Synthesis of a series of perfluoroalkyl containing spiro cyclic barbituric acid derivatives

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An efficient and versatile method for the preparation of a series of perfluoroalkyl containing spiro cyclic barbituric acid derivatives is described. 7,9-Dimethyl-2-(iodomethyl)-3-(perfluoroalkylmethyl) 7,9-diazaspiro[4.5]decane-6,8,10-trione were prepared in good yields from 1,3-dimethylbarbituric acid. The structures of these compounds were confirmed by ^{1}H NMR, ^{13}C NMR, IR, MS spectra and elemental analysis.

Keywords: barbituric acid derivatives, perfluoroalkyl group, spiro cyclic compounds

Barbituric acid derivatives are sedative drugs, acting as central nervous system (CNS) depressants.[1] Recently, barbituric acid derivatives are found totally new biomedicinal applications in the fields such as cancer and AIDS therapy,[2] and matrix metalloproteinase inhibitors.[3] On the other hand, selective introduction of fluorine atom and fluoroalkyl groups into those heterocyclic compounds, which may have potential biological activities, can either enhance their pharmacological properties or increase their therapeutic efficiency.[4]

The spiro functionality has long been known to be present in phytochemicals either in alkaloids, lactones or terpenoids. Spiroketals are reported to be sub-units of many naturally occurring substances of biological interest such as insect pheromones, antecedents and polyether antibiotics. Spiro compounds represent an important class of naturally occurring substances characterised by their highly pronounced biological properties.[5,6]

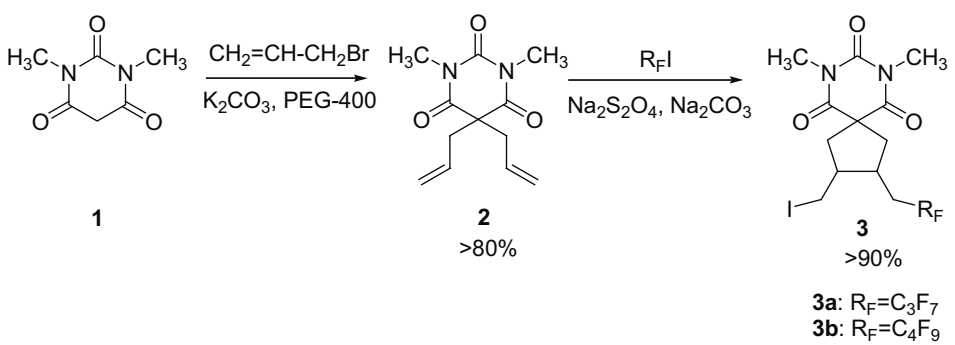
A facile synthesis of a series of long chain perfluoroalkyl-containing spiro barbituric acid derivatives from 1,3-dimethyl barbituric acid is reported; these perfluoroalkyl-containing spiro compounds could be useful.

Results and discussion

The first report of a fluorinated barbituric acid was by Huber and Bruce in 1953 who developed an approach to 5-fluoropropyl and 5-fluoropentyl derivatives.[7] Other structurally related 5-ethyl-5-fluoroalkyl barbituric acids have since been prepared following an analogous strategy from the starting material. But this kind of synthesis of fluorinated barbituric acid derivatives was restricted by their low yield and the harsh conditions, which limited its commercial use. This paper describes an efficient and versatile method for the preparation of a series of perfluoroalkyl containging spiro cyclic barbituric acid derivatives. As depicted in Scheme 1, 1,3-dimethylpyrimidine-2,4,6(*1H,3H,5H*)-trione **1** reacted with allyl bromide in the presence K_2CO_3 and PEG-400 in chloroform to get 5,5-diallyl-1,3-dimethylpyrimidine-2,4,6(*1H,3H,5H*)-trione **2**. The reaction of compound **2** with perfluoroalkyl iodides was carried out in a heterogeneous system consisting of water and acetonitrile (1:8, volume ratio) as solvent, using sodium dithionite as initiator to start the free radical reactions to afford spiro cyclic compounds **3a–b**.

The key material 5,5-diallyl-1,3-dimethylpyrimidine-2,4,6(*1H,3H,5H*)-trione **2** was obtained when the two hydrogen of methylene were substituted by two allyl groups. In this process, an excess of fresh distilled allyl bromide was used, K_2CO_3 was dried at 115 °C for 2 h, and the use of it was a bit more than the stoichiometric amount (2.01 equiv.); KOH also could be used, and the yield was almost the same. PEG-400 was used as phase transfer catalyst, and the stoichiometric amount was (2 equiv.); when the catalytic amount (0.015 equiv.) of PEG-400 served as phase transfer catalyst, the yield was slightly decreased. Benzyltriethylammonium chloride could be used as phase transfer catalyst, but it was difficult to remove.

The formation of **3** from **2** was a free radical reaction, which was assumed to be as shown in Scheme 2. R_F· generated from perfluoroalkyl iodide in the presence of sodium dithionite reacted with the carbon–carbon double bond to form spirocyclic compounds. Sodium dithionite was used as the initiator and sodium carbonate was used to slow down the decomposition rate of sodium dithionite. The molar ratio of sodium dithionite and sodium carbonate was 1 :1. The mixture



Scheme 1

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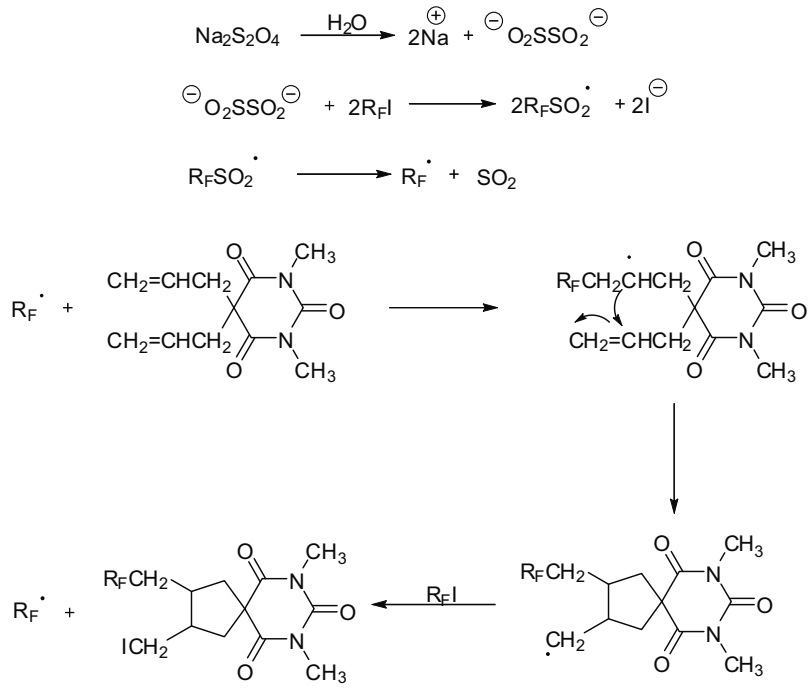


Scheme 2

of acetonitrile and water (8 : 1) was used as a solvent, different volume ratios 10 : 1, 9 : 1, 7 : 1 were also tested, but the yield was lower than the ratio of 8 : 1. A mixture of dichloromethane and water was also used, but the reaction did not occur.

Conclusion

In summary, we have synthesised polyfunctional organo-fluoro heterocyclic compounds in two steps from 1,3-dimethylbarbituric acid. This method is simple, efficient and versatile with good to excellent yields and the reaction conditions are mild. It can be used to synthesise a series of fluorinated spiro cyclic compounds.

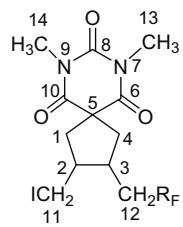
Experimental

Melting and boiling points were uncorrected. Solvents were distilled prior to use. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded at Bruker AV 500 MHz spectrometer. ^{1}H NMR and ^{13}C NMR data are given in parts per million (ppm) downfield from tetramethylsilane (TMS) as an internal standard; ^{19}F NMR data are given in ppm upfield from $CFCl_3$ (an external standard). Observation frequency: ^{1}H NMR 500.130 MHz, spectrum width 10330.578 Hz; ^{13}C NMR 125.757 MHz, spectrum width 30030.029 Hz, ^{19}F NMR 470.54 MHz, spectrum width 100000 Hz. The abbreviations used are: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Coupling constants (*J* values) are given in Hz. MS analyses were performed using an HP 5989A mass spectrometer (EI at 70 ev); IR analyses were performed using an Avatar 370 IR spectrometer; Elemental analyses were performed using a vario EL III element analyser.

Synthesis of 1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (**1**): Malonic acid (4 g, 38 mmol) was added to 20 mL acetic acid, when it was completely dissolved, acetic anhydride (7 mL, 74 mmol) was added dropwise. The mixture was heated for 13 h at 70 °C then refluxed for 1 h. After removing most of the solvent, distilled water (15 mL) was added and the mixture was extracted with ethyl acetate. Most solvent was removed and the residue was then put into the freezer overnight. The crude product was recrystallised from ethyl acetate. A white needle crystal **1** was precipitated out for further reaction. Yield: 57%; m.p. 121.3–123.1 (lit.,[9] 121–122 °C); ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ(ppm): 3.28 (s, 6H, 2 × CH_3), 4.08 (s, 2H, CH_2).

Synthesis of 5,5-diallyl-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (**2**):[10] 1,3-Dimethyl barbituric acid (1.12 g, 7 mmol), K_2CO_3 (2 g, 14.5 mmol), chloroform (10 mL) was added to PEG-400 (5.71 g, 14.2 mmol). Allyl bromide (1.5 mL, 17.4 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 1 h, and then stirred at r.t. for 24 h. After removing most of the solvent, distilled water (30 mL) was added and extracted three times with ethyl acetate. After removing most of the solvent, a lot of white solid appeared, the crude product was washed many times with a large amount of water, a white powder solid **2** was obtained. Yield: 85%; m.p. 50.4–51.0 °C (lit.,[10]: 58–59 °C); **IR** (KBr) (cm^{-1}): 3081 ($\nu_{=CH}$), 2964 (ν_{C-H}), 2926 (ν_{C-H}), 1745 ($\nu_{C=O}$), 1675 ($\nu_{C=O}$), 1643 ($\nu_{=C}$), 1086 (ν_{C-N}), 1036 (ν_{C-N}), 936 (δ_{C-H}); ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ(ppm): 2.72 (d, 4H, CH_2, ^3J = 7.5 Hz), 3.28 (d, 6H, 2 × CH_3), 5.05–5.13 (m, 4H, =CH_2), 5.47–5.55 (m, 2H, =CH); ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ(ppm): 29.3, 43.7, 57.2, 120.6, 130.8, 151.1, 170.8.

Synthesis of perfluoroalkyl-containing spiro compounds (**3a**) *and* (**3b**): The mixture of 8 mL acetonitrile and 1 mL water was used as a solvent, $CF_3CF_2CF_2I$ (0.17 mL, 1 mmol) and 5,5-diallyl-1,3-dimethylpyrimidine-2,4,6(*1H,3H,5H*)-trione (0.224 g, 0.95 mmol) was reacted in the presence of sodium dithionite (0.21 g, 1.2 mmol) and sodium carbonate (0.13 g, 1.2 mmol) performing as initiators (sodium carbonate was used to slow down the decomposition rate of sodium dithionite), the mixture was stirred in the ice water for 4 h. The reaction was quenched by adding distilled water and extracted with ethyl acetate. After the solvent was completely removed, a light green glassy state substance was obtained.



3a: R_F=$^{15}CF_2{}^{16}CF_2{}^{17}CF_3$
3b: R_F=$^{15}CF_2{}^{16}CF_2{}^{17}CF_2{}^{18}CF_3$

$C_{15}H_{16}F_7IN_2O_3$ (**3a**): 7,9-Dimethyl-3-(2,2,3,3,4,4,4-heptafluorobutyl)-2-(iodomethyl) 7,9-diazaspiro[4.5]decane-6,8,10-trione IR (KBr): 2960 (ν_{C-H}), 1748 ($\nu_{C=O}$), 1681 ($\nu_{C=O}$), 1225 (ν_{C-F}), 1044 (ν_{C-N}), 536 (ν_{C-I}); ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ(ppm): 2.30–2.36 (m, 2H, H-1), 2.84–2.95 (m, 1H, H-2), 2.84–2.95 (m, 1H, H-3), 2.40–2.50 (m, 2H, H-4), 3.24 (q, 1H, H-11, ^2J = 10 Hz, ^3J = 5 Hz), 3.39 (t, 1H, H-11, ^2J = 10 Hz, ^3J = 5 Hz), 2.23–2.30 (m, 2H, H-12), 3.21 (s, 3H, H-13), 3.22 (s, 3H, H-14); ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ(ppm): 42.3 (s, C-1), 36.7 (s, C-2), 46.8 (s, C-3), 43.6 (s, C-4), 55.1

(s, C-5), 172.7 (s, C-6), 151.0 (s, C-8), 172.8 (s, C-10), 5.3 (s, C-11), 29.1 (t, C-12, ^2J = 21.25Hz), 29.2 (s, C-13), 29.1 (s, C-14), 117.8 (t-t, C-15, $^1J_{F\text{-}C}$ = 253.125 Hz, $^2J_{F\text{-}C}$ = 29.875 Hz), 108.5 (t-h, C-16, $^1J_{F\text{-}C}$ = 260.87 Hz, $^2J_{F\text{-}C}$ = 37.15 Hz), 117.9 (q-t, C-17, $^1J_{F\text{-}C}$ = 287.375 Hz, $^2J_{F\text{-}C}$ = 32.25 Hz; ^{19}F NMR (470.54 MHz, $CFCl_3$) δ(ppm): –114.36 (t-t-q, 2F, F-13, $^2J_{F\text{-}F}$ = 276.65 Hz, $^3J_{F\text{-}F}$ = 12.29 Hz, $^3J_{H\text{-}F}$ = 11.86 Hz), –127.69 (t-q, 2F, F-14, $^3J_{F\text{-}F}$ = 9.4 Hz, $^3J_{F\text{-}F}$ = 14.1 Hz), –80.35 (m, 3F, F-15, $^3J_{F\text{-}F}$ = 10.15 Hz, $^4J_{F\text{-}F}$ = 22.40 Hz); EI-MS, 70eV, *m/z*(rel, int.): 58 $[C_2H_4NO]^+$(23), 84 $[C_3H_4N_2O]^+$(88), 86 $[C_3H_6N_2O]^+$(57), 112 $[C_3H_4O_2N_2]^+$(16), 127 $[I]^+$(4), 143 $[C_5H_7N_2O_3]^+$(14), 263 $[C_{10}H_{10}F_7]^+$(20), 387 $[M\text{-}I\text{-}H_2O]^+$(17), 405 $[M\text{-}I]^+$(100); Anal. Calcd for $C_{15}H_{16}F_7IN_2O_3$: C, 33.85; H, 3.03; N, 5.26. Found: C, 33.90; H, 3.05; N, 5.35%.

$C_{16}H_{16}F_9IN_2O_3$ (**3b**): 7,9-Dimethyl-2-(iodomethyl)-3-(2,2,3,3,4,4,5,5,5-nonafluoropentyl) 7,9-diazaspiro[4.5]decane-6,8,10-trione IR (KBr): 2959($\nu_{C\text{-}H}$), 1749 ($\nu_{C=O}$), 1678($\nu_{C=O}$), 1223($\nu_{C\text{-}F}$), 1041 ($\nu_{C\text{-}N}$), 1022($\nu_{C\text{-}N}$), 531 ($\nu_{C\text{-}I}$); ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ(ppm): 2.23–2.28 (m, 2H, H-1), 2.76–2.87 (m, 1H, H-2), 2.76–2.87 (m, 1H, H-3), 2.32–2.43 (m, 2H, H-4), 3.18 (q, 1H, H-11, ^2J = 10 Hz, ^3J = 5.5 Hz), 3.33 (t, 1H, H-11), 2.18–2.23 (m, 2H, H-12), 3.21 (s, 3H, H-13), 3.22 (s, 3H, H-14); ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ(ppm): 42.2 (s, C-1), 36.6 (s, C-2), 46.7 (s, C-3), 43.5 (s, C-4), 55.1(s, C-5), 172.6 (s, C-6), 150.9 (s, C-8), 172.8 (s, C-10), 5.4 (s, C-11), 29.0 (t, C-12, ^2J = 21.67 Hz), 29.1 (s, C-13), 28.9 (s, C-14), 118.3 (t-t, C-15, $^1J_{F\text{-}C}$ = 286.13 Hz, $^2J_{F\text{-}C}$ = 33.13 Hz), 110.3 (t-p, C-16, $^1J_{F\text{-}C}$ = 263.75 Hz, $^2J_{F\text{-}C}$ = 32.00 Hz), 108.8 (t-h, C-17, $^1J_{F\text{-}C}$ = 227.73 Hz, $^2J_{F\text{-}C}$ = 33.00 Hz), 117.2(q-t, C-18, $^1J_{F\text{-}C}$ = 254.00 Hz, $^2J_{F\text{-}C}$ = 31.25 Hz); ^{19}F NMR (470.54 MHz, $CFCl_3$) δ(ppm): –113.72 (t-t-q, 2F, F-13, $^2J_{F\text{-}F}$ = 274.02 Hz, $^3J_{F\text{-}F}$ = 12.99 Hz, $^3J_{H\text{-}F}$ = 11.52 Hz), –126.15 (t-t, 2F, F-14, $^3J_{F\text{-}F}$ = 9.4 Hz, $^3J_{F\text{-}F}$ = 14.2 Hz), –124.57 (t-q, 2F, F-15, $^3J_{F\text{-}F}$ = 4.70 Hz, $^3J_{F\text{-}F}$ = 9.40 Hz), –81.32 (t, 3F, F-16, $^3J_{F\text{-}F}$ = 8.75 Hz); EI-MS, 70ev, *m/z*(rel.int.): 58 $[C_2H_4NO]^+$(42), 84 $[C_3H_4N_2O]^+$(88), 86 $[C_3H_6N_2O]^+$(57), 112 $[C_4H_4O_2N_2]^+$(12), 127 $[I]^+$(4), 143 $[C_5H_7N_2O_3]^+$(13), 313 $[C_{11}H_{10}F_9]^+$(20), 437 $[M\text{-}I\text{-}H_2O]^+$(18), 455 $[M\text{-}I]^+$(100); Anal. Calcd for $C_{16}H_{16}F_9IN_2O_3$: C, 33.01; H, 2.77; N, 4.81. Found: C, 33.05; H, 2.85; N, 4.50%.

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