SYNTHESIS OF TRIFLUOROMETHYLPYRIMIDINES *FROM FLUORINATED ENAMINODIKETONES*

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Abstract - 4-Trifluoromethylpyrimidines (**2, 7**) were easily synthesized by reaction of enamino diketones (**1** , **6**) with *N,N*-dimethylguanidine, *O*-methylisourea or guanidine. The 4,6-bistrifluoromethylpyrimidine (**11**) was obtained from **10** and *O*-methylisourea. Hydrolysis of the 2-methoxypyrimidines (**2c**, **7c**, **12**) gave the 4-hydroxypyrimidones (**3**, **8**, **13**).

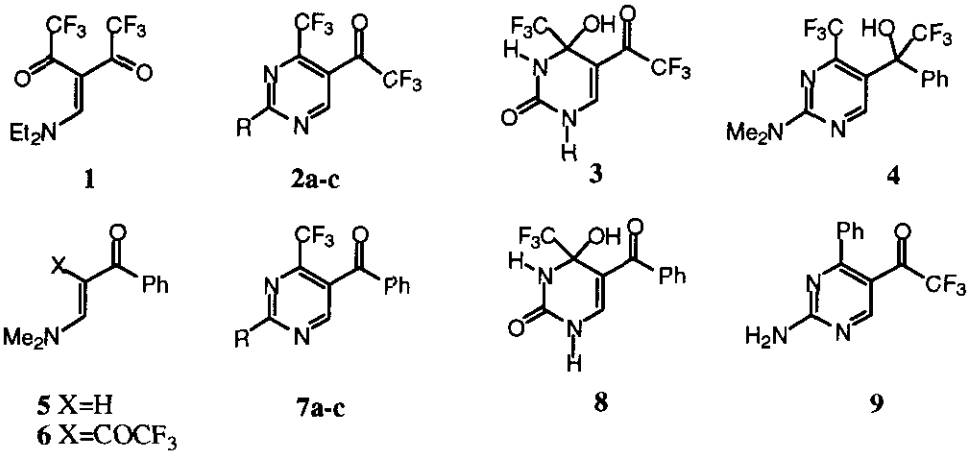
In a previous paper, we have described a simple and efficient synthesis of various trifluoromethylated nitrogen heterocycles from *N,N*-diethylaminomethylene-1,1,1,5,5,5-hexafluoroacetylacetone (**1**) (DAMFA), an enamino diketone easily obtained by reacting trifluoroacetic anhydride with triethylamine.[1-3] Especially, DAMFA undergoes facile cyclocondensation with *N,N*-dimethylguanidine and *O*-methylisourea to give the 5-trifluoroacetyl-4-trifluoromethylpyrimidines (**2a**) and (**2c**) with good yields.[2]

The increasing interest for fluoroheterocyclic compounds in medecinal and agricultural fields[4] and recent developments of new synthetic methodologies towards such compounds[5] prompted us to apply our approach to other N-C-N nucleophiles and other CF_3 containing enamino ketones.

As expected, condensation of DAMFA (**1**) with guanidine yielded the 2-aminopyrimidine (**2b**) (82%). However attempts at reacting **1** with urea were fruitless (acidic or alkaline conditions) and we envisioned therefore an indirect method to access to 2-hydroxypyrimidines. Thus *O*-demethylation of the pyrimidine (**2c**) was achieved by treatment with hydrobromic acid/acetic acid, but hydration of the 3,4-double bond occurred, leading to the 4-hydroxydihydropyrimidone (**3**). The result is not unexpected as fluoro imines are known to easily react with nucleophiles to form stable adducts.[6] Compound (**3**) was also obtained through deamination of the 2-aminopyrimidine (**2b**) with nitrous acid. The structure of **3** was clearly established on the basis of its spectral data: the ^1H NMR spectrum showed four singlets at 10.63, 8.91,

7.86, 7.68 ppm and the C-4 signal on the ^{13}C NMR spectrum was shielded to 82.1 ppm, disclosing the lack of aromaticity.

In order to prepare benzylpyrimidine derivatives, **2a** was reacted with phenyllithium to give compound (**4**) (29%).

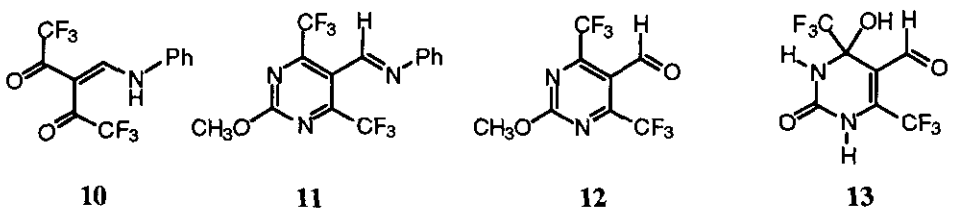


Scheme 1 **a**: R = NMe_2; **b**: R = NH_2; **c**: R = OMe

As an extension of this work, we investigated the synthesis of 5-aroyl-4-trifluoromethylpyrimidines from enamino diketone (**6**), which was easily prepared in two steps: condensation of *N,N*-dimethylformamide dimethylacetal with acetophenone led to enaminone (**5**) whose trifluoroacetylation provided **6**.[8] Similarly to DAMFA enamino diketone (**6**) reacted with *N,N*-dimethylguanidine, guanidine and *O*-methylisourea to give the desired pyrimidines (**7a-c**) respectively, with moderate yields (60-70%). With guanidine, the phenylpyrimidine (**9**) was isolated as a by product (30%). The structural distinction between **7b** and **9** was established as follows:

- the ^{13}C NMR spectra showed the carbonyl carbon as a singlet at 192.2 ppm for **7b** and a quadruplet at 179.5 ppm ($^2J_{CF}$=37.4) for **9**;
- on the MS spectra, the base peaks were seen at m/z 105 (loss of COPh) for **7b** and at m/z 170 (loss of $COCF_3$) for **9**.

Treatment of **7c** with HBr/AcOH afforded the 4-hydroxydihydropyrimidone (**8**), analogous to **3**.



Scheme 2

Synthesis of bistrifluoromethylpyrimidines was also performed from DAMFA (**1**) by replacing the diethylamino group by a less labile group, in order to favor the nucleophilic addition to the two carbonyl groups. Thus, cyclocondensation of **10** (available by nucleophilic substitution of DAMFA with aniline[2]) with *O*-methylisourea led to the imine (**11**) whose hydrolysis gave aldehyde (**12**). The transformation of **12** to dihydropyrimidone (**13**) was carried out under the conditions used for **2c**.

Thus, the fluorinated enamino ketones (**1**, **6** and **10**) constitute useful synthetic blocks for efficient syntheses of pyrimidines bearing one or two trifluoromethyl groups at C-4 and C-6 positions.

EXPERIMENTAL

Melting points were determined on a Reichert melting point apparatus and are uncorrected. IR spectra (ν cm^{-1}) were recorded on a BOMEM MB series apparatus. ^1H (300 MHz) and ^{13}C (75 MHz)-NMR spectra were obtained on a Bruker AC 300 instrument with TMS as internal standard; the chemical shifts are expressed in ppm and coupling constants in Hz. MS spectra were recorded on a UG Autospec spectometer. Elemental analyses were performed with a Perkin Elmer CHN 2400 analyzer.
Monitoring of reactions was carried out using Merck TLC aluminium sheets (Kieselgel 60 PF 254). Preparative TLC (Kiesegel 60 PF 254) and column chromatographies (Kieselgel 60 70-230 mesh) were performed with indicated eluents.

2-Amino-5-trifluoroacetyl-4-trifluoromethylpyrimidine (2b):

To a solution of **1** (1 g, 3.44 mmol) in MeCN (7 mL) were added guanidinium nitrate (430 mg, 3.52 mmol) and K_2CO_3 (486 mg, 3.52 mmol). The reaction mixture was stirred at 65°C for 20 h. After filtration of the precipitate and evaporation of the solvent, the crude product was chromatographed on silica gel (CH_2Cl_2/MeOH 5:1) to give **2b** (730 mg; 82%): mp 138-139°C (hexane); IR (KBr) 3358, 1734, 1665, 1591; ^1H NMR (DMSO-d_6) 8.90 (s, 1H), 8.65 (br s, 1H) 8.66 (br s, 1H); ^{13}C NMR (DMSO-d_6) 176.9 (q, J_{CF}=35.6), 163.7, 162.4, 156.5 (q, J_{CF}=36.4), 119.9 (q, J_{CF}=275.8), 116.2 (q, J_{CF}=290.2), 110.9; EIMS: m/z (%) = 259 ($M^{+\cdot}$, 62), 190 (98), 163 (100), 121 (52), 69 (47). Anal. Calcd for $C_7H_3N_3OF_6$ C 32.43, H 1.17, N 16.22. Found C 32.41, H 0.90, N 15.84.

5- Trifluoroacetyl-4-trifluoromethyl-4-hydroxy-1,2,3,4-tetrahydropyrimidin-2-one (3):

from 2c: A solution of pyrimidine (**2c**) (900 mg, 3.28 mmol) and 33% HBr in acetic acid (15 mL) was left at rt for 24 h. The reaction mixture was then concentrated under reduced pressure to give a solid residue which was recrystallized from acetone to give **3** (660 mg, 72%): mp 145-146°C; IR (KBr) 3358, 3229, 3128, 1726, 1676; ^1H NMR (DMSO-d_6) 10.63 (d, 1H, J=4.5), 8.91 (br s, 1H), 7.86 (br s, 1H), 7.68 (d, 1H, J=4.5); ^{13}C NMR (DMSO-d_6) 173.7 (q, J_{CF}=32.3), 148.6, 147.1, 123.8 (q, J_{CF}=298.8), 116.6 (q,

J_{CF}=292.2), 101.3, 82.1 (q, J_{CF}=33.8); CIMS: m/z (%) = 279 (MH^+, 38), 261 (100), 241 (12), 209 (35), 191 (10), 139 (10), 83 (30); HRMS calcd for [(M+H)] $C_7H_5N_2O_3F_6$ 279.0204, found 279.0168.

from 2b: 2b (150 mg, 0.58 mmol) was dissolved in acetone/water/acetic acid(1 :1 :1) (4.5 mL) and $NaNO_2$ (870 mg, 12.61 mmol) was added. This mixture was stirred at 80°C for 24 h. After cooling to rt, the reaction solution was quenched with 10% $NaHCO_3$ (40 mL), extracted with EtOAc (3x40 mL). The combined organic layers were washed with water (20 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was chromatographed on silica gel (CH_2Cl_2/MeOH 4:1) affording **3** (120 mg, 74%).

1-Phenyl-1-(2-*N,N*-dimethylamino-4-trifluoromethylpyrimidin-5-yl)-2,2,2-trifluoroethanol (4):

A solution of **2a** (287 mg, 1 mmol) in dry THF was cooled to –80°C, and 1.8 M phenyllithium (0.83 mL, 1.5 mmol) in cyclohexane/Et_2O was added. The reaction mixture was stirred at –80°C for 2 h. Then H_2O was added and the mixture was extracted three times with CH_2Cl_2. The combined organic phases were washed (brine), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue (289 mg) was purified by column chromatography (hexane/40-60% CH_2Cl_2) to yield **4** (107 mg, 29%): white amorphous solid ; IR (KBr) 3235, 1601; ^1H NMR ($CDCl_3$) 8.59 (s, 1H), 7.46-7.27 (m, 5H), 3.64 (s, 1H), 3.20 (s, 6H); ^{13}C NMR ($CDCl_3$) 160.3, 159.5, 154.3 (q, J_{CF}=37), 138.5, 128.9, 128.2, 127.0, 124.9 (q, J_{CF}=286), 120.5 (q, J_{CF}=275), 116.7, 78.4 (q, J_{CF}=29), 36.8; EIMS: m/z (%) =365 ($M^{+\cdot}$, 41), 296 (100), 276 (58), 218 (44), 121 (8), 105 (58); HRMS calcd for $C_{15}H_{13}N_3OF_6$ 365.0963, found 365.0948.

3- Benzoyl-1,1,1-trifluoro-4-*N,N*-dimethylaminobut-3-en-2-one (6):

Trifluoroacetic anhydride (5 mL, 35.5 mmol) was added dropwise to a solution of enamino ketone (**5**) (1.5 g, 8.57 mmol) in CH_2Cl_2 (12 mL). The resulting solution was kept at rt for 3 days. The reaction mixture was quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2. The organic phase was washed (H_2O), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was chromatographed on silica gel (CH_2Cl_2) to give **6** (1.84 g, 79%) : mp 68°C (hexane); IR (KBr) 1672, 1614; ^1H-NMR ($CDCl_3$) 7.85 (d, 2H, J=7.5), 7.75 (s, 1H), 7.55 (t, 1H, J=7.5), 7.44 (t, 2H, J=7.5), 3.29 (s, 3H), 2.70 (s, 3H); ^{13}C-NMR ($CDCl_3$) 194.2, 176.9 (q, J_{CF}=32.2), 157.2, 138.9, 132.9, 129.1, 128.5, 117.3 (q, J_{CF}=290.6), 105.8, 47.9, 41.5; EIMS: m/z (%) = 271 ($M^{+\cdot}$, 22), 202 (40), 194 (10), 174 (8), 129 (9), 105 (100); HRMS calcd for $C_{13}H_{12}NO_2F_3$ 271.0820, found 271.0817.

5-Benzoyl-4-trifluoromethyl-2-*N,N*-dimethylaminopyrimidine (7a):

A solution of enamino diketone (**6**) (1457 mg, 5.38 mmol) and *N,N*-dimethylguanidine (475 mg, 5.46 mmol) in acetonitrile (20 mL) was left at rt for 16 h. After evaporation of the solvent, the crude product was chromatographed on silica gel (CH_2Cl_2) to give **7a** (1108 mg, 70%): oil ; IR (film) 1678, 1590; ^1H NMR ($CDCl_3$) 8.48 (s, 1H), 7.80 (d, 2H, J=7.5), 7.58 (t, 1H, J=7.5), 7.46 (t, 2H, J=7.5), 3.27 (s, 6H); ^{13}C

NMR ($CDCl_3$) 192.3, 161.3, 160.1, 154.3 (q, J_{CF}=35.6), 137.1, 133.5, 129.7, 128.5, 120.2 (q, J_{CF}=275.8), 117.7, 36.9; EIMS m/z (%) = 295 ($M^{+\cdot}$, 94), 280 (24), 266 (27), 226 (16), 218 (100), 105 (44); HRMS calcd for $C_{14}H_{12}N_3OF_3$ 295.0932, found: 295.0933.

2-Aminopyrimidines (7b and 9):

To a solution of enamino diketone (**7**) (600 mg, 2.21 mmol) in MeCN (6 mL) were added guanidinium nitrate (280 mg, 2.30 mmol) and K_2CO_3 (317 mg, 2.30 mmol). The reaction mixture was heated to 65°C for 14 h. After filtration of the precipitate and evaporation of the solvent, the crude product was purified by TLC (98:2 CH_2Cl_2/MeOH) to afford **7b** (355 mg, 60%) and **9** (177 mg, 30%).

2-Amino-5-benzoyl-4-trifluoromethylpyrimidine (7b): mp 136-137°C ($CHCl_3$); IR (KBr) 3360, 1675, 1601; ^1H NMR (DMSO-d_6) 8.56 (s, 1H), 7.88 (br s, 2H), 7.82 (d, 2H, J=7.5), 7.73 (t, 1H, J=7.5), 7.57 (t, 2H, J=7.5); ^{13}C NMR (DMSO-d_6) 192.2, 163.4, 161.1, 153.3 (q, J_{CF}=35.2), 136.8, 134.1, 129.9, 129.1, 120.5 (q, J_{CF}=275.3), 118.7; EIMS: m/z (%) = 267 ($M^{+\cdot}$, 60), 198 (7), 190 (92), 163 (11), 121 (7), 105 (100); HRMS calcd for $C_{12}H_8N_3OF_3$ 267.0619, found: 267.0554.

2-Amino-5-trifluoroacetyl-4-phenylpyrimidine (9): mp 153-154°C($CHCl_3$); IR (KBr) 3378, 1668, 1597; ^1H NMR (DMSO-d_6) 8.75 (s, 1H), 8.15 (br s, 2H), 7.57-7.41 (m, 5H); ^{13}C NMR (DMSO-d_6) 179.5 (q, J_{CF}=37.4), 170.8, 163.6, 161.6, 138.3, 130.0, 128.4, 128.3, 116.4 (q, J_{CF}=292.1), 113.0; EIMS: m/z (%) = 267 ($M^{+\cdot}$, 72), 198 (100), 170 (13), 156 (12), 143 (10), 129 (49), 116 (27), 104 (63). Anal. Calcd for $C_{12}H_8N_3OF_3$ C 53.92, H 3.02, N 15.73. Found C 53.77, H 2.67, N 15.58.

5-Benzoyl-4-trifluoromethyl-2-methoxypyrimidine (7c):

To a solution of enamino diketone (**6**) (1.5 g, 5.54 mmol) in MeCN (12 mL) were added *O*-methylisourea hydrogen sulfate (964 mg, 5.60 mmol) and K_2CO_3 (773 mg, 5.60 mmol). The reaction mixture was stirred at rt for 20 h. After filtration of the precipitate and evaporation of the solvent, the crude product was chromatographed on silica gel (CH_2Cl_2/hexane 4:1) to give **7c** (985 mg; 63%): oil; IR (film) 1674, 1586; ^1H NMR ($CDCl_3$) 8.71 (s, 1H), 7.81 (d, 2H, J=7.5), 7.68 (t, 1H, J=7.5), 7.52 (t, 2H, J=7.5), 4.18 (s, 3H); ^{13}C NMR ($CDCl_3$) 191.2, 165.6, 161.1, 155.0 (q, J_{CF}=36.8), 136.1, 134.5, 129.8, 128.8, 124.7, 119.8 (q, J_{CF}=275.1), 55.9; EIMS: m/z (%) = 282 ($M^{+\cdot}$, 70), 262 (7), 252 (7), 213 (12), 205 (54), 110 (21), 105 (100). Anal. Calcd for $C_{13}H_9N_2O_2F_3$ C 55.30, H 3.21, N 9.93. Found C 55.35, H 2.78, N 9.72.

5-Benzoyl-4-trifluoromethyl-4-hydroxy-1,2,3,4-tetrahydropyrimidin-2-one (8):

A solution of pyrimidine (**7c**) (200 mg, 0.68 mmol) and 33% HBr in acetic acid (15 mL) was left at rt for 24 h. The reaction mixture was then concentrated under reduced pressure to give a solid residue which was recrystallized from acetone to give **8** (148 mg, 76%): mp 172-173 °C; IR (KBr) 3225, 3123, 1709,

1655, 1613; ^{1}H NMR (DMSO-d_6) 10.08 (br s, 1H), 8.79 (br s, 1H), 7.78 (s, 1H), 7.65-7.50 (m, 5H), 7.14 (d, 1H, J=4.5); ^{13}C NMR (DMSO-d_6) 193.9, 149.3, 144.9, 138.6, 132.2, 128.9, 128.8, 124.1 (q, J_{CF}=288.2), 104.6, 82.7 (q, J_{CF}=32.8); EIMS: m/z (%) = 268 ($M^{+\cdot}$ -18, 13), 217 (80), 191 (7), 139 (100), 105 (88); HRMS calcd for [(M-H_2O)] $C_{12}H_7N_2O_2F_3$ 268.0459, found 268.0450.

4,6- Bis(trifluoromethyl)-2-methoxy-5-(phenyliminomethyl)pyrimidine (11):

Compound (**10**) (900 mg, 2.89 mmol) was added to a mixture of *O*-methylisourea hydrogen sulfate (500 mg, 2.91 mmol) and potassium carbonate (402 mg, 2.91 mmol) in MeCN (6 mL). After stirring at rt for 20 h, the precipitate was filtered off and the solvent was evaporated. The resulting product was recrystallized from hexane/chloroform to give **11** (730 mg; 72%) : mp 116°C; IR (KBr) 1647, 1589; ^{1}H NMR ($CDCl_3$) 8.67 (m, 1H), 7.44 (t, 2H, J=7.5), 7.31 (t, 1H, J=7.5), 7.18 (d, 2H, J=7.5), 4.21 (s, 3H); ^{13}C NMR ($CDCl_3$) 164.6, 158.4 (q, J_{CF}=36.2), 150.8, 150.6, 129.4, 127.3, 120.8, 120.6, 118.0 (q, J_{CF}=284.6), 56.5; EIMS: m/z (%) = 349 ($M^{+\cdot}$, 10), 348 (70), 104 (35), 77 (100). Anal. Calcd for $C_{14}H_9N_3OF_6$ C 48.13, H 2.59, N 12.03. Found C 48.03, H 2.19, N 11.72.

4,6- Bis(trifluoromethyl)-2-methoxypyrimidine-5-carbaldehyde (12):

Pyrimidine (**11**) (600 mg, 1.72 mmol) was stirred with 10% HCl (15 mL) in THF (25 mL) at rt for 48 h. The reaction mixture was extracted twice with ethyl acetate. The combined organic layer were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (CH_2Cl_2/hexane 2:1) yielded **12** (460 mg, 98%) : oil; IR (film) 1721, 1586; ^{1}H NMR ($CDCl_3$) 10.42 (m, 1H), 4.23 (s, 3H); ^{13}C NMR ($CDCl_3$) 184.9, 165.3, 159.0 (q, J_{CF}=36.6), 120.9, 119.5 (q, J_{CF}=286.2), 57.0; EIMS: m/z (%) = 274 ($M^{+\cdot}$, 65), 273 (48), 244 (35), 147 (22), 110 (100), 69 (48). Anal. Calcd for $C_8H_4N_2O_2F_6$ C 35.03, H 1.47, N 10.22. Found C 35.21, H 1.32; N 10.30.

4,6- Bis(trifluoromethyl)-4-hydroxy-1,2,3,4-tetrahydropyrimidin-2-one-5-carbaldehyde (13):

This product was obtained from pyrimidine (**12**) using the procedure described for tetrahydropyrimidone (**3**) (from **2c**): yield 92%; mp 127-128 °C (acetone); IR (KBr) 3443, 3262, 3204, 3162, 1726, 1668; ^{1}H NMR (DMSO-d_6) 10.99 (br s, 1H), 9.68 (s, 1H), 9.24 (s, 1H), 8.36 (br s, 1H); ^{13}C NMR (DMSO-d_6) 185.6, 148.7, 138.3 (q, J_{CF}=36.2), 123.5 (q, J_{CF}=286.6), 119.4 (q, J_{CF}=276.6), 107.1, 81.9 (q, J_{CF}=33.8); EIMS: m/z (%) = 279 ($M^{+\cdot}$+1, 7), 261 (33), 241 (10), 223 (45), 216 (30), 209 (100), 180 (20), 166 (785), 138 (94); HRMS calcd for [(MH+)] $C_7H_5N_2O_3F_6$; 279.0204, found 279.0205. Anal. Calcd for $C_7H_4N_2O_3F_6$ C 30.21, H 1.45, N 10.07. Found C 30.48, H 1.21, N 9.88.

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