Modification of biologically active amides and amines with fluorine-containing heterocycles

2*. *N*-(2-Thienyl)imines on the base of methyl trifluoropyruvate in cyclocondensation with 1,3-*N*,*N*-binucleophiles

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An approach to the modification of the biologically active compounds, substituted 2-aminothiophenes, with fluorine-containing five-membered heterocycles is proposed. The reaction of 2-aminothiophenes with methyl trifluoropyruvate yields the corresponding *N*-(2-thienyl)imines, their subsequent cyclocondensation with 1,3-*N,N*-binucleophiles (2-aminothiazoline and benzamidines) furnished 5-oxo-6-trifluoromethyl-2,3,5,6-tetrahydroimidazothiazoles and 5-oxo-2-phenyl-4-trifluoromethyl-4,5-dihydro-1*H*-imidazoles.

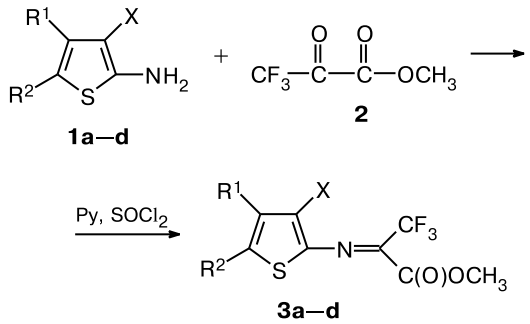
Key words: substituted 2-aminothiophenes, methyl trifluoropyruvate, methyl (2-thienylimino)-3,3,3-trifluoropropionate, 2-aminothiazoline, benzamidines, 5-oxo-6-trifluoromethyl-2,3,5,6-tetrahydroimidazotriazoles, 5-oxo-2-phenyl-4-trifluoromethyl-4,5-dihydro-1*H*-imidazoles, cyclocondensation.

Substituted 2-aminothiophenes, which can be synthesized by the Gewald reaction,[2,3] present a class of promising biologically active compounds widely used in medicine and agriculture.[4—6] The main approaches to the molecular design of 2-aminothiophenes involve the introduction of substituents, including the trifluoromethyl group, in the thiophene ring,[7,8] incorporation of a 2-aminothiophene fragment into a heterocyclic system,[9] modification of the substituents at the amino group.[10,11] The aim of the present study was the modification of 2-aminothiophenes with fluorine-containing heterocycles. This conversion involved the reaction of 2-aminothiophenes **1** with methyl trifluoropyruvate (**2**) followed by cyclocondensations of the resulting 2-(2-thienylimino)-3,3,3-trifluoropropionates **3** with 2-aminothiazoline (**4**) or benzamidines **6**. The premise of the present work was our data that have previously been obtained in the study of cyclocondensations of *N*-substituted imines derived from methyl trifluoropyruvate with 1,3-binucleophiles.[12—15]

The proposed procedure for the synthesis of hitherto unknown 2-thienylimines **3a—d** involved successive addition of equimolar amounts of pyridine, methyl trifluoropyruvate (**2**), and $SOCl_2$ to a solution of 2-aminothiophenes **1a—d** (Scheme 1).

Imines **3a—d** are crystalline solids. Their compositions and the structures were determined based on the data from ^1H and ^{19}F NMR spectroscopy and elemental analysis.

Scheme 1



1,3	a	b	c	d
R^1R^2	$(CH_2)_3$	$(CH_2)_4$	$(CH_2)_4$	$(CH_2)_5$
X	$C(O)OCH_3$	CN	$C(O)OCH_3$	CN

The ^{19}F NMR spectra exhibited signals in the range of δ 7—10 characteristic of *N*-heterylimines derived from methyl trifluoropyruvate.[16]

2-Thienylimines **3a—d** reacted exothermally with fairly reactive 1,3-binucleophiles, such as 2-aminothiazoline (**4**) and benzamidines **6a—c** following the cyclocondensation pattern: 1,3-binucleoiphile adds to the C=N bond of imine **3** with subsequent cyclization and elimination of methanol. These conversions resulted in the corresponding 5-oxo-6-trifluoromethyl-2,3,5,6-tetrahydroimidazo-[2,1-*b*]thiazoles **5a—d** and 5-oxo-2-phenyl-4-(2-thi-

* For Part 1, see Ref. 1.

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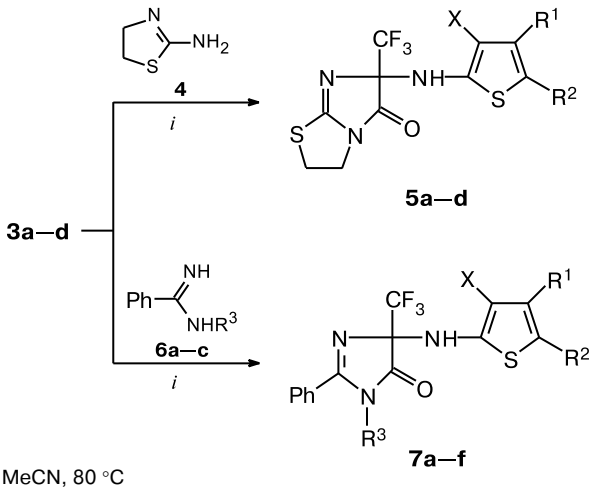
enyl)amino-4-triflioromethyl-4,5-dihydro-1*H*-imidazoles **7a—f** (Scheme 2).

Scheme 2



i. MeCN, 80 °C

Compound	R^1R^2	X
5a, 7a	$(CH_2)_3$	C(O)OMe
5b, 7b	$(CH_2)_4$	CN
5c, 7c,d	$(CH_2)_4$	C(O)OMe
5d, 7e,f	$(CH_2)_5$	CN

R^3 = H (**6a, 7b,c**), CH_2Ph (**6b, 7a,d,e**), CH_2CH_2Ph (**6c, 7f**)

Compounds **5** and **7** are crystalline solids. Their compositions and the structures were established based on the data from ^1H and ^{19}F NMR spectroscopy and elemental analysis. The ^{19}F NMR spectra showed the characteristic signal in the range of δ 0.01—1.

In summary, hitherto unknown 2-thienylimines derived from methyl trifluoropyruvate are promising reagents for the synthesis of a variety of fluorine-containing *N*-heteryl-substituted 2-aminothiophenes. The proposed synthetic approach to the modification of 2-aminothiophenes makes it possible to combine two biologically active fragments in one molecule, *viz.*, 2-aminothiophene and a heterocyclic moiety with a pharmacophoric 3,3,3-trifluoroalanine fragment, which is known to possess the high bacteriostatic activity.[17]

Experimental

The ^1H and ^{19}F NMR spectra were recorded on a Bruker DPX 200 instrument at 200.13 MHz and 188.29 MHz relative to tetramethylsilane (internal standard) and CF_3COOH (external standard), respectively. Melting points were determined in open capillaries. The starting 2-aminothiophene **1** was synthesized according to the known procedure,[18] 2-aminothiazoline (**4**), benzamidines **6**, methyl trifluoropyruvate (**2**) were used as purchased (Aldrich).

Methyl 2-[(*Z*)-1-methoxycarbonyl-2,2,2-trifluoroethylideneamino]-5,6-dihydro-4*H*-cyclopenta[*b*]thiophene-3-carboxylate (3a). To a stirred solution of 2-aminothiophene **1a** (9.9 g, 0.05 mol) in benzene (50 mL), pyridine (7.8 g, 0.1 mol) and methyl trifluoropyruvate **2** (7.8 g, 0.1 mol) were successively added at 20 °C. The reaction mixture was stirred for 30 min, then $SOCl_2$ (6.0 g, 0.05 mol) was added and stirring was continued for 1 h. The precipitate that formed was filtered off, the filtrate was concentrated *in vacuo*, and the residue was recrystallized from hexane to give compound **3a** in a yield of 12.6 g (75%), m.p. 91—93 °C. ^1H NMR ($CDCl_3$), δ: 2.42 (m, 2 H, CH_2); 2.97 (overlapping d, 4 H, CH_2 + CH_2, J = 7.7 Hz); 3.84 (s, 3 H, CH_3O); 3.91 (s, 3 H, CH_3O). ^{19}F NMR ($CDCl_3$), δ: 6.97 s. Found (%): C, 46.75; H, 3.43; N, 4.01. $C_{13}H_{12}F_3NO_4S$. Calculated (%): C, 46.57; H, 3.61; N, 4.18.

Methyl 2-[(3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)imino]-3,3,3-trifluoropyruvate (3b) was synthesized as described for **3a** in a yield of 11.7 g (74%), m.p. 79—81 °C. ^1H NMR ($CDCl_3$), δ: 1.93 (m, 4 H, CH_2); 2.78 (m, 4 H, CH_2); 4.01 (s, 3 H, CH_3O). ^{19}F NMR ($CDCl_3$), δ: 9.53 s. Found (%): C, 49.22; H, 3.38; N, 8.72. $C_{13}H_{11}F_3N_2O_2S$. Calculated (%): C, 49.37; H, 3.51; N, 8.86.

Methyl 2-[(*Z*)-1-methoxycarbonyl-2,2,2-trifluoroethylideneamino]-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (3c) was synthesized as described for **3a** in a yield of 13.5 g (77%), m.p. 86—88 °C. ^1H NMR ($CDCl_3$), δ: 1.83 (m, 4 H, CH_2); 2.74 (m, 4 H, CH_2); 3.85 (s, 3 H, CH_3O); 3.93 (s, 3 H, CH_3O). ^{19}F NMR (DMSO-d_6), δ: 8.99 s. Found (%): C, 48.27; H, 4.16; N, 4.19. $C_{14}H_{14}F_3NO_4S$. Calculated (%): C, 48.14; H, 4.04; N, 4.01.

Methyl 2-[(3-cyano-5,6,7,8-tetrahydro-4*H*-cyclohepta[*b*]-thiophen-2-yl)imino]-3,3,3-trifluoropyruvate (3d) was synthesized as described for **3a** in a yield of 12.1 g (73%), m.p. 68—69 °C. ^1H NMR ($CDCl_3$), δ: 1.72 (m, 4 H, CH_2); 1.92 (m, 2 H, CH_2); 2.88 (m, 4 H, CH_2); 4.00 (s, 3 H, CH_3O). ^{19}F NMR (DMSO-d_6), δ: 9.65 s. Found (%): C, 50.73; H, 3.79; N, 8.31. $C_{14}H_{13}F_3N_2O_2S$. Calculated (%): C, 50.91; H, 3.97; N, 8.48.

Methyl 2-[(5-oxo-6-trifluoromethyl-2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazol-6-yl)amino]-5,6-dihydro-4*H*-cyclopenta[*b*]-thiophene-3-carboxylate (5a). To a solution of imine **3a** (3.35 g, 0.01 mol) in MeCN (20 mL), 2-aminothiazoline **4** (1.02 g, 0.01 mol) was added. The reaction mixture was refluxed for 1 h and poured into water (50 mL), the precipitate that formed was recrystallized from 50% EtOH to give compound **5a** in a yield of 3.1 g (77%), m.p. 133—134 °C. ^1H NMR (DMSO-d_6), δ: 2.34 (m, 2 H, CH_2); 2.77 (m, 4 H, CH_2); 3.82 (s, 3 H, CH_3O); 3.86—4.06 (m, 4 H, CH_2); 8.77 (s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: –0.43 s. Found (%): C, 44.26; H, 3.26; N, 10.61. $C_{15}H_{14}F_3N_3O_3S_2$. Calculated (%): C, 44.44; H, 3.48; N, 10.36.

2-[(5-Oxo-6-trifluoromethyl-2,3,5,6-tetrahydroimidazo-[2,1-*b*]thiazol-6-yl)amino]-4,5,6,7-tetrahydrobenzo[*b*]thiophen-3-carbonitrile (5b) was synthesized as described for **5a** in a yield of 2.9 g (75%), m.p. 138—140 °C. ^1H NMR (DMSO-d_6), δ: 1.79 (m, 4 H, CH_2); 2.53 (m, 4 H, CH_2); 3.87 (m, 4 H, CH_2); 7.66 (s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: 0.89 s. Found (%): C, 46.49; H, 3.27; N, 14.33. $C_{15}H_{13}F_3N_4OS_2$. Calculated (%): C, 46.62; H, 3.39; N, 14.50.

Methyl 2-[(5-oxo-6-trifluoromethyl-2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazol-6-yl)amino]-4,5,6,7-tetrahydrobenzo[*b*]-thiophene-3-carboxylate (5c) was synthesized as described for **5a** in a yield of 3.0 g (72%), m.p. 128—129 °C. ^1H NMR (DMSO-d_6), δ: 1.77 (m, 4 H, CH_2); 2.52 (m, 2 H, CH_2); 2.68 (m, 2 H, CH_2); 3.77 (s, 3 H, CH_3O); 3.91 (m, 4 H, CH_2); 9.14 (s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: 0.44 s. Found (%): C, 45.69; H, 3.71; N, 10.15. $C_{16}H_{16}F_3N_3O_3S_2$. Calculated (%): C, 45.82; H, 3.84; N, 10.02.

2-[(5-Oxo-6-trifluoromethyl-2,3,5,6-tetrahydroimidazo-[2,1-*b*]thiazol-6-yl)amino]-5,6,7,8-tetrahydro-4*H*-cyclohepta-[*b*]thiophene-3-carbonitrile (5d) was synthesized as described for **5a** in a yield of 3.2 g (80%), m.p. 118—120 °C. ^{1}H NMR (DMSO-d_6), δ: 1.67 (m, 4 H, CH_2); 1.84 (m, 2 H, CH_2); 2.64 (m, 4 H, CH_2); 3.72—4.02 (m, 4 H, CH_2 + CH_2); 7.45 (s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: 0.61 s. Found (%): C, 48.18; H, 3.61; N, 13.72. $C_{16}H_{15}F_3N_4OS_2$. Calculated (%): C, 47.99; H, 3.78; N, 13.99.

Methyl 2-[(1-benzyl-5-oxo-4-trifluoromethyl-2-phenyl-4,5-dihydro-1*H*-imidazol-4-yl)amino]-5,6-dihydro-4*H*-cyclopenta-[*b*]thiophene-3-carboxylate (7a). To a solution of imine **3a** (3.35 g, 0.01 mol) in MeCN (20 mL), amidine **6a** (2.1 g, 0.01 mol) was added. The reaction mixture was refluxed of 1 h and poured into water (50 mL), the precipitate that formed was recrystallized from 50% EtOH to give compound **7a** in a yield of 3.8 g (74%), m.p. 192—194 °C.^{1}H NMR (DMSO-d_6), δ: 2.35 (m, 2 H, CH_2); 2.80 (m, 4 H, CH_2); 3.86 (s, 3 H, CH_3O); 4.90 (AB-system, 2 H, CH_2, J = 16.7); 7.00 (m, 2 H, CH_{AR}); 7.26 (m, 3 H, CH_{AR}); 7.4—7.78 (m, 5 H, CH_{AR}); 8.86 (s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: 0.04 s. Found (%): C, 60.73; H, 4.69; N, 8.31. $C_{26}H_{22}F_3N_3O_3S$. Calculated (%): C, 60.81; H, 4.32; N, 8.18.

2-[(5-Oxo-2-phenyl-4-trifluoromethyl-4,5-dihydro-1*H*-imidazol-4-yl)amino]-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile (7b) was synthesized as described for **7a** in a yield of 3.1 g (77%), m.p. 184—185 °C. ^{1}H NMR (DMSO-d_6), δ: 1.79 (m, 4 H, CH_2); 2.53 (m, 4 H, CH_2); 7.23 (s, 1 H, NH); 7.55 (m, 3 H, CH_{Ar}); 8.14 (d, 2 H, CH_{Ar}, J = 7.9 Hz); 12.38 (s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: 0.78 s. Found (%): C, 56.73; H, 3.89; N, 13.61. $C_{19}H_{15}F_3N_4OS$. Calculated (%): C, 56.43; H, 3.74; N, 13.85.

Methyl 2-[(5-oxo-2-phenyl-4-trifluoromethyl-4,5-dihydro-1*H*-imidazol-4-yl)amino]-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (7c) was synthesized as described for **7a** in a yield of 3.2 g (73%), m.p. 166—167 °C. ^{1}H NMR (DMSO-d_6), δ: 1.74 (m, 4 H, CH_2); 2.52 (m, 4 H, CH_2); 3.83 (s, 3 H, CH_3O); 7.61 (m, 3 H, CH_{Ar}); 8.18 (d, 2 H, CH_{Ar}, J = 7.9 Hz); 9.11 (s, 1 H, NH); 12.53 (s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: –0.41 s. Found (%): C, 54.73; H, 3.99; N, 9.34. $C_{20}H_{18}F_3N_3O_3S$. Calculated (%): C, 54.92; H, 4.15; N, 9.61.

Methyl 2-[(1-benzyl-5-oxo-2-phenyl-4-trifluoromethyl-4,5-dihydro-1*H*-imidazol-4-yl)amino]-4,5,6,7-tetrahydrobenzo[*b*]-thiophene-3-carboxylate (7d) was synthesized as described for **7a** in a yield of 3.7 g (70%), m.p. 118—119 °C. ^{1}H NMR (DMSO-d_6), δ: 1.74 (m, 4 H, CH_2); 2.49 (m, 2 H, CH_2); 2.66 (m, 2 H, CH_2); 3.77 (s, 3 H, CH_3O); 4.85 (AB-system, 2 H, CH_2, J = 11.2 Hz); 6.96 (m, 2 H, CH_{AR}); 7.22 (m, 3 H, CH_{AR}); 7.49 (m, 2 H, CH_{AR}); 7.63 (m, 3 H, CH_{AR}); 9.16 (s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: 0.77 s. Found (%): C, 61.71; H, 4.79; N, 8.21. $C_{27}H_{24}F_3N_3O_3S$. Calculated (%): C, 61.47; H, 4.59; N, 7.96.

2-[(1-Benzyl-5-oxo-2-phenyl-4-trifluoromethyl-4,5-dihydro-1*H*-imidazol-4-yl)amino]-5,6,7,8-tetrahydro-4*H*-cyclohepta[*b*]thiophene-3-carbonitrile (7e) was synthesized as described for **7a** in a yield of 3.5 g (69%), m.p. 123—124 °C. ^{1}H NMR (DMSO-d_6), δ: 1.70 (m, 4 H, CH_2); 1.87 (m, 2 H, CH_2); 2.68 (m, 4 H, CH_2); 4.84 (s, 2 H, CH_2); 6.98 (m, 2 H, CH_{Ar}); 7.24 (m, 3 H, CH_{Ar}), 7.41—7.68 (m, 6 H, CH_{Ar} + NH). Спектр ^{19}F NMR (DMSO-d_6), δ: 0.91 s. Found (%): C, 63.58; H, 4.79; N, 11.27. $C_{27}H_{23}F_3N_4OS$. Calculated (%): C, 63.77; H, 4.56; N, 11.02.

2-[(5-Oxo-1-phenethyl-2-phenyl-4-trifluoromethyl-4,5-dihydro-1*H*-imidazol-4-yl)amino]-5,6,7,8-tetrahydro-4*H*-cyclohepta[*b*]thiophene-3-carbonitrile (7f) was synthesized as described for **7a** in a yield of 3.7 g (71%), m.p. 120—121 °C. ^{1}H NMR (DMSO-d_6), δ: 1.84 (m, 4 H, CH_2); 2.01 (m, 2 H, CH_2); 2.86 (m, 6 H, CH_2); 3.72—4.01 (t, 2 H, CH_2, J = 7.6 Hz); 7.12 (m, 2 H, CH_{Ar}); 7.31 (m, 3 H, CH_{Ar}); 7.57 (s, 1 H, NH); 7.62—7.82 (m, 5 H, CH_{Ar}). ^{19}F NMR (DMSO-d_6), δ: 1.09 s. Found (%): C, 64.19; H, 4.63; N, 10.51. $C_{28}H_{25}F_3N_4OS$. Calculated (%): C, 64.35; H, 4.82; N, 10.72.

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