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One-Step Solvent-Free Synthesis of Fluoroalkyl-Substituted 4-Hydroxy-2-oxo(thioxo)hexahydropyrimidines in the Presence of 1-Butyl-3-methylimidazolium Tetrafluoroborate

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Abstract—A convenient procedure has been developed for the synthesis of fluoroalkyl-substituted 6-aryl-4-hydroxy-2-oxo-(thioxo)hexahydropyrimidine derivatives by three-component condensation of fluorinated β-dicarbonyl compounds with aromatic aldehydes and urea or thiourea in the absence of a solvent using 6 mol % of 1-butyl-3-methylimidazolium tetrafluoroborate as catalyst.

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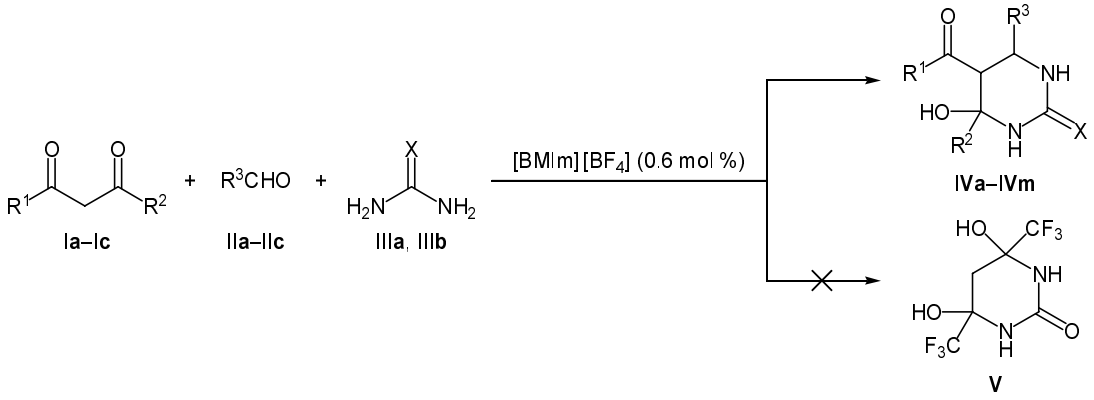
Compounds including a pyrimidine fragment are known to be components of natural substances and synthetic medical agents [1]. Some fluorinated pyrimidines, e.g., fluorouracil, are used in chemotherapy of tumors [2]. A convenient one-step procedure for the synthesis of fluoroalkyl-substituted hexahydropyrimidine derivatives is based on three-component cyclocondensation of fluorinated β-dicarbonyl compounds with benzaldehyde and urea or thiourea [3] (a version of the Biginelli reaction [4]). However, under standard conditions (ethanol, HCl) this reaction does not always give the desired heterocyclic compounds in high yields. In addition, hexafluoroacetylacetone reacts with urea in alcoholic medium without involving benzaldehyde; as a result, symmetrically substituted 4,6-bis(trifluoromethyl)-4,6-dihydroxyhexahydropyrimidin-2-one is formed [3].

We recently revealed that trialkylammonium, tetraalkylammonium, 1,3-dialkylimidazolium, and 1,2,3-trialkylimidazolium salts with BF_4^-, PF_6^-, $AlCl_4^-$, or $Al_2Cl_7^-$ as counterion (so-called ionic liquids [5]), effectively catalyze the Biginelli reaction involving various β-dicarbonyl compounds [6]. The reaction occurs on mixing the reactants under solvent-free conditions and is characterized by an acceptable yield. Presumably, the catalytic activity of the above salts arises from their ability to generate the corresponding hydrogen halides during the process.

In the present communication we describe a convenient solvent-free procedure for the synthesis of 6-aryl(hetaryl)-4-fluoroalkyl-4-hydroxytetrahydropyrimidin-2(1*H*)-one(thione) derivatives **IV** by three-component condensation of fluorinated β-dicarbonyl compounds **I** with aromatic (or heteroaromatic) aldehydes **II** and urea (**IIIa**) or thiourea (**IIIb**) in the presence of a catalytic amount of 1-butyl-3-methylimidazolium tetrafluoroborate [BMIm][BF_4]; the latter is among the most accessible and most widely used ionic liquids [5]. We have found no published data on the application of ionic liquids in the synthesis of fluorine-containing compounds of the pyrimidine series.

As fluorinated β-dicarbonyl compounds we used ethyl trifluoroacetoacetate (**Ia**), 4,4,5,5-tetrafluoro-1-phenylpentane-1,3-dione (**Ib**), and 1,1,1,5,5,5-hexafluoropentane-2,4-dione (**Ic**). The aldehyde components were benzaldehyde (**IIa**), 4-fluorobenzaldehyde (**IIb**), and thiophene-2-carbaldehyde (**IIc**). As reported in [6], the reactions were performed by adding 0.6 mol % of [BMIm] [BF_4] to a mixture of the reactants in the absence of a solvent. In all cases, we isolated the target tetrahydropyrimidin-2(1*H*)-one(thione) derivatives **IVa**–**IVm** whose yields appreciably exceeded those given in [3, 7] (Scheme 1).

Scheme 1.

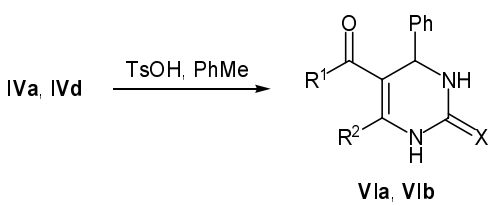


I, R^1 = OEt, R^2 = CF_3 (**a**), R^1 = Ph, R^2 = CHF_2CF_2 (**b**), R^1 = R^2 = CF_3 (**c**); **II**, R^3 = Ph (**a**), 4-FC_6H_4 (**b**), 2-thienyl (**c**); **III**, X = O (**a**), S (**b**); **IV**, R^1 = OEt, R^2 = CF_3, R^3 = Ph, X = O (**a**), S (**b**), R^3 = 4-FC_6H_4, X = S (**c**); R^1 = Ph, R^2 = CHF_2CF_2, R^3 = Ph, X = O (**d**), S (**e**), R^3 = 4-FC_6H_4, X = O (**f**), S (**g**), R^3 = 2-thienyl, X = O (**h**); R^1 = R^2 = CF_3, R^3 = Ph, X = O (**i**), S (**j**), R^3 = 2-thienyl, X = O (**k**), R^3 = 4-FC_6H_4, X = O (**l**), S (**m**).

The condensation conditions depended on the initial fluorinated β-dicarbonyl compound. Ethyl trifluoroacetoacetate (**Ia**) reacted with aldehydes **IIa**–**IIc** and urea **IIIa** or thiourea (**IIIb**) in the presence of [BMIm][BF_4] only at 100°C, and the reaction time was 6 h. The reactions with 4,4,5,5-tetrafluoro-1-phenylpentane-1,3-dione (**Ib**) occurred at a higher rate (in 2 h) and under milder conditions (80°C). Among the examined fluorinated β-dicarbonyl compounds, the most reactive was hexafluoroacetylacetone (**Ic**). In the condensations with compound **Ic**, heterocyclic products **IVi**–**IVm** were obtained even at room temperature, and no 4,6-bis(trifluoromethyl)-4,6-dihydroxyhexahydropyrimidin-2-one (**V**) was formed as by-product.

The reactions with unsymmetrically substituted 1,3-diketone **Ib** were regioselective, and the condensation products **IVd**–**IVh** contained the fluoroalkyl group in the 4-position. Compounds **IVa**, **IVb**, **IVd**, **IVe**, **IVi**, and **IVj** were reported previously; they were identified by comparing their physical constants and spectral parameters with those given in [3, 7]. The structure of pyrimidines **IVa** and **IVd** was also confirmed by chemical transformation: they were converted into the corresponding 6-fluoroalkyl-4-phenyltetrahydropyrimidines **VIa** and **VIb** by heating in boiling toluene in the presence of *p*-toluenesulfonic acid according to [3, 7] (Scheme 2). By analogy, the newly synthesized compounds **IVc**, **IVf**–**IVh**, and **IVk**–**IVm** were assigned the structure of 4-fluoroalkyl-4-hydroxytetrahydropyrimidin-2(1*H*)-ones(thiones).

Scheme 2.



VI, R^1 = OEt, R^2 = CF_3 (**a**), R^1 = Ph, R^2 = CHF_2CF_2 (**b**).

It should be emphasized that, unlike reactions in the system EtOH–HCl [3], the products of [BMIm][BF_4]-catalyzed condensation of hexafluoroacetylacetone (**Ic**) with aromatic (heteroaromatic) aldehydes and urea (thiourea) were always 6-aryl(hetaryl)-4-hydroxy-5-trifluoroacetyl-4-trifluoromethyltetrahydropyrimidin-2(1*H*)-ones(thiones) **IVi**–**VIm**. The observed reaction direction may be rationalized by the absence in the reaction system of a hydroxy-containing solvent capable of adding at the carbonyl groups of diketone **Ic** and hampering participation of the aldehyde component. The formation of compounds **IVi** and **IVj** was reported previously in the reaction of hexafluoroacetylacetone (**Ic**) with benzaldehyde and urea in the system THF–TsOH; however, their yield did not exceed 20–30%.

Thus we have developed a convenient procedure for the synthesis of 6-aryl(hetaryl)-4-fluoroalkyl-4-hydroxytetrahydropyrimidin-2(1*H*)-ones(thiones) via three-component condensation of fluorinated β-dicarbonyl compounds with aromatic (heteroaromatic) aldehydes and urea (thiourea) in the presence of 1-butyl-3-methylimidazolium tetrafluoroborate. The procedure is simple; it requires no organic solvent and ensures high yields of the target products which attract interest as starting compounds for the preparation of biologically active fluorine-containing pyrimidine derivatives.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker WM-250 instrument at 250.3 MHz. The elemental compositions were determined on a Perkin–Elmer 2400 analyzer. 1-Butyl-3-methylimidazolium tetrafluoroborate was synthesized according to the procedure described in [8].

Condensation of β-dicarbonyl compounds with aromatic (heteroaromatic) aldehydes and urea (thiourea) (*general procedure*). A mixture of 3.0 mmol of fluorinated β-dicarbonyl compounds **Ia**–**Ic**, 3.0 mmol of aldehyde **IIa**–**IIc**, 3.0 mmol of urea (**IIIa**) or thiourea (**IIIb**), and 0.018 mmol of 1-butyl-3-methylimidazolium tetrafluoroborate was heated until the reaction was complete (according to the TLC data). The crystalline product was washed in succession with hot water (2 × 4 ml) and petroleum ether (2 × 4 ml) and was recrystallized from isopropyl alcohol–water (4 : 1) or carbon tetrachloride–chloroform (2 : 1).

Ethyl 4-hydroxy-2-oxo-6-phenyl-4-trifluoromethylhexahydropyrimidine-5-carboxylate (IVa). The reactants were heated for 6 h at 100–125°C. Yield 78%, mp 165–167°C; published data [7]: yield 70% (EtOH–HCl), 80% (THF–polyphosphoric acid); mp 162°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.44 s (1H, NH), 7.32 m (5H, C_6H_5), 7.26 s (1H, OH), 7.17 s (1H, NH), 4.79 d (1H, 6-H, J = 11.5 Hz), 3.80 q (2H, CH_2, J = 7.5 Hz), 2.92 d (1H, **5**-H, J = 11.5 Hz), 0.87 t (3H, CH_3, J = 7.5 Hz). Found, %: C 50.83; H 4.71; N 8.28. $C_{14}H_{15}F_3N_2O_4$. Calculated, %: C 50.61; H 4.55; N 8.43.

Compounds **IVb** and **IVc** were synthesized under analogous conditions.

Ethyl 4-hydroxy-6-phenyl-2-thioxo-4-trifluoromethylhexahydropyrimidine-5-carboxylate (IVb). Yield 85%, mp 188–189°C; published data [3]: yield 43% (EtOH–HCl), mp 190–191°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.40–7.48 m (3H, C_6H_5), 7.32–7.40 m (2H, C_6H_5), 7.00 s (1H, NH), 6.88 s (1H, NH), 5.65 s (1H, OH), 4.85 d (1H, 6-H, J = 11.8 Hz), 3.92 q (2H, CH_2, J = 7.1 Hz), 3.18 d (1H, 5-H, J = 11.8 Hz), 0.85 t (3H, CH_3, J = 7.1 Hz). Found, %: C 48.42; H 4.49; N 7.89; S 9.07. $C_{14}H_{15}F_3N_2O_3S$. Calculated, %: C 48.27; H 4.34; N 8.04; S 9.21.

Ethyl 6-(4-fluorophenyl)-4-hydroxy-2-thioxo-4-trifluoromethylhexahydropyrimidine-5-carboxylate (IVc). Yield 77%, mp 212–214.5°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 8.97 s (1H, NH), 8.27 s (1H, NH), 7.74 s (1H, OH), 7.38 d.d (2H, C_6H_4F, J_{HH} = 8.5, J_{HF} = 6.5 Hz), 7.10 t (2H, C_6H_4F, J_{HH} = 8.5, J_{HF} = 6.5 Hz), 4.83 d (1H, 6-H, J = 11.6 Hz), 3.86 q (2H, CH_2, J = 7.2 Hz), 3.00 d (1H, 5-H, J = 11.6 Hz), 0.95 t (3H, CH_3, J = 7.2 Hz). Found, %: C 46.00; H 3.77; N 7.58; S 8.69. $C_{14}H_{14}F_4N_2O_3S$. Calculated, %: C 45.90; H 3.85; N 7.65; S 8.75.

5-Benzoyl-4-hydroxy-6-phenyl-4-(1,1,2,2-tetrafluoroethyl)hexahydropyrimidin-2-one (IVd). The reactants were heated for 1–2 h at 80–100°C. Yield 62%, mp 222–224°C; published data [3]: yield 38% (EtOH–HCl), mp 233–234°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.52 d (2H, *o*-H, J = 7.5 Hz), 7.41 t (1H, *p*-H, J = 7.5 Hz), 7.03–7.32 m (8H, C_6H_5, OH), 7.05 s (1H, NH), 6.74 s (1H, NH), 6.60 t.t (1H, CF_2H, $^2J_{HF}$ = 51.0, $^3J_{HF}$ = 5.9 Hz), 4.94 d (1H, 6-H, J = 11.0 Hz), 4.26 d (1H, 5-H, J = 11.4 Hz). Found, %: C 57.65; H 4.00; N 7.12. $C_{19}H_{16}F_4N_2O_3$. Calculated, %: C 57.58; H 4.07; N 7.07.

Compounds **IVe**–**IVh** were synthesized under similar conditions.

5-Benzoyl-4-hydroxy-6-phenyl-4-(1,1,2,2-tetrafluoroethyl)hexahydropyrimidine-2-thione (IVe). Yield 66%, mp 232–233°C; published data [3]: yield 36% (EtOH–HCl), mp 233–234°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 9.08 s (1H, NH), 8.04 s (1H, NH), 7.55 d (2H, *o*-H, J = 7.2 Hz), 7.00–7.43 m (9H, C_6H_5, OH), 6.70 t.t (1H, CHF_2, $^2J_{HF}$ = 51.0, $^3J_{HF}$ = 5.9 Hz), 4.98 d (1H, 6-H, J = 11.3 Hz), 4.35 d (1H, 5-H, J = 11.3 Hz). Found, %: C 55.58; H 4.04; F 18.29; N 6.86. $C_{19}H_{16}F_4N_2O_2S$. Calculated, %: C 55.34; H 3.91; F 18.43; N 6.79.

5-Benzoyl-6-(4-fluorophenyl)-4-hydroxy-4-(1,1,2,2-tetrafluoroethyl)hexahydropyrimidin-2-one (IVf). Yield 92%, mp 185.5–187°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.58 d (2H, *o*-H, J = 8.0 Hz), 7.43 t (1H, *p*-H, J = 8.0 Hz), 7.25–7.40 m (5H, C_6H_5, C_6H_4, NH), 7.08 s (1H, OH), 6.85 t (2H, 4-FC_6H_4, J_{HH} = 8.5, J_{HF} = 8.5 Hz), 6.77 s (1H, NH), 6.60 t.t (1H, CHF_2, $^2J_{HF}$ = 52.0, $^3J_{HF}$ = 6.5 Hz), 4.96 d (1H, 6-H, J = 10.8 Hz), 4.30 d (1H, 5-H, J = 10.8 Hz). Found, %: C 55.00; H 3.76; N 6.84. $C_{19}H_{15}F_5N_2O_3$. Calculated, %: C 55.08; H 3.65; N 6.76.

5-Benzoyl-6-(4-fluorophenyl)-4-hydroxy-4-(1,1,2,2-tetrafluoroethyl)hexahydropyrimidine-2-thione (IVg). Yield 84%, mp 195–197°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 9.08 s (1H, NH), 7.97 s (1H, NH), 7.59 d (2H, *o*-H, J = 8.5 Hz), 7.26–7.47 m (6H, C_6H_5, 4-FC_6H_4, OH), 6.84–6.94 t (2H, 4-FC_6H_4,), 6.66 t.t (1H, CF_2H, $^2J_{HF}$ = 52.0, $^3J_{HF}$ = 6.3 Hz), 5.00 d

(1H, 6-H, J = 11.4 Hz), 4.39 d (1H, 5-H, J = 11.4 Hz). Found, %: C 53.15; H 3.45; N 6.59; S 7.38. $C_{19}H_{15}F_5N_2O_2S$. Calculated, %: C 53.02; H 3.51; N 6.51; S 7.45.

5-Benzoyl-4-hydroxy-4-(1,1,2,2-tetrafluoroethyl)-6-(thiophen-2-yl)hexahydropyrimidin-2-one (IVh). Yield 34%, mp 202–203.5°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.62 d (2H, *o*-H, J = 8.0 Hz), 7.48 t (1H, *o*-H, J = 8.0 Hz), 7.30–7.40 m (3H, *m*-H, NH), 7.15 d (1H, C_4H_3S, J = 4.6 Hz), 7.10 s (1H, NH), 6.82–6.89 m (2H, C_4H_3S), 6.69 s (1H, OH), 6.58 t.t (1H, CF_2H, $^2J_{HF}$ = 51.0, $^3J_{HF}$ = 6.0 Hz), 5.30 d (1H, 6-H, J = 11.1 Hz), 4.25 d (1H, 5-H, J = 11.1 Hz). Found, %: C 50.68; H 3.45; N 7.12; S 7.89. $C_{17}H_{14}F_4N_2O_3S$. Calculated, %: C 50.75; H 3.51; N 6.96; S 7.97.

4-Hydroxy-6-phenyl-5-(2,2,2-trifluoroacetyl)-4-trifluoromethylhexahydropyrimidin-2-one (IVi). The reactants were kept for 30 min at 20–30°C. Yield 75%, mp 197–199°C; published data [3]: yield 30% (THF–TsOH), mp 200–201°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 8.05 s (1H, NH), 7.90 s (1H, NH), 7.45 s (1H, OH), 7.30 m (5H, C_6H_5), 4.90 d (1H, 6-H, J = 11.2 Hz), 3.75 d (1H, 5-H, J = 11.2 Hz). Found, %: C 44.02; H 2.95; F 31.83; N 7.70. $C_{13}H_{10}F_6N_2O_3$. Calculated, %: C 43.83; H 2.83; F 32.00; N 7.86.

Compounds **IVj**–**VIm** were synthesized under analogous conditions.

4-Hydroxy-6-phenyl-5-(2,2,2-trifluoroacetyl)-4-trifluoromethylhexahydropyrimidine-2-thione (IVj). Yield 88%, mp 210–212°C; published data [3]: yield 20% (EtOH–HCl), mp 215–216°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 9.11 s (1H, NH), 8.98 s (1H, NH), 8.26 s (1H, OH), 7.33 m (5H, C_6H_5), 4.90 d (1H, 6-H, J = 11.3 Hz), 3.75 d (1H, 5-H, J = 11.3 Hz). Found, %: C 42.10; H 2.79; F 30.46; N 7.44. $C_{13}H_{10}F_6N_2O_2S$. Calculated, %: C 41.94; H 2.71; F 30.62; N 7.52.

4-Hydroxy-6-(thiophen-2-yl)-5-(2,2,2-trifluoroacetyl)-4-trifluoromethylhexahydropyrimidin-2-one (IVk). Yield 92%, mp 150–152°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.89 s (1H, NH), 7.85 s (1H, NH), 7.50 s (1H, OH), 7.40 d (1H, C_4H_3S, J = 4.6 Hz), 6.94 m (2H, C_4H_3S), 5.25 d (1H, 6-H, J = 11.1 Hz), 3.68 d (1H, 5-H, J = 11.1 Hz). Found, %: C 36.60; H 2.34; N 7.50; S 8.78. $C_{11}H_8F_6N_2O_3S$. Calculated, %: C 36.47; H 2.23; N 7.73; S 8.85.

6-(4-Fluorophenyl)-4-hydroxy-5-(2,2,2-trifluoroacetyl)-4-trifluoromethylhexahydropyrimidin-2-one (IVl). Yield 83%, mp 153–155°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.81 s (2H, NH), 7.37 d.d (2H, C_6H_4, J_{HH} = 8.5, J_{HF} = 7.2 Hz), 7.33 s (1H, OH), 7.08 d.d (2H, C_6H_4, J_{HH} = 8.5, J_{HF} = 7.2 Hz), 4.92 d (1H, 6-H, J = 11.2 Hz), 3.72 d (1H, 5-H, J = 11.2 Hz). Found, %: C 41.65; H 2.34; N 7.20. $C_{13}H_9F_7N_2O_3$ Calculated, %: C 41.72; H 2.42; N 7.49.

6-(4-Fluorophenyl)-4-hydroxy-5-(2,2,2-trifluoroacetyl)-4-trifluoromethylhexahydropyrimidine-2-thione (IVm). Yield 82%, mp 173–175°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 9.17 s (1H, NH), 9.00 s (1H, NH), 8.25 s (1H, OH), 7.80 t (2H, C_6H_4, J_{HH} = 8.5, J_{HF} = 8.5 Hz), 7.36 m (2H, C_6H_4), 4.92 d (1H, 6-H, J = 11.5 Hz), 3.82 d (1H, 5-H, J = 11.5 Hz). Found, %: C 39.87; H 2.25; N 7.08; S 8.45. $C_{13}H_9F_7N_2O_2S$. Calculated, %: C 40.01; H 2.32; N 7.18; S 8.22.

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