Cyclization of Bifunctional 3,5-Diamino-1*H*-1,2,4-triazole-1-carboximidamide, 5-Amino-3-hydrazinotriazole and 3,6-Diguanidino-1,2,4,5-tetrazine: A One-Step Route to Fluorinated Heteropolycycles

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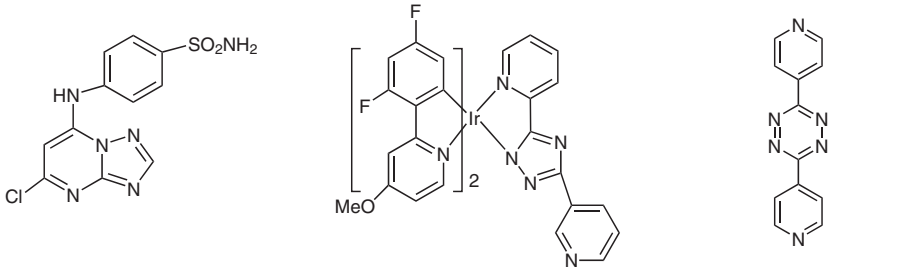
Abstract: A series of new fluorine-containing triazolylpyrimidines and pyrimidinoaminotetrazines results from one-pot reactions of 3,5-diamino-1*H*-1,2,4-triazole-1-carboximidamide hydrochloride and 1,4-diguanidino-2,3,4,5-tetrazine with fluoro-1,3-diketones. Bicyclization of a variety of fluorinated 1,3-diketones gave three fluorinated heterocyclic pyrazolo[1,2,4]triazolo[1,5-*a*]pyrimidines in moderate yield in a single step.

Key words: cyclization, bifunctional heterocycles, fluorinated polyheterocycles, triazolylpyrimidines, pyrazolo[1,2,4]triazolo[1,5-*a*]pyrimidines

It is well-known that introduction of a fluorine atom or a fluoroalkyl group into heterocyclic compounds has a profound influence on their chemical, physical and biological properties.[1] Fluorinated heterocycles are widely recognized as important species in the development of new pharmaceuticals and agrochemicals.[2] In the formation of these heterocyclic compounds, cyclic addition reactions have been mainly applied to the synthesis of fluorinated five-membered heterocyclic rings, such as furan, pyrazole, isoxazole, 1,2,3-triazole, and six-membered heterocyclic rings, such as pyrimidine, quinoline and pyridine.[3] It is worthwhile developing new fluorinated heterocyclic rings which may have advantageous properties. Fluorinated heteropolycyclic systems are among some new fluorinated heterocyclic rings that are currently attracting attention.[4] For example, the bicyclic heterocycle, 1,2,4-triazolo[1,5-*a*]pyrimidine, a subtype of a purine bioisosteric analogue, is reported to be useful in controlling noxious fungi, and to be a potent and selective A_{2A} adenosine receptor antagonist, in addition to possessing potential anti-tumor activities (Figure 1).[5] The properties of 1,2,4-triazole–iridium complexes, such as flexibility, make them well-suited for organic light-emitting materials and devices.[6] The tricyclic heterocyclic tetrazine compound shown in Figure 1 has also been shown to retard the ripening or senescence of fruit or other plants.[7]

Previously, a bicyclic triazolopyrimidine was prepared by condensation of 3-amino-1,2,4-triazole or 3-amino-5-benzylthio-1,2,4-triazole and dicarbonyl compounds,[8] or by a multiple-step process.[9] However, the efficient syntheses of fluorinated bicyclic or polycyclic triazoloaminopyrimidine, pyrazolo-triazolopyrimidine, or pyrimidinotetrazine compounds have not been reported. Our efforts have been directed toward the development of new synthetic methodologies for the successful preparation of fluorinated heterocyclic compounds as bioactive molecules as well as nitrogen-rich energetic materials.[10] A large number of fluorinated pyrazole, triazole and tetrazole quaternary salts are ionic liquids.[11]

While 3,5-diamino-1*H*-1,2,4-triazole-1-carboximidamide,[12] 5-amino-3-hydrazino-1,2,4-triazole[13] and 1,4-diguanidino-2,3,4,5-tetrazine[14] are bifunctional heteronucleophiles (Scheme 1), there appears to be no reports of



[1,2,4]triazolo[1,5-a]pyrimidine as anticancer agent[a]

organic light-emitting materials 1,2,4-triazole iridium complex[b]

tetrazine retards ripening of fruit and plants[c]

[a] Ref. 5, [b] Ref. 6, [c] Ref. 7

Figure 1 Triazole and tetrazine heterocycles

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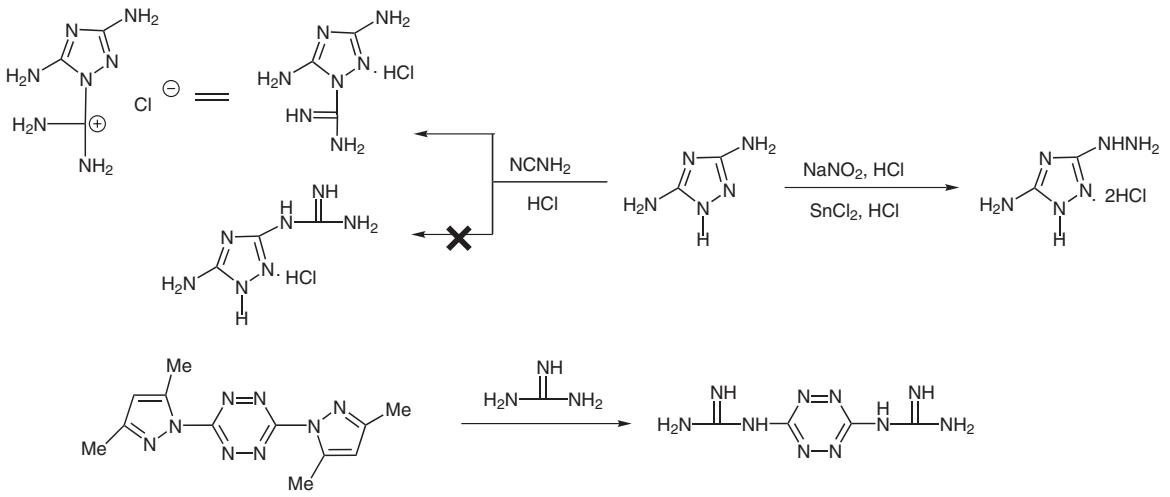
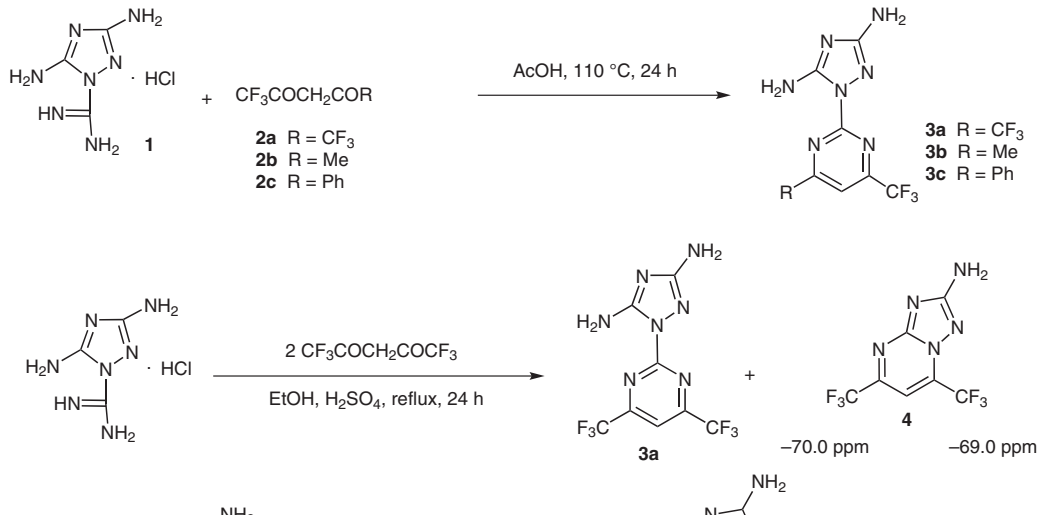


Scheme 1 Synthesis of bifunctional heterocyclic nucleophiles

cyclization reactions of such materials to yield fluorinated heteropolycyclic compounds. Therefore, we now report the facile and straightforward syntheses of fluorinated triazolylaminopyrimidine, pyrazolo-triazolopyrimidine, and pyrimidino(amino)tetrazine heteropolycycles by cyclizing 3,5-diamino-1*H*-1,2,4-triazole-1-carboximidamide, 5-amino-3-hydrazino-1,2,4-triazole, and 1,4-diguanidino-2,3,4,5-tetrazine with fluorine-containing 1,3-diketones.

The commercially available starting material, 3,5-diamino-1,2,4-triazole, was reacted with cyanamide in ethanol under reflux for six hours to form 3,5-diamino-1*H*-1,2,4-triazole-1-carboximidamide, not the previously reported product 5-amino-3-guanidino-1,2,4-triazole,[15] which, after workup, was isolated as the hydrochloride salt, **1**, in 75% yield (Scheme 2). Previously, 2-(3,5-diamino-1*H*-1,2,4-triazol-1-yl)-4,6-dimethylpyrimidine was isolated from the reaction of 4,6-dimethyl-2-hydrazinopyrimidine hydrochloride and dicyandiamide in pyrimidine,[16] or from the 3,5-diamino-1*H*-1,2,4-triazole-1-carboximidamide.[17] Cyclization of **1** with fluorine-containing 1,3-diketones **2a**–**c** (1:1), in acetic acid at 110 °C for 24 hours, generated the fluorinated triazolylaminopyrimidines **3a**–**c** in high yields (Scheme 2). An attempt to form the bicyclic product, 4,6-bis(trifluoromethyl)-2-(1,2,4-triazolo[1,5-*a*]pyrimidin-5-ylamino)pyrimidine, by treating **3a** with additional 1,1,1,5,5,5-hexafluoropentane-2,4-dione (**2a**) in acetic acid at 110 °C was unsuccessful. After refluxing **1** and **2a** (1:2 ratio) in ethanol with sulfuric acid as catalyst, the ^{19}F NMR spectrum of the reaction mixture showed resonances at δ = –68.8 ppm (**3a**), and at δ = –69.0 ppm and –70.0 ppm (**4**). Separation of the reaction mixture gave **3a** (70% yield) and **4** (30%).

While no bicyclization reactions occurred, it was found that **4** could also be obtained in 60% yield by reacting 3,5-diamino-1,2,4-triazole with **2a** under the same conditions. The formation of compound **4** from the 3,5-diamino-1*H*-



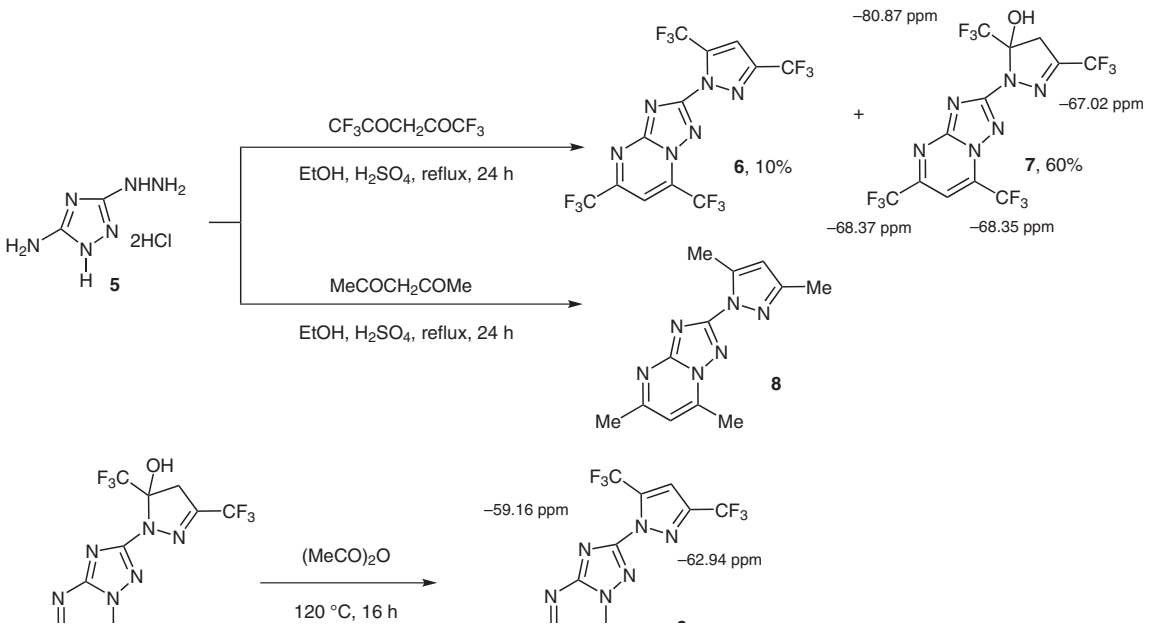
Scheme 2 Cyclization reactions of 3,5-diamino-1*H*-1,2,4-triazole-1-carboximidamide.

1,2,4-triazole-1-carboximidamide hydrochloride, **1**, may involve an initial solvolysis of the guanyl moiety to yield 3,5-diamino-1,2,4-triazole which would react with the diketone to produce **4**.

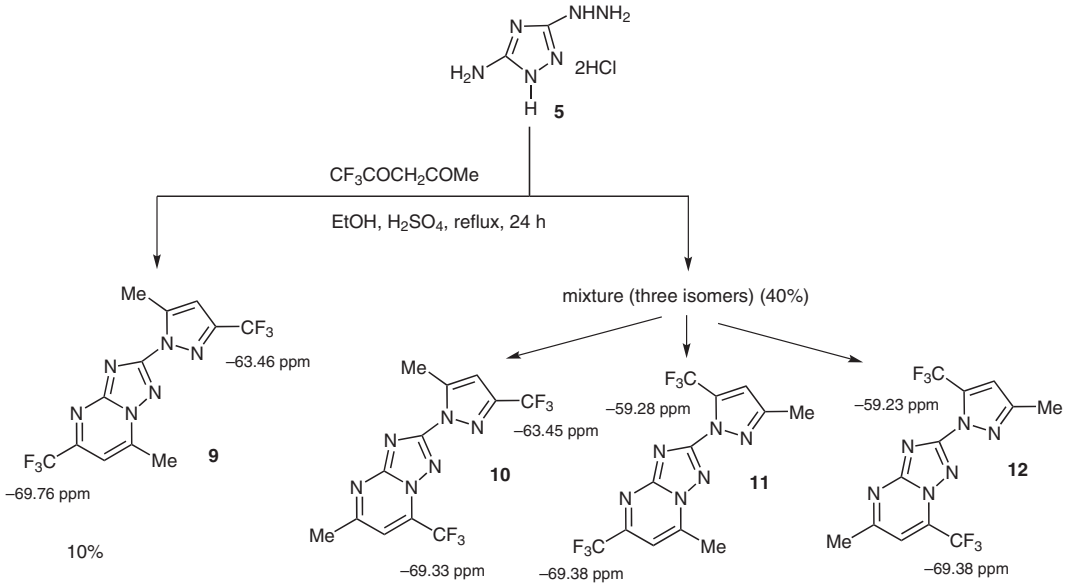
The bicyclization of 5-amino-3-hydrazino-1,2,4-triazole dihydrochloride (**5**) to three fluorinated pyrazolo[1,2,4]triazolo[1,5-*a*]pyrimidine heterocycles in one step was also investigated; the starting material, **5**, was produced in two steps from 3,5-diamino-1,2,4-triazole.[13] In an effort to prepare 5-amino-3-[3,5-bis(trifluoromethyl)pyrazolo]-1,2,4-triazole, **5** was reacted with **2a** to give a mixture of 5,7-bis(trifluoromethyl)-2-[3,5-bis(trifluoromethyl)pyrazolo]-[1,2,4]-triazolo[1,5-*a*]pyrimidine (**6**) and the corresponding dihydro compound **7** (Scheme 3). The mixture was easily separated by chromatography to give **6** (10%) and **7** (60%). The structure of compound **6** was confirmed by ^{19}F and ^{1}H NMR, mass spectrometry and elemental analysis [four ^{19}F NMR resonances (δ = –68.38, –68.26, –62.94 and –59.16 ppm), and aromatic proton signals in the ^{1}H NMR spectrum (δ = 8.21 and 7.54 ppm)]. The structure of **7** was unambiguously assigned using ^{1}H (^{1}H–^{13}C HSQC, HMBC) and ^{19}F NMR spectroscopy, mass spectrometry, and elemental analysis. In the ^{1}H HSQC spectrum of **7**, a clear decoupled ^{1}H singlet at δ = 6.21 ppm could be assigned to the hydroxyl group. When **5** and pentane-2,4-dione were heated at reflux for 24 hours under the same conditions, only 5,7-dimethyl-2-(3,5-dimethylpyrazolo)-[1,2,4]-triazolo[1,5-*a*]pyrimidine (**8**) was obtained in 70% yield. Based on the observed formation of a single compound, **8**, it can be seen that the formation of **7** arises either as a direct result of the presence of a high concentration of the enol isomer of bis(trifluoromethyl)acetylacetone or because the dehydration step is more difficult under the reaction conditions when a fluorinated group is present.[18] Dehydration of **7** under the influence of acetic anhydride at 120 °C, gave **6** in 90% yield. This is thus a simple and convenient one-step route for the preparation of fluorinated heteropolycyclic derivatives of pyrazolo-[1,2,4]-triazolo[1,5-*a*]pyrimidine.

The result obtained with **2a** encouraged us to extend this approach to the synthesis of asymmetrically fluorinated pentane-2,4-diones in order to synthesize the fluorinated heteropolycycles, pyrazolo-1,2,4-triazolo-pyrimidines, using 1,1,1-trifluoropentane-2,4-dione (**2b**; Scheme 4). Upon column chromatographic purification of the reaction mixture, 7-methyl-5-trifluoromethyl-2-(5-methyl-3-trifluoromethylpyrazolo)-[1,2,4]-triazolo[1,5-*a*]pyrimidine (**9**), and a three-component isomeric mixture were obtained. Compound **9** was identified using ^{1}H (^{1}H–^{13}C HMBC) and ^{19}F NMR spectroscopy, mass spectra, elemental analysis and single-crystal X-ray structure determination. The ^{19}F NMR signals at δ = –69.76 and –63.46 ppm were assigned to the trifluoromethyl groups on the pyrimidine and pyrazole rings, respectively, based on ^{1}H–^{13}C HMBC and ^{19}F NMR spectroscopy; the coupling constants (J_{C-F}) between the fluorine atoms of the trifluoromethyl groups and the carbon atom were 275 and 266 Hz, respectively. The mixture containing the isomeric compounds **10**, **11** and **12** could not be separated by normal column chromatography because of their very similar polarities. The GC-MS chromatogram, however, exhibited three peaks at 14.1 (*m*/*z* =350), 14.6 (*m*/*z* = 350) and 15.7 (*m*/*z* = 350) minutes, corresponding to the three isomers. These isomeric structures were identified by comparison of the ^{19}F NMR spectra with those of **6** and **9**.

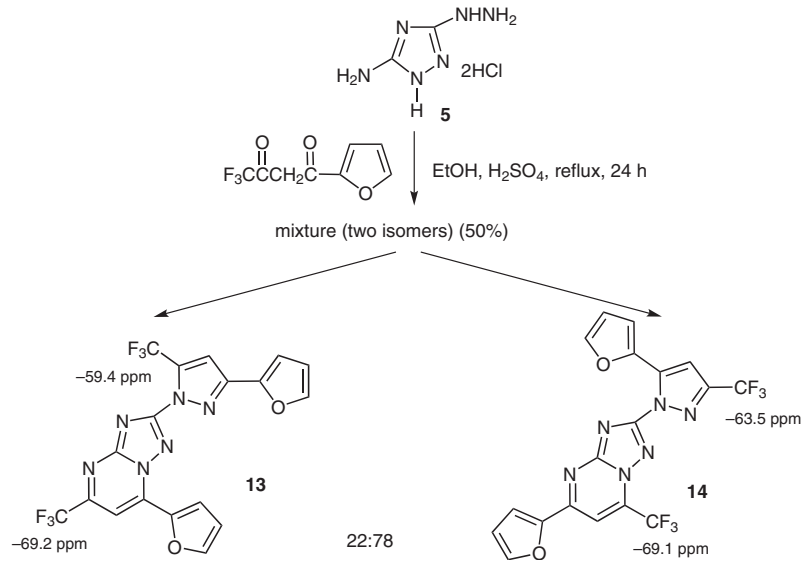
Furyl pyrimidine derivatives have been reported to be important antitumor agents.[19] Condensation of furyl-substi-



Scheme 3 Cyclization reactions of 5-amino-3-hydrazino-1,2,4-triazole



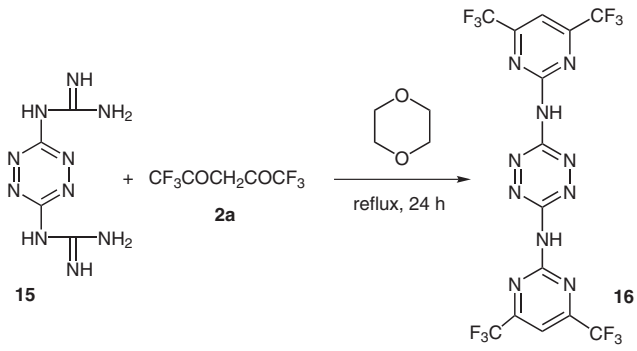
Scheme 4 Synthesis of asymmetrically fluorinated pyrazolo-1,2,4-triazolo-pyrimidines



Scheme 5 Synthesis of asymmetrically fluorinated pyrazolo-1,2,4-triazolo-pyrimidines

tuted 4,4,4-trifluoro-1-(2-furyl)butane-1,3-dione with **5**, gave a mixture of two isomers **13** and **14** (Scheme 5). The GC-MS chromatogram exhibited two peaks at 19.9 (m/z = 454) and 20.3 (m/z = 454) minutes. The ratio of **13** and **14** was 22:78, based on comparison of peak intensities in the ^{19}F NMR spectra. Their structures were assigned by comparison with the ^{19}F NMR spectra of **6** and **9**.

The synthesis of 3,6-bis[4,6-bis(trifluoromethyl)pyrimidino-2-amino]tetrazine (**16**), a fluorinated heteropolycyclic, in 75% yield also succeeded by heating 3,6-diguanidino-1,2,4,5-tetrazine (**15**)[14] and **2a**, at reflux in dioxane (Scheme 6). However, no reaction occurred when **15** was heated under the same conditions with 1,1,1-trifluoropentane-2,4-dione (**2b**).



Scheme 6 Synthesis of fluorinated pyrimidinotetrazine

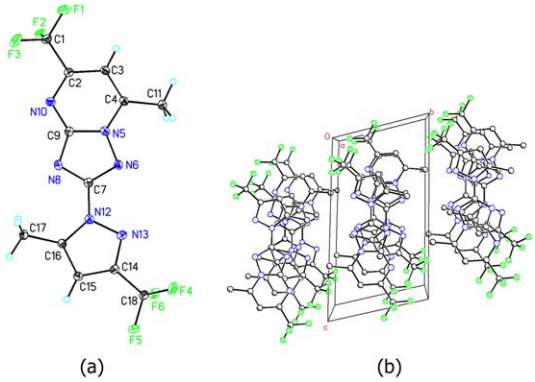


Figure 2 (a) Molecular structure of **9** (30% thermal displacement) showing the numbering scheme. Hydrogen atoms are shown (arbitrary spheres) but are unlabelled for clarity. (b) Packing diagram of **9** (ball and stick) viewed down the a-axis, showing the alternating stacks. Hydrogen atoms have been omitted for clarity.

The solid-state structure of **9** was confirmed by single-crystal X-ray diffraction as shown in Figure 2. Suitable colorless plate crystals were obtained by slow concentration of an ethyl acetate/hexane solution of **9**. A notable feature of this molecule is the approximate co-planarity of the pyrazole and pyrimidine moieties (only a 2.2° angle between the pyrazole and pyrimidine mean planes). This, as well as the short C–N bond length joining the two systems [C7–N12, 1.394(2) Å], indicates a delocalization of the aromaticity across both ring-systems. This conformation enables the molecules to pack in alternating ABAB stacks parallel to the a-axis with a gap of ~3.45 Å between each 'planar' unit as shown in Figure 2b.

In conclusion, a new and highly effective one-step route has been developed for the preparation of fluorine-containing heteropolycycles. Cyclization of bifunctional nucleophiles, 3,5-diamino-1*H*-1,2,4-triazole-1-carboximidamide hydrochloride and 3,6-diguanidino-1,2,4,5-tetrazine, with fluorine-containing 1,3-diketones results in the formation of fluorinated triazolylaminopyrimidines and pyrimidinoaminotetrazines in high yield. Combination of 5-amino-3-hydrazino-1,2,4-triazole dihydrochloride with a variety of fluorinated 1,3-diketones yields three symmetric and asymmetric fluorinated heterocycles, pyrazolo[1,2,4]triazolo[1,5-*a*]pyrimidines, in one step in moderate yields.

All the reagents used were analytical reagents purchased from commercial sources and used as received. The following materials were prepared and purified according to reported procedures: 5-amino-3-hydrazino-1,2,4-triazole dihydrochloride[13] and 3,6-diguanidino-1,2,4,5-tetrazine.[14]

^{1}H, ^{19}F and ^{13}C NMR spectra were recorded on a Bruker 300 MHz NMR spectrometer operating at 300.13, 282 and 75.48 MHz, respectively. ^{1}H–^{13}C HSQC and HMBC spectra were recorded on a Bruker Avance 500 MHz NMR spectrometer. Chemical shifts are reported relative to TMS (^{1}H and ^{13}C NMR) or CCl_3F (^{19}F NMR). The solvent used was CD_3CN unless otherwise specified. Melting points were recorded on a differential scanning calorimeter (DSC) at a scan rate of 10 °C/min. Elemental analyses were performed on an EXETER CE-440 Elemental Analyzer. GC-MS spectra were recorded on a Shimadzu GCMS-QP5050A using a capillary column.

3,5-Diamino-1*H*-1,2,4-triazole-1-carboximidamide Hydrochloride (1)

To a round-bottom flask fitted with a reflux condenser, was added 3,5-diamino-1,2,4-triazole hydrochloride (3 mmol) and cyanamide (3 mmol) in EtOH (30 mL). The reaction was heated at reflux for 6 h, then the mixture was filtered and washed with EtOH (15 mL), and the white solid was recrystallized from methanol to give **1**. Yield: 75% white solid; mp (DSC) 210 ºC (dec.).

^{1}H NMR (DMSO-d_6): δ = 8.8 (s, 4 H), 7.4 (s, 2 H), 5.8 (s, 2 H).

^{13}C NMR (DMSO-d_6): δ = 164.3, 157.6, 152.7.

Anal. Calcd for $C_3H_8ClN_7$: C, 20.29; H, 4.54; N, 55.21. Found: C, 20.39; H, 4.47; N, 55.21.

Preparation of Fluorinated Triazolylpyrimidines 3a–c; General Procedure

To a round-bottom flask fitted with a reflux condenser, was added 3,5-diamino-1*H*-1,2,4-triazole-1-carboximidamide hydrochloride (**1**; 1 mmol) and fluorinated 1,3-β-diketone (1 mmol) in AcOH (10 mL). The reaction was heated at reflux for 24 h then AcOH was removed under reduced pressure and the residue was recrystallized from 1,4-dioxane to give **3a**–**c** in good yields.

2-(3,5-Diamino-1*H*-1,2,4-triazol-1-yl)-4,6-di(trifluoromethyl)pyrimidine (3a)

Yield: 80%; yellow solid; mp 319 °C.

^{1}H NMR (DMSO-d_6): δ = 8.1 (s, 1 H), 7.5 (s, 2 H), 5.8 (s, 2 H).

^{13}C NMR (DMSO-d_6): δ = 164.1, 159.5 (q, $J_{C–F}$ = 37.0 Hz, CCF_3), 157.9, 156.5, 126.9 (q, $J_{C–F}$ = 276.0 Hz, CF_3), 108.9.

^{19}F NMR (DMSO-d_6): δ = –68.8 (s, 6 F).

GC-MS (EI): m/z = 313 [M^+].

Anal. Calcd for $C_8H_5F_6N_7$: C, 30.68; H, 1.61; N, 31.31. Found: C, 30.94; H, 1.52; N, 30.91.

2-(3,5-Diamino-1*H*-1,2,4-triazol-1-yl)-4-methyl-6-trifluoromethylpyrimidine (3b)

Yield: 70%; yellow solid; mp 322 °C.

^{1}H NMR (DMSO-d_6): δ = 7.6 (s, 1 H), 7.5 (s, 2 H), 5.6 (s, 2 H), 2.5 (s, 3 H).

^{13}C NMR (DMSO-d_6): δ = 172.6, 162.1 156.3, 155.32, 154.8 (q, $J_{C–F}$ = 35.0 Hz, CCF_3), 121.5 (q, $J_{C–F}$ = 274.0 Hz, CF_3), 111.1, 24.0.

^{19}F NMR (DMSO-d_6): δ = –69.0 (s, 3 F).

GC-MS (EI): m/z = 259 [M^+].

Anal. Calcd for $C_8H_8F_3N_7$: C, 37.07; H, 3.11; N, 37.83. Found: C, 37.00; H, 2.95; N, 37.67.

2-(3,5-Diamino-1*H*-1,2,4-triazol-1-yl)-4-phenyl-6-trifluoromethylpyrimidine (3c)

Yield: 62%; yellow solid; mp 324 °C.

^{1}H NMR (DMSO-d_6): δ = 8.3 (d, J = 6.8 Hz, 2 H), 8.2 (s, 1 H), 7.8 (s, 2 H), 7.6 (m, 3 H).

^{13}C NMR (DMSO-d_6): δ = 169.3, 161.4, 157.4 (q, $J_{C–F}$ = 35.0 Hz, CCF_3), 156.7, 135.9, 134.0, 130.6, 129.3, 121.7 (q, $J_{C–F}$ = 275.0 Hz, CF_3), 109.5.

^{19}F NMR (DMSO-d_6): δ = –68.6 (s, 3 F).

GC-MS (EI): m/z = 321 [M^+].

Anal. Calcd for $C_{13}H_{10}F_3N_7 \cdot 0.5(C_4H_8O_2)$: C, 49.32; H, 3.86; N, 26.84. Found: C, 49.08; H, 3.20; N, 26.43.

Preparation of 3a and 5,7-Bis(trifluoromethyl)-[1,2,4]-triazolo[1,5-*a*]pyrimidine-2-amine (4); Method 1

To a round-bottom flask fitted with a reflux condenser, **1** (1 mmol), 1,1,1,5,5,5-hexafluoropentane-2,4-dione (**2a**; 2 mmol) and concd H_2SO_4 (6 drops) in EtOH (15 mL) was brought to reflux for 24 h. The mixture was cooled to r.t. and neutralized with sat $NaHCO_3$. EtOH was removed under reduced pressure, MeCN (40 mL) was added to the residue and the solution was stirred for 1 h. The solution was filtered and the residue was recrystallized (1,4-dioxane) to yield a yellow solid (**3a**), which was identified by ^{1}H NMR, ^{19}F NMR, GC-MS. The filtrate was concentrated and the residue was purified by column chromatography (hexane–EtOAc, 3:1) to give **4**.

Yield: 30%; colorless solid; mp 252 °C.

^{1}H NMR (CD_3CN): δ = 7.7 (s, 1 H), 5.7 (s, 2 H).

^{19}F NMR (CD_3CN): δ = –70.0, –69.0.

GC-MS (EI): *m*/*z* = 271 [M^+].

Anal. Calcd for $C_7H_3F_6N_5$: C, 31.01; H, 1.12; N, 25.83. Found: C, 31.16; H, 1.09; N, 25.56.

Preparation of 4; Method 2

The reaction was carried out as described above with 3,5-diamino-1,2,4-triazole (1 mmol) and **2a** (1 mmol). After the solvent was removed, the crude product was purified by column chromatography (hexane–EtOAc, 3:1) to give **4** (isolated yield 70%), which was identified by ^{1}H NMR, ^{19}F NMR, GC-MS.

Preparation of 5,7-Bis(trifluoromethyl)-2-[3,5-bis(trifluoromethyl)pyrazolo]-[1,2,4]-triazolo[1,5-*a*]pyrimidine (6) and 7

The reaction was carried as described above with **5** (1 mmol) and **2a** (2 mmol). After the addition of $NaHCO_3$, H_2O (15 mL) was added, the solution was extracted with EtOAc (3 × 15 mL) and the organic extracts were dried over anhydrous Na_2SO_4. The solvent was removed and the crude product was purified by column chromatography (hexane–EtOAc, 10:1 then 5:1) to give **6** and **7**.

5,7-Bis(trifluoromethyl)-2-[3,5-bis(trifluoromethyl)pyrazolo]-[1,2,4]-triazolo[1,5-*a*]pyrimidine (6)

Yield: 10%; colorless solid; mp 167 °C.

^{1}H NMR (CD_3CN): δ = 8.2 (s, 1 H), 7.5 (s, 1 H).

^{13}C NMR (CD_3CN): δ = 161.3, 155.9, 154.2 (q, $J_{C–F}$ = 38.0 Hz, CCF_3), 146.1 (q, $J_{C–F}$ = 40.0 Hz, CCF_3), 138.7 (q, $J_{C–F}$ = 40.0 Hz, CCF_3), 136.6 (q, $J_{C–F}$ = 42.0 Hz, CCF_3), 122.8 (CF_3), 120.9 (CF_3), 120.6 (CF_3), 117.6 (CF_3), 111.9, 108.7.

^{19}F NMR (CD_3CN): δ = –68.4 (s, 3 F), –68.3 (s, 3 F), –62.9 (s, 3 F), –59.2 (s, 3 F).

GC-MS (EI): *m*/*z* = 458 [M^+].

Anal. Calcd for $C_{12}H_2F_{12}N_6$: C, 31.46; H, 0.44; N, 18.34. Found: C, 31.58; H, 0.37; N, 18.06.

7

Yield: 60%; colorless solid; mp 140 °C.

^{1}H NMR ($CDCl_3$): δ = 7.7 (s, 1 H), 6.2 (s, 1 H, OH), 3.6 (AB, $J_{A–B}$ = 53 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 163.2, 154.0, 144.4 (q, $J_{C–F}$ = 40.0 Hz, CCF_3), 136.7 (q, $J_{C–F}$ = 40.0 Hz, CCF_3), 123.6 (q, CF_3), 121.3 (q, CF_3), 119.2 (q, CF_3), 117.0 (q, CF_3), 104.2, 95.7 (q, $J_{C–F}$ = 21.0 Hz, CCF_3), 41.7 (CH_2).

^{19}F NMR ($CDCl_3$): δ = –80.9 (s, 3 F), –68.4 (s, 3 F), –68.4 (s, 3 F), –67.0 (s, 3 F).

GC-MS (EI): *m*/*z* = 458 [$M^+ – H_2O$].

Anal. Calcd for $C_{12}H_4F_{12}N_6O$: C, 30.27; H, 0.85; N, 17.65. Found: C, 30.37; H, 0.87; N, 17.26.

Dehydration of 7 to 6

A sample of **7** (50 mg) was dissolved in Ac_2O (10 mL) and heated at 120 °C for 16 h. The solvent was removed under reduced pressure and the residue was recrystallized (CH_2Cl_2–hexane) to give **6** (90% yield).

Preparation of 5,7-Dimethyl-2-[3,5-bis(trifluoromethyl)pyrazolo]-[1,2,4]-triazolo[1,5-*a*]pyrimidine (8)

The reaction was carried out as described above with 5-amino-3-hydrazino-1,2,4-triazole dihydrochloride (**5**; l mmol) and pentane-2,4-dione (2 mmol). The solvent was removed and the crude product was recrystallized (EtOH) to give **8**.

Yield: 70%; colorless solid; mp 172 °C.

^{1}H NMR (CD_3CN): δ = 7.0 (s, 1 H), 6.1 (s, 1 H), 2.7 (s, 3 H), 2.6 (s, 3 H), 2.6 (s, 3 H), 2.3 (s, 3 H).

^{13}C NMR (CD_3CN): δ = 165.9, 161.2, 155.5, 151.9, 148.1, 143.5, 111.8, 109.5, 24.9, 17.0, 13.6, 13.5.

GC-MS (EI): *m*/*z* = 242 [M^+].

Anal. Calcd for $C_{12}H_{14}N_6$: C, 59.49; H, 5.82; N, 34.69. Found: C, 59.15; H, 5.68; N, 34.64.

Preparation of Pyrazolo-1,2,4-triazolopyrimidines 9–12

The reaction was carried out as described above with **5** (1 mmol) and **2b** (2 mmol). After addition of $NaHCO_3$, H_2O (15 mL) was added, the solution was extracted with EtOAc (3 × 15 mL) and the organic extracts were dried over anhydrous Na_2SO_4. After the solvent was removed, the crude product was purified by column chromatography (hexane–EtOAc, 5:1 then 2:1) to give **9** and a mixture of the three isomers **10**, **11** and **12** (30:40:10 mixture by ^{19}F NMR spectra).

7-Methyl-5-trifluoromethyl-2-(5-methyl-3-trifluoromethyl-pyrazolo)-[1,2,4]-triazolo[1,5-*a*]pyrimidine (9)

Yield: 10%; colorless solid; mp 162 °C.

^{1}H NMR (CD_3CN): δ = 7.6 (s, 1 H), 6.7 (s, 1 H), 2.9 (s, 3 H), 2.7 (s, 3 H).

^{13}C NMR (CD_3CN): δ = 162.2, 153.5, 152.3 (q, $J_{C–F}$ = 37.0 Hz, CCF_3), 146.5, 145.5 (q, $J_{C–F}$ = 38.0 Hz, CCF_3), 122.4 (q, $J_{C–F}$ = 275.0 Hz, CF_3), 121.7 (q, $J_{C–F}$ = 275.0 Hz, CF_3), 108.6 (q, $J_{C–F}$ = 2.4 Hz, $CHCCF_3$), 107.6 (q, $J_{C–F}$ = 1.8 Hz, $CHCCF_3$), 18.0 (CH_3), 13.9 (CH_3).

^{19}F NMR (CD_3CN): δ = –69.3 (s, 3 F), –63.5 (s, 3 F).

GC-MS (EI): *m*/*z* = 350 [M^+].

Anal. Calcd for $C_{12}H_8F_6N_6$: C, 41.15; H, 2.30; N, 24.00. Found: C, 41.16; H, 2.34; N, 23.36.

10, 11 and 12

Isolated as a mixture of three isomers. The yield ratio of **10**:**11**:**12** was 40:50:10.

Yield: 40%; colorless solid; GC peaks at 14.3 min, 14.5 min and 15.0 min.

^{1}H NMR (CD_3CN): δ = 7.6 (t, *J* = 5.9 Hz, 1 H), 6.9 (s, 1 H), 6.7 (s, 1 H), 2.9, 2.8, 2.7, 2.4 (4 s, 3 H each).

^{19}F NMR (CD_3CN): δ = –69.4, –69.3, –63.5, –59.3, –59.2.

GC-MS (EI): *m*/*z* = 350 [M^+] (14.3 min), 350 [M^+] (14.5 min), 350 [M^+] (15.0 min).

Anal. Calcd for $C_{12}H_8F_6N_6$: C, 41.15; H, 2.30; N, 24.00. Found: C, 41.48; H, 2.57; N, 23.39.

Preparation of Pyrazolo-1,2,4-triazolopyrimidines 13 and 14

The reaction was performed as described above with **5** (1 mmol) and 4,4,4-trifluoro-1-(2-furyl)butane-1,3-dione (2 mmol). After ad-

dition of $NaHCO_3$, H_2O (15 mL) was added, the mixture was extracted with EtOAc (3 × 15 mL) and the organic extracts were dried over anhydrous Na_2SO_4. The solvent was removed and the crude product was purified by column chromatography (hexane–EtOAc, 5:1) to give a mixture of the two isomers **13** and **14**.

Yield: 50% (isolated yield of **13** + **14** in 22:78 ratio based on ^{19}F NMR spectra); colorless solid; GC peaks at 19.9 min and 20.3 min.

^1H NMR (CD_3CN): δ = 8.05 (s, 1 H), 7.90 (m, 1 H), 7.62 (d, *J* = 3.5 Hz, 1 H), 7.58 (m, 1 H), 7.13 (s, 1 H), 6.84 (m, 1 H), 6.77 (q, *J* = 1.7 Hz, 1 H), 6.54 (q, *J* = 1.7 Hz, 1 H).

^{19}F NMR (CD_3CN): δ = –69.19, –69.14, –63.46, –59.40.

GC-MS (EI): *m*/*z* = 454 [M^+] (19.9 min), 454 [M^+] (20.3 min).

Anal. Calcd for $C_{18}H_8F_6N_6O_2$: C, 47.59; H, 1.77; N, 18.50. Found: C, 47.62; H, 1.64; N, 18.26.

Preparation of 3,6-Bis[4,6-bis(trifluoromethyl)pyrimidino-2-amino]tetrazine (16)

The reaction was carried out as described above with **15** (0.5 mmol) and **2a** (1 mmol) in 1,4-dioxane (10 mL) under reflux. The mixture is refluxed for 24 h then cooled to r.t. and filtered. The residue was washed with EtOH (3 × 15 mL) and dried in vacuo to give **16**.

Yield: 75%; red solid; mp 225 °C.

^1H NMR (DMSO-d_6): δ = 12.4 (s, 2 H), 8.0 (s, 2 H).

^{19}F NMR (DMSO-d_6): δ = –68.8 (s, 6 F).

Anal. Calcd for $C_{14}H_4F_{12}N_{10}\cdot(C_4H_8O_2)$: C, 34.41; H, 1.92; N, 22.29. Found: C, 33.96; H, 1.61; N, 22.66.

X-ray Crystallographic Analysis of 9

Crystals of compound **9** were removed from the flask and a suitable crystal was selected, attached to a glass fiber and data were collected at 90(2) K using a Bruker/Siemens SMART APEX instrument (Mo Kα radiation, λ = 0.71073 Å) equipped with a Cryocool NeverIce low-temperature device. Data were measured using omega scans of 0.3° (omega and phi scans of 0.5°) per frame for 20 s for **9**, and a full sphere of data was collected. A total of 2400 (2565) frames were collected with a final resolution of 0.83 Å. Cell parameters were retrieved using SMART software[20] and refined using SAINTPlus[21] on all observed reflections. Data reduction and correction for Lp and decay were performed using the SAINTPlus software. Absorption corrections were applied using SADABS.[22] The structure was solved by direct methods and refined by least-squares method on F^2 using the SHELXTL program package.[23] The structure was solved by analysis of systematic absences. All non-hydrogen atoms were refined anisotropically. No decomposition was observed during data collection.

X-ray crystal data for **9**;[24] Empirical formula: $C_{12}H_8F_6N_6$; Formula weight 350.24; Crystal system = triclinic; Space group $P\bar{1}$ (#2); T = 90(2) K; *a* = 7.0943(4) Å, *b* = 7.3652(4) Å, *c* = 13.4329(7) Å, *α* = 102.400(10)°, *β* = 103.171(2)°, *γ* = 97.1310(10)°; *V* = 656.33(6) Å^3; *Z* = 2; *F*(000) = 352; *μ* = 0.174 mm^{-1}; reflections collected = 7561, independent reflections = 2574 [R_{int} = 0.0158]; *R*1, w*R*2 [*I* > 2σ(I)] = 0.0421, 0.0444.

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