SYNTHESIS OF TRIFLUOROMETHYL-PYRIMIDINES FROM FLUORINATED ENAMINO-DIKETONES

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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. 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.

The increasing interest for fluoroheterocyclic compounds in medical and agricultural fields and recent developments of new synthetic methodologies towards such compounds prompted us to apply our approach to other N-C-N nucleophiles and other CF₃ 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. 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%).

As an extension of this work, we investigated the synthesis of 5-arylo-4-trifluoromethylpyrimidines from enamino diketone (6), which was easily prepared in two steps: condensation of $N,N$-dimethylformamide dimethylacetal with acetophenone led to enamino (5) whose trifluoroacetylation provided 6. 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 (10), analogous to 3.

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Treatment of 7c with HBr/AcOH afforded the 4-hydroxydihydropyrimidone (10), analogous to 3.
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 (\(\nu\) cm\(^{-1}\)) were recorded on a BOMEM MB series apparatus. \(^1\)H (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 spectrometer. 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 (Kieselgel 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\(_2\)Cl\(_2\)/MeOH 5:1) to give 2b (730 mg; 82%): mp 138-139°C (hexane); IR (KBr) 3358, 1734, 1665, 1591; \(^1\)H 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\(^{+}\), 62), 190 (98), 163 (100), 121 (52), 69 (47). Anal. Calcd for C\(_7\)H\(_3\)N\(_3\)O\(_6\)F\(_6\) 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; \(^1\)H 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,
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1~~292.2), 101.3, 82.1 (q, JCF=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)I C7H5N2O3F6 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 NaN02 (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% NaHC03 (40 mL), extracted with EtOAc (3x40 mL). The combined organic layers were washed with water (20 mL), dried (Na2SO4), and concentrated under reduced pressure. The residue was chromatographed on silica gel (CH2Cl2/MeOH 4:1) affording 3 (120 mg, 74%).

A solution of ta (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/Et2O was added. The reaction mixture was stirred at -80°C for 2 h. Then H2O was added and the mixture was extracted three times with CH2Cl2. The combined organic phases were washed (brine), dried (Na2SO4), filtered and concentrated under reduced pressure. The residue (289 mg) was purified by column chromatography (hexane/40-60% CH2Cl2) to yield 4 (107 mg, 29%): white amorphous solid; IR (KBr) 3235, 1601; 1H NMR (CDC13) 8.59 (s, 1H), 7.46-7.27 (m, 5H), 3.64 (s, 1H), 3.20 (s, 6H); 13C NMR (CDC13) 160.3, 159.5, 154.3 (q, JCF=37), 138.5, 128.9, 128.2, 127.0, 124.9 (q, JCF=28), 120.5 (q, JCF=27), 116.7, 78.4 (q, JCF=29), 36.8; EIMS: m/z (%) =365 (M+, 41), 296 (17), 276 (58), 218 (44), 121 (8), 105 (58); HRMS calcd for C15H13N30F6 365.0963, found 365.0948.

Trifluoroacetic anhydride (5 mL, 35.5 mmol) was added dropwise to a solution of enamino ketone (5) (1.5 g, 8.57 mmol) in CH2Cl2 (12 mL). The resulting solution was kept at rt for 3 days. The reaction mixture was quenched with saturated NaHC03 and extracted with CH2Cl2. The organic phase was washed (H2O), dried (Na2SO4) and concentrated under reduced pressure. The residue was chromatographed on silica gel (CH2Cl2) to give 6 (1.84 g, 79%): mp 68°C (hexane); IR (KBr) 1672, 1614; 1H-NMR (CDC13) 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); 13C-NMR (CDC13) 194.2, 176.9 (q, JCF=32.2), 157.2, 138.9, 132.9, 129.1, 128.5, 117.3 (q, JCF=290.6), 105.8, 47.9, 41.5; EIMS: m/z (%) =271 (M+, 22), 202 (40), 194 (10), 174 (8), 129 (9), 105 (100); HRMS calcd for C13H12NO2F3 271.0820, found 271.0817.

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 (CH2Cl2) to give 7a (1108 mg, 70%): oil; IR (film) 1678, 1590; 1H NMR (CDC13) 8.48 (d, 2H, J=7.5), 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); 13C
NMR (CDCl₃) 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⁺, 94), 280 (24), 266 (27), 226 (16), 218 (100), 105 (44); HRMS calcd for C₁₄H₁₂N₃O₃F₃ 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 K₂CO₃ (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 CH₂Cl₂/MeOH) to afford 7b (355 mg, 60%) and 9 (177 mg, 30%).

2-Amino-5-benzoyl-4-trifluoromethylpyrimidine (7b): mp 136-137°C (CHCl₃); IR (KBr) 3360, 1675, 1601; ¹H NMR (DMSO-d₆) 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); ¹³C NMR (DMSO-d₆) 192.2, 163.4, 161.1, 153.3 (q, J_C=35.2), 136.8, 134.1, 129.9, 129.1, 120.5 (q, J_CF=275.3), 118.7; EIMS: m/z (%) = 267 (M⁺, 60), 198 (7), 190 (92), 190 (19), 163 (11), 121 (7), 105 (100); HRMS calcd for C₁₂H₈N₃O₃F₃ 267.0619, found: 267.0554.

2-Amino-5-trifluoroacetyl-4-phenylpyrimidine (9): mp 153-154°C (CHCl₃); IR (KBr) 3378, 1668, 1597; ¹H NMR (DMSO-d₆) 8.75 (s, 1H), 8.15 (br s, 2H), 7.57-7.41 (m, 5H); ¹³C NMR (DMSO-d₆) 179.5 (q, J_C=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⁺, 72), 198 (100), 170 (13), 156 (12), 143 (10), 129 (49), 116 (27), 104 (63). Anal. Calcd for C₁₂H₉N₃O₂F₃ 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 K₂CO₃ (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 (CH₂Cl₂/hexane 4:1) to give 7c (985 mg; 63%): oil; IR (film) 1674, 1586; ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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⁺, 70), 262 (7), 252 (7), 213 (12), 205 (54), 110 (21), 105 (100). Anal. Calcd for C₁₃H₉N₂O₂F₃ 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; 1H NMR (DMSO-d6) 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); 13C NMR (DMSO-d6) 193.9, 149.3, 144.9, 138.6, 132.2, 128.9, 128.8, 124.1 (q, JCF=288.2), 104.6, 82.7 (q, JCF=32.8); EIMS: m/z (%) = 268 (M+-18, 13), 217 (80), 191 (7), 139 (100), 105 (88); HRMS calcd for [(M-H2O)] C12H7N2O2F3 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; 1H NMR (CDCl3) 8.67 (m, 1H), 7.44 (t, 2H, J=7.5), 7.31 (1, 1H, J=7.5), 7.18 (d, 2H, J=7.5), 4.21 (s, 3H); 13C NMR (CDCl3) 164.6, 158.4 (q, Jc~=36.2), 150.8, 150.6, 129.4, 127.3, 120.8, 120.6, 118.0 (q, JCF=284.6), 56.5; EIMS: m/z (%) = 349 (M+., 10), 348 (70), 104 (35), 77 (100). Anal. Calcd for C14H9N30F6 C 48.13, H 2.59, N 12.03. Found C 48.03, H 2.19, N 11.72.

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 (Na2SO4), filtered and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (CH2Cl2/hexane 2:1) yielded 12 (460 mg, 98%): oil; IR (film) 1721, 1586; 1H NMR (CDCl3) 10.42 (m, 1H), 4.23 (s, 3H); 13C NMR (CDCl3) 184.9, 165.3, 159.0 (q, Jc~=36.6), 120.9, 119.5 (q, JCF=286.2), 57.0; EIMS: m/z (%) = 274 (M+., 65), 273 (48), 244 (35), 147 (22), 110 (100), 69 (48). Anal. Calcd for C8H4N2O2F6 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 tetrahydropyrimidinone (3) (from 2e): yield 92%; mp 127-128 °C (acetone); IR (KBr) 3443, 3262, 3204, 3162, 1726, 1668; 1H NMR (DMSO-d6) 10.99 (br s, 1H), 9.68 (s, 1H), 9.24 (s, 1H), 8.36 (br s, 1H); 13C NMR (DMSO-d6) 185.6, 148.7, 138.3 (q, JCF=36.2), 123.5 (q, JCF=286.6), 119.4 (q, JCF=276.6), 107.1, 81.9 (q, JCF=33.8); EIMS: m/z (%) = 279 (M+:+1, 7), 261 (33), 241 (10), 223 (45), 216 (30), 209 (100), 180 (20), 166 (785), 138 (94); HRMS calcd for [(MH+)] C7H5N2O2F6; 279.0204, found 279.0205. Anal. Calcd for C7H5N2O2F6 C 30.21, H 1.45, N 10.07. Found C 30.48, H 1.21, N 9.88.

ACKNOWLEDGEMENTS

We thank C. Peterman and P. Sigaut for recording the NMR and MS spectra.
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Received, 21st May, 1999