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Synthesis and biological activity of novel 2-methyl-4-trifluoromethyl-thiazole-5-carboxamide derivatives

Chang-Ling Liu[a,b], Zheng-Ming Li[a,*], Bin Zhong[a]

[a]*Institute of Elemento-Organic Chemistry, State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, PR China*
[b]*Shenyang Research Institute of Chemical Industry, Shenyang 110021, PR China*

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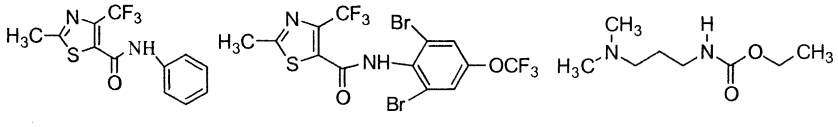
Abstract

Nine novel 2-methyl-4-trifluoromethylthiazole-5-carboxamide derivatives were designed and synthesized utilizing ethyl 4,4,4-trifluoroacetoacetate as a starting material. Subsequently, the biological activity of the compounds was evaluated in the greenhouse. Results indicated that all of the compounds have some fungicidal and insecticidal activity but no herbicidal activity. Compound **1** has fungicidal activity with 90% control of tomato late blight at 375 g ai/ha, while two compounds **2F** and **2H** show insecticidal activity with 80 and 100% control, respectively, against potato leafhopper at 600 g ai/ha.

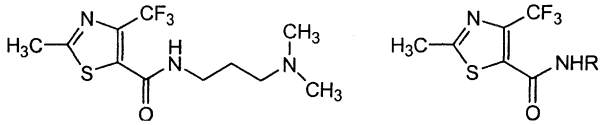
Keywords: Synthesis; Biological activity; 2-Methyl-5-trifluoromethyl-thiazolecarboxamides

1. Introduction

The thiazole nucleus plays a vital role in many biological activities making it one of the extensively studied heterocycles [1–9]. For example 2,4-dimethylthiazole-5-carboxamide and 2-methyl-4-trifluoromethylthiazole-5-carboxamide derivatives such as metsulfovax [10] and thifluzamide [11] are known as agricultural fungicides where the 4-trifluoromethylthiazole-5-carboxamide derivatives are usually better than the 4-methylthiazole-5-carboxamides [3]. Propamocarb [12] is also a known agricultural fungicide and with the goal of discovering new fungicides we incorporated the two active moieties of thifuzamide and propamocarb into a single compound, **1**. The hydrochloride salt (**2A**), and additional analogs (**2B–2D**) and comparative compounds (**2E–2H**) were synthesized, and their biological activities were evaluated in the greenhouse.



metsulfovax thifuzamide propamocarb



1 **2**

2. Results and discussion

2.1. Synthesis

Scheme 1 illustrates the synthetic route used to prepare the derivatives.

Compound **6** was synthesized from ethyl 4,4,4-trifluoroacetoacetate [13] and reacted easily with amines in acetonitrile to afford **1** and **2** in high purity and yield. Compound

* Corresponding author.
E-mail addresses: liuchangling@vip.163.com (C.-L. Liu), nkzml@nk.sina.net (Z.-M. Li).

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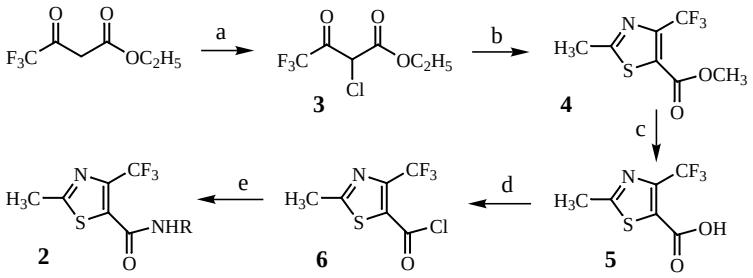
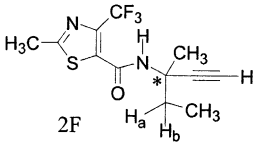


Scheme 1. Synthesis of 2-methyl-4-trifluoromethyl-thiazole-5-carboxamide derivatives. (a) $SO_2Cl_2CCl_4$; (b) thioacetamide/DMF; (c) $NaOH/H_2O$, HCl (aq); (d) $SOCl_2$; (e) amine/Et_3N/CH_3CN. R: **2A**, 3-(dimethylamino)propyl HCL salt; **2B**, 3-(diethylamino)propyl; **2C**, 3-(1*H*-imidazol-1-yl)propyl; **2D**, 3-(2-oxo-pyrrolidin-1-yl)propyl; **2E**, 1,1-dimethyl-prop-2-ynyl; **2F**, 1-ethyl-1-methyl-prop-2-ynyl; **2G**, *tert*-butyl; **2H**, (*N*-*tert*-butyl)amino.

2A was prepared from **1** with hydrochloride acid in methanol.

The synthesized compounds **1** and **2** were characterized by IR, ^{1}H NMR, mass spectra and elemental analyses were consistent with the assigned structures. The IR spectra of compounds showed NH and C=O stretching bands at 3240–3440 and 1640–1675 cm^{-1}, respectively. The ^{1}H NMR of spectra of compounds **1** and **2** showed signals at δ 5.98–8.45 ppm attributed to NH, while the $\underline{CH_2}$ of compound **2F** was affected by CH_3 and chiral carbon simultaneously, and showed two groups of quadruple peak 2.11–2.15 (m, 1H, $J = 7.5$ Hz, CH_aMe), and 1.85–1.92 (m, 1H, $J = 7.5$ Hz, CH_bMe).



2F

2.2. Biological activities

The biological activities were evaluated at Rohm and Haas Co. using a previously reported procedure [14–17]. All of the compounds have some flingicidal and insecticidal activity with no herbicidal activity, where 100% is complete control of the flingus. Compound **1** showed good activity of tomato late blight providing 90% at 375 g ai/ha. Additionally, two compounds, **2F** and **2H**, have insecticidal activity with 80 and 100% control, respectively, against potato leafhopper at 600 g ai/ha.

3. Experimental

Melting points were determined on a Büchi melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded with Mercury 300 (Varian, 300 MHz) spectrometer with CDCl3 as the solvent and TMS as the internal standard. Infrared spectra were measured on KBr disks using a PF-983G instrument (Perkin-Elmer). Mass spectra (GC–MS) were obtained on an MD-800 (Fisons) instrument. Combustion analyses for elemental composition were made with an EA 1106 analyzer (Fisons). All chemicals or reagents were purchased from standard commercial suppliers.

3.1. Preparation of N-(3-(dimethylamino)propyl)-2-methyl-4-trifluoromethylthiazole-5-carboxamide (*1*)

To the solution of 3-(dimethylaniino)propylamine (1.1 g, 0.01 mol) and triethylamine (1.0 g, 0.01 mol) in 10 mL acetonitrile was added 2-methyl-4-trifluoromethylthiazole-5-carbonyl chloride (**6**) [13] (2.3 g, 0.01 mol), the mixture was heated to reflux for 10 min, rotovaped to remove the acetonitrile. Water was added and extracted with ethyl acetate, washed with saturated aqueous $NaHCO_3$, water and brine, dried over magnesium sulfate and rotovaped to give 2.36 g of the target compound (**1**) as an oil, yield 80%. IR (KBr) *v*: 3300 (N–H), 2960, 2840, 1660, 1565, 1495, 1465, 1360, 1295, 1175, 1140, 910, 730 cm^{-1}; GC–MS, *m*/*z* (%): 295 (M^+, 15%), 273 (25%), 254, 245 (10%), 232 (8%), 222 (88%), 206 (10%), 194 (75%), 181 (18%), 166 (70%), 147, 125 (40%), 106 (10%), 97 (100%), 84 (20%), 71 (25%), 58 (25%), 42 (80%); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.45 (bs, 1H, NH), 3.53 (d, 2H, $J = 5.4$ Hz, CH_2), 2.73 (s, 3H, CH_3), 2.60 (t, 2H, $J = 6$ Hz, CH_2), 2.34 (s, 6H, NMe_2), 1.82 (t, 2H, $J = 6$ Hz, CH_2); Anal. Calc. (%) for $C_{11}H_{16}F_3N_3OS$: C, 44.73; H, 5.46; N, 14.24. Found: C, 44.49; H, 5.56; N, 14.28.

3.2. Preparation of N-(3-(dimethylamino)propyl)-2-methyl-4-trifluoromethylthiazole-5-carboxamide hydrochloride salt (*2A*)

Yield 90%, 143–144 °C. IR (KBr) *v*: 3440 (N–H), 2980, 2960, 1640, 1520, 1505, 1475, 1440, 1320, 1250, 1160, 1135, 1080, 905, 850, 710 cm^{-1}; GC–MS, *m*/*z* (%): 331 (M^+), 295 (13%), 280, 275, 251, 194 (15%), 166 (22%), 151, 125 (22%), 106 (5%), 84 (10%), 72 (20%), 58 (100%); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 11.76 (bs, 1H, HCl), 8.22 (bs, 1H, NH), 3.60 (bs, 2H, CH_2), 3.15 (bs, 2H, CH_2), 2.84 (d, 6H, $J = 3.6$ Hz, NMe_2), 2.73 (s, 3H, CH_3), 2.18 (bs, 2H, CH_2).

3.3. Preparation of N-(3-(diethylamino)propyl)-2-methyl-4-trifluoromethylthiazole-5-carboxamide (**2B**)

Oil, yield 86%. IR(KBr) *v*: 3280 (N–H), 2980, 2820, 1660, 1565, 1490, 1360, 1295, 1200, 1175, 1135, 910, 730 cm^{-1}; GC–MS, *m/z* (%): 323 (M^+, 15%), 308 (68%), 294 (45%), 231 (5%), 223 (8%), 183 (3%), 166 (65%), 125 (50%), 112 (20%), 100 (22%), 86 (100%), 72 (75%), 58 (65%), 42 (38%); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.44 (bs, 1H, NH), 3.56 (d, 2H, $J = 6$ Hz, CH_2), 2.70–2.81 (m, 9H, CH_3, $3CH_2$), 1.92 (t, 2H, $J = 6$ Hz, CH_2), 1.13–1.18 (m, 6H, $2CH_3$); Anal. Calc. (%) for $C_{13}H_{20}F_3N_3OS$: C, 48.29; H, 6.23; N 12.99. Found: C, 48.40; H, 6.18; N 12.78.

3.4. Preparation of N-(3-(1H-imidazol-1-yl)propyl)-2-methyl-4-trifluoromethylthiazole-5-carboxamide (**2C**)

Oil, yield 78%. IR (KBr) *v*: 3240 (N–H), 2950, 2880, 1660, 1570, 1505, 1495, 1440, 1360, 1295, 1230, 1205, 1175, 1140, 1090, 910, 820, 730, 670 cm^{-1}; GC–MS, *m/z* (%): 318 (M^+, 5%), 300, 275, 341, 259 (6%), 251, 203 (3%), 194 (80%), 183 (15%), 175 (18%), 166 (90%), 146 (8%), 125 (65%), 107 (42%), 95 (100%), 82 (85%), 69 (28%), 55 (45%), 41 (35%); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.62 (bs, 1H, NH), 7.45 (s, 1H, CH), 6.95 (s, 2H, CH=CH), 4.04 (t, 2H, $J = 6.6$ Hz, CH_2), 3.38 (d, 2H, $J = 6.3$ Hz, CH_2), 2.73 (s, 3H, CH_3), 2.10 (t, 2H, $J = 6.6$ Hz, CH_2); Anal. Calc. (%) for $C_{12}H_{13}F_3N_4OS$: C, 45.27; H, 4.12; N 17.61. Found: C, 45.08; H, 4.25; N 17.45.

3.5. Preparation of N-(3-(2-oxo-pyrrolidin-1-yl)propyl)-2-methyl-4-trifluoromethylthiazole-5-carboxamide (**2D**)

Oil, yield 85%. IR (KBr) *v*: 3265 (N–H), 2940, 2880, 1675, 1655, 1560, 1500, 1475, 1440, 1365, 1295, 1205, 1175, 1140, 905, 820, 730 cm^{-1}; GC–MS, *m/z* (%): 335 (M^+, 30%), 315, 302, 287 (5%), 266 (10%), 251 (5%), 237 (15%), 224 (23%), 211, 194 (62%), 183 (15%), 175 (12%), 166 (62%), 146 (3%), 141 (12%), 125 (64%), 112 (78%), 98 (100%), 84 (38%), 70 (64%), 56 (52%), 41 (49%); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.66 (bs, 1H, NH), 3.33–3.46 (m, 6H, $3CH_2$), 2.73 (s, 3H, CH_3), 2.43 (t, 2H, $J = 8.1$ Hz, CH_2), 2.11 (m, 2H, CH_2), 1.80 (m, 2H, CH_2); Anal. Calc. (%) for $C_{13}H_{16}F_3N_3O_2S$: C, 46.55; H, 4.81; N, 12.54. Found: C, 46.72; H, 4.67; N, 12.62.

3.6. Preparation of N-(1,1-dimethyl-prop-2-ynyl)-2-methyl-4-trifluoromethylthiazole-5-carboxamide (**2E**)

Yield 95%, 99–100 °C. IR (KBr) *v*: 3320 (C≡CH), 3290 (N–H), 2980, 2920, 2180 (C≡C), 1660, 1560, 1530, 1485, 1360, 1295, 1205, 1175, 1135, 1000, 905, 850, 730, 665, 640 cm^{-1}; GC–MS, *m/z* (%): 276 (M^+, 50%), 261 (60%), 256 (78%), 241 (15%), 228 (12%), 220 (8%), 207 (15%), 194 (100%), 187 (60%), 171 (15%), 166 (88%), 146 (15%), 125 (78%), 106 (50%), 96 (15%), 84 (55%), 67 (48%), 52 (39%), 41 (65%); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.21 (bs, 1H, NH), 2.73 (s, 3H, CH_3), 2.42 (s, 1H, ≡CH), 1.73 (s, 6H, $2CH_3$); Anal. Calc. (%) for $C_{11}H_{11}F_3N_2OS$: C, 47.82; H, 4.02; N, 10.15. Found: C, 47.68; H, 3.90; N, 10.28.

3.7. Preparation of N-(1-ethyl-1-methyl-prop-2-ynyl)-2-methyl-4-trifluoromethylthiazole-5-carboxamide (**2F**)

Yield 95%, 79–80 °C. IR (KBr) *v*: 3310 (C≡CH), 3280 (N–H), 2980, 2940, 2880, 2180 (C≡C), 1665, 1575, 1540, 1485, 1485, 1465, 1360, 1320, 1295, 1205, 1185, 1135, 1000, 910, 840, 730, 675, 635 cm^{-1}; GC–MS, *m/z* (%): 291 ($M + 1$, 2%), 275 (10%), 261 (100%), 255 (15%), 242 (70%), 235, 221, 194 (90%), 173 (10%), 166 (80%), 146 (15%), 125 (65%), 106 (32%), 96 (15%), 79 (52%), 65 (12%), 53 (25%), 42 (20%); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.20 (bs, 1H, NH), 2.73 (s, 3H, CH_3), 2.11–2.15 (m, $J = 7.5$, 1H, CH_aMe), 1.85–1.92 (m, $J = 7.5$, 1H, CH_bMe), 2.43 (s, 1H, C≡CH), 1.71 (s, 3H, CH_3), 1.58 (t, 3H, $J = 7.2$ Hz, CH_3); Anal. Calc. (%) for $C_{12}H_{13}F_3N_2OS$: C, 49.64; H, 4.52; N, 9.65. Found: C, 49.45; H, 4.42; N, 9.78.

3.8. Preparation of N-tert-butyl-2-methyl-4-trifluoromethylthiazole-5-carboxamide (**2G**)

Yield 95%, 110–112 °C. IR (KBr) *v*: 3300 (N–H), 2980, 2940, 1650, 1575, 1540, 1495, 1375, 1305, 1200, 1175, 1140, 910, 850, 730, 695 cm^{-1}; GC–MS, *m/z* (%): 266 (M^+, 35%), 251 (88%), 231, 223, 211 (60%), 194 (100%), 171 (44%), 166 (88%), 151 (25%), 146 (10%), 125 (75%), 118 (20%), 106 (30%), 96 (8%), 87 (5%), 70 (8%), 56 (48%), 42 (41%); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.98 (bs, 1H, NH), 2.72 (s, 3H, CH_3), 1.44 (s, 9H, $3CH_3$); Anal. Calc. (%) for $C_{10}H_{13}F_3N_2OS$: C, 45.10; H, 4.92; N, 10.53. Found: C, 45.29; H, 4.78; N, 10.37.

3.9. Preparation of N-((N-tert-butyl)amino)-2-methyl-4-trifluoromethylthiazole-5-carboxamide (**2H**)

Yield 85%, 123–124 °C. IR (KBr) *v*: 3260 (N–H), 3205 (N–NH), 2980, 1675, 1530, 1460, 1375, 1340, 1210, 1155, 910, 865, 780, 715 cm^{-1}; GC–MS, *m/z* (%): 281 (M^+, 20%), 266 (52%), 246 (15%), 225 (75%), 205 (25%), 194 (100%), 186 (10%), 166 (45%), 148 (2%), 146 (3%), 125 (30%), 106 (10%), 87 (15%), 75 (4%), 576 (95%), 41 (55%); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.64 (bs, 1H, NH), 3.56 (bs, 1H, NH), 2.75 (s, 3H, CH_3), 1.14 (s, 9H, $3CH_3$); Anal. Calc. (%) for $C_{10}H_{14}F_3N_3OS$: C, 42.69; H, 5.02; N, 14.95. Found: C, 42.88; H, 5.21; N, 14.78.

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