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Biginelli condensations of fluorinated 3-oxo esters and 1,3-diketones [1]

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Abstract

Condensation of fluorinated 3-oxo esters or 1,3-diketones with benzaldehyde and (thio)urea results in the diastereoselective formation of 4-fluoroalkyl-4-hydroxy-2-oxo(thioxo)-6-phenyl-hexahydropyrimidine-5-carboxylates from which by dehydration under acidic conditions the corresponding 6-fluoroalkyl-2-oxo(thioxo)-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylates were obtained. Under the same conditions, hexafluoroacetylacetone furnishes 4,6-dihydroxy-4,6-di(trifluoromethyl)-hexahydropyrimidin-2-one. Some further reactions of these pyrimidine derivatives leading to fused heterocycles are described.

Keywords: Fluoroalkyl 3-oxo esters and 1,3-diketones; Biginelli reaction; Hexahydropyrimidines

1. Introduction

The cyclocondensation of acetoacetic esters with aromatic aldehydes and (thio)urea, known as the Biginelli reaction, has attracted considerable attention in recent years [2]. The resulting 1,2,3,4-tetrahydropyrimidine derivatives have been shown to possess a variety of interesting pharmacological properties and therefore many synthetic methods for the synthesis of this heterocyclic scaffold are now available [3]. Recently, we have discovered that using a fluorinated acetoacetic ester derivative (i.e. ethyl trifluoroacetoacetate) the reaction takes a different course and a hexahydropyrimidine is obtained [4]. The structure and relative stereochemistry of this material was established unequivocally by X-ray analysis [4]. In this article we show that this reaction is rather general and that a number of fluorinated 3-oxo esters or 1,3-dicarbonyl compounds can be employed in this novel three-component condensation leading to fluorine-containing heterocycles of potential biological activity.

2. Experimental details

Melting points were measured in open capillaries and are reported uncorrected. Infrared spectra were measured on a Specord 75 IR spectrometer. ^{1}H- and ^{19}F-NMR spectra were recorded on a Tesla BS-587A instrument (^{1}H: 80 MHz, using TMS as an internal standard, ^{19}F: 75 MHz, using C_6F_6 as an internal standard). Microanalyses were performed with a Carlo Erba CHNS-O EA 1108 elemental analyzer. Thin-layer chromatography was performed on 'Silufol-UV 254' plates.

2.1. Materials

3-Oxo esters **1a–e** were prepared by the methods described previously [5]. 1,3-Diketones **2a–d** were prepared via a known procedure [6].

2.2. Synthesis of hexahydropyrimidines *3a–h, 4a–g, i, 7*

A mixture of benzaldehyde (0.21 g, 2.0 mmol), 1,3-dicarbonyl compound (**1a–e**, **2a–d**) (2.0 mmol) (Scheme 1), (thio)urea (3.0 mmol) and 8 ml of ethanol, containing two drops of concentrated HCl, was refluxed for 6 h. The reaction mixture was stored at 4°C overnight. The precipitate was filtered and recrystallized from ethanol to give hexahydropyrimidines **3a–h**, **4a–g, i, 7** as white solids.

2.2.1. Ethyl ester of 4-difluoromethyl-4-hydroxy-2-oxo-6-phenylhexahydropyrimidine-5-carboxylic acid (*3a*)

Yield, 75%; m.p., 204–205°C. ^{1}H NMR (DMSO-d_6) δ: 0.87 (3H, t, CH_3, $J_{(H–H)} = 7.0$ Hz); 2.92 (1H, d, H^5, $J_{(H5–H6)} = 11.6$ Hz); 3.82 (2H, q, CH_2, $J_{(H–H)} = 7.0$ Hz); 4.80 (1H, d, H^6, $J_{(H6–H5)} = 11.6$ Hz); 5.88 (1H, t, HCF_2, $J_{(H–F)} =$

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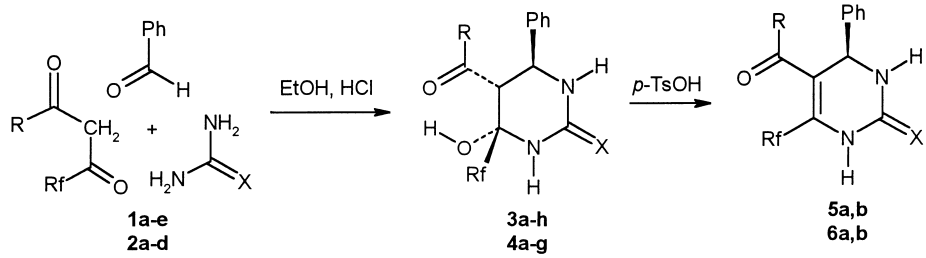


R^f =HCF_2, R=OEt (**1a**), X=O (**3a**);
R^f =$H(CF_2)_2$, R=OMe (**1b**), X=O (**3b**), S (**3e**);
R^f =C_3F_7, R=OMe (**1c**), X=O (**3c**), S (**3f**);
R^f =C_4F_9, R=OEt (**1d**), X=O (**3d, 5a**), S (**3g, 5b**);
R^f =CF_3, R=OEt (**1e**), X=S (**3h**);
R^f =CF_3, R=Me (**2a**), X=O (**4a**), S (**4e**);
R^f =CF_3, R=Ph (**2b**), X=O (**4b**), S (**4f**);
R^f =$H(CF_2)_2$, R=Me (**2c**), X=O (**4c**);
R^f =$H(CF_2)_2$, R=Ph (**2d**), X=O (**4d, 6a**), S (**4g, 6b**).

Scheme 1.

55.2 Hz); 7.33 (5H, s, C_6H_5); 6.67, 7.00, 7.15 (3H, 3 ws, 2NH, OH) ppm. ^{19}F NMR (DMSO-d_6) δ: 30.38 (2F, m, HCF_2, AB-system, $\Delta\nu = 236.0$, $J_{(F–F)} = 274.9$, $J_{(F–H)} = 55.2$ Hz) ppm. IR: 3315, 3200, 1585 (NH, OH); 3090 (CH); 1720 (CO_2Et); 1665 (C=O); 1500 (C=C); 1170–1070 (C–F) cm^{-1}. Analysis: Found: C, 53.39; H, 5.17; F, 12.44; N, 8.65. Calc. for $C_{14}H_{16}F_2N_2O_4$: C, 53.50; H, 5.13; F, 12.09; N, 8.91%.

2.2.2. Methyl ester of 4-hydroxy-2-oxo-6-phenyl-4-(1,1,2,2-tetrafluoroethyl)-hexahydropyrimidine-5-carboxylic acid (*3b*)

Yield, 79%; m.p., 190–192°C. ^{1}H NMR (DMSO-d_6) δ: 3.00 (1H, d, H^5, $J_{(H5–H6)} = 11.1$ Hz); 3.27 (3H, s, OCH_3); 4.79 (1H, d, H^6, $J_{(H6–H5)} = 11.1$ Hz); 6.70 (1H, t.t, $H(CF_2)_2$, $^2J_{(H–F)} = 51.4$, $^3J_{(H–F)} = 5.1$ Hz); 7.32 (5H, s, C_6H_5); 7.10 (H, ws, OH); 7.20 (2H, ws, 2NH) ppm. ^{19}F NMR (DMSO-d_6) δ: 27.57 (2F, m, HCF_2CF_2); 35.14 (2F, m, HCF_2CF_2, AB-system, $\Delta\nu = 166.12$, $^2J_{(F–F)} = 266.0$, $^3J_{(F–H)} = 5.1$ Hz) ppm. IR: 3440, 3220, 1585 (NH, OH); 3055 (CH); 1740 (CO_2Me); 1660 (C = O); 1500 (C = C); 1160–1090 (C–F) cm^{-1}. Analysis: Found: C, 48.13; H, 4.16; F, 22.14; N, 8.06. Calc. for $C_{14}H_{14}F_4N_2O_4$: C, 48.00; H, 4.03; F, 21.70; N, 8.00%.

2.2.3. Methyl ester of 4-heptafluoropropyl-4-hydroxy-2-oxo-6-phenyl-hexahydropyrimidine-5-carboxylic acid (*3c*)

Yield, 73%; m.p., 204–205°C. ^{1}H NMR (DMSO-d_6) δ: 3.04 (1H, d, H^5, $J_{(H5–H6)} = 11.0$ Hz); 3.28 (3H, s, OCH_3); 4.81 (1H, d, H^6, $J_{(H6–H5)} = 11.0$ Hz); 7.33 (5H, s, C_6H_5); 7.17, 7.53, 7.61 (3H, 3 ws, OH, 2NH) ppm. ^{19}F NMR (DMSO-d_6) δ: 40.39 (2F, m, CF_2); 43.76 (2F, m, CF_2); 82.26 (2F, m, CF_3) ppm. IR: 3450, 3205, 1630 (NH, OH); 3080 (CH); 1740 (CO_2Me); 1670 (C = O); 1490 (C = C); 1230–1100 (C–F) cm^{-1}. Analysis: Found: C, 43.25; H, 3.14; F, 31.91; N, 6.70. Calc. for $C_{15}H_{13}F_7N_2O_4$: C, 43.07; H, 3.13; F, 31.80; N, 6.70%.

2.2.4. Ethyl ester of 4-hydroxy-4-nonafluorobutyl-2-oxo-6-phenyl-hexahydropyrimidine-5-carboxylic acid (*3d*)

Yield, 80%; m.p., 191–192°C. ^{1}H NMR (DMSO-d_6) δ: 0.78 (3H, t, CH_3, $J_{(H–H)} = 7.1$ Hz); 3.03 (1H, d, H^5, $J_{(H5–H6)} = 11.1$ Hz); 3.74 (2H, q, CH_2, $J_{(H–H)} = 7.1$ Hz); 4.81 (1H, d, H^6, $J_{(H6–H5)} = 11.1$ Hz); 7.33 (5H, s, C_6H_5); 5.39, 7.11, 7.48 (3H, 3 ws, 2NH, OH) ppm. ^{19}F NMR (DMSO-d_6) δ: 37.25 (2F, m, CF_2); 44.66–43.51 (4F, m, $2CF_2$); 82.42 (3F, m, CF_3) ppm. IR: 3420, 3190, 1620 (NH, OH); 3075 (CH); 1720 (CO_2Et); 1675 (C = O); 1530 (C = C); 1220–1090 (C–F) cm^{-1}. Analysis: Found: C, 42.34; H, 3.13; F, 35.45; N, 5.81. Calc. for $C_{17}H_{15}F_9N_2O_4$: C, 42.29; H, 3.21; F, 35.53; N, 5.96%.

2.2.5. Methyl ester of 4-hydroxy-6-phenyl-4-(1,1,2,2-tetrafluoroethyl)-2-thioxohexahydro-pyrimidine-5-carboxylic acid (*3e*)

Yield, 50%; m.p., 212–213°C. ^{1}H NMR (DMSO-d_6) δ: 3.09 (1H, d, H^5, $J_{(H5–H6)} = 11.7$ Hz); 3.28 (3H, s, OCH_3); 4.81 (1H, d, H^6, $J_{(H6–H5)} = 11.7$ Hz); 6.79 (1H, t.t, $H(CF_2)_2$, $^2J_{(H–F)} = 51.4$, $^3J_{(H–F)} = 6.6$ Hz); 7.33 (5H, s, C_6H_5); 7.73, 8.31, 9,19 (3H, ws, OH, 2NH) ppm. ^{19}F NMR (DMSO-d_6) δ: 27.46 (2F, m, HCF_2CF_2); 35.14 (2F, m, HCF_2CF_2) ppm. IR: 3400, 3200, 1600 (NH, OH); 3090 (CH); 1735 (CO_2Me); 1580, 1565, 1500 (C = C); 1220–1100 (C–F) cm^{-1}. Analysis: Found: C, 46.21; H, 4.12; F, 20.38; N, 7.65; S, 8.65. Calc. for $C_{14}H_{14}F_4N_2O_3S$: C, 45.90; H, 3.85; F, 20.74; N, 7.65; S, 8.75%.

2.2.6. Methyl ester of 4-heptafluoropropyl-4-hydroxy-6-phenyl-2-thioxo-hexahydropyrimidine-5-carboxylic acid (*3f*)

Yield, 47%; m.p., 215–217°C. ^{1}H NMR (DMSO-d_6) δ: 3.14 (1H, d, H^5, $J_{(H5–H6)} = 11.3$ Hz); 3.30 (3H, s, OCH_3); 4.83 (1H, d, H^6, $J_{(H6–H5)} = 11.3$ Hz); 7.34 (5H, s, C_6H_5); 8.13 (1H, ws, OH); 9.35 (2H, ws, 2NH) ppm. ^{19}F NMR (DMSO-d_6) δ: 40.38 (2F, m, CF_2); 44.05 (2F, m, CF_2); 82.35

(2F, m, CF_3) ppm. IR: 3440, 3200, 1600 (NH, OH); 3100 (CH); 1740 (CO_2Me); 1585, 1565, 1490 (C=C); 1280–1170 (C–F) cm^{-1}. Analysis: Found: C, 41.45; H, 3.23; F, 30.62; N, 6.68; S, 7.34. Calc. for $C_{15}H_{13}F_7N_2O_3S$: C, 41.48; H, 3.02; F, 30.62; N, 6.42; S, 7.38%.

*2.2.7. Ethyl ester of 4-hydroxy-4-nonafluorobutyl-6-phenyl-2-thioxo-hexahydropyrimidine-5-carboxylic acid (**3g**)*

Yield, 45%; m.p., 212–213°C. ^{1}H NMR (DMSO-d_6) δ: 0.81 (3H, t, CH_3, $J_{(H–H)} = 7.1$ Hz); 3.13 (1H, d, H^5, $J_{(H5–H6)} = 11.5$ Hz); 3.78 (2H, q, CH_2, $J_{(H–H)} = 7.1$ Hz); 4.84 (1H, d, H^6, $J_{(H6–H5)} = 11.5$ Hz); 7.35 (5H, s, C_6H_5); 7.90, 7.98, 9.24 (3H, 3 ws, 2NH, OH) ppm. ^{19}F NMR (DMSO-d_6) δ: 37.08 (2F, m, CF_2); 43.73 (2F, m, CF_2); 44.86 (2F, m, CF_2); 82.33 (3F, m, CF_3) ppm. IR: 3440, 3185, 1600 (NH, OH); 3100 (CH); 1730 (CO_2Et); 1580, 1500 (C=C); 1230–1130 (C–F) cm^{-1}. Analysis: Found: C, 40.98; H, 3.13; F, 34.26; N, 5.67; S, 6.48. Calc. for $C_{17}H_{15}F_9N_2O_3S$: C, 40.97; H, 3.03; F, 34.21; N, 5.62; S, 6.43%.

*2.2.8. Ethyl ester of 4-hydroxy-6-phenyl-2-thioxo-4-trifluoromethylhexahydropyrimidine-5-carboxylic acid (**3h**)*

Yield, 43%; m.p., 190–191°C (lit. mp. 190°C [7]). ^{1}H NMR (DMSO-d_6) δ: 0.81 (3H, t, CH_3, $J_{(H–H)} = 7.1$ Hz); 3.02 (1H, d, H^5, $J_{(H5–H6)} = 11.8$ Hz); 3.79 (2H, q, CH_2, $J_{(H–H)} = 7.1$ Hz); 4.79 (1H, d, H^6, $J_{(H6–H5)} = 11.8$ Hz); 7.34 (5H, s, C_6H_5); 7.88, 8.89, 9.09 (3H, 3 ws, 2NH, OH) ppm. ^{19}F NMR (DMSO-d_6) δ: 82.30 (3F, m, CF_3) ppm. IR: 3430, 3190, 1600 (NH, OH); 3100 (CH); 1735 (CO_2Et); 1570 (C=C); 1260–1170 (C–F) cm^{-1}. Analysis: Found: C, 48.18; H, 4.32; F, 16.34; N, 8.01. Calc. for $C_{14}H_{15}F_3N_2O_3S$: C, 48.27; H, 4.34; F, 16.36; N, 8.04%.

*2.2.9. 5-Acetyl-4-hydroxy-6-phenyl-4-trifluoromethyl-hexahydropyrimidin-2-one (**4a**)*

Yield, 32%; m.p., 180–182°C. ^{1}H NMR (DMSO-d_6) δ: 1.88 (3H, s, CH_3); 3.11 (1H, d, H^5, $J_{(H5–H6)} = 11.7$ Hz); 4.84 (1H, d, H^6, $J_{(H6–H5)} = 11.7$ Hz); 7.35 (5H, s, C_6H_5); 7.19, 7.52, 7.61 (3H, 3 ws, 2NH, OH) ppm. ^{19}F NMR (DMSO-d_6) δ: 82.04 (3F, m, CF_3) ppm. IR: 3400, 3390, 3220, 1610 (NH, OH); 3080, 3050 (CH); 1720, 1705 (COMe); 1680, 1660 (C=O); 1500 (C=C); 1190–1170 (C–F) cm^{-1}. Analysis: Found: C, 51.49; H, 4.28; F, 18.85; N, 9.28. Calc. for $C_{13}H_{13}F_3N_2O_3$: C, 51.66; H, 4.34; F, 18.86; N, 9.27%.

*2.2.10. 5-Benzoyl-4-hydroxy-6-phenyl-4-trifluoromethyl-hexahydropyrimidin-2-one (**4b**)*

Yield, 42%; m.p., 204–205°C. ^{1}H NMR (DMSO-d_6) δ: 4.68 (2H, m, H^5, H^6, AB-system, $\Delta\nu = 41.94$, $J_{(H5–H6)} = 11.1$ Hz); 7.10–7.40 (10H, m, $2C_6H_5$); 7.60, 7.72 (3H, 3 ws, 2NH, OH) ppm. ^{19}F NMR (DMSO-d_6) δ: 82.71 (3F, s, CF_3) ppm. IR: 3430, 3190, 1590 (NH, OH); 3060 (CH); 1675 (COPh); 1660 (C=O); 1500 (C=C); 1200–1175 (C–F) cm^{-1}. Analysis: Found: C, 59.23; H, 4.05; F, 15.69; N, 7.54. Calc. for $C_{18}H_{15}F_3N_2O_3$: C, 59.34; H, 4.15; F, 15.64; N, 7.69%.

*2.2.11. 5-Acetyl-4-hydroxy-6-phenyl-4-(1,1,2,2-tetrafluoroethyl)-hexahydropyrimidin-2-one (**4c**)*

Yield, 33%; m.p., 184–185°C. ^{1}H NMR (DMSO-d_6) δ: 1.80 (3H, s, CH_3); 3.10 (1H, d, H^5, $J_{(H5–H6)} = 11.4$ Hz); 4.82 (1H, d, H^6, $J_{(H6–H5)} = 11.4$ Hz); 6.71 (1H, t.t, $H(CF_2)_2$, $^2J_{(H–F)} = 51.5$ Hz, $^3J_{(H–F)} = 6.8$ Hz); 7.34 (5H, s, C_6H_5); 7.21, 7.28 (3H, 2 ws, 2NH, OH) ppm. ^{19}F NMR (DMSO-d_6) δ: 27.64 (2F, m, HCF_2CF_2); 36.69 (2F, m, HCF_2CF_2, AB-system, $\Delta\nu = 116.83$, $^2J_{(F–F)} = 267.0$ Hz, $^3J_{(F–H)} = 6.8$ Hz) ppm. IR: 3450, 3390, 3210, 1590 (NH, OH); 3090 (CH); 1700 (COMe); 1690 (C=O); 1480 (C=C); 1160–1110 (C–F) cm^{-1}. Analysis: Found: C, 50.39; H, 4.27; F, 22.74; N, 8.43. Calc. for $C_{14}H_{14}F_4N_2O_3$: C, 50.30; H, 4.22; F, 22.73; N, 8.38%.

*2.2.12. 5-Benzoyl-4-hydroxy-6-phenyl-4-(1,1,2,2-tetrafluoroethyl)-hexahydropyrimidin-2-one (**4d**)*

Yield, 38%; m.p., 233–234°C. ^{1}H NMR (DMSO-d_6) δ: 4.65 (2H, m, H^5, H^6, AB-system, $\Delta\nu = 41.45$, $J_{(H5–H6)} = 11.0$ Hz); 6.72 (1H, t.t, $H(CF_2)_2$, $^2J_{(H–F)} = 51.3$ Hz, $^3J_{(H–F)} = 6.7$ Hz); 7.04–7.46 (10H, m, $2C_6H_5$); 7.54, 7.62 (3H, 2 ws, 2NH, OH) ppm. ^{19}F NMR (DMSO-d_6) δ: 27.79 (2F, m, HCF_2CF_2, AB-system, $\Delta\nu = 159.34$, $^2J_{(F–F)} = 300.0$ Hz, $^2J_{(F–H)} = 51.3$ Hz); 38.11 (2F, m, HCF_2CF_2,) ppm. IR: 3430, 3190, 1590 (NH, OH); 3050 (CH); 1675 (COPh); 1660 (C=O); 1490 (C=C); 1140–1100 (C–F) cm^{-1}. Analysis: Found: C, 57.44; H, 4.12; F, 19.12; N, 7.04. Calc. for $C_{19}H_{16}F_4N_2O_3$: C, 57.58; H, 4.07; F, 19.17; N, 7.07%.

*2.2.13. 5-Acetyl-4-hydroxy-6-phenyl-4-trifluoromethyl-hexahydropyrimidine-2-thione (**4e**)*

Yield, 22%; m.p., 211–212°C. ^{1}H NMR (DMSO-d_6) δ: 1.89 (3H, s, CH_3); 3.19 (1H, d, H^5, $J_{(H5–H6)} = 11.8$ Hz); 4.86 (1H, d, H^6, $J_{(H6–H5)} = 11.8$ Hz); 7.35 (5H, s, C_6H_5); 8.02, 8.96, 9.09 (3H, 3 ws, 2NH, OH) ppm. ^{19}F NMR (DMSO-d_6) δ : 82.90 (3F, m, CF_3) ppm. IR: 3380, 3260, 1580 (NH, OH); 3050 (CH); 1690 (COMe); 1550, 1500 (C=C); 1240–1160 (C–F) cm^{-1}. Analysis: Found: C, 49.05; H, 4.14; F, 17.83; N, 8.78; S, 10.14. Calc. for $C_{13}H_{13}F_3N_2O_2S$: C, 49.05; H, 4.12; F, 17.91; N, 8.80; S, 10.07%.

*2.2.14. 5-Benzoyl-4-hydroxy-6-phenyl-4-trifluoromethyl-hexahydropyrimidine-2-thione (**4f**)*

Yield, 30%; m.p., 229–230°C. ^{1}H NMR (DMSO-d_6) δ: 4.75 (2H, m, H^5, H^6, AB-system, $\Delta\nu = 38.80$, $J_{(H5–H6)} = 11.5$ Hz); 7.15–7.70 (10H, m, $2C_6H_5$); 7.75, 8.95, 9.09 (3H, 3 ws, 2NH, OH) ppm. ^{19}F NMR (DMSO-d_6) δ: 83.61 (3F, s, CF_3) ppm. IR: 3430, 3180, 1585 (NH, OH); 3090 (CH); 1665 (COPh); 1560, 1500 (C=C); 1250–1120 (C–F) cm^{-1}. Analysis: Found: C, 56.95; H, 3.84; F, 14.76; N, 7.36; S, 8.47. Calc. for $C_{18}H_{15}F_3N_2O_2S$: C, 56.84; H, 3.97; F, 14.98; N, 7.36; S, 8.43%.

*2.2.15. 5-Benzoyl-4-hydroxy-6-phenyl-(1,1,2,2-tetrafluoroethyl)-hexahydropyrimidine-2-thione (**4g**)*

Yield, 36%; m.p., 233–234°C. ^{1}H NMR (DMSO-d_6) δ: 4.72 (2H, m, H^5, H^6, AB-system, $\Delta\nu = 41.79$, $J_{(H5–H6)} = 11.5$ Hz); 6.84 (1H, t.t, H$(CF_2)_2$, $^2J_{(H–F)} = 51.5$ Hz, $^3J_{(H–F)} = 6.0$ Hz); 7.09–7.58 (10H, m, 2C_6H_5); 7.66, 8.30, 9.20 (3H, 3 ws, 2NH, OH) ppm. ^{19}F NMR (DMSO-d_6) δ: 27.50 (2F, m, *HCF*$_2$CF$_2$); 38.65 (2F, m, HCF$_2$*CF*$_2$, AB-system, $\Delta\nu = 80.22$, $^2J_{(F–F)} = 264.4$ Hz, $^3J_{(F–H)} = 6.0$ Hz) ppm. IR: 3440, 3190, 1595 (NH, OH); 3100 (CH); 1680 (COPh); 1560, 1500 (C=C); 1220–1150 (C–F) cm^{-1}. Analysis: Found: C, 55.25; H, 4.06; F, 18.54; N, 6.69; S, 7.70. Calc. for $C_{19}H_{16}F_4N_2O_2S$: C, 55.34; H, 3.91; F, 18.43; N, 6.79; S, 7.77%.

*2.2.16. 4-Hydroxy-6-phenyl-5-trifluoroacetyl-4-trifluoromethylhexahydropyrimidine-2-thione (**4i**)*

Yield, 20%; m.p., 215–216°C. ^{1}H NMR (DMSO-d_6) δ: 3.97 (1H, d, H^5, $J_{(H5–H6)} = 11.5$ Hz); 4.89 (1H, d, H6, $J_{(H6–H5)} = 11.5$ Hz); 7.35 (5H, m, C_6H_5); 8.38, 9.29, 9.46 (3H, 3 ws, 2NH, OH) ppm. ^{19}F NMR (DMSO-d_6) δ: 82.59 (3F, q, CF_3, $J = 5.4$ Hz); 84.59 (3F, q, CF_3, $J = 5.4$ Hz) ppm. IR: 3160, 1580 (NH, OH); 3100 (CH); 1740 ($COCF_3$); 1560, 1510 (C=C); 1200–1170 (C–F) cm^{-1}. Analysis: Found: C, 41.99; H, 2.75; F, 30.74; N, 7.56; S, 8.35. Calc. for $C_{13}H_{10}F_6N_2O_2S$: C, 41.94; H, 2.71; F, 30.62; N, 7.52; S, 8.61%.

*2.2.17. 4,6-Di(hydroxy)-4,6-di(trifluoromethyl)-hexahydropyrimidin-2-one (**7**)*

Yield, 44%; m.p., 211–212°C. ^{1}H NMR (DMSO-d_6) δ: 2.15 (2H, m, H^{5a}, H^{5e}, AB-system, $\Delta\nu = 18.28$, $J_{(H–H)} = 13.7$ Hz); 6.94, 7.97 (4H, 2s, 2NH, 2OH) ppm. ^{19}F NMR (DMSO-d_6) δ: 78.60 (6F, s, CF_3) ppm. IR: 3290, 3130, 1590 (NH, OH); 1680 (COPh); 1560, 1500 (C=C); 1220–1150 (C–F) cm^{-1}. Analysis: Found: C, 55.25; H, 4.06; F, 18.54; N, 6.69; S, 7.70. Calc. for $C_{19}H_{16}F_4N_2O_2S$: C, 55.34; H, 3.91; F, 18.43; N, 6.79; S, 7.77%.

Method **B**: A mixture of 1,3-diketone **2e** (0.42 g, 2.0 mmol) and urea (0.18 g, 3.0 mmol) was refluxed in 8 ml of ethanol containing two drops of concentrated HCl for 2 h. The solvent was removed under reduced pressure. The residue was washed with chloroform (10 ml). Recrystallization of the mixture from ethanol–water (1:1) gave **7** (0.39 g, 72%). The physical data were identical to those listed above.

*2.3. 4-Hydroxy-6-phenyl-5-trifluoroacetyl-4-trifluoromethyl-hexahydropyrimidin-2-one (**4h**)*

A mixture of benzaldehyde (0.21 g, 2.0 mmol), 1,3-diketone **2e** (0.42 g, 2.0 mmol), urea (0.18 g, 3.0 mmol) and *p*-toluenesulfonic acid (0.09 g, 1.5 mmol) in 8 ml of tetrahydrofuran was refluxed for 2 h. Precipitation by water gave **4g** (0.21 g, 30%) as a white powder (m.p., 200–201°C). ^{1}H NMR (DMSO-d_6) δ: 3.83 (1H, d, H^5, $J_{(H5–H6)} = 11.5$ Hz); 4.88 (1H, d, H^6, $J_{(H6–H5)} = 11.5$ Hz); 7.34 (5H, m, C_6H_5); 7.44, 7.95, 8.09 (3H, 3 ws, 2NH, OH) ppm. ^{19}F NMR (DMSO-d_6) δ: 81.17 (3F, q, CF_3, $J = 5.3$ Hz); 84.03 (3F, q, CF_3, $J = 5.3$ Hz) ppm. IR: 3390, 3200, 1610 (NH, OH); 3060 (CH); 1745 ($COCF_3$); 1660 (C=O); 1480 (C=C); 1200–1100 (C–F) cm^{-1}. Analysis: Found: C, 43.74; H, 2.82; F, 32.14; N, 7.93. Calc. for $C_{13}H_{10}F_6N_2O_3$: C, 43.83; H, 2.83; F, 32.00; N, 7.86%.

*2.4. Synthesis of tetrahydropyrimidines **5a,b** and **6a,b***

To a solution of hexahydropyrimidine **3d,g**, **4d,g** (2.0 mmol) (Scheme 1) in 15 ml of toluene, 0.1 g of *p*-toluenesulfonic acid was added. The mixture was refluxed for 6 h with azeotropic removal of water. The reaction mixture was cooled to room temperature and filtered from a small amount of solid material. Reprecipitation of this residue from ethanol/water gave compounds **5a,b**, **6a,b**.

*2.4.1. Ethyl ester of 6-nonafluorobutyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid (**5a**)*

Yield, 56%; m.p., 154–155°C. ^{1}H NMR (DMSO-d_6) δ: 1.03 (3H, t, CH_3, $J_{(H–H)} = 7.1$ Hz); 4.00 (2H, q, CH_2, $J_{(H–H)} = 7.1$ Hz); 5.25 (1H, s, H^4); 7.34 (5H, s, C_6H_5); 7.96, 9.60 (2H, 2 ws, 2NH) ppm. ^{19}F NMR (DMSO-d_6) δ : 36.92 (2F, m, CF_2); 42.85 (2F, m, CF_2); 52.62 (2F, m, CF_2); 82.25 (3F, m, CF_3) ppm. IR: 3270, 3210, 1650 (NH); 3080 (CH); 1730 (CO_2Et); 1670 (C=O); 1560 (C=C); 1240–1140 (C–F) cm^{-1}. Analysis: Found: C, 43.93; H, 2.86; F, 36.91; N, 6.14. Calc. for $C_{17}H_{13}F_9N_2O_3$: C, 43.98; H, 2.82; F, 36.83; N 6.03%.

*2.4.2. Ethyl ester of 6-nonafluorobutyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid (**5b**)*

Yield, 48%; m.p., 137–138°C. ^{1}H NMR (DMSO-d_6) δ: 1.08 (3H, t, CH_3, $J_{(H–H)} = 7.1$ Hz); 4.07 (2H, q, CH_2, $J_{(H–H)} = 7.1$ Hz); 5.25 (1H, d, H^4, $^3J_{(H–H)} = 3.1$ Hz); 7.21–7.46 (5H, m, C_6H_5); 9.20 (1H, d, NH, $^3J_{(H–H)} = 3.1$ Hz); 10.71 (1H, ws, NH) ppm. ^{19}F NMR (DMSO-d_6) δ: 36.85 (2F, m, CF_2); 42.88 (2F, m, CF_2); 52.86 (2F, m, CF_2); 82.19 (3F, m, CF_3) ppm. IR: 3295, 3180, 1580 (NH); 3100 (CH); 1710 (CO_2Et); 1670 (C=C); 1560 (C=C); 1220–1130 (C–F) cm^{-1}. Analysis: Found: C, 43.93; H, 2.86; F, 36.91; N, 6.14. Calc. for $C_{17}H_{13}F_9N_2O_3$: C, 43.98; H, 2.82; F, 36.83; N, 6.03%.

*2.4.3. 5-Benzoyl-4-phenyl-6-(1,1,2,2-tetrafluoroethyl)-1,2,3,4-tetrahydropyrimidin-2-one (**6a**)*

Yield, 44%; m.p., 152–153°C. ^{1}H NMR (DMSO–d_6) δ: 5.13 (1H, ws, H^4); 6.65 (1H, t.t, H$(CF_2)_2$, $^2J_{(H–F1,2)} = 52.0$ Hz, $^3J_{(H–F3)} = 7.4$ Hz, $^3J_{(H–F4)} = 4.6$ Hz); 7.18–7.65 (10H, m, 2C_6H_5); 7.86, 9.43 (2H, 2 ws, 2NH) ppm. ^{19}F NMR (DMSO-d_6) δ: 25.08 (2F, d.t, *HCF*$_2$CF$_2$, $^2J_{(F1,2–H)} = 52.0$ Hz, $^3J_{(F1,2–F3,4)} = 7.9$ Hz); 46.04 (2F, m, HCF$_2$*CF*$_2$, AB-system, $\Delta\nu = 363.3$, $^2J_{(F3–F4)} = 269.6$ Hz, $^3J_{(F3,4–F1,2)} = 7.9$ Hz, $^3J_{(F3–H)} = 7.4$ Hz, $^3J_{(F4–H)} = 4.6$ Hz) ppm. IR:

3235, 1600 (NH); 3100 (CH); 1710 (COPh); 1675 (C=O); 1660 (C=C); 1490 (C=C); 1170–1100 (C–F) cm^{-1}. Analysis: Found: C, 60.07; H, 3.68; F, 19.85; N, 7.50. Calc. for $C_{19}H_{14}F_4N_2O_2$: C, 60.32; H, 3.73; F, 20.09; N, 7.40%.

*2.4.4. 5-Benzoyl-4-phenyl-6-(1,1,2,2-tetrafluoroethyl)-1,2,3,4-tetrahydropyrimidine-2-thione (**6b**)*

Yield, 40%; m.p., 123–124°C. ^{1}H NMR (DMSO-d_6) δ: 5.10 (1H, ws, H^4); 6.76 (1H, t.t, $H(CF_2)_2$, $^2J_{(H–F)} = 51.9$ Hz, $^3J_{(H–F)} = 6.0$ Hz); 7.20–7.67 (10H, m, $2C_6H_5$); 9.70, 10.67 (2H, 2 ws, 2NH) ppm. ^{19}F NMR (DMSO-d_6) δ: 24.75 (2F, m, HCF_2CF_2,); 46.90 (2F, m, HCF_2CF_2) ppm. IR: 3150, 1590 (NH); 3090 (CH); 1665 (COPh); 1650 (C=C); 1570 (C=C); 1210–1100 (C–F) cm^{-1}. Analysis: Found: C, 57.70; H, 3.52; F, 19.04; N, 7.04. Calc. for $C_{19}H_{14}F_4N_2OS$: C, 57.86; H, 3.58; F, 19.27; N, 7.10%.

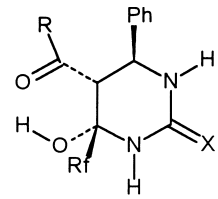
*2.5. Ethyl ester of 7-nonafluorobutyl-5-phenyl-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidine-6-carboxylic acid, hydrobromide salt (**9**)*

To a refluxing solution of tetrahydropyrimidine **5b** (0.96 g, 2.0 mmol) in 5 ml of DMF, dibromoethane (0.39 g, 2.1 mmol) was added. The mixture was refluxed for 25 min. After cooling, the resulting precipitate was collected by filtration. Recrystallization from ethanol gave **9** (0.49 g, 42%) as a white powder (m.p., 200–201°C). ^{1}H NMR (CF_3COOD) δ: 1.11 (3H, t, CH_3, $J_{(H–H)} = 7.0$ Hz); 3.71 (2H, m, H^{2a},H^{2e}, $J_{(H–H)} = 6.5$ Hz); 4.17 (2H, q, CH_2, $J_{(H–H)} = 7.0$ Hz); 4.58 (2H, m, H^{3a},H^{3e}, $J_{(H–H)} = 6.5$ Hz); 5.92 (1H, s, H^5); 7.50 (5H, m, C_6H_5) ppm. IR: 2770, 2745, 2700 (NH+); 3060 (CH); 1730 (CO_2Et); 1660, 1500 (C=C, C=N); 1240–1140 (C–F) cm^{-1}. Analysis: Found: C, 38.85; H, 2.74; F, 29.13; N, 4.75; S, 5.48. Calc. for $C_{19}H_{15}F_9N_2O_2S$ HBr: C, 38.86; H, 2.75; F, 29.11; N, 4.77; S, 5.46%.

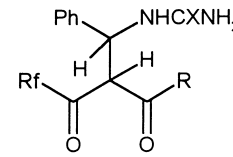
3. Results and discussion

In the present work, the Biginelli-type cyclocondensations of a number of fluorine-containing 3-oxo esters **1a–e** and 1,3-diketones **2a–e** have been studied. In analogy to the reaction with ethyl trifluoroacetoacetate **1e** with benzaldehyde and urea [4], we find that both fluorinated 3-oxo esters **1a–e** and fluorinated 1,3-diketones **2a–d** in general react with (thio)urea and benzaldehyde to furnish hexahydropyrimidines **3a–h**, and **4a–g**, respectively (Scheme 1). These reactions were conveniently carried out in refluxing ethanol in the presence of a catalytic amount of concentrated HCl for 5–6 h providing hexahydropyrimidine products in moderate to good yields.

In principle, one has to consider two isomeric structures for these condensation products, namely the hexahydropyrimidine structure of type **A**, or the isomeric acyclic ureidopropionate structure of type **B** (which may exist as mixture of keto- and enol tautomers). It has to be mentioned that an earlier report on the condensation of ethyl trifluoroacetoacetate with thiourea and benzaldehyde postulated the formation of the corresponding ureidopropionate **B** ($R^f = CF_3$, R = OEt, X = S) under essentially similar reaction conditions [7]. Based on comparison of melting points and spectral data we assume that the identical material has been isolated. However, we assign the structure of the corresponding hexahydropyrimidine of type **A** (**3h**) to this product based on the detailed spectroscopic characterization that we have carried out.



A



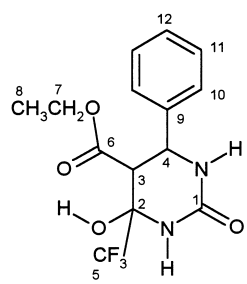
B

Spectral examination (^{1}H and ^{19}F NMR) of products **3a–h**, **4a–g** confirms the formation of one single isomer in all cases. The IR spectra of products **3a–h**, **4a–g** are characterized by the absence of two narrow absorption bands corresponding to the asymmetric and symmetric vibration of the NH_2-groups in structures **B**. However, sharp and intense signals for the OH functionality in structure **A** are present in all cases. In the ^{1}H NMR spectra of compounds **3a–h**, and **4a–g**, the most characteristic signals are two doublets corresponding to the two *trans*-axial methine protons in **A** (H^5–H^6). The observed coupling constants ($J = 11.0$–11.8 Hz) agree very well with the values previously found for our reference compound **A** ($R^f = CF_3$, R = OEt, X = O) [4]. It is therefore reasonable to assume that the same relative stereochemistry as shown in **A** and ring orientation is observed in all cases.

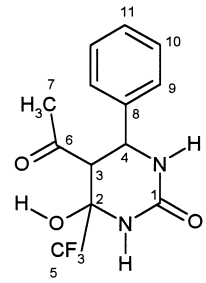
In addition, the cyclic nature of compound **3h** was confirmed by ^{13}C NMR spectroscopy. In the spectrum, a quartet for the carbon atom connected with the trifluoromethyl substituent is located at 79.61 ppm ($^3J_{(C–F)} = 31.13$ Hz) (Table 1) which is typical for a quarternary carbon rather than a carbonyl carbon atom [8]. Therefore, all the spectroscopic data clearly confirm the cyclic structure of type **A** for the products obtained, in agreement with the X-ray analysis obtained previously for a single analog [4].

When non-symmetrical 1,3-diketones are employed in the above Biginelli-type cyclocondensation process two isomeric products may possibly be formed. Cyclization of the pyrimidine nucleus may occur on the carbonyl group at the fluorinated substituent or the carbonyl group connected with the non-fluorinated substituent to form the corresponding heterocycles **C** or **D**, respectively, or a mixture of both isomers. Literature data indicate that condensation of amines with non-symmetrical 1,3-diketones having

Table 1
^{13}C NMR spectra of compounds **3h**, **4a** (δ_C, ppm; $J(^{13}C–^{19}F)$, Hz) in DMSO-d_6



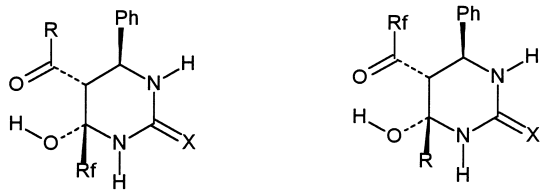
3h



4a

N	C^1	C^2	C^3	C^4	C^5	C^6	C^7	C^8	C^9	C^{10}	C^{11}	C^{12}
3h	177.17	79.61 (31.13)	54.30	60.37	122.84 (288)	166.40	49.36	13.36	136.89	128.06	128.31	128.55
4a	164.22	80.69 (30.52)	53.21	57.21	123.21 (288)	203.89	30.58	153.72	127.97	128.52	138.04	

one fluorinated substituent preferably occurs at the carbonyl group attached to the non-fluorinated radical [9].



C **D**

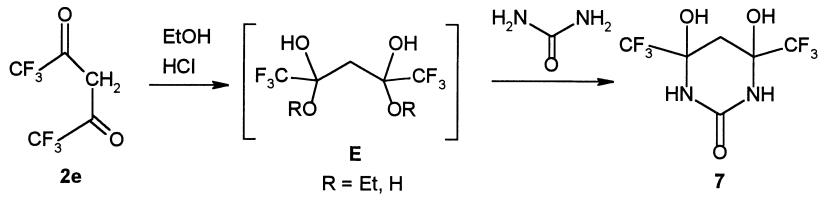
$R^f = CF_3, H(CF_2)_2$;
R = Me, Ph;
X = O, S

In the NMR spectra of compounds **4a–g**, signals for only one isomer are observable. The distinction between structures **C** and **D** was easily made on the basis of ^{13}C NMR spectroscopic data, as the quartet signal of the carbon atom attached to the trifluoromethyl group ($^3J_{C–F} = 30.52$ Hz) is located at 80.69 ppm, which is typical for a quarternary carbon atom (structure **C**, O–C–N) rather than a carbonyl carbon in structure **D** [8]. Thus, the above cyclocondensation occurs regioselectively on the carbonyl group at the fluorinated substituent.

In contrast to the reactions of 3-oxo esters **1a–d** and 1,3-diketones **2a–d** described above, hexafluoroacetylacetone **2e** reacts with urea and benzaldehyde (under identical reaction conditions) in a different manner yielding 4,6-di(trifluoromethyl)-hexahydropyrimidin-2-one **7** (Scheme 2). The formation of the latter evidently proceeds without the participation of the aldehyde component, and is competitive to the Biginelli condensation (see below). The addition of water or alcohols on both carbonyl groups with the formation of stable adducts (tetraols and bis-semiketals) is typical for hexafluoroacetylacetone [9]. Under the reaction conditions in an ethanol/water medium, hexafluoroacetylacetone probably spontaneously forms bis-semiketal or tetraol **E**, which do not have an activated methylene group and therefore cannot react with the *N*-acyliminium ion intermediate formed from the benzaldehyde and urea components [10].

Hexahydropyrimidine **7** may exist in two diastereoisomeric forms (*cis*- and *trans*-isomers). The character of the non-equivalent methylene proton signals as an AB-system ($J_{(H–H)} = 13.7$ Hz) in the ^1H NMR spectrum of **7** and one single signal for the trifluoromethyl group in the ^{19}F NMR spectrum suggests that the *cis*-isomer is the only one formed. This was further supported by semiempirical AM1 calculations, showing that the *cis*-isomer is ca. 4 kcal/mol more stable than the *trans*-isomer. A representation of the AM1 optimized geometry is given in Fig. 1.

The formation of the originally anticipated hexahydropyrimidine **4h** is only possible using anhydrous conditions in the three-component reaction and an aprotoic solvent such as THF in the presence of a catalytic amount of *p*-toluenesulfonic acid (Scheme 3). In contrast to the reaction



2e **E** R = Et, H **7**

Scheme 2.

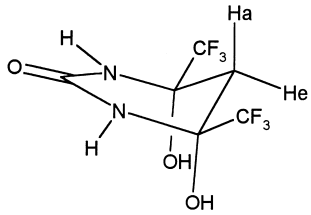
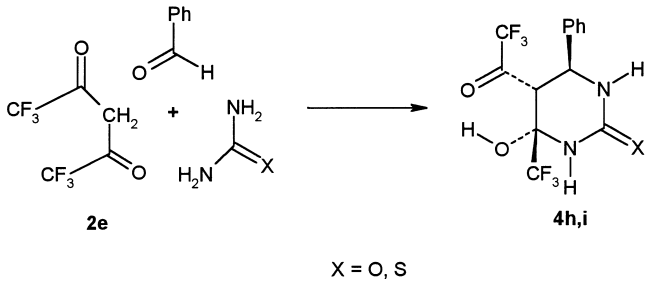


Fig. 1. AM1 optimized geometry of *cis*-hexahydropyrimidine **7** (schematic representation).

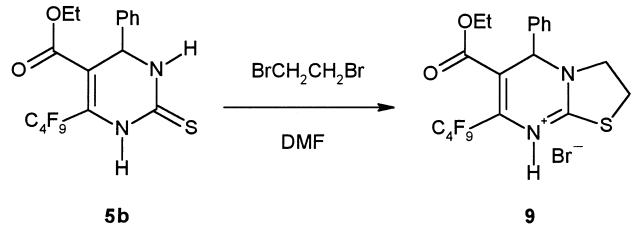


Scheme 3.

with urea, interaction of hexafluoroacetylacetone **2e** with thiourea and benzaldehyde results in the formation of hexahydropyrimidine **4i** even under classical reaction conditions (EtOH/HCl). In this case, the Biginelli-type three-component condensation apparently occurs faster than the competitive addition of thiourea on both carbonyl groups of the 1,3-diketone. Probably, this is a result of the greater basicity of thiourea ($pK_b = 11.97$) as compared to urea ($pK_b = 13.82$).

The experimental data obtained herein allow us to conclude that the replacement of non-fluorinated 3-oxo ester components in the Biginelli reaction by 1,3-dicarbonyl compounds containing partially or completely fluorinated substituents results in the formation of hexahydropyrimidine derivatives in a diastereoselective fashion. The formation of stable hydrated heterocycles due to the presence of a strong electron-withdrawing group is typical for the reactions of fluorinated 1,3-dicarbonyl compounds with nucleophilic reagents [11–13].

We were also able to show that e.g. hexahydropyrimidines **3d,f** and **4d,f** underwent successful dehydration in refluxing toluene in the presence of *p*-toluenesulfonic acid with azeotropic removal to form 1,2,3,4-tetrahydropyrimidines **5a,b** and **6a,b** (see Scheme 1) [4]. Such tetrahydro-



Scheme 4.

pyrimidines may be used as precursors for the synthesis of fused heterocyclic systems. For example, tetrahydropyrimidine **5b** on refluxing with dibromoethane in DMF affords the substituted thiazolopyrimidine **9** as hydrobromide salt (Scheme 4) [14].

In conclusion, we have shown that a family of novel fluoroalkyl substituted hexahydropyrimidines is readily available by Biginelli-type three-component cyclocondensation reaction of fluorinated 1,3-dicarbonyl compounds with benzaldehyde and (thio)urea. The biological properties of these substances are currently under investigation.

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