.82) | | |
| **13b** | $C_{21}H_{14}ClF_4N_3S$ | | | | | 451.0531 (451.0533) |
| **13c** | $C_{23}H_{23}ClFN_3S$ | 64.51 (64.86) | 5.02 (4.97) | 9.78 (9.86) | | |
| **13d** | $C_{23}H_{21}ClFN_3OS$ | | | | | 441.1074 (441.1078) |
| **13e** | $C_{22}H_{16}ClF_4N_3S$ | | | | | 465.0687 (465.0690) |
| **13f** | $C_{22}H_{16}ClF_4N_3OS$ | | | | | 481.0641 (481.0639) |
| **13g** | $C_{24}H_{23}ClFN_3S$ | | | | | 439.1281 (439.1284) |
| **13h** | $C_{21}H_{16}Cl_2FN_3S$ | | | | | 431.0427 (431.0426) |

8.4 Hz, 1H), 7.19 (d, $J = 8.0$ Hz, 1H), 7.03 (ddd, $J = 0.85$, 8.0, 8.4 Hz, 1H), 2.65 (s, 3H); EIMS, *m*/*z* 470 ($[M - Cl]^+$). 4,5-Dibromo-3-chlorothiophene-2-carboxylic acid (2-chloro-6-fluorophenyl)methylsulfanyl methyleneamide (2.14 g, 4.22 mmol) was dissolved in toluene (42 mL) under $N_2$. To this solution was added methylhydrazine (0.90 mL, 16.9 mmol), and the mixture was stirred at 25 °C for 40 h. The mixture was concentrated and triturated with hexanes to give the crude product. The crude product was dissolved in a minimum of $CH_2Cl_2$, and a few drops of hexanes were added. The solution was allowed to crystallize over 48 h, providing the product as a tan solid (499 mg, 24% yield): mp 180−182 °C; $^1$H NMR ($CDCl_3$), $\delta$ 7.40−7.27 (m, 2H), 7.14−7.08 (m, 1H), 4.03 (s, 3H); EIMS, *m*/*z* 485 ($[M]^+$).

The following compounds were prepared according to the procedure below:

**5-[4-Bromo-3-chloro-5-(4-trifluoromethoxyphenyl)thiophen-2-yl]-3-(2-chloro-6-fluorophenyl)-1-methyl-1*H*-[1,2,4]triazole (16a).** 3-(2-Chloro-6-fluorophenyl)-5-(4,5-dibromo-3-chlorothiophen-2-yl)-1-methyl-1*H*-[1,2,4]triazole (**15**, 203 mg, 0.418 mmol), 4-trifluoromethoxyphenyl boronic acid (87.2 mg, 0.423 mmol), and $K_2CO_3$ (85.8 mg, 0.620 mmol) were taken up in $PhCH_3$ (4 mL). The mixture was degassed with $N_2$ for 15 min, and then $Pd(PPh_3)_4$ (cat.) was added. The reaction mixture was stirred at 90−95 °C under $N_2$ for 7.5 h. TLC (20% $Et_2O$/hexanes) showed the presence of **15**. More $Pd(PPh_3)_4$ was added, and the mixture was stirred at 90−95 °C for 16 h. Reaction was still incomplete. The reaction mixture was quenched with 1 N HCl (50 mL) and was extracted with $Et_2O$ (3 × 50 mL). The combined organic extracts were washed with saturated aqueous NaCl (50 mL), dried ($Na_2SO_4$), filtered, and concentrated. Column chromatography (20% $Et_2O$/hexanes) provided the product as a white solid (44 mg, 18% yield): mp 170−172 °C; $^1$H NMR ($CDCl_3$), $\delta$ 7.69 (d, $J = 8.7$ Hz, 2H), 7.38−7.29 (m, 4H), 7.23−7.09 (m, 1H), 4.09 (s, 3H); EIMS, *m*/*z* 567 ($[M]^+$).

**5-[4-Bromo-3-chloro-5-(4-trifluoromethylphenyl)thiophen-2-yl]-3-(2-chloro-6-fluorophenyl)-1-methyl-1*H*-[1,2,4]triazole (16b).** The product was isolated as a white solid (28% yield): mp 167−170 °C; $^1$H NMR ($CDCl_3$), $\delta$ 7.50 (dd, $J = 8.7$, 2.0 Hz, 2H), 7.39−7.29 (m, 2H), 7.15 (s, 1H), 7.14−7.08 (m, 1H), 6.96−6.92 (m, 1H), 4.11 (m, 5H), 1.44 (t, $J = 7.1$ Hz, 3H); EIMS, *m*/*z* 551 ($[M]^+$).

**5-[4-Bromo-3-chloro-5-(4-ethoxyphenyl)thiophen-2-yl]-3-(2-chloro-6-fluorophenyl)-1-methyl-1*H*-[1,2,4]triazole (16c).** The product was isolated as a white solid (41% yield): mp 145−150 °C; $^1$H NMR ($CDCl_3$), $\delta$ 7.58 (d, $J = 8.7$ Hz, 2H), 7.40−7.30 (m, 2H), 7.14−7.08 (m, 1H), 6.99 (d, $J = 8.7$ Hz, 2H), 4.13−4.03 (m, 5H), 1.45 (t, $J = 6.9$ Hz, 3H); EIMS, *m*/*z* 527 ($[M]^+$).

**General Procedure for the Preparation of 5, 18, and 19.** The triazole (**12** or **13**, 1.20 mmol) was dissolved in $CH_2Cl_2$ (12 mL) under $N_2$ and was cooled to 0 °C. To this was added $BBr_3$ (1.0 M solution in $CH_2Cl_2$; 2.0 mL, 2.0 mmol) dropwise via syringe. The cooling bath was removed immediately, and the reaction mixture was allowed to warm to 25 °C and stirred for 20 h. The mixture was poured onto $H_2O$ (100 mL) and stirred at 25 °C for 30 min. The layers were partitioned, and the aqueous layer was extracted with $CH_2Cl_2$ (2 × 50 mL). The combined organic extracts were washed with $H_2O$ (50 mL) and saturated aqueous NaCl (50 mL), dried ($Na_2SO_4$), filtered, and concentrated. Column chromatography gave the corresponding phenol. The phenol (0.438 mmol) was taken up in DMF (1.6 mL) to which was added 25% NaOH (a few drops). The mixture became a bright yellow color and was stirred at 25 °C for 10 min. Bromotrifluoroethylene, chlorotrifluoroethylene, or hexafluoropropene (g, excess) was then bubbled through the mixture for 10−15 min. TLC showed little reaction, so more 25% NaOH (a few drops) was added, followed by the bubbling of more gas for 10 min. TLC (30% $Et_2O$/hexanes) at this time showed no starting material, only a less polar spot. The mixture was stirred at 25 °C for 1 h. The mixture was poured onto $H_2O$ (50 mL) and was extracted with $Et_2O$ (3 × 50 mL). The combined organic extracts were washed with $H_2O$ (50 mL) and saturated aqueous NaCl (50 mL), dried ($Na_2SO_4$), filtered, and concentrated to a tan solid. Column chromatography, eluting with an acetone/, ether/, or ethyl acetate/hexane mixture, gave the product. Preparative information and mass spectral and proton NMR, as well as microanalytical and HRMS, data for compounds **5**, **18a**−**h**, and **19a**−**h** can be found in **Tables 3** and **4**, respectively.

**5-{5-Bromo-4-[4-(2-bromo-1,1,2-trifluoroethoxy)phenyl]-3-methylthiophen-2-yl}-3-(2-chloro-6-fluorophenyl)-1-methyl-1*H*-[1,2,4]-triazole (20).** Bromine (0.03 g, 0.2 mmol) in HOAc (0.5 mL) was added dropwise to a solution of 5-{4-[4-(2-bromo-1,1,2-trifluoroethoxy)-phenyl]-3-methylthien-2-yl}-3-(2-chloro-6-fluorophenyl)-1-methyl-1*H*-[1,2,4]triazole (**19**, X = Br, Y = Cl, R1 = $CH_3$, R4 = H; 0.1 g, 0.2 mmol) in HOAc (1 mL) at 0 °C. The reaction was allowed to warm to 25 °C and stirred for 50 h. The reaction mixture was made basic with saturated aqueous $NaHCO_3$ (30 mL) and was extracted with $Et_2O$ (3 × 30 mL). The combined extracts were washed with saturated aqueous NaCl, dried ($Na_2SO_4$), filtered, and concentrated. Column chromatography (20% $Et_2O$/hexanes) gave the product (88 mg, 77% yield) as a clear oil: $^1$H NMR ($CDCl_3$), $\delta$ 7.40−7.29 (m, 6H), 7.14−7.08 (m, 1H), 6.58 (dt, $J = 47.6$, 5.1, 4.0, 4.4 Hz, 1H), 4.06 (s, 3H), 2.19 (s, 3H); EIMS, *m*/*z* 636 ($[M + H]^+$).

**Table 3.** Preparative Information and Mass Spectral and Proton NMR Data for Compounds **5**, **18a**–**h**, and **19a**–**g**[a]

| compd | Y | R1 | R2 | R3 | R4 | yield (%) | mp (°C) | MS[b] (*m*/*z*) | $^1$H NMR data ($CDCl_3$) |
|---|---|---|---|---|---|---|---|---|---|
| **5** | Cl | $CH_3$ | 4-$OCF_2CHFCl$ | H | H | 65 | 115–116 | 515 ($[M-H]^+$) | 7.55 (d, 2H), 7.31–7.11 (m, 5H), 7.02 (t, 1H), 6.30 and 6.13 (t, 1H), 3.99 (s, 3H), 2.34 (s, 3H) |
| **18a** | Cl | Cl | 4-$OCF_2CHFBr$ | H | H | 68 | 137–140 | 581 ($[M]^+$) | 7.60 (m, 2H), 7.40–7.25 (m, 5H), 7.14–7.08 (m, 1H), 6.56 (dt, $J_{H,F(gem)}$ = 47.6 Hz, $J_{H,F(vic)}$ = 4.67 Hz, 1H), 4.08 (s, 3H) |
| **18b** | Cl | $CH_3$ | 4-$OCF_2CHCl_2$ | H | H | 72 | 119–120 | 534 ($[M+H]^+$) | 7.55 (d, 2H), 7.31–7.21 (m, 3H), 7.15 (s, 1H), 7.02 (t, 1H), 5.85 (t, 1H), 3.99 (s, 3H), 2.34 (s, 3H) |
| **18c** | Cl | $CH_3$ | 4-$OCF_2CHFCF_3$ | H | H | 58 | oil | 550 ($[M+H]^+$) | 7.48 (d, 2H), 7.22–7.15 (m, 3H), 7.11 (s, 1H), 6.99 (t, 1H), 4.95–4.79 (m, 1H), 3.93 (s, 3H), 2.27 (s, 3H) |
| **18d** | Cl | Cl | 4-$OCF_2CHFCl$ | H | H | 72 | 135–138 | 535 ($[M]^+$) | 7.60 (m, 2H), 7.40–7.28 (m, 5H), 7.14–7.08 (m, 1H), 6.29 (dt, $J_{H,F(gem)}$ = 47.9 Hz, $J_{H,F(vic)}$ = 3.93 Hz, 1H), 4.08 (s, 3H) |
| **18e** | Cl | $CH_3$ | 4-$OCF_2CHFBr$ | H | H | 82 | oil | 562 ($[M+H]^+$) | 7.53–7.50 (m, 1H) 7.46–7.44 (m, 1H), 7.41 (d, $J$ = 0.73 Hz, 1H), 7.38 (s, 1H), 7.37–7.29 (m, 2H), 7.21–7.18 (m, 1H), 7.13–7.07 (m, 1H), 6.57 (dt, $J$ = 47.6, 4.76 Hz, 1H), 4.08 (s, 3H), 2.43 (s, 3H) |
| **18f** | Cl | $CH_3$ | 3-$OCF_2CHFCl$ | H | H | 78 | oil | 516 ($[M]^+$) | 7.54–7.51 (m, 1H), 7.42 (s, 1H), 7.45 (s, 1H), 7.40 (s, 1H), 7.38–7.29 (m, 1H), 7.25 (s, 1H), 7.21–7.18 (m, 1H), 7.14–7.08 (m, 1H), 6.30 (dt, $J$ = 48.3, 4.0 Hz, 1H), 4.08 (s, 3H), 2.43 (s, 3H) |
| **18g** | Cl | $CH_3$ | 4-$OCF_2CHFCl$ | H | $CH_3$ | 90 | 140–142 | 530 ($[M]^+$) | 7.50–7.46 (m, 2H) 7.39–7.29 (m, 4H), 7.14–7.08 (m, 1H), 6.30 (dt, $J$ = 48.3, 4.0 Hz, 1H), 4.05 (s, 3H), 2.32 (s, 3H), 2.24 (s, 3H) |
| **18h** | Cl | $CH_3$ | 4-$OCF_2CHFBr$ | H | $CH_3$ | 80 | 121–124 | 576 ($[M+H]^+$) | 7.48 (d, $J$ = 8.4 Hz, 2H), 7.39–7.29 (m, 4H), 7.19–7.08 (m, 1H), 6.56 (dt, $J$ = 48.0, 4.4, 5.1, 4.8 Hz, 1H), 4.05 (s, 3H), 2.32 (s, 3H), 2.24 (s, 3H) |
| **19a** | Cl | $CH_3$ | 4-$OCF_2CHFBr$ | H | H | 70 | foam | 560 ($[M+H]^+$) | 7.41 (d, $J$ = 7.3 Hz, 3H), 7.37–7.28 (m, 4H), 7.14–7.08 (m, 1H), 6.57 (dt, $J$ = 47.9, 5.1, 4.4 Hz, 1H), 4.07 (s, 3H), 2.32 (s, 3H) |
| **19b** | Cl | $CH_3$ | 4-$OCF_2CHFCl$ | H | H | 71 | oil | 516 ($[M+H]^+$) | 7.43–7.27 (m, 7H), 7.14–7.08 (m, 1H), 6.30 (dt, $J$ = 48.1, 4.1 Hz, 1H), 4.07 (s, 3H), 2.32 (s, 3H) |
| **19c** | Cl | $CH_3$ | 4-$OCF_2CHFCF_3$ | H | H | 44 | oil | 549 ($[M+H]^+$) | 7.44–7.39 (m, 3H), 7.37–7.29 (m, 4H), 7.14–7.08 (m, 1H), 5.03 (m, 1H), 4.06 (s, 3H), 2.32 (s, 3H) |
| **19d** | Cl | $CH_3$ | 4-$OCF_2CHCl_2$ | H | H | 53 | 114–116 | 532 ($[M+H]^+$) | 7.42–7.39 (m, 3H), 7.38–7.28 (m, 4H), 7.14–7.08 (m, 1H), 5.95 (t, $J$ = 4.8, 4.4 Hz, 1H), 4.07 (s, 3H), 2.32 (s, 3H) |
| **19e** | Cl | $CH_3$ | 4-$OCFCCl_2$ | H | H | 10 | oil | 512 ($[M+H]^+$) | 7.42–7.38 (m, 3H), 7.37–7.29 (m, 2H), 7.17–7.08 (m, 3H), 4.06 (s, 3H), 2.31 (s, 3H) |
| **19f** | Cl | $CH_3$ | 4-$OCF_2CHFCl$ | H | $CH_3$ | 65 | 123–124 | 530 ($[M+H]^+$) | 7.38–7.27 (m, 4H), 7.24 (d, $J$ = 2.2 Hz, 2H), 7.13–7.07 (m, 1H), 6.30 (dt, $J$ = 48.3, 4.0, 4.4, 3.7 Hz, 1H), 4.06 (s, 3H), 2.36 (s, 3H), 2.14 (s, 3H) |
| **19g** | Cl | $CH_3$ | 4-$OCF_2CHFBr$ | H | $CH_3$ | 74 | 123–127 | 576 ($[M+H]^+$) | 7.38–7.26 (m, 4H), 7.24–7.23 (m, 2H), 7.13–7.07 (m, 1H), 6.57 (dt, $J$ = 48.0, 4.0, 5.1, 4.4 Hz, 1H), 4.06 (s, 3H), 2.36 (s, 3H), 2.14 (s, 3H) |

[a] See **Figure 4** for structures. [b] Electron-impact ionization.

**Table 4.** Microanalytical and High-Resolution Mass Spectral (HRMS) Data for Compounds in **Table 3**

| compd | molecular formula | % C (theory) | % H (theory) | % N (theory) | HRMS (theory) |
|---|---|---|---|---|---|
| **5** | $C_{22}H_{15}Cl_2F_4N_3OS$ | | | | 515.0250 (515.0249) |
| **18a** | $C_{21}H_{12}BrCl_2F_4N_3OS$ | 43.51 (43.40) | 2.10 (2.08) | 7.11 (7.23) | |
| **18b** | $C_{22}H_{15}Cl_3F_3N_3OS$ | | | | 530.9950 (530.9954) |
| **18c** | $C_{23}H_{15}ClF_7N_3OS$ | | | | 549.0504 (549.0513) |
| **18d** | $C_{21}H_{12}Cl_3F_4N_3OS$ | 46.99 (46.99) | 2.25 (2.31) | 7.83 (7.69) | |
| **18e** | $C_{22}H_{15}BrClF_4N_3OS$ | 47.19 (47.12) | 2.80 (2.70) | 7.32 (7.49) | |
| **18f** | $C_{22}H_{15}Cl_2F_4N_3OS$ | | | | 515.0246 (515.0249) |
| **18g** | $C_{23}H_{17}Cl_2F_4N_3OS$ | 51.79 (52.09) | 3.26 (3.23) | 7.73 (7.29) | |
| **18h** | $C_{23}H_{17}BrClF_4N_3OS$ | 48.04 (48.06) | 2.98 (2.98) | 7.26 (7.31) | |
| **19a** | $C_{22}H_{15}BrClF_4N_3OS$ | 47.35 (47.12) | 2.78 (2.70) | 7.36 (7.49) | |
| **19b** | $C_{22}H_{15}Cl_2F_4N_3OS$ | 50.45 (51.18) | 3.01 (2.93) | 7.86 (8.14) | |
| **19c** | $C_{23}H_{15}ClF_7N_3OS$ | 50.36 (50.24) | 3.01 (2.75) | 7.39 (7.64) | |
| **19d** | $C_{22}H_{15}Cl_3F_3N_3OS$ | 49.29 (49.60) | 2.84 (2.84) | 7.70 (7.89) | |
| **19e** | $C_{22}H_{14}Cl_3F_2N_3OS$ | 51.22 (51.53) | 3.13 (2.75) | 8.01 (8.19) | |
| **19f** | $C_{23}H_{17}Cl_2F_4N_3OS$ | 51.92 (52.09) | 3.31 (3.23) | 7.70 (7.92) | |
| **19g** | $C_{23}H_{17}BrClF_4N_3OS$ | 47.86 (48.06) | 2.91 (2.98) | 7.07 (7.31) | |

**Insecticidal Test for Tobacco Budworm (*Heliothis virescens*), Beet Armyworm (*Spodoptera exigua*), and Cabbage Looper (*Trichoplusia ni*).** To prepare the test solution, the test compound was formulated at 400 ppm in 7.5 mL of 2:1 acetone/distilled water. Two hundred and fifty microliters of the test solution was pipetted upon the surface of 8 mL of lepidopteran diet (Multispecies diet, Southland Products, Lake Village, AR) contained in each of five 1 oz plastic cups (one cup = 1 replication). A second-instar beet armyworm was placed upon the treated diet in each cup once the solvent had air-dried. The solutions remaining after completing applications to the 1 oz cups were then used as leaf-dip solutions for 3.5 cm leaf disks cut from cabbage leaves and cotton cotyledons. Five disks of each type of plant were dipped until thoroughly coated into each rate of each compound (=5 replications of each treatment). After air-drying, the treated leaf disks were placed individually into 1 oz plastic cups. Each dried, treated cotton cotyledon disk was infested with a second-instar tobacco budworm larva, and each cabbage leaf disk was infested with a second-instar cabbage looper larva. Cups containing the treated substrates and larvae were capped and then held in a growth chamber at 25 °C, 50−55% relative humidity (RH), and 14 h light/10 h dark for 5 days. The number of dead insects of five per species per treatment was then determined,

**Table 5.** Greenhouse Laboratory Data To Demonstrate SAR Trends

| entry | ID | Y | R1 | R2 | R3 | R4 | cotton aphid[a] | green peach aphid[b] | two-spotted spider mite[c] | tobacco budworm[d] | beet armyworm[d] | cabbage looper[d] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3-Position Thiophene Substitution | | | | | | | | | | | | |
| 1 | **4** | Cl | $CH_3$ | 4-$OCF_3$ | H | H | *0.5* (**12.8**)[e] | *13.7* | *<0.04* (**0.151**) | *225* | *<1.6* | *<1.6* |
| 2 | **12a** | Cl | Cl | 4-$OCF_3$ | H | H | 78/80 | 65 | 100 | *62* | (**<1.6**) | *4.02* (**69.2**) |
| 3 | **12p** | Cl | H | 4-$OCF_3$ | H | H | 72/47 | 9.6 | 0 | *122* | 49.9 (**59.9**) | 20.6 (**27.7**) |
| C-to-D-Ring Connection (4- versus 5-Position) | | | | | | | | | | | | |
| 4 | **4** | Cl | $CH_3$ | 4-$OCF_3$ | H | H | *0.5* (**12.8**) | *13.7* | *<0.04* (**0.151**) | *225* | *<1.6* | *<1.6* |
| 5 | **3** | Cl | $CH_3$ | 4-$OCF_3$ | H | H | *0.07* (**22.2**) | *23.3* | *<0.293* | *>400* | *21.9* (**243**) | 15.8 |
| D-Ring Mono- versus Disubstitution | | | | | | | | | | | | |
| 6 | **4** | Cl | $CH_3$ | 4-$OCF_3$ | H | H | *0.5* (**12.8**) | *13.7* | *<0.04* (**0.151**) | *225* | *<1.6* | *<1.6* |
| 7 | **12h** | Cl | $CH_3$ | 3-Cl | 4-F | H | *9.28* | 55 | 100 | 0/0 | 60/0 | 100/60 |
| 8 | **12q** | Cl | $CH_3$ | 3-F | 4-F | H | *4.41* (**22.3**) | 88 | 100 | 20/20 | 60/0 | 100/40 |
| 9 | **12r** | Cl | $CH_3$ | 2-F | 4-Cl | H | *4.93* | 91 | 100 | 20/20 | 100/0 | 100/40 |
| 10 | **12s** | Cl | $CH_3$ | 3-F | 4-Cl | H | *0.923* (**933**) | 89 | 100 | 19.4 | *65* (**323**) | *30.2* (**40.3**) |
| Fluoroalkyl Ethers | | | | | | | | | | | | |
| 11 | **4** | Cl | $CH_3$ | 4-$OCF_3$ | H | H | *0.5* (**12.8**) | *13.7* | *<0.04* (**0.151**) | *225* | *<1.6* | *<1.6* |
| 12 | **5** | Cl | $CH_3$ | 4-$OCF_2CFCl$ | H | H | *<5.0* | *<3.1* | *<0.1* (**2.07**) | **<1.6** | **<1.79** | **<1.6** |
| 13 | **18a** | Cl | Cl | 4-$OCF_2CFBr$ | H | H | 51/54 | 70 | 75 | **53.7** | **<1.6** | **<1.6** |
| 14 | **18d** | Cl | Cl | 4-$OCF_2CFCl$ | H | H | 69/72 | 78 | 0 | **<1.6** | **<1.6** | **<1.6** |
| 15 | **18e** | Cl | $CH_3$ | 4-$OCF_2CFBr$ | H | H | 92/89 | 62 | 0 | 3.93 | **2.17** | **<1.6** |
| 16 | **18f** | Cl | $CH_3$ | 3-$OCF_2CFCl$ | H | H | 89/91 | 75 | 75 | *4.38* (**151**) | **23.1** | **<1.6** |

[a] Percent mortality of CA at 50/5 ppm. [b] Percent mortality of GPA at 50 ppm. [c] Percent mortality of TSSM at 2.5 ppm. [d] Percent mortality of BAW, CL, and TBW at 400/25 ppm. [e] *$LC_{50}$* or (**$LC_{90}$**) in ppm.

**Table 6.** Laboratory Data[a] for Phenyl Thiophen-2-yl Triazoles and Commercial Standards

| compd | cotton aphid | green peach aphid | two-spotted spider mite | tobacco budworm | beet army-worm | cabbage looper |
|---|---|---|---|---|---|---|
| **3 (4-phenyl)** | **0.0656** | **23.3** | **<0.293** | **>400** | **21.9** | **15.8** |
| **4 (5-phenyl)** | **0.5** | **13.7** | **<0.04** | **225** | **<1.6** | **<1.6** |
| **5 (5-phenyl)** | **<5.0** | **<3.1** | **<0.1** | **<1.6** | **<1.6** | **<1.6** |
| **19b** (4-phenyl) | <5 | <5 | <2.5 | 4.38 | 1.56 | <1.56 |
| cypermethrin | | | | 1.3 | 1.6 | 0.6 |
| **1** | 0.7 | 0.8 | 0.29 | | | |
| spinosad | 65 | | 14 | 0.8 | 1.3 | 0.1 |
| imidacloprid | 0.05 | 1.7 | | | | |

[a] $LC_{50}$ in ppm.

and the results are given in **Tables 5** and **6** and Supporting Information Tables 1 and 2.

**Insecticidal Test for Cotton Aphid (*Aphis gossypii*).** To prepare spray solutions, 1 mg of each test compound was dissolved into 1 mL of 90:10 acetone/ethanol. One milliliter of this chemical solution was added to 19 mL of water containing 0.05% Tween 20 surfactant to produce a 50 ppm spray solution.

One-week-old Crookneck squash plants, trimmed to one cotyledon per plant, were infested with cotton aphid (all life stages). Prior to spraying (16−20 h), sections of heavily infested colony squash leaves were placed on the untreated squash cotyledons. As the infested sections dried out, the aphids moved to the succulent plant material. Plants were examined for good infestation prior to application. A hand-held Devilbiss, air-brush sprayer was used to apply compound spray solution to the squash plants. The plants were sprayed individually until runoff on all sides. Then, all four plants of that treatment were sprayed with a sweeping action with the remaining solution until completely used. Each rate was applied to four plants (1 plant = 1 replication). The plants were allowed to air-dry and held for 3 days in a controlled room at 26 °C and 40% RH prior to grading. Evaluation was by actual live count using a dissecting microscope. Percent control was calculated by comparison of test counts to solution-only (no test compound) sprayed plants. Results are given in **Tables 5** and **6** and Supporting Information Tables 1 and 2.

**Insecticidal Test for Two-Spotted Spider Mite (*Tetranychus urticae*). Ovicide Method.** Ten adult female two-spotted spider mites were placed on eight 2.2 cm leaf disks of cotton leaf, allowed to oviposit over 24 h, and thereafter removed. The leaf disks were sprayed with a 100 ppm test solution using a hand syringe and then were allowed to dry with 16 disks left untreated as a negative control. Disks were placed on an agar substrate and held at 24 °C and 90% RH for 6 days. Percent control based on the number of hatched larvae on treated disks and the number on untreated disks is reported in **Tables 5** and **6** and Supporting Information Tables 1 and 2.

**Insecticidal Test for Sweetpotato Whitefly (*Bemisia tabaci*).** Four milligrams of each test compound was dissolved by adding 4 mL of 90:10 acetone/ethanol to the vial containing the sample compound. This solution was added to 16 mL of water containing 0.05% Tween 20 surfactant to produce 20 mL of a 200 ppm spray solution. Five-week-old cotton plants reared in a greenhouse were stripped of all foliage except for the two uppermost true leaves that were >5 cm in diameter. These plants were then placed into a laboratory colony of whiteflies for 2 days for oviposition by the colony females. All whiteflies were then removed from the test plants with pressurized air. The spray solution was then applied to the test plants with a hand-held syringe fitted with a hollow cone nozzle. One milliliter of spray solution was applied to each leaf top and bottom for a total of 4 mL per plant. Four replications of each test compound utilized a total of 16 mL of spray solution. Plants were air-dried and then placed in a holding chamber (28 °C and 60% RH) for 13 days. Compound efficacy was evaluated by counting, under an illuminated magnifying glass, the number of large nymphs (third/fourth instar) per leaf. Percent control based on reduction of large nymphs of a test compound compared to solution-only (no test compound) sprayed plants is reported in Supporting Information Tables 1 and 2.

## RESULTS AND DISCUSSION

**SAR Development Rationale for Phenylthiophenes.** To find the best chewing and sap-feeding insect pest coactive, different areas of the phenylthiophenes were varied (**Figure 2**). Previous work in the 2,6-dihalo area has demonstrated that, in general, 2,6-dihaloaryl A-rings (typically, difluorophenyl or chlorofluorophenyl) are the most active. An *N*-methyl 1,2,4-triazole is the B-ring of choice, as demonstrated in earlier work in the dihalo area. The greatest points of diversity were incorporated on the C-ring thiophene and the D-ring. The only constant was the connection between the B- and C-rings: the 2-position of the thiophene. Substitutions on the 3-position of the thiophene

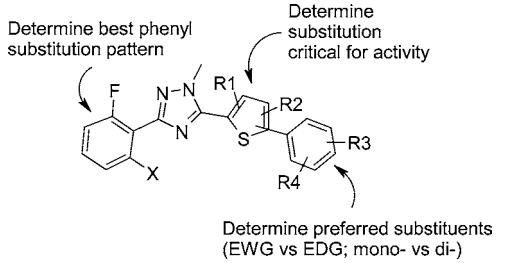
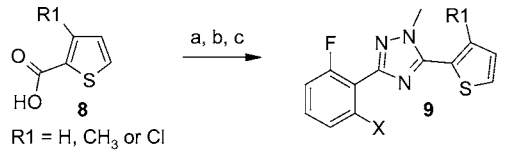



**Figure 2.** Determining structural requirements to maximize spectrum of activity and efficacy.

**Scheme 1.** General Synthetic Route to the ABC-Rings of Thiophen-2-yl Triazoles[a]

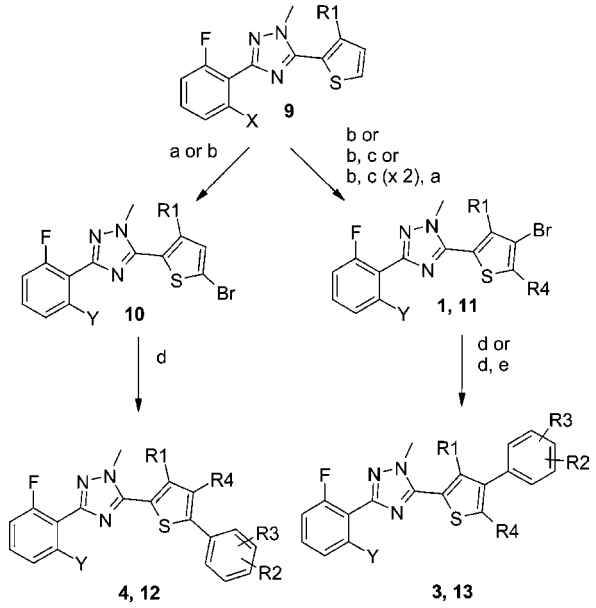



[a]Reagents and conditions: (a) $SOCl_2$, cat. DMF, DCE (b) *N*′-[(2,6-Difluorophenyl)iminomethyl]-*N*-methylhydrazine carboxylic acid tert-butyl ester, $PhCH_3$, 110 °C or 2-chloro-6-fluoro-thiobenzimidic acid methyl ester hydrogen bromide or methyl sulfate, pyr, DCE, 25 °C; (c) $CH_3NHNH_2$, $PhCH_3$, 25 or 110 °C, 16 h.

included methyl, as on **1**, chloro, as on **7**, and a proton. The D-ring was positioned at either the 4- or 5-position of the thiophene ring, providing the extended lipophilicity needed for lepidopteran activity. Heteroaryl and substituted aryl groups were incorporated into the molecules, generally by Suzuki cross-coupling methods. Variations in substitution pattern were examined (ortho, meta, and para substituents), as well as number of substituents (mono- and disubstitution), to evaluate steric requirements for activity. Electronic requirements for activity were evaluated by varying the substituents from electron-withdrawing to electron-donating (for example, $OCF_3$, $CF_3$, $CH_3$, and OEt). Finally, substituted cycloalkyl and cycloalkenyl groups were installed as D-rings to determine if the extended lipophilicity demanded aromatic functionality. In this way, the molecules were systematically varied to maximize efficacy and spectrum of activity against both chewing and sap-feeding insect pests.

**Synthetic Strategy and Execution.** The substituted thiophen-2-yl triazoles were synthesized by the general routes shown in **Schemes 1** and **2**. The acid chloride of a 2-thiophenecarboxylic acid **8** was formed by reaction of the acid with thionyl chloride and catalytic DMF in refluxing DCE. This intermediate was then allowed to react with either *N*′-[(2,6-difluorophenyl)-iminomethyl]-*N*-methylhydrazine carboxylic acid *tert*-butyl ester in refluxing toluene or 2-chloro-6-fluorothiobenzimidic acid methyl ester hydrogen bromide or methyl sulfate in DCE at ambient temperature to generate the intermediate amide. Cyclization with methylhydrazine provided the three-ring system **9**, containing a dihalogenated A-ring, *N*-methyl triazole B-ring, and thiophene C-ring (**Scheme 1**). Bromination of the C-ring thiophene could be effected in either the 4-position or the 4- and 5-positions (in the case of methyl only), depending upon the temperature of the reaction, to afford the corresponding mono- (**10**) and dibrominated thiophenes (not shown, **Scheme 2**). The monobrominated thiophenes **10** could then be converted to the four-ring compounds **12** via classical Suzuki cross-coupling conditions, to furnish compounds such as **4** (R1 = $CH_3$, R2 = 4-$OCF_3$, R3, R4 = H, **Scheme 2**), with or without further functionalization. Alternatively, the dibrominated thiophene

**Scheme 2.** General Synthetic Routes to the Four-Ring Phenyl Thiophen-2-yl Triazoles[a]



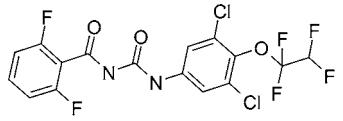

[a]Reagents and conditions: (a) $Br_2$, NaOAc, HOAc, 25 °C; (b) $Br_2$, NaOAc, HOAc, 75 °C; (c) *n*-BuLi, THF, -78 °C; electrophile; (d) boronic acid, $Pd(PPh_3)_2Cl_2$, $Na_2CO_3$, (*o*-tolyl)$_3$P, $CH_3CN/H_2O$ (10:1); (e) LDA, electrophile, -78 to 25 °C.

could be subjected to metal−halogen exchange followed by reaction with an electrophile (water, iodomethane, etc.) to give **1** (R4 = H) or **11** (R4 = $CH_3$). Compound **1** or **11** could be further elaborated via a variety of chemical conditions (Suzuki cross-coupling, bromination, alkylation, reduction, or substitution conditions) to provide the 4-phenyl compounds **13**, including **3** (R1 = $CH_3$, R2 = 4-$OCF_3$, R3, R4 = H, **Figure 1**).

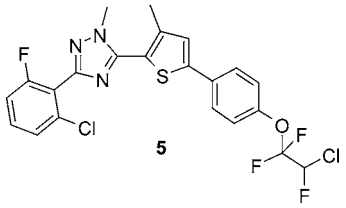
Most of the compounds in Supporting Information Tables 1 and 2 were synthesized by the routes shown in **Schemes 1** and **2**. Representative examples of the synthetic steps within the sequences can be found under Materials and Methods.

Some thiophene substitution patterns were difficult to achieve by the routes given in **Schemes 1** and **2**. As a result, less convergent synthetic sequences were needed. In the case of the electron-deficient 3-chlorothiophene-2-carboxylic acid (**8**, R1 = Cl, **Scheme 1**), it was necessary to functionalize the thiophene prior to completing the synthesis. Attempts to dibrominate the three-ring system **9** (R1 = Cl, **Scheme 2**) were unsuccessful, yielding only the monobrominated product **10** (R1 = Cl, R4 = H) under a variety of stringent bromination conditions. Commercially available 3-chlorothiophene-2-carboxylic acid (**8**) was esterified via the acid chloride, and was brominated and saponified, yielding the fully functionalized 4,5-dibromo-3-chlorothiophene-2-carboxylic acid (**14**) in reasonable yield after four steps (**Scheme 3**). Formation of the corresponding acid chloride and reaction of it with 2-chloro-6-fluorothiobenzimidic acid methyl ester methyl sulfate yielded the amide, which was cyclized to the *N*-methyl triazole with methylhydrazine in modest yield. A competing reaction of the methylhydrazine with the 5-position bromine accounted for the less than optimal cyclization yield. Suzuki coupling of bromide **15** under standard conditions, although different from those in **Scheme 2**, provided the four-ring compounds **16** (R = $OCF_3$, $CF_3$, OEt) in reasonable yields.

Given that the most active compounds tended to contain the electron-withdrawing trifluoromethoxy group, the SAR around

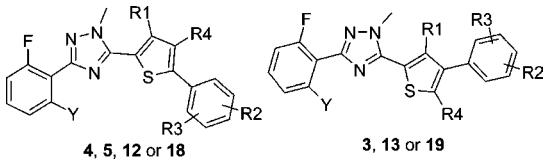


Hexaflumuron (**17**)



**5**

**Figure 3.** Structurally relevant perhaloalkyl ether compounds.



**4**, **5**, **12** or **18** **3**, **13** or **19**

**Figure 4.** General structures for compounds from **Tables 5** and **6**.

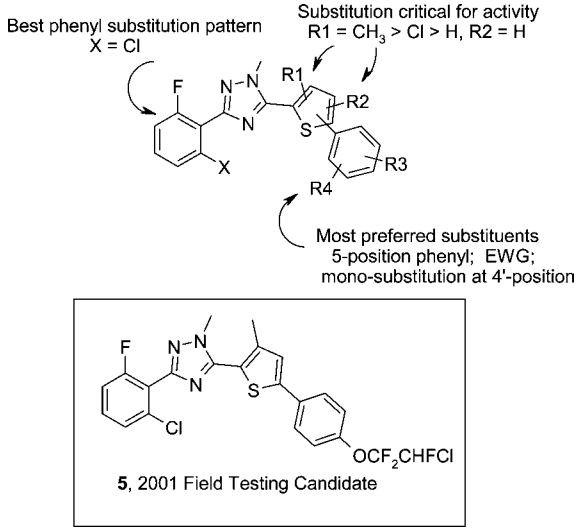
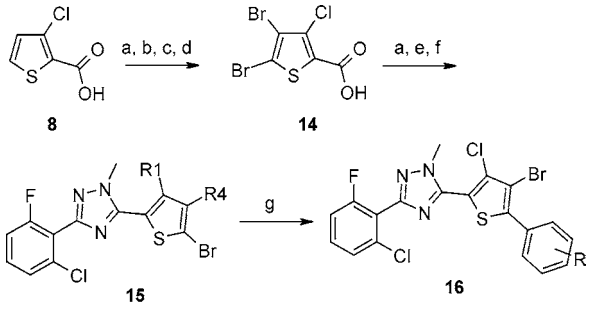



**Figure 5.** Pictorial summary of SAR trends.

**Scheme 3.** Synthetic Route to Phenyl Thiophen-2-yl Triazoles[a]



**8** **14** **15** **16**

[a]Reagents and conditions: (a) $SOCl_2$, cat. DMF, DCE; (b) EtOH, DCE; (c) $Br_2$, NaOAc, HOAc, 55-75 °C; (d) LiOH, THF/$H_2O$ (1:1); (e) 2-Chloro-6-fluorothiobenzimidic acid methyl ester methyl sulfate, pyr, DCE; (f) $CH_3NHNH_2$, $PhCH_3$, rt, 16 h; (g) phenylboronic acid, $Pd(PPh_3)_4$, $K_2CO_3$, $PhCH_3$.

the D-ring was expanded by generating perhaloalkyl ethers similar to that found in hexaflumuron (**17**, {*N*-[[[3,5-dichloro-4-(1,1,2,2-tetrafluoroethoxy)phenyl]amino]carbonyl]-2,6-difluorobenzamide}, the active ingredient in Recruit II (trademark of Dow AgraSciences LLC) termite bait in the Sentricon (trademark of Dow AgraSciences LLC) *Termite Colony Elimination System*, **Figure 3**). Thus, the ethyl group was removed from the ethyl phenyl ether **12** or **13** with boron tribromide in dichloromethane to provide the phenol, which was subsequently alkylated with base and gaseous bromo- or chlorotrifluoroethylene or hexafluoropropene, to afford the desired perhaloalkylether **18** or **19** (**Scheme 4**). These compounds proved to be even more active than their predecessors in this series (for example, **4**). Included in this latter group is **5** (**Figure 5**), a field testing candidate in the northern hemisphere in the summer of 2001. Further elaboration, like bromination, could be accomplished under standard conditions to yield **20**.

**Biological Activity, SAR Trends, and Field Results.** Tables 1 and 2 in the Supporting Information provide greenhouse laboratory data against tobacco budworm (TBW), beet armyworm (BAW), cabbage looper (CL), cotton aphid (CA), two-spotted spider mite (TSSM), and whitefly (WF). **Table 5** was created to compare and contrast major points of the SAR of the phenyl thiophen-2-yl triazoles, including substitution on the C-ring thiophene (3-position R group), C-to-D-ring connectivity (4- vs 5-position aryl), and D-ring substitution (mono- vs disubstitution, electron-withdrawing vs electron-donating substituents). **Figure 4** provides the general structures for the following tables.

By comparison of the efficacy and spectrum of activity of the compounds, the following SAR trends were established. The 3-position C-ring thiophene substitution adheres to the following: $CH_3$ > Cl > H ≫ Ph (entries 1−3; some data not shown). 5-Position C-to-D-ring connectivity was preferred over the 4-position D-rings (entries 4 and 5). Monosubstituted D-rings were preferred over disubstituted D-rings, with the para position being favored over the ortho and meta positions (entries 6−10). Electron-withdrawing groups generally had the best activity (e.g., **4**); however, increasing the number of halogens, as in **5**, increased the lepidopteran activity over that of the testing candidate **4** (entries 11−16). These SAR trends are shown pictorially in **Figure 5**.

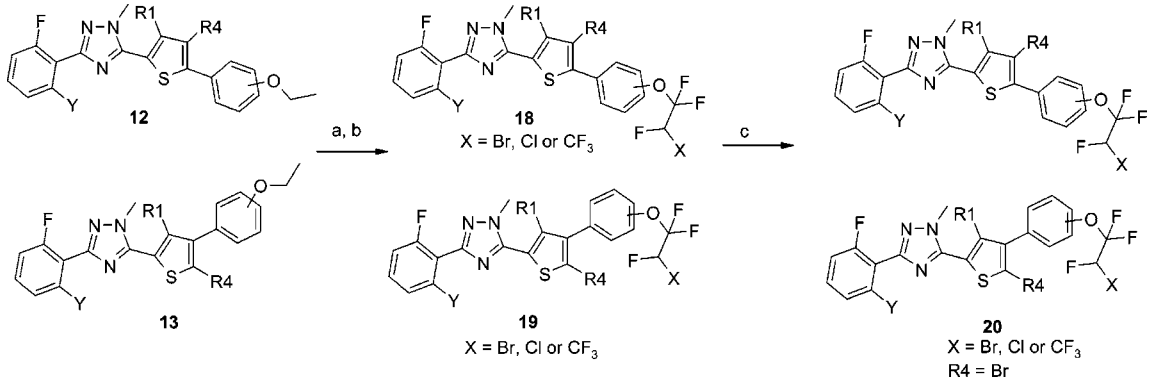
**Table 6** provides laboratory data ($LC_{50}$ in ppm) for the leading phenyl thiophen-2-yl triazoles in comparison to other testing candidates, field testing candidates, and commercial standards. In the laboratory, compound **5** has activity comparable to that of other field testing molecules. All three **boldfaced** compounds show activity comparable to those of commercial standards with superior activity against mites.

Extending the lipophilicity of the first-generation dihalo actives provided the desired lepidopteran activity in the phenylthiophene series while retaining the sap-feeding insect pest activity. SAR development afforded the first lead compound, **4**, which was selected for field testing. It was also observed that attachment of the D-ring phenyl systems was preferred at the 5- as compared to the 4-position. Subsequent exploration revealed that perhaloalkyl ethers in the para position of the D-ring gave optimal efficacy and, in particular, chlorotrifluoroethyl ether derivative **5** stood out as the best and was sent for advanced field testing. Although these compounds were highly active in laboratory tests, their activity in the field was not sufficient to warrant any further advancement. Although the phenyl thiophen-2-yl triazole series afforded exciting activity, the corresponding phenyl thiophen-3-yl triazoles, as well as other nitrogen heterocycles/bioisosteres for triazoles, were also investigated and will be the subject of subsequent publications.

## ABBREVIATIONS USED

**1**, 5-(4-bromo-3-methylthiophen-2-yl)-3-(2-chloro-6-fluorophenyl)-1-methyl-1*H*-[1,2,4]triazole; **2**, 3-(2-chloro-6-fluo-

**Scheme 4.** Synthetic Sequence for Generating Perhaloalkylethers[a]




[a]Reagents and conditions: (a) $BBr_3$, $CH_2Cl_2$, 0 °C; (b) 25% NaOH, DMF, $CF_2CFX$ (g); (c) $Br_2$, HOAc, 0 to 25 °C.

rophenyl)-5-[3,4-dichloro-5-(4-ethoxyphenylethynyl)thiophen-2-yl]-1-methyl-1*H*-[1,2,4]triazole; **3**, 3-(2-chloro-6-fluorophenyl)-1-methyl-5-[3-methyl-4-(4-trifluoromethoxyphenyl)thiophen-2-yl]-1*H*-[1,2,4]triazole; **4**, 3-(2-chloro-6-fluorophenyl)-1-methyl-5-[3-methyl-5-(4-trifluoromethoxyphenyl)thiophen-2-yl]-1*H*-[1,2,4]triazole; **5**, 3-(2-chloro-6-fluorophenyl)-5-{5-[4-(2-chloro-1,1,2-trifluoroethoxy)phenyl]-3-methylthiophen-2-yl}-1-methyl-1*H*-[1,2,4]triazole; **6**, 2-chloro-5-[5-(2-chloro-6-fluorophenyl)-2-methyl-2*H*-[1,2,4]triazol-3-yl]pyridine; **7**, 3-(2-chloro-6-fluorophenyl)-1-methyl-5-(3,4,5-trichlorothiophen-2-yl)-1*H*-[1,2,4]triazole; **9a**, 3-(2-chloro-6-fluorophenyl)-5-(3-chlorothiophen-2-yl)-1-methyl-1*H*-[1,2,4]triazole; **10a**, 5-(5-bromo-3-chlorothiophen-2-yl)-3-(2-chloro-6-fluorophenyl)-1-methyl-1*H*-[1,2,4]triazole; **10b**, 5-(5-bromo-3-chlorothiophen-2-yl)-3-(2,6-difluorophenyl)-1-methyl-1*H*-[1,2,4]triazole; **11a**, 5-(4-bromo-3,5-dimethylthiophen-2-yl)-3-(2-chloro-6-fluorophenyl)-1-methyl-1*H*-[1,2,4]triazole; **12a**, 3-(2-chloro-6-fluorophenyl)-5-[3-chloro-5-(4-trifluoromethoxyphenyl)thiophen-2-yl]-1-methyl-1*H*-[1,2,4]triazole; **12b**, 3-(2-chloro-6-fluorophenyl)-5-[3-chloro-5-(4-trifluoromethylphenyl)-thiophen-2-yl}-1-methyl-1*H*-[1,2,4]triazole; **12c**, 3-(2-chloro-6-fluorophenyl)-5-(3-chloro-5-*p*-tolylthiophen-2-yl)-1-methyl-1*H*-[1,2,4]triazole; **12d**, 5-[3-chloro-5-(4-ethoxyphenyl)thiophen-2-yl]-3-(2-chloro-6-fluorophenyl)-1-methyl-1*H*-[1,2,4]triazole; **12e**, 5-[5-(4-bromophenyl)-3-chlorothiophen-2-yl]-3-(2-chloro-6-fluorophenyl)-1-methyl-1*H*-[1,2,4]triazole; **12f**, 3-(2-chloro-6-fluorophenyl)-5-[3-chloro-5-(4-methylsulfanylphenyl)thiophen-2-yl}-1-methyl-1*H*-[1,2,4]triazole; **12g**, 3-(2-chloro-6-fluorophenyl)-1-methyl-5-[3-methyl-5-(4-trifluoromethylphenyl)thiophen-2-yl]-1*H*-[1,2,4]triazole; **12h**, 3-(2-chloro-6-fluorophenyl)-5-[5-(3-chloro-4-fluorophenyl)-3-methylthiophen-2-yl]-1-methyl-1*H*-[1,2,4]triazole; **12i**, 3-(2-chloro-6-fluorophenyl)-5-[5-(3-ethoxyphenyl)-3-methylthiophen-2-yl]-1-methyl-1*H*-[1,2,4]triazole; **12j**, 3-(2-chloro-6-fluorophenyl)-5-[5-(4-ethoxyphenyl)-3,4-dimethylthiophen-2-yl]-1-methyl-1*H*-[1,2,4]triazole; **12k**, 3-(2-chloro-6-fluorophenyl)-5-[3,4-dimethyl-5-(4-trifluoromethoxyphenyl)-thiophen-2-yl]-1-methyl-1*H*-[1,2,4]triazole; **12l**, 5-[3-chloro-5-(4-trifluoromethoxyphenyl)thiophen-2-yl]-3-(2,6-difluorophenyl)-1-methyl-1*H*-[1,2,4]triazole; **12m**, 5-(3-chloro-5-*p*-tolylthiophen-2-yl)-3-(2,6-difluorophenyl)-1-methyl-1*H*-[1,2,4]triazole; **12n**, 5-[3-chloro-5-(4-ethoxyphenyl)thiophen-2-yl]-3-(2,6-difluorophenyl)-1-methyl-1*H*-[1,2,4]triazole; **12o**, 5-[3-chloro-5-(4-trifluoromethylphenyl)thiophen-2-yl}-3-(2,6-difluorophenyl)-1-methyl-1*H*-[1,2,4]triazole; **13a**, 3-(2-chloro-6-fluorophenyl)-5-[4-(4-ethoxyphenyl)-3-methylthiophen-2-yl]-1-methyl-1*H*-[1,2,4]triazole; **13b**, 3-(2-chloro-6-fluorophenyl)-1-methyl-5-[3-methyl-4-(4-trifluoromethylphenyl)thiophen-2-yl]-1*H*-[1,2,4]triazole; **13c**, 3-(2-chloro-6-fluorophenyl)-5-[4-(4-isopropylphenyl)-3-methylthiophen-2-yl]-1-methyl-1*H*-[1,2,4]-triazole; **13d**, 3-(2-chloro-6-fluorophenyl)-5-[4-(4-ethoxyphenyl)-3,5-dimethylthiophen-2-yl]-1-methyl-1*H*-[1,2,4]triazole; **13e**, 3-(2-chloro-6-fluorophenyl)-5-[3,5-dimethyl-4-(4-trifluoromethylphenyl)thiophen-2-yl]-1-methyl-1*H*-[1,2,4]triazole; **13f**, 3-(2-chloro-6-fluorophenyl)-5-[3,5-dimethyl-4-(4-trifluoromethoxyphenyl)thiophen-2-yl]-1-methyl-1*H*-[1,2,4]triazole; **13g**, 3-(2-chloro-6-fluorophenyl)-5-[4-(4-isopropylphenyl)-3,5-dimethylthiophen-2-yl]-1-methyl-1*H*-[1,2,4]triazole; **13h**, 3-(2-chloro-6-fluorophenyl)-5-[4-(4-chlorophenyl)-3,5-dimethylthiophen-2-yl]-1-methyl-1*H*-[1,2,4]triazole; **14**, 4,5-dibromo-3-chlorothiophene-2-carboxylic acid; **15**, 3-(2-chloro-6-fluorophenyl)-5-(4,5-dibromo-3-chlorothiophen-2-yl)-1-methyl-1*H*-[1,2,4]triazole; **16a**, 5-[4-bromo-3-chloro-5-(4-trifluoromethoxyphenyl)thiophen-2-yl]-3-(2-chloro-6-fluorophenyl)-1-methyl-1*H*-[1,2,4]triazole; **16b**, 5-[4-bromo-3-chloro-5-(4-trifluoromethylphenyl)thiophen-2-yl]-3-(2-chloro-6-fluorophenyl)-1-methyl-1*H*-[1,2,4]triazole; **16c**, 5-[4-bromo-3-chloro-5-(4-ethoxyphenyl)thiophen-2-yl]-3-(2-chloro-6-fluorophenyl)-1-methyl-1*H*-[1,2,4]triazole; **17**, *N*-{[[3,5-dichloro-4-(1,1,2,2-tetrafluoroethoxy)phenyl]amino]carbonyl}-2,6-diflubenzamide; **18a**, 5-{5-[4-(2-bromo-1,1,2-trifluoroethoxy)phenyl]-3-chlorothiophen-2-yl}-3-(2-chloro-6-fluorophenyl)-1-methyl-1*H*-[1,2,4]triazole; **18b**, 3-(2-chloro-6-fluorophenyl)-5-{5-[4-(2,2-dichloro-1,1-difluoroethoxy)phenyl]-3-methylthiophen-2-yl}-1-methyl-1*H*-[1,2,4]triazole; **18c**, 3-(2-chloro-6-fluorophenyl)-5-{5-[4-(1,1,2,3,3,3-hexafluoropropoxy)phenyl]-3-methylthiophen-2-yl}-1-methyl-1*H*-[1,2,4]triazole; **18d**, 5-{3-chloro-5-[4-(2-chloro-1,1,2-trifluoroethoxy)phenyl]thiophen-2-yl}-3-(2-chloro-6-fluorophenyl)-1-methyl-1*H*-[1,2,4]triazole; **18e**, 5-{5-[3-(2-bromo-1,1,2-trifluoroethoxy)phenyl]-3-methylthiophen-2-yl}-3-(2-chloro-6-fluorophenyl)-1-methyl-1*H*-[1,2,4]triazole; **18f**, 3-(2-chloro-6-fluorophenyl)-5-{5-[3-(2-chloro-1,1,2-trifluoroethoxy)phenyl]-3-methylthiophen-2-yl}-1-methyl-1*H*-[1,2,4]triazole; **18g**, 3-(2-chloro-6-fluorophenyl)-5-{5-[4-(2-chloro-1,1,2-trifluoroethoxy)phenyl]-3,4-dimethylthiophen-2-yl}-1-methyl-1*H*-[1,2,4]triazole; **18h**, 5-{5-[4-(2-bromo-1,1,2-trifluoroethoxy)phenyl]-3,4-dimethylthiophen-2-yl}-3-(2-chloro-6-fluorophenyl)-1-methyl-1*H*-[1,2,4]triazole; **19a**, 5-{4-[4-(2-bromo-1,1,2-trifluoroethoxy)phenyl]-3-methylthiophen-2-yl}-3-(2-chloro-6-fluorophenyl)-1-methyl-1*H*-[1,2,4]triazole; **19b**, 3-(2-chloro-6-fluorophenyl)-5-{4-[4-(2-chloro-1,1,2-trifluoroethoxy)phenyl]-3-methylthiophen-2-yl}-1-methyl-1*H*-[1,2,4]triazole; **19c**, 3-(2-chloro-6-fluorophenyl)-5-{4-[4-(1,1,2,3,3,3-hexafluoropropoxy)phenyl]-3-methylthiophen-2-yl}-1-methyl-1*H*-[1,2,4]triazole; **19d**, 3-(2-chloro-6-fluorophenyl)-5-{4-[4-(2,2-dichloro-1,1-difluoroethoxy)phenyl]-3-methylthiophen-2-yl}-1-methyl-1*H*-[1,2,4]triazole; **19e**, 3-(2-

chloro-6-fluorophenyl)-5-{4-[4-(2,2-dichloro-1-fluorovinyloxy)phenyl]-3-methylthiophen-2-yl}-1-methyl-1*H*-[1,2,4]triazole; **19f**, 3-(2-chloro-6-fluorophenyl)-5-{4-[4-(2-chloro-1,1,2-trifluoroethoxy)phenyl]-3,5-dimethylthiophen-2-yl}-1-methyl-1*H*-[1,2,4]triazole; **19g**, 5-{4-[4-(2-bromo-1,1,2-trifluoroethoxy)phenyl]-3,5-dimethylthiophen-2-yl}-3-(2-chloro-6-fluorophenyl)-1-methyl-1*H*-[1,2,4]triazole; **20**, 5-{5-bromo-4-[4-(2-bromo-1,1,2-trifluoroethoxyphenyl]-3-methylthiophen-2-yl}-3-(2-chloro-6-fluorophenyl)-1-methyl-1*H*-[1,2,4]triazole.

## ACKNOWLEDGMENT

We thank Jeff Gilbert and Jeff Godbey for conducting HRMS analyses.

**Supporting Information Available:** Greenhouse laboratory data are provided for the phenyl 4- and 5-substituted thiophenes. This material is available free of charge via the Internet at http://pubs.acs.org.

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**Received for review May 22, 2007. Revised manuscript received July 2, 2007. Accepted July 2, 2007.**

JF071498S