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# SYNTHESIS OF 2-TRIHALOMETHYL-3,4-DIHYDROTHIENO[2,3-*d*]PYRIMIDIN-4-ONES

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*At room temperature, N-(1-chloro-2,2,2-trihaloethylidene)-O-methyl urethanes react with 2-aminothiophenes to form N-(2-thienyl)-N'-(methoxycarbonyl)trihaloacetamidines, which when heated in boiling toluene undergo ring closure to form 2-trihalomethyl-3,4-dihydrothieno[2,3-d]pyrimidin-4-ones.*

**Keywords:** 2-aminothiophenes, N-(2-thienyl)-N'-methoxycarbonylamidines, 2-trihalomethyl-3,4-dihydrothieno[2,3-*d*]pyrimidin-4-ones, N-(1-chloro-2,2,2-trihaloethylidene)-O-methyl urethanes, intramolecular cyclization.

Among the derivatives of thieno[2,3-*d*]pyrimidines, substances have been observed that have antiviral, fungicidal, and insecticidal activity [1], antibacterial and antiparasitic properties [2], antihypertensive [3], antitumor [4], and antihistaminic [5] action. Two methods are most often used to synthesize the indicated condensed heterocyclic system. The first method includes annelation of 6-chloro-5-formyl(cyano)pyrimidines by 2-mercaptoacetates [6, 7]. The second method is based on condensation of 3-alkoxycarbonyl-2-aminothiophenes with amides [8] and guanidines [9], and proves to be an effective way to obtain 3,4-dihydro[2,3-*d*]pyrimidin-4-ones which in turn are the basic compounds for functionalization of the position 4 with various nucleophilic groups [10, 11]. 3,4-Dihydrothieno[2,3-*d*]pyrimidin-4-ones with trihalomethyl substituents in the position 2 have not been described in the literature so far, although we should expect that introducing a trifluoromethyl group on the pyrimidine ring should increase the lipophilic properties of the molecule [12].

We have proposed a novel and convenient approach to synthesis of such compounds, based on reaction of N-(1-chloro-2,2,2-trihaloethylidene)-O-methyl urethanes **1a,b** [13] with 2-aminothiophenes **2a,b**. A detailed study of the discovered reaction allowed us to establish that, despite the biphilic nature of the reagents, the reaction is regioselective and at room temperature proceeds according to the scheme involving N-iminoalkylation of aminothiophenes to form N-(2-thienyl)-N'-(methoxycarbonyl)trihaloacetamidines **3a-d** (Table 1). The structure of the latter is consistent with the results of measurements of the $^1$H NMR spectra (Table 2), in which for compounds **3a,b** there are doublets for the $C_{(3)}H$ and $C_{(4)}H$ protons in the ranges 7.03-7.15 ppm and 7.68-7.70 ppm, while for compounds **3c,d** we see singlets in the 6.91-7.04 ppm region from the $C_{(3)}H$ proton of the thiophene ring. The IR spectra are characterized by absorption bands for the bonds N–H (3230-3300 cm$^{-1}$), C=O (1690-1750 cm$^{-1}$), while for compounds **3b,d** we also see an absorption band for the C=N bond (1650 cm$^{-1}$).

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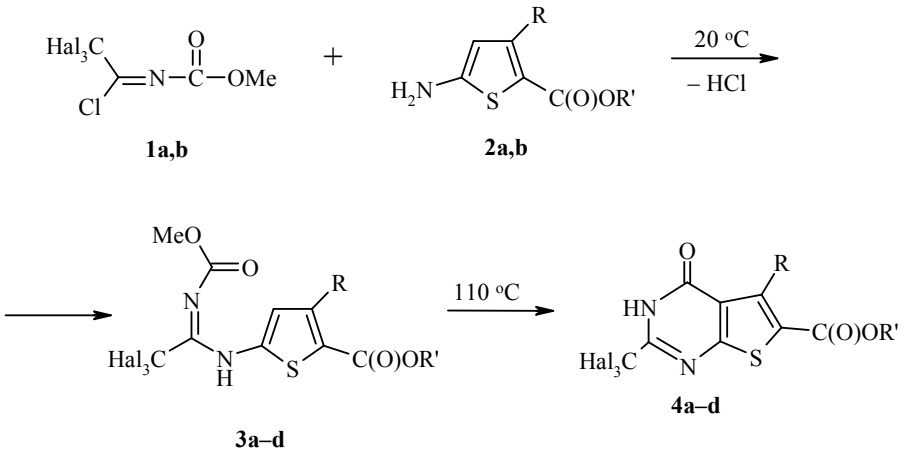
Compounds **3a-d**, when heated in boiling toluene (3 h), undergo intramolecular cyclization to form thieno[2,3-*d*]pyrimidin-4-ones **4a-d** (see Table 1) as a result of electrophilic attack by the carbonyl group at the π-electron-rich $C_{(3)}$ atom of the thiophene ring. The factor determining the cyclization process is probably the increased electrophilicity of the carbonyl group, due to a significant degree to the effect of the trihaloamidine moiety. In the case of aminal **3e** with a less electrophilic C=O group, obtained from N-ethylidene urethane **1c** [14] and aminothiophene **2b**, we did not observe formation of compound **4e** either at the temperature indicated in the scheme or at a higher temperature (140°C).




**1 a** Hal = F, **b** Hal = Cl; **2 a** R = H, R' = Me; **b** R = Me, R' = Et; **3**, **4 a** Hal = F, R = H, R' = Me; **b** Hal = Cl, R = H, R' = Me; **c** Hal = F, R = Me, R' = Et; **d** Hal = Cl, R = Me, R' = Et

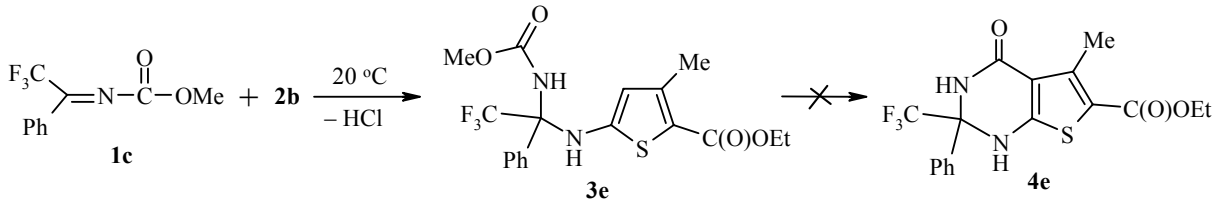



TABLE 1. Characteristics of Synthesized Compounds **3a-d, 4a-d**

| Compound | Empirical formula | Found, % / Calculated, % | | mp, °C | Yield, % |
|---|---|---|---|---|---|
| | | N | Hal | | |
| **3a** | $C_{10}H_9F_3N_2O_4S$ | 9.29 / 9.03 | 17.84 / 18.37 | 110-111 | 78 |
| **3b** | $C_{10}H_9Cl_3N_2O_4S$ | 7.60 / 7.79 | 29.23 / 29.58 | 107-108 | 73 |
| **3c** | $C_{12}H_{13}F_3N_2O_4S$ | 8.45 / 8.28 | 17.07 / 16.85 | 118-119 | 84 |
| **3d** | $C_{12}H_{13}Cl_3N_2O_4S$ | 7.58 / 7.23 | 27.89 / 27.44 | 97-98 | 80 |
| **4a** | $C_9H_5F_3N_2O_3S$ | 9.72 / 10.07 | 20.63 / 20.49 | 227-228 | 76 |
| **4b** | $C_9H_5Cl_3N_2O_3S$ | 8.85 / 8.55 | 32.74 / 32.47 | 238-239 | 79 |
| **4c** | $C_{11}H_9F_3N_2O_3S$ | 8.86 / 9.15 | 18.97 / 18.61 | 159-160 | 74 |
| **4d** | $C_{11}H_9Cl_3N_2O_3S$ | 8.17 / 7.88 | 30.27 / 29.91 | 220-221 | 77 |

The IR and $^{1}H$, $^{19}F$ (Table 2), and $^{13}C$ (Table 3) NMR spectral data provide support for a cyclic structure for the synthesized compounds, but do not give an unambiguous answer concerning the location of the proton in the amidine system of bonds, which may be substantially affected by a strong acceptor trihalomethyl group. For this reason, we carried out an X-ray diffraction study of compound **4d** and established that in the crystal, the proton is located on the nitrogen atom in the position 3, i.e., the target compounds have the structure of 3,4-dihydrothieno[2,3-*d*]pyrimidin-4-ones.

TABLE 2. Spectral Characteristics of Compounds **3a-d, 4a-d**

| Compound | IR spectrum, ν, $cm^{-1}$ | | $^{1}H$ NMR spectrum, δ, ppm, spin-spin coupling constant (*J*, Hz) | $^{19}F$ NMR spectrum, δ, ppm |
|---|---|---|---|---|
| | NH | CO | | |
| **3a** | 3285 | 1690<br>1730 | 3.76 (3H, s, $OCH_3$); 3.90 (3H, s, $OCH_3$);<br>7.03 (1H, d, *J* = 3.8, CH); 7.18 (1H, s, NH);<br>7.70 (1H, d, *J* = 3.8, CH) | 72.3 |
| **3b** | 3230 | 1650*<br>1700<br>1735 | 3.73 (3H, s, $OCH_3$); 3.89 (3H, s, $OCH_3$);<br>7.19 (2H, m, CH + NH); 7.68 (1H, d, *J* = 3.9, CH) | |
| **3c** | 3250 | 1700<br>1750 | 1.37 (3H, t, *J* = 7.1, $CH_3$); 2.51 (3H, s, $CH_3$);<br>3.78 (3H, s, $OCH_3$); 4.32 (2H, q, *J* = 7.1, $OCH_2$);<br>6.91 (1H, s, $C_{(3)}H$); 7.08 (1H, s, NH) | 71.8 |
| **3d** | 3300 | 1650*<br>1700<br>1730 | 1.36 (3H, t, *J* = 7.2, $CH_3$); 2.51 (3H, s, $CH_3$);<br>3.74 (3H, s, $OCH_3$); 4.32 (2H, q, *J* = 7.2, $OCH_2$);<br>7.04 (1H, s, $C_{(3)}H$); 7.08 (1H, s, NH) | |
| **4a** | 3110 | 1700<br>1735 | 3.90 (3H, s, $OCH_3$); 8.04 (1H, s, $C_{(5)}H$);<br>14.5 (1H, br. s, NH) | 69.0 |
| **4b** | 3200 | 1700<br>1740 | 3.90 (3H, s, $OCH_3$); 8.05 (1H, s, $C_{(5)}H$);<br>14.0 (1H, br. s, NH) | |
| **4c** | 3200 | 1675<br>1720 | 1.33 (3H, t, *J* = 7.1, $CH_3$); 2.83 (3H, s, $CH_3$);<br>4.35 (2H, q, *J* = 7.1, $OCH_2$); 13.8 (1H, br. s, NH) | 68.9 |
| **4d** | 3200 | 1720<br>1735 | 1.37 (3H, t, *J* = 7.1, $CH_3$); 2.86 (3H, s, $CH_3$);<br>4.33 (2H, q, *J* = 7.1, $OCH_2$); 13.3 (1H, br. s, NH) | |

* $\nu_{(C=N)}$.

TABLE 3. $^{13}C$ NMR Spectra, δ, ppm, Spin–spin Coupling Constant (*J*, Hz) of Compounds **4a-d**

| Compound | R | OR' | $CHal_3$ | $C_{(4a)}$ | $C_{(5)}$ |
|---|---|---|---|---|---|
| **4a** | — | 52.88 | 118.02 (q, $^{1}J_{C-F}$ = 276.1) | 124.47 | 126.89 |
| **4b** | — | 52.88 | 92.98 | 122.76 | 126.92 |
| **4c** | 14.52 | 61.36 ($OCH_2$)<br>13.92 ($CH_3$) | 117.87 (q, $^{1}J_{C-F}$ =276.3) | 123.75 | 142.21 |
| **4d** | 14.61 | 61.39 ($OCH_2$)<br>14.00 ($CH_3$) | 92.46 | 124.76 | 142.24 |

| Compound | $C_{(6)}$ | $C_{(2)}$ | $C_{(7a)}$ | C=O | $C_{(4)}$ |
|---|---|---|---|---|---|
| **4a** | 131.53 | 147.13 (q, $^{2}J_{C-F}$ = 37.8) | 159.86 | 161.14 | 165.36 |
| **4b** | 131.42 | 155.92 | 160.36 | 161.20 | 165.22 |
| **4c** | 124.66 | 146.41 (q, $^{2}J_{C-F}$ = 37.6) | 160.11 | 161.35 | 163.69 |
| **4d** | 122.31 | 154.88 | 160.49 | 161.49 | 163.46 |

We observed that in the crystal of compound **4d**, there are two symmetrically independent molecules (**A** and **B**) having quite complex geometric parameters. A general view of these molecules is shown in Fig. 1; the principal bond lengths and bond angles are given in Table 4. The central bicyclic system in the **A** and **B**

TABLE 4. Principal Bond Lengths (*d*) and Bond Angles (ω) in a Molecule of Compound **4d**

| Bond | *d*, Å | Angle | ω, deg. |
|---|---|---|---|
| $S_{(1)}–C_{(1)}$ | 1.745(6) | $C_{(1)}–S_{(1)}–C_{(4)}$ | 90.7(3) |
| $S_{(1)}–C_{(4)}$ | 1.690(6) | $C_{(12)}–S_{(2)}–C_{(15)}$ | 90.2(2) |
| $S_{(2)}–C_{(12)}$ | 1.721(5) | $C_{(4)}–N_{(1)}–C_{(5)}$ | 114.9(5) |
| $S_{(2)}–C_{(15)}$ | 1.714(5) | $C_{(5)}–N_{(2)}–C_{(6)}$ | 123.7(5) |
| $O_{(1)}–C_{(6)}$ | 1.226(7) | $C_{(15)}–N_{(3)}–C_{(17)}$ | 113.8(5) |
| $O_{(4)}–C_{(16)}$ | 1.235(6) | $C_{(16)}–N_{(4)}–C_{(17)}$ | 124.3(5) |
| $N_{(1)}–C_{(4)}$ | 1.384(7) | $S_{(1)}–C_{(1)}–C_{(2)}$ | 113.4(4) |
| $N_{(1)}–C_{(5)}$ | 1.279(7) | $C_{(1)}–C_{(2)}–C_{(3)}$ | 110.6(5) |
| $N_{(2)}–C_{(5)}$ | 1.364(7) | $C_{(2)}–C_{(3)}–C_{(4)}$ | 112.7(5) |
| $N_{(2)}–C_{(6)}$ | 1.385(8) | $C_{(4)}–C_{(3)}–C_{(6)}$ | 118.5(5) |
| $N_{(3)}–C_{(15)}$ | 1.356(6) | $S_{(1)}–C_{(4)}–C_{(3)}$ | 112.7(4) |
| $N_{(3)}–C_{(17)}$ | 1.290(7) | $N_{(1)}–C_{(4)}–C_{(3)}$ | 124.9(5) |
| $N_{(4)}–C_{(16)}$ | 1.377(6) | $N_{(1)}–C_{(5)}–N_{(2)}$ | 124.6(5) |
| $N_{(4)}–C_{(17)}$ | 1.354(7) | $N_{(2)}–C_{(6)}–C_{(3)}$ | 113.4(5) |
| $C_{(1)}–C_{(2)}$ | 1.354(8) | $S_{(2)}–C_{(12)}–C_{(13)}$ | 114.6(4) |
| $C_{(2)}–C_{(3)}$ | 1.433(8) | $C_{(12)}–C_{(13)}–C_{(14)}$ | 109.7(4) |
| $C_{(3)}–C_{(4)}$ | 1.383(8) | $C_{(13)}–C_{(14)}–C_{(15)}$ | 113.6(5) |
| $C_{(3)}–C_{(6)}$ | 1.430(8) | $C_{(15)}–C_{(14)}–C_{(16)}$ | 116.8(4) |
| $C_{(12)}–C_{(13)}$ | 1.365(8) | $S_{(2)}–C_{(15)}–C_{(14)}$ | 112.0(4) |
| $C_{(13)}–C_{(14)}$ | 1.423(7) | $N_{(3)}–C_{(15)}–C_{(14)}$ | 127.4(5) |
| $C_{(14)}–C_{(15)}$ | 1.379(7) | $N_{(4)}–C_{(16)}–C_{(14)}$ | 113.3(5) |
| $C_{(14)}–C_{(16)}$ | 1.437(8) | $N_{(3)}–C_{(17)}–N_{(4)}$ | 124.3(5) |

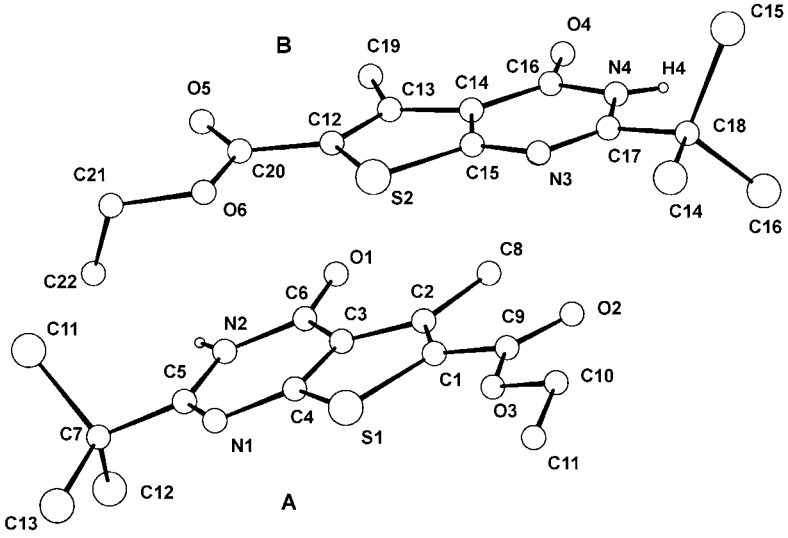



Fig. 1 General view of two symmetrically independent **A** and **B** molecules of compound **4d** (of the hydrogen atoms, only the $H_{(2)}$ and $H_{(4)}$ atoms are shown).

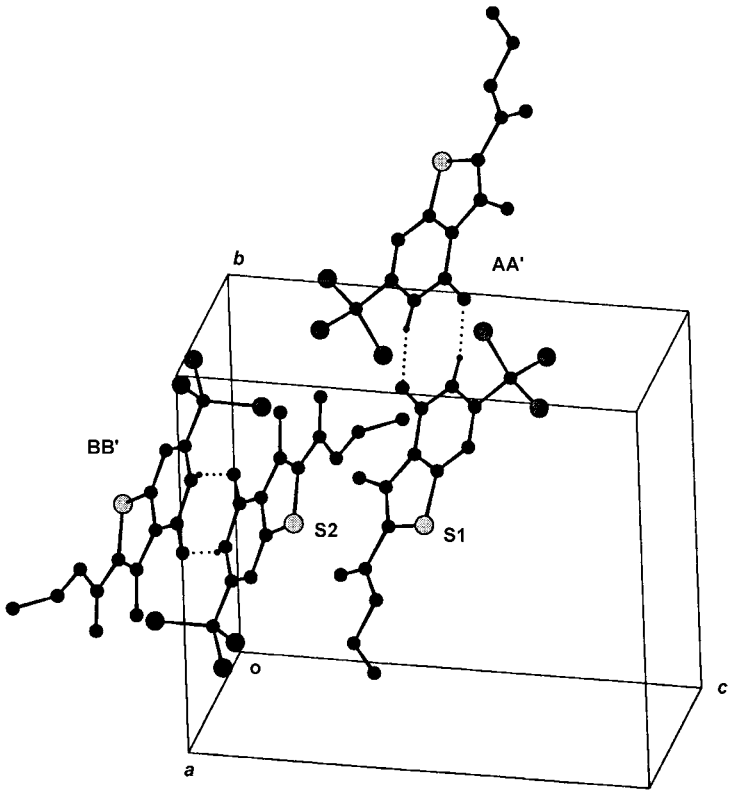



Fig. 2 Fragment of the crystal packing of compound **4d**.
The dotted lines indicate intermolecular hydrogen bonds N–H···O.

molecules is in fact planar: the deviations of the atoms from the mean-square plane are not greater than 0.039 Å and 0.023 Å respectively, and the dihedral angle between the 6-membered and 5-membered rings is only 2.4° and 1.2°. The geometric parameters of the bicyclic system suggest substantial delocalization of the electron density [15, 16]. The exocyclic system of bonds ($C_{(1)}$–$C_{(9)}$(=$O_{(2)}$)–$O_{(3)}$ in the **A** molecule and $C_{(12)}$–$C_{(20)}$(=$O_{(5)}$)–$O_{(6)}$ in the **B** molecule) lies in the plane of the bicycle: the corresponding dihedral angles are 3.1° and 8.2°. In the crystal of compound **4d**, the molecules are joined into centrosymmetric dimers **AA'** and **BB'** by means of a relatively strong [17] hydrogen bond N–H···O (Fig. 2). The principal geometric parameters of these H bonds are as follows: $N_{(2)}$···$O_{(1)}$ 2.759(7), $H_{(2)}$···$O_{(1)}$ 1.86(6), $N_{(2)}$–$H_{(2)}$ 0.91(6) Å, $N_{(2)}H_{(2)}O_{(1)}$ 169(4)°; $N_{(4)}$···$O_{(4)}$ 2.816(6), $H_{(4)}$···$O_{(4)}$ 2.02(5), $N_{(4)}$–$H_{(4)}$ 0.82(5) Å, $N_{(4)}H_{(4)}O_{(4)}$ 163(4)°.

## EXPERIMENTAL

The IR spectra were recorded on a UR-20 in KBr disks. The $^{1}H$, $^{13}C$, and $^{19}F$ NMR spectra were obtained on a Varian VXR-300 spectrometer (300 MHz, 75.5 MHz, and 282 MHz respectively) in $CDCl_3$ solutions for compounds **3a-d**, $(CD_3)_2SO$ for compounds **4a-d**, internal standards TMS ($^{1}H$, $^{13}C$) and $CCl_3F$ ($^{19}F$).

**An X-ray Diffraction Study of a Single Crystal of Compound 4d** with linear dimensions 0.28 × 0.38 × 0.50 mm was carried out at room temperature on an Enraf-Nonius CAD-4 automatic four-circle diffractometer (CuKα radiation, ratio of scanning rates $\omega/2\theta = 1.2$, $\theta_{max} = 70°C$, spherical segment $0 \le h \le 9$, $-13 \le k \le 13$, $-17 \le l \le 17$).

We collected a total of 5105 reflections, of which 4782 were symmetrically independent (averaging *R* factor 0.051). The crystals of compound **4d** were triclinic, $a$ = 10.615(2), $b$ = 11.213(3), $c$ = 14.440(2) Å; $\alpha$ = 95.67(2), $\beta$ = 111.39(1), $\gamma$ = 107.23(2)°; $V$ = 1486.5(6) Å$^3$; M = 369.63; $Z$ = 4; $d_{calc}$ = 1.69 g/cm$^3$; $\mu$ = 73.02 cm$^{-1}$; space group $P\bar{1}$ (N 2). Absorption in the crystal was taken into account by the azimuthal scanning method [18]. The structure was deciphered by the direct method and least-squares refined in the full-matrix anisotropic approximation using the CRYSTALS software package [19]. In the refinement, we used 3117 reflections with $I > 3\sigma(I)$ (369 refined parameters, number of reflections times the parameter 8.4). All the hydrogen atoms were determined from a difference electron density synthesis and included in the calculation with fixed positions and thermal parameters; only the $H_{(2)}$ and $H_{(4)}$ atoms were refined isotropically. In the refinement, we used the Chebyshev weighting scheme [20] with parameters 2.75, -0.74, 0.87, and -1.08. The final values for the *R* factors were $R$ = 0.069 and $R_w$ = 0.073, *GOF* = 1.090. The residual electron density from a difference Fourier series was 0.45 and -0.48 e/Å$^3$. The complete set of crystallographic data was deposited in the Cambridge Structural Database (No. 165118).

**N-(2-Thienyl)-N'-(methoxycarbonyl)trihaloacetamidines (3a-d).** A solution of aminothiophene **2a,b** (5.0 mmol) and triethylamine (0.5 g, 5.0 mmol) in benzene (10 ml) was added with stirring at room temperature to a solution of N-ethylidene urethane **1a,b** (5.0 mmol) in benzene (10 ml). After 2 h of stirring, the reaction mixture was heated to boiling and the precipitate of triethylamine hydrochloride was filtered out; the target products precipitated from the filtrate as it cooled.

**1-(N-Methoxycarbonylamino)-1-(5-ethoxycarbonyl-4-methyl-2-thienylamino)-1-phenyl-2,2,2-trifluoroethane (3e).** Aminothiophene **2b** (0.93 g, 5.0 mmol) was added to a solution of N-ethylidene urethane **1c** (1.15 g, 5.0 mmol) in benzene (10 ml); the reaction mixture was allowed to stand at room temperature for 12 h, and then it was refluxed for 1 h. The residue after evaporation of the solvent was crystallized from a 1:3 hexane–benzene mixture. Yield 72%; mp 150°C. IR spectrum, $\nu$, cm$^{-1}$: 1720-1760 (C=O), 3300, 3340 (NH). $^1$H NMR spectrum, $\delta$, ppm ($J$, Hz): 1.24 (3H, t, $J$ = 7.2, $CH_3$); 2.29 (3H, s, $CH_3$); 3.53 (3H, s, $CH_3$); 4.13 (2H, q, $J$ = 7.2, $CH_2O$); 6.09 (1H, s, CH); 7.42 (3H, m, $H_{arom}$); 7.66 (2H, m, $H_{arom}$); 7.88 (1H, s, NH); 8.59 (1H, s, NH). $^{19}$F NMR spectrum, $\delta$, ppm: -78.1 (s). Found, %: C 52.13; H 4.72; N 6.58. $C_{18}H_{19}F_3N_2O_4S$. Calculated, %: C 51.92; H 4.60; N 6.73.

**2-Trihalomethyl-3,4-dihydrothieno[2,3-*d*]pyrimidin-4-ones (4a-d).** A solution of compound **3a-d** (3.0 mmol) in toluene (10 ml) was refluxed for 3 h. The product precipitating after cooling was filtered out and crystallized from ethanol.

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