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CHEMISTRY

Methyl Trifluoropyruvate and Hexafluoroacetone *N*-(2-Pyrimidinyl)imines in Heterocyclization Reactions

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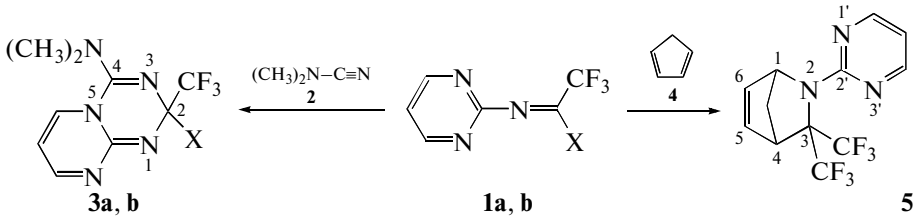
Trifluoromethyl-containing heterodienes are important precursors for the preparation of fluorine-containing heterocyclic compounds, a promising class of biologically active compounds applied in medical and agrochemical practice [1–3]. Acylimines of hexafluoroacetone (HFA) and methyl trifluoropyruvate (MTFP) are the most studied in heterocyclization reactions (cycloaddition and cyclocondensation). These studies provide data on the behavior of HFA and MTFP acylimines in the aza Diels–Alder reaction [4] and cyclocondensation reactions with 1,3-bisnucleophilic reagents [5–11].

The aim of this work is to develop the methodology of the use of trifluoromethyl-containing heterodienes in the synthesis of heterocyclic compounds. We studied *N*-(2-pyrimidinyl)imines of HFA (**1a**) and MTFP (**1b**) in the heterocyclization reactions of three types: cycloaddition, defluorocyclization, and cyclocondensation.

N-(2-Pyrimidinyl)imines **1a** and **1b** in (2 + 4) cycloaddition reaction behave as electron-deficient heterodienes and dienophiles. Thus, **1a** and **1b** react with dimethylcyanamine **2** at 90°C to give the products of aza Diels–Alder reaction, pyrimidotriazines **3a** and **3b**, in 86 and 83% yield, respectively. Hexafluoroacetone *N*-(2-pyrimidinyl)imine **1a** reacts with cyclopentadiene **4** on prolonged (30 h) heating in benzene to form azabicyclo[2.2.1]hept-5-ene **5** (Scheme 1).



1, **3**: X = CF_3 (**a**), $C(O)OCH_3$ (**b**)

Scheme 1.

Under the action of trimethyl phosphite **6**, MTFP *N*-(2-pyrimidinyl)imine undergoes defluorocyclization to yield methyl 3-fluoroimidazo[1,2-*a*]pyrimidine-2-carboxylate **8**, while trimethyl phosphite **6** is converted into difluorotrimethoxyphosphorane. The reaction proceeds exothermically and, judging from the similar reactions of HFA acylimines with tin dichloride [12], carbene **7** is the primary reaction product that undergoes heterocyclization to afford compound **8** (Scheme 2).

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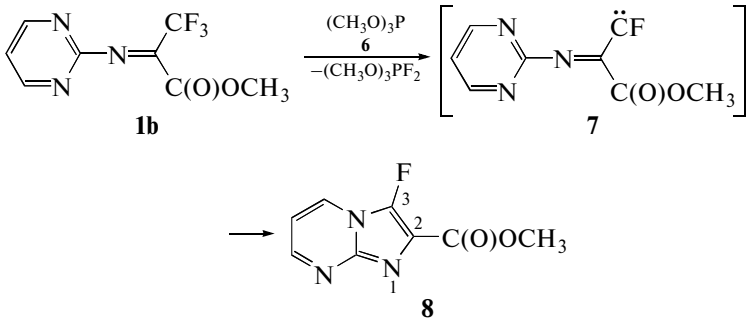


1b **7** **8**

Scheme 2.

In the cyclocondensation reactions, compound **1b** behaves as a 1,2-biselectrophilic reagent and reacts with 1,3-bisnucleophiles by a two-stage mechanism: addition of the bisnucleophile to the C=N bond with subsequent heterocyclization accompanied by methanol elimination. *N*-Butylurea (**9**), 4-phenylaminopent-3-en-2-one (**10**), 2-aminothiazoline (**11**), *N*-cyclohexylbenzamidine (**12**), 3-aminocrotonate (**13**), and 6-aminouracil (**14**) were studied in these transformations as bisnucleophiles (Scheme 3).

Compounds **10**–**13** exothermically react with imine **1b** to give 2,3-dihydropyrrol-2-one (**16**), 4,5-dihydroimidazo[2,1-*b*]thiazol-5-one (**17**), 4,5-dihydroimidazol-5-one (**18**), and 4,5-dihydro-1H-pyrrole (**19**), respectively; the heterocyclization requires a short heating (20 min) at 60°C to complete. Less nucleophilic *N*-butylurea (**9**) and 6-aminouracil (**14**) react with imine **1b** on heating in DMF for 2 h at 80°C in the presence of catalytic amounts of Et_3N to give imidazolidine-2,4-dione (**15**) and 5,6-dihydro-1H-pyrrolo[2,3-*d*]pyrimidine-2,4,6-trione (**20**), respectively.

The composition and structure of all obtained compounds were proved by the data of elemental analysis and ^1H and ^{19}F NMR spectra.

Thus, by the example of transformations of hexafluoroacetone and methyl trifluoropyruvate *N*-(2-pyrimidinyl)imines, we showed the synthetic capabilities of these compounds as promising precursors in the synthesis of fluorine-containing heterocyclic compounds.

EXPERIMENTAL

^1H and ^{19}F NMR spectra were recorded on a Bruker DXP 200 spectrometer operating at 200.13 and 188.29 MHz relative to tetramethylsilane (internal reference) and CF_3COOH (external reference), respectively. Melting points were determined in glass capillary tubes. Initial HFA and MTFP *N*-(2-pyrimidinyl)imines and 6-aminouracil **14** were prepared by procedures [13] and [14], respectively, *N*-butylurea **9**, 4-phenylaminopent-3-en-2-one **10**, 2-aminothiazoline **11**, *N*-cyclohexylbenzamidine **12**, and 3-aminocrotonate **13** (Aldrich) were used as purchased.

(2,2-Bistrifluoromethyl-2H-pyrimido[1,2-*a*]-1,3,5-triazin-4-yl)dimethylamine (3a). A solution of 0.01 mol of imine **1a** and 0.01 mol of dimethylcyanamine **2** in 20 mL of benzene was heated at reflux for 5 h and concentrated, and the residue was recrystallized from hexane to give 2.7 g (86%) of the title compound, mp 145–147°C.

^1H NMR ($CDCl_3$, δ, ppm, *J*, Hz): 2.83 (s, 6 H Me_2N), 6.10 (dd, 1H, CH_{Ar}, $J_1 = 7.3$, $J_2 = 3.4$), 7.52 (dd, 1H, CH_{Ar}, $J_1 = 7.1$, $J_2 = 2.2$), 8.36 (dd, 1H, CH_{Ar}, $J_1 = 3.4$, $J_2 = 2.1$).

^{19}F NMR ($CDCl_3$, δ, ppm, *J*, Hz): –1.34 s.

For $C_{10}H_9F_6N_5$ anal. calcd. (%): C, 38.35; H, 2.90; N, 22.36.

Found (%): C, 38.51; H, 2.71; N, 22.18.

Methyl 4-dimethylamino-2-trifluoromethylpyrimido[1,2-*a*]-1,3,5-triazine-2-carboxylate (3b) was obtained similarly to compound **3a** from 0.01 mol of imine **1b** and 0.01 mol of dimethylcyanamine **2**. Yield 2.5 g (83%), mp 122–124°C.

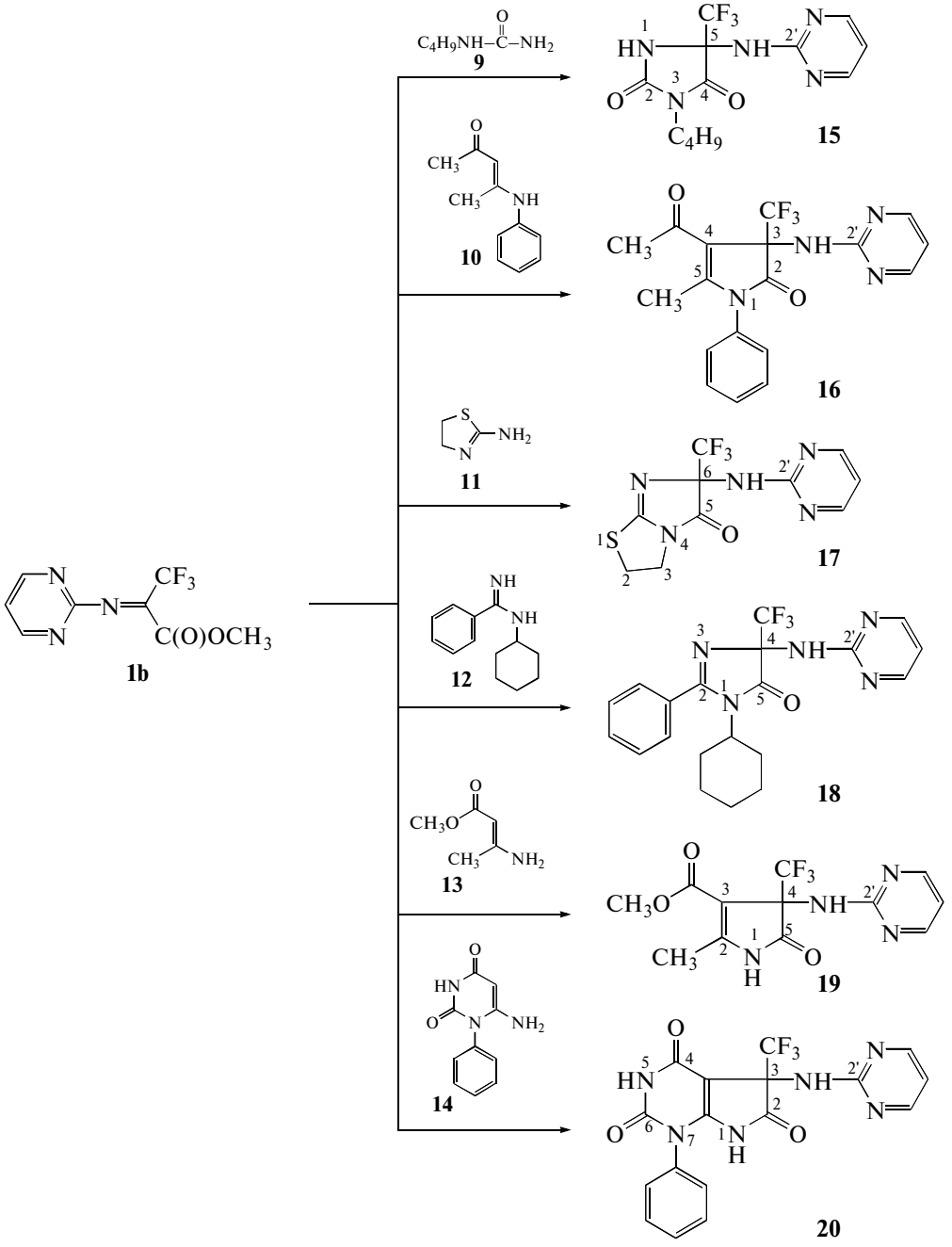
^1H NMR ($CDCl_3$, δ, ppm, *J*, Hz): 3.05 (s, 6H, Me_2N), 3.96 (s, 3H, MeO), 6.11 (dd, 1 H, CH_{Ar}, J_1 6.5 J_2 3.5), 7.50 (dd, 1 H, CH_{Ar}, J_1 6.6, J_2 2.1), 8.27 (dd, 1H, CH_{Ar}, J_1 3.5, J_2 2.2).

^{19}F NMR ($CDCl_3$, δ, ppm, *J*, Hz): –0.94 s.

For $C_{11}H_{12}F_3N_5O_2$ anal. calcd. (%): C, 43.57; H, 3.99; N, 23.06.

Found (%): C, 43.72; H, 3.81; N, 22.86.

2-(2'-Pyrimidinyl)-3,3-bistrifluoromethyl-2-azabicyclo[2.2.1]hept-5-ene (5). A solution 0.01 mol of 2-pyrimidinylimine **1a** and 0.01 mol of cyclopentadiene **4** in 20 mL of benzene was heated at reflux for 30 h, concentrated, the residue was recrystallized from hexane to give 2.5 g (81%) of the title compound, mp 71–73ºC.



Scheme 3.

^{1}H NMR ($CDCl_3$, δ, ppm, *J*, Hz): 1.52 (d, 1H, CH_2, *J* = 9.3), 2.21 (d, 1H, CH_2, *J* = 9.3), 3.61 (s, 1H, CH), 5.27 (s, 1H, CH), 6.11 (m, 1H, CH), 6.38 (t, 1H, CH_{Ar}, *J* = 4.1), 6.48 (m, 1H, CH), 7.98 (d, 2H, CH_{Ar}, *J* = 4.1).

^{19}F NMR ($CDCl_3$, δ, ppm, *J*, Hz): 10.16 (q, CF_3, *J* = 10.1), 20.65 (q, CF_3, *J* = 10.2).

For $C_{12}H_9F_6N_3$ anal. calcd. (%): C, 46.61; H, 2.93; N, 13.59.

Found (%): C, 46.79; H, 3.11; N, 13.41.

Methyl 3-fluoroimidazo[1,2-*a*]pyrimidine-2-carboxylate (8). Trimethyl phosphite **6** (0.01 mol) was added to a solution of 0.01 mol of imine **1b** in 20 mL of CH_3CN with stirring. After an exothermic reaction completed, the reaction mixture was refluxed for 1 h, poured into 50 mL of water, and neutralized with a 5% K_2CO_3 solution, and the resultant precipitate was separated by filtration and recrystallized from 50% EtOH to give 1.6 g (82%) of compound **8**, mp 219–221°C.

^{1}H NMR (DMSO-d_6, δ, ppm, J, Hz): 3.87 (s, 3H, MeO), 7.18 (dt, 1H, $J_d = 7.7$, $J_t = 2.3$), 8.65 (t, 1H, J = 2.3), 8.81 (d, 1H, $J = 7.7$).

^{19}F NMR (DMSO-d_6, δ, ppm, J, Hz): –63.70 m.

For $C_8H_6FN_3O_2$ anal. calcd. (%): C 49.24; H 3.10; N 21.53.

Found (%): C 49.01; H 3.33; N 21.75.

3-Butyl-5-(pyrimidin-2'-ylamino)-5-trifluoromethylimidazolidine-2,4-dione (15). A solution of 0.01 mol of imine **1b** and 0.01 mol of *N*-butylurea **9** in 20 mL of DMF was stirred at 80°C for 1 h, 0.1 g of Et_3N was added, the mixture was heated for 6 h at 90°C, cooled, and poured into 50 mL of water, and the resultant precipitate was recrystallized from 50% EtOH to give 2.6 g (82%) of the title compound, mp 126–128°C.

^{1}H NMR (DMSO-d_6, δ, ppm, J, Hz): 1.07 (t, 3H, Me, $J = 7.4$), 1.45 (m, 2H, CH_2), 1.66 (m, 2H, CH_2), 3.42 (m, 2H, CH_2), 6.57 (t, 1H, CH_{Ar}, $J = 4.3$), 8.01 (d, 2H, CH_{Ar}, $J = 4.2$), 8.43 (s, 1H, NH), 8.67 (s, 1H, NH).

^{19}F NMR (DMSO-d_6, δ, ppm, J, Hz): –0.44 s.

For $C_{12}H_{14}F_3N_5O_2$ anal. calcd. (%): C, 45.43; H, 4.45; N, 22.07.

Found (%): C, 45.58; H, 4.62; N, 22.26.

4-Acetyl-5-methyl-3-(pyrimidin-2'-ylamino)-3-trifluoromethyl-1-phenyl-2,3-dihydropyrrol-2-one (16). Enamine **10** was added to a solution of 0.01 mmol of imine **1b** in 10 mL of DMF at 20°C with stirring. The reaction mixture was stirred for 20 min at 60°C, cooled, and poured into 50 mL of water, and the resultant precipitate was crystallized from 50% EtOH to give 2.9 g (77%) of the title compound, mp 202–204°C.

^{1}H NMR (DMSO-d_6, δ, ppm, J, Hz): 2.15 (s, 3H, Me), 2.24 (s, 3H, Me), 6.75 (t, 1H, CH_{Ar}, $J = 4.7$), 7.75 (d, 2H, CH_{Ar}, $J = 6.4$), 7.52 (m, 3H, CH_{Ar}), 8.37 (d, 2H, CH_{Ar}, $J = 4.7$), 9.03 (s, 1H, NH).

^{19}F NMR (DMSO-d_6, δ, ppm, J, Hz): 4.39 s.

For $C_{18}H_{15}F_3N_4O_2$ anal. calcd. (%): C, 57.45; H, 4.02; N, 14.89.

Found (%): C, 57.23; H, 4.21; N, 15.06.

6-(Pyrimidin-2'-ylamino)-6-trifluoromethyl-2,3-dihydroimidazo[2,1-*b*]thiazol-5-one (17) was obtained similarly to compound **16** from 0.01 mol of imine **1b** and 0.01 mol of 2-aminothiazoline **11**. Yield 2.4 g (79%), mp 147–149°C.

^{1}H NMR (DMSO-d_6, δ, ppm, J, Hz): 3.15 (m, 1H, CH_2), 3.56–3.74 (m, 2H, CH_2), 3.83 (m, 1H, CH_2), 6.61 (t, 1H, CH_{Ar}, $J = 4.4$), 8.12 (d, 2H, CH_{Ar}, J = 4.4), 8.87 (s, 1H, NH).

^{19}F NMR (DMSO-d_6, δ, ppm, J, Hz): 1.26 s.

For $C_{10}H_8F_3N_5OS$ anal. calcd. (%): C, 39.61; H, 2.66; N, 23.08.

Found (%): C, 39.80; H, 2.45; N, 22.89.

4-(Pyrimidin-2'-ylamino)-4-trifluoromethyl-2-phenyl-1-cyclohexyl-4,5-dihydroimidazol-5-one (18) was obtained similarly to compound **16** from 0.01 mol of imine **1b** and 0.01 mol of amidine **12**. Yield 3.2 g (79%), mp 145–147°C.

^{1}H NMR (DMSO-d_6, δ, ppm, J, Hz): 1.03–1.24 (m, 3H, CH_2), 1.47–1.90 (m, 5H, CH_2), 2.02–2.23 (m, 2H, CH_2), 3.50 (t, 1H, CH, J = 11.2), 6.73 (t, 1H, CH_{Ar}, J = 4.9), 7.39–7.61 (m, 5H, CH_{Ar}), 8.29 (d, 2H, CH_{Ar}, $J = 4.9$), 8.66 (s, 1H, NH).

^{19}F NMR (DMSO-d_6, δ, ppm, J, Hz): 0.30 s.

For $C_{20}H_{20}F_3N_5O$ anal. calcd. (%): C, 59.55; H, 5.00; N, 17.36.

Found (%): C, 59.73; H, 5.19; N, 17.18.

Methyl 2-methyl-5-oxo-4-(pyrimidin-2'-ylamino)-4-trifluoromethyl-4,5-dihydropyrrole-3-carboxylate (19) was obtained similarly to compound **16** from 0.01 mol of imine **1b** and 0.01 mol of 3-aminocrotonate **13**. Yield 2.4 g (76%), mp 163–165°C.

^{1}H NMR (DMSO-d_6, δ, ppm, J, Hz): 2.37 (s, 3H, Me), 3.60 (s, 3H, MeO), 6.68 (t, 1H, CH_{Ar}, $J = 5.4$), 7.56 (s, 1H, NH), 8.25 (d, 2H, CH_{Ar}, $J = 5.4$), 10.86 (s, 1H, NH).

^{19}F NMR (DMSO-d_6, δ, ppm, J, Hz): 3.15 s.

For $C_{12}H_{11}F_3NO_3$ anal. calcd. (%): C, 45.58; H, 3.51; N, 17.72.

Found (%): C, 45.77; H, 3.29; N, 17.91.

3-(Pyrimidin-2'-ylamino)-3-trifluoromethyl-7-phenyl-5,6-dihydropyrrolo[2,3-*b*]pyrimidin-2,4,6-trione (20) was obtained similarly to compound **15** from 0.01 mol of imine **1b** and 0.01 mol of 6-aminouracil **14**. Yield 3.1 g (76%), mp 249–251°C.

^{1}H NMR (DMSO-d_6, δ, ppm, J, Hz): 7.14 (t, 1H, CH_{Ar}, J = 4.6), 7.75 (m, 2H, CH_{Ar}), 7.92 (m, 3H, CH_{Ar}), 8.68 (d, 2H, CH_{Ar}, $J = 4.5$), 8.76 (s, 1H, NH), 11.28 (s, 1H, NH), 11.54 (s, 1H, NH).

^{19}F NMR (DMSO-d_6, δ, ppm, J, Hz): 3.99 s.

For $C_{17}H_{11}F_3N_6O_3$ anal. calcd. (%): C, 50.50; H, 2.74; N, 20.79.

Found (%): C, 50.77; H, 2.93; N, 20.61.

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