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METHYL TRIFLUOROPYRUVATE *N*-(PYRIMIDIN-2-YL)IMINES IN CYCLOCONDENSATION REACTIONS WITH 1,3-BINUCLEOPHILIC REAGENTS

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Cyclocondensation reactions of methyl trifluoropyruvate N-(pyrimidin-2-yl)imines with N-substituted ureas, N-benzylbenzamidine, 2-aminothiazoline, methyl 3-aminocrotonate, and 6-aminouracils leading to imidazolidine-2,4-diones, 3,5-dihydroimidazol-4-ones, 2,3-dihydroimidazo[2,1-d][1,3]thiazol-5(6H)-one, 4,5-dihydro-1H-pyrroles, and 5,7-dihydro-1H-pyrrolo[2,3-d]pyrimidine-2,4,6-triones have been studied.

Keywords: 2-aminothiazoline, 6-aminouracils, *N*-benzylbenzamidine, 3,5-dihydroimidazol-4-ones, 2,3-dihydroimidazo[2,1-*d*][1,3]thiazol-5(6*H*)-one, 4,5-dihydro-1*H*-pyrroles, 5,7-dihydro-1*H*-pyrrolo[2,3-*d*]-pyrimidine-2,4,6-triones, imidazolidine-2,4-dione, methyl 3-aminocrotonate, methyl trifluoropyruvate *N*-(pyrimidin-2-yl)imines, *N*-substituted ureas, cyclocondensation.

The modification of physiologically active compounds (PACs) is one of the most fruitful directions in organic chemistry. In this context the functionalization of PACs with fluorine-containing (including heterocyclic) substituents is particularly attractive. The introduction of fluorine-containing fragments into PAC molecules does not generally lead to a lowering of biological activity, but rather induces specific physicochemical properties which, in turn, can bring about an improvement and, in certain examples, a tunable change in the pharmacological parameters [1-5].

We have previously studied the behavior of methyl trifluoropyruvate (MTFP) *N*-substituted imines and hexafluoroacetone in cyclocondensation reactions with 1,3-C,N-, 1,3-C,O-, and 1,3-N,N-binucleophiles and demonstrated the synthetic potential of these reactions for obtaining various trifluoromethyl-containing five- and six-membered heterocycles [6-10]. This allowed us to propose an original approach to the molecular design of biologically active amides and amines.

The aim of this work was to study the cyclocondensation reactions of our previously synthesized MTFP *N*-(pyrimidin-2-yl)imines [11] with 1,3-binucleophilic reagents: *N*-substituted ureas, *N*-benzylbenzamidine, 2-aminothiazoline, methyl 3-aminocrotonate, and 6-aminouracils. It should be noted that the 2-aminopyrimidine pharmacophoric fragment occurs in the structures of diverse biologically active compounds including, for example, inhibitors of dihydrofolate reductase [12], tyrosine kinase [13], and protein kinases [14].

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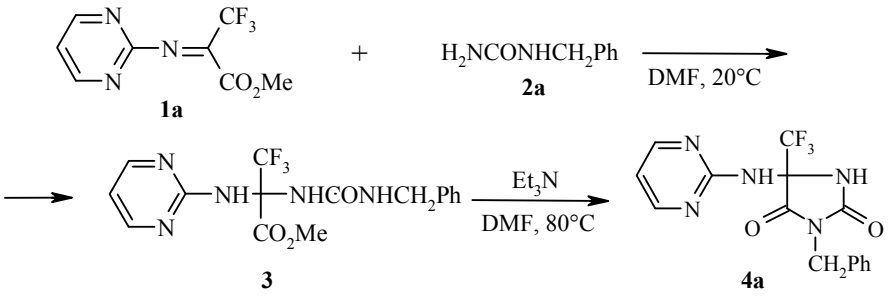
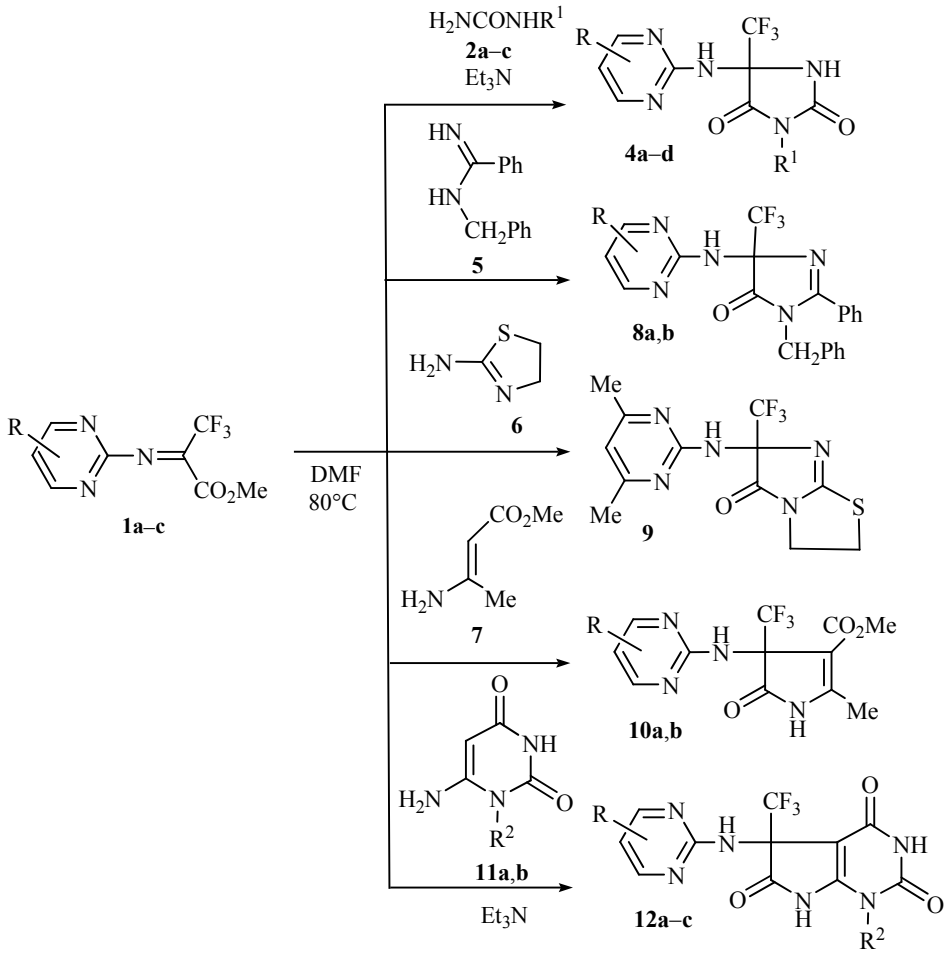
We have shown that the MTFP *N*-(pyrimidin-2-yl)imines behaved as 1,2-bielectrophiles in the examined reactions and reacted with the aforementioned 1,3-N,N- and 1,3-C,N-binucleophiles in two stages. The binucleophile at first added to the C=N bond, followed by heterocyclization with elimination of methanol. In the case of MTFP *N*-(pyrimidin-2-yl)imine (**1a**) reaction with *N*-benzylurea (**2a**) we isolated the amide **3** as the addition product, heating of which for 2 h in DMF at 80°C in the presence of a catalytic amount of triethylamine gave the imidazolidine-2,4-dione **4a**.



1a **3** **4a**

The imidazolidine-2,4-diones **4b-d** were prepared without isolation of the intermediate addition products (type **3** amides) by heating equimolar amounts of the reagents in DMF in the presence of catalytic amounts of Et_3N.



1a, **4a**,**b**, **8a**, **10a**, **12a**,**b** R = H, **1b**, **4c**, **8b**, **10b**, **12c** R = 4,6-Me_2, **1c**, **4d** R = 5-Br;
2a, **4a**,**c** R^1 = CH_2Ph, **2b**, **4d** R^1 = Me, **2c**, **4b** R^1 = CH_2CH_2Ph;
11a, **12a** R^2 = CH_2CH_2Ph, **11b**, **12b**,**c** R^2 = 2-furylmethyl

The *N*-benzylbenzamidine (**5**), 2-aminothiazoline (**6**), and methyl 3-aminocrotonate (**7**) reacted exothermically with the MTFP *N*-(pyrimidin-2-yl)imines **1a-c** without a catalyst to form the 3,5-dihydroimidazol-4-ones **8a**,**b**, the 2,3-dihydro-6*H*-imidazo[2,1-*d*]thiazol-5-one **9**, and the 4,5-dihydro-1*H*-pyrroles **10a**,**b**. Complete heterocyclization required heating for 1 h at 80°C. The less nucleophilic 6-aminouracils **11a**,**b** reacted with the MTFP *N*-(pyrimidin-2-yl)imines **1a**,**b** when heated for 2 h in DMF at 80°C in the presence of catalytic amounts of Et_3N, to give the 5,7-dihydro-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4,6-triones **12a-c**.

The synthesized compounds **4a-d**, **8a**,**b**, **9**, **10a**,**b**, and **12a-d** were solid, colorless crystals, the composition and structure of which were confirmed by elemental analysis and by ^1H and ^{19}F NMR spectroscopy.

Hence, the examined cyclocondensation reactions of MTFP *N*-(pyrimidin-2-yl)imines with 1,3-N,N- and 1,3-C,N-binucleophiles allowed the functionalization of pharmaceutically significant 2-aminopyrimidines with trifluoromethyl-containing five-membered heterocycles.

EXPERIMENTAL

The ^1H and ^{19}F NMR spectra were recorded on a Bruker DPX-200 instrument (200 and 188 MHz, respectively) using DMSO-d_6 relative to TMS as internal standard and CF_3COOH as external standard, respectively. Elemental analysis was performed on a vario MICRO cube CHNS/O analyzer. Melting points were determined in glass capillaries on a Manual Mel-Temp instrument. The *N*-(pyrimidin-2-yl)imines **1a-c** were synthesized by method [11]. The *N*-substituted ureas **2a-c**, *N*-benzylbenzamidine (**5**), 2-aminothiazoline (**6**), methyl 3-aminocrotonate (**7**), and 6-aminouracils **11a**,**b** (Sigma-Aldrich) were used without preliminary purification.

Methyl 2-(3-Benzylcarbamoylamino)-2-(pyrimidin-2-ylamino)-3,3,3-trifluoropropionate (3). Urea **2a** (1.50 g, 10 mmol) was added to a solution of the imine **1a** (2.33 g, 10 mmol) in DMF (20 ml). The reaction mixture was stirred for 2 h at 20°C, poured into water, and the precipitate formed was filtered off and recrystallized from 50% ethanol. Yield 3.50 g (90%). Mp 102-104°C. ^1H NMR spectrum, δ, ppm (*J*, Hz): 3.82 (3H, s, CH_3); 4.06-4.22 (2H, m, CH_2); 6.61 (1H, t, *J* = 4.7, H Ar); 7.20-7.41 (5H, m, H Ph); 7.89 (2H, d, *J* = 4.7, H Ar); 8.06 (1H, t, *J* = 5.1, NH); 8.79 (1H, s, NH); 9.13 (1H, s, NH). ^{19}F NMR spectrum, δ, ppm: 2.51 (s). Found, %: C 50.31; H 4.39; N 18.42. $C_{16}H_{16}F_3N_5O_3$. Calculated, %: C 50.13; H 4.21; N 18.27.

3-Benzyl-5-(pyrimidin-2-ylamino)-5-(trifluoromethyl)imidazolidine-2,4-dione (4a). A. Et_3N (0.1 g, 0.1 mmol) was added to a solution of compound **3** (1.9 g, 5.0 mmol) in DMF (10 ml). The reaction mixture was heated at 80°C for 2 h, poured into water, the precipitate formed was filtered off and recrystallized from 50% ethanol. Yield 1.5 g (85%).

B. Urea **2a** (0.75 g, 5.0 mmol) was added to a solution of imine **1a** (1.17 g, 5.0 mmol) in DMF (20 ml). The reaction mixture was stirred for 2 h at 20°C and treated with Et_3N (0.1 g, 0.1 mmol). The reaction mixture was then heated at 80°C for 2 h, poured into water, and the precipitate formed was filtered off and recrystallized from 50% ethanol. Yield 1.40 g (80%). Mp 134-135°C. ^1H NMR spectrum, δ, ppm (*J*, Hz): 4.67 (2H, s, CH_2); 6.67 (1H, t, *J* = 4.8, H Ar); 7.27-7.48 (5H, m, H Ph); 7.93 (2H, d, *J* = 4.8, H Ar); 8.79 (1H, s, NH); 9.13 (1H, s, NH). ^{19}F NMR spectrum, δ, ppm: -0.11 (s). Found, %: C 51.10; H 3.26, N 20.11. $C_{15}H_{12}F_3N_5O_2$. Calculated, %: C 51.29; H 3.44; N 19.94.

3-(2-Phenylethyl)-5-(pyrimidin-2-ylamino)-5-trifluoromethylimidazolidine-2,4-dione (4b). Prepared similarly to compound **4a** (method B) from the imine **1a** (1.2 g, 5 mmol) and the urea **2c** (0.8 g, 5 mmol). Yield 1.6 g (88%). Mp 123-124°C. ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.98 (2H, t, *J* = 7.7, CH_2); 3.65-3.75 (2H, m, CH_2); 6.80 (1H, t, *J* = 5.1, H Ar); 7.14-7.38 (5H, m, H Ph); 8.34 (2H, d, *J* = 5.1, H Ar); 8.82 (1H, s, NH); 9.08 (1H, s, NH). ^{19}F NMR spectrum, δ, ppm: -0.22 (s). Found, %: C 52.40; H 3.68, N 19.33. $C_{16}H_{14}F_3N_5O_2$. Calculated, %: C 52.61; H 3.86; N 19.17.

3-Benzyl-5-(4,6-dimethylpyrimidin-2-ylamino)-5-(trifluoromethyl)imidazolidine-2,4-dione (4c). Prepared similarly to compound **4a** (method B) from the imine **1b** (1.30 g, 5 mmol) and the urea **2a** (0.75 g, 5 mmol). Yield 1.50 g (79%). Mp 135-137°C. ^{1}H NMR spectrum, δ, ppm: 2.19 (6H, s, $2CH_3$); 4.67 (2H, s, CH_2); 6.52 (1H, s, H Ar); 7.25-7.41 (5H, m, H Ph); 8.48 (1H, s, NH); 9.06 (1H, s, NH). ^{19}F NMR spectrum, δ, ppm: -0.27 (s). Found, %: C 53.66; H 4.42; N 18.29. $C_{17}H_{16}F_3N_5O_2$. Calculated, %: C 53.83; H 4.25; N 18.46.

5-(5-Bromopyrimidin-2-ylamino)-3-methyl-5-(trifluoromethyl)imidazolidine-2,4-dione (4d). Obtained similarly to compound **4a** (method B) from the imine **1c** (1.6 g, 5 mmol) and the urea **2b** (0.37 g, 5 mmol). Yield 1.4 g (79%). Mp 166-168°C. ^{1}H NMR spectrum, δ, ppm: 3.01 (3H, s, CH_3); 8.43 (2H, s, H Ar); 9.09 (1H, s, NH); 9.18 (1H, s, NH). ^{19}F NMR spectrum, δ, ppm: -0.16 (s). Found, %: C 30.35; H 2.22, N 19.94. $C_9H_7BrF_3N_5O_2$. Calculated, %: C 30.53; H 1.99; N 19.78.

3-Benzyl-2-phenyl-5-(pyrimidin-2-ylamino)-5-trifluoromethyl-3,5-dihydro-4*H*-imidazol-4-one (8a). The amidine **5** (1.05 g, 5 mmol) was added to a solution of the imine **1a** (1.2 g, 5 mmol) in DMF (20 ml). The reaction mixture was stirred for 1 h at 20°C, heated at 80°C for 1 h, poured into water, the precipitate was filtered off, and recrystallized from 50% ethanol. Yield 1.7 g (83%). Mp 177-179°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.77 (2H, s, CH_2); 6.69 (1H, t, *J* = 4.7, H Ar); 7.07-7.19 (2H, m, H Ph); 7.21-7.29 (3H, m, H Ph); 7.29-7.52 (5H, m, H Ph); 8.12 (2H, d, *J* = 7.3, H Ar); 8.80 (1H, s, NH). ^{19}F NMR spectrum, δ, ppm: 0.83 (s). Found, %: C 61.13; H 3.71; N 17.23. $C_{21}H_{16}F_3N_5O$. Calculated, %: C 61.31; H 3.92; N 17.02.

3-Benzyl-5-(4,6-dimethylpyrimidin-2-ylamino)-2-phenyl-5-trifluoromethyl-3,5-dihydroimidazol-4-one (8b). Obtained similarly to compound **8a** from the imine **1b** (1.30 g, 5 mmol) and compound **5** (1.05 g, 5 mmol). Yield 1.70 g (77%). Mp 181-182°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.34 (6H, s, $2CH_3$); 4.65 (1H, d, *J* = 15.1) and 5.12 (1H, d, *J* = 15.1, CH_2); 6.61 (1H, s, H Ar); 7.29 (2H, d, *J* = 7.3, H Ph); 7.41-7.49 (3H, m, H Ph); 7.52-7.60 (4H, m, H Ph); 7.63-7.71 (1H, m, H Ph); 8.67 (1H, s, NH). ^{19}F NMR spectrum, δ, ppm: 0.92 (s). Found, %: C 62.66; H 4.41; N 16.15. $C_{23}H_{20}F_3N_5O$. Calculated, %: C 62.87; H 4.59; N 15.94.

6-(4,6-Dimethylpyrimidin-2-ylamino)-6-trifluoromethyl-2,3-dihydroimidazo[2,1-*d*][1,3]thiazol-5(6*H*)-one (9). Prepared similarly to compound **8a** from the imine **1b** (1.2 g, 5 mmol) and compound **6** (0.5 g, 5 mmol). Yield 1.2 g (73%). Mp 145-147°C. ^{1}H NMR spectrum, δ, ppm: 2.27 (6H, s, $2CH_3$); 3.09-3.21 (1H, m, CH_2); 3.56-3.74 (2H, m, CH_2); 3.78-3.88 (1H, m, CH_2); 6.56 (1H, s, H Ar); 8.87 (1H, s, NH). ^{19}F NMR spectrum, δ, ppm: 1.19 (s). Found, %: C 43.33; H 3.83; N 21.36. $C_{12}H_{12}F_3N_5OS$. Calculated, %: C 43.50; H 3.65; N 21.14.

Methyl 2-Methyl-5-oxo-4-(pyrimidin-2-ylamino)-4-trifluoromethyl-4,5-dihydro-1*H*-pyrrole-3-carboxylate (10a). Obtained similarly to compound **8a** from the imine **1a** (1.2 g, 5 mmol) and compound **7** (0.6 g, 5 mmol). Yield 1.2 g (76%). Mp 163-164°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.37 (3H, s, CH_3); 3.60 (3H, s, CH_3O); 6.68 (1H, t, *J* = 5.4, H Ar); 7.56 (1H, s, NH); 8.25 (2H, d, *J* = 5.4, H Ar); 10.86 (1H, s, NH). ^{19}F NMR spectrum, δ, ppm: 3.15 (s). Found, %: C 45.77; H 3.29; N 17.91. $C_{12}H_{11}F_3N_4O_3$. Calculated, %: C 45.58; H 3.51; N 17.72.

Methyl 2-Methyl-4-(4,6-dimethylpyrimidin-2-ylamino)-5-oxo-4-trifluoromethyl-4,5-dihydro-1*H*-pyrrole-3-carboxylate (10b). Prepared similarly to compound **8a** from the imine **1b** (1.3 g, 5 mmol) and compound **7** (0.6 g, 5 mmol). Yield 1.2 g (76%). Mp 173-175°C. ^{1}H NMR spectrum, δ, ppm: 2.19 (6H, s, $2CH_3$); 2.32 (3H, s, CH_3); 3.58 (3H, s, CH_3O); 6.39 (1H, s, H Ar); 7.02 (1H, s, NH); 10.75 (1H, s, NH). ^{19}F NMR spectrum, δ, ppm: 3.25 (s). Found, %: C 48.66; H 4.15; N 16.08. $C_{14}H_{15}F_3N_4O_3$. Calculated, %: C 48.84; H 4.39; N 16.27.

1-(2-Phenylethyl)-5-(pyrimidin-2-ylamino)-5-trifluoromethyl-5,7-dihydro-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4,6(3*H*)-trione (12a). The uracil **11a** (1.16 g, 5 mmol) was added to a solution of the imine **1a** (1.2 g, 5 mmol) in DMF (20 ml). The reaction mixture was stirred for 2 h at 20°C, Et_3N (0.1 g, 0.1 mmol) was added. The mixture was then heated at 80°C for 2 h, poured into water, and the precipitate formed was filtered off and recrystallized from 50% ethanol. Yield 1.6 g (74%). Mp 211-213°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.89 (2H, t, *J* = 5.0, CH_2); 3.98-4.12 (2H, m, CH_2); 6.65 (1H, t, *J* = 5.0, H Ar); 7.17-7.32 (5H, m, H Ph); 8.25 (2H, d,

J = 5.2, H Ar); 8.40 (1H, s, NH); 10.87 (1H, s, NH); 12.09 (1H, s, NH). ^{19}F NMR spectrum, δ, ppm: 3.52 (s). Found, %: C 52.61; H 3.69; N 19.25. $C_{19}H_{15}F_3N_6O_3$. Calculated, %: C 52.78; H 3.50; N 19.44.

1-(2-Furylmethyl)-5-(pyrimidin-2-ylamino)-5-trifluoromethyl-5,7-dihydro-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4,6(3*H*)-trione (12b). Prepared similarly to compound **12a** from the imine **1a** (1.2 g, 5 mmol) and the uracil **11b** (1.04 g, 5 mmol). Yield 1.5 g (78%). Mp 223-225°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.07 (2H, AB system, *J* = 18.4, CH_2); 6.32-6.44 (2H, m, H furan); 6.65 (1H, t, *J* = 5.0, H Ar); 7.50-7.62 (1H, m, H furan); 8.18 (2H, d, *J* = 5.2, H Ar); 8.35 (1H, s, NH); 10.96 (1H, s, NH); 12.11 (1H, s, NH). ^{19}F NMR spectrum, δ, ppm: 3.61 (s). Found, %: C 47.25; H 2.88; N 20.39. $C_{16}H_{11}F_3N_6O_4$. Calculated, %: C 47.07; H 2.72; N 20.58.

1-(2-Furylmethyl)-5-(4,6-dimethylpyrimidin-2-ylamino)-5-trifluoromethyl-5,7-dihydro-1*H*-pyrrolo-[2,3-*d*]pyrimidine-2,4,6(3*H*)-trione (12c). Prepared similarly to compound **12a** from the imine **1b** (1.30 g, 5 mmol) and the uracil **11b** (1.04 g, 5 mmol). Yield 1.65 g (73%). Mp 231-233°C. ^{1}H NMR spectrum, δ, ppm: 2.16 (6H, s, $2CH_3$); 4.99-5.17 (2H, m, CH_2); 6.34-6.42 (2H, m, H furan); 6.45-6.51 (1H, m, H furan); 7.49 (1H, s, H Ar); 7.73 (1H, s, NH); 10.94 (1H, s, NH); 12.06 (1H, s, NH). ^{19}F NMR spectrum, δ, ppm: 3.64 (s). Found, %: C 49.34; H 3.22; N 19.02. $C_{18}H_{15}F_3N_6O_4$. Calculated, %: C 49.55; H 3.46; N 19.26.

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