One-step hetarylation of steroids: regioselective synthesis of new estrone derivatives

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New estrone derivatives containing 1,2,4-triazin-5-one moieties were synthesised through direct C–C coupling of estrone 3-methyl ether with 1,2,4-triazinones.

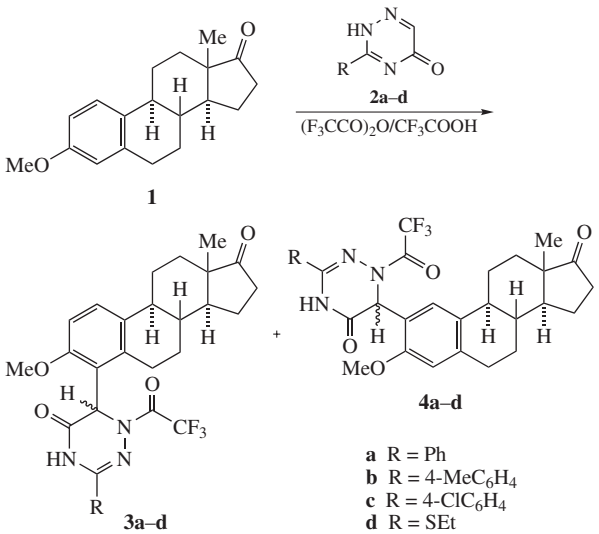
Steroids are a biologically important class of compounds, which are of importance for pharmaceutical industry.[1] Estrone, one of the three naturally occurring estrogens, is of interest for the treatment and prevention of prostate[2] and breast cancer.[3–5] Modification of the estrone structure, especially in A and D rings, can bring about remarkable changes in the pharmacological activity of estrone.[6] For example, functionalization of A ring by pharmacophore fragments results in potential steroid sulfatase inhibition.[7]

Earlier, we succeeded in the functionalization of 1,2,4-triazines by π-excess carbo- and heterocycles such as phenols, crown ethers, calixpyrroles, calixarenes and resorcinarenes using a nucleophilic attack on an unsubstituted carbon atom in azines (A_N- and S_N^H-processes).[8] Here we propose to modify estrone 3-methyl ether by heterocyclic moieties through direct one-step C–C coupling.

Despite of the presence of aza groups in the molecule of 3-substituted-1,2,4-triazin-5-ones, they usually do not react with aromatic C-nucleophiles. We found that the interaction of 1,2,4-triazin-5(2*H*)-ones with aromatic C-nucleophiles in a mixture of trifluoroacetic acid and a carboxylic acid anhydride results in the formation of stable products of nucleophilic addition to the unsubstituted C(6) atom of the 1,2,4-triazine ring.[9] This reaction is accompanied by acylation of the nitrogen atom adjacent to the reaction centre. The synthesis of hetaryl-containing estrone derivatives was achieved in a similar fashion.

Thus, using the general procedure for the reaction of 1,2,4-triazin-5(2*H*)-ones with aromatic C-nucleophiles, the coupling of estrone derivatives with 3-substituted-1,2,4-triazin-5-ones **2a–d** results in the formation of a difficult-to-separate mixture of the stable regioisomeric products **3a–d**, **4a–d** of nucleophilic addition to the unsubstituted C(6) atom of the triazine ring (Scheme 1).†

The formation of such a mixture can be avoided by using previously synthesised 2-acetyl-1,2,4-triazinones **5**‡ as starting compounds. The trifluoroacetic acid-promoted reaction between **1** and **5a**,**b**,**e** in refluxing chloroform afforded stable adducts. In this case, we succeeded to carry out a regioselective reaction.



Scheme 1

Only diastereomeric compounds **6a**,**b**,**e** and **7a**,**b**,**e** were synthesised in a ratio of 1:1 (Scheme 2).§

It has been shown by flash chromatography of filtrate that there are no other by-products in an Et_2O solution. It is possible

† Flash chromatography was performed on Lancaster silica gel (230–400 mesl). All melting points are uncorrected and have been obtained on a Boetius melting point apparatus. Elemental analyses were performed on a Perkin Elmer 2400 CHN analyzer. The ^{1}H NMR spectra were recorded on a Bruker DRX 400 (400 MHz) spectrometer with TMS as an internal standard. The ^{19}F NMR spectra were recorded on a Tesla (80 MHz) spectrometer with hexafluorobenzene as an internal standard. All signals are given in ppm.

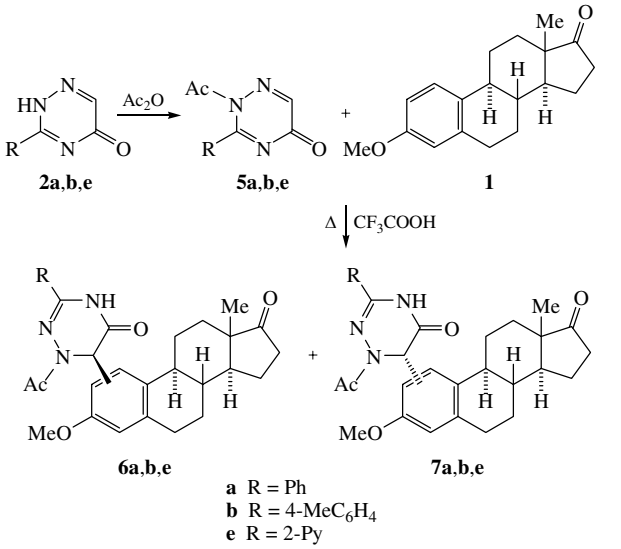
General procedure for preparation of 3-substituted 2-(1-trifluoroacetyl-5-oxo-1,4,5,6-tetrahydro-1,2,4-triazin-6-yl)-3-methoxy-D-hydroxymethylestra-1,3,5(10)-trien-17-one **3**, **4**. A suspension of 3-substituted-1,2,4-triazin-5(2*H*)-one (0.25 mmol) and 3-methoxy-D-hydroxymethylestra-1,3,5(10)-trien-17-one (0.25 mmol) in a mixture of TFA (2 ml) and trifluoroacetic anhydride (1 ml) was stirred at 20 °C until reagents were completely dissolved. The reaction mixture was evaporated to dryness. The residue was mashed with diethyl ether. The obtained precipitate was filtered off and recrystallised from methanol.

2-(1-Trifluoroacetyl-5-oxo-3-phenyl-1,4,5,6-tetrahydro-1,2,4-triazin-6-yl)-3-methoxy-D-hydroxymethylestra-1,3,5(10)-trien-17-one **3a**, **4a**: yield 75%, mp 240–242 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 0.92, 0.96 (br. s, 3H, Me), 1.31–1.40, 1.65–2.07, 2.59–2.64 (m, 12H, CH_2), 3.38–3.40 (m, 3H, CH), 3.50, 3.51, 3.57, 3.59 (s, 3H, OMe), 5.85, 5.88 (set of singlets, 1H, $C^{triaz}_{sp^3}H$), 6.17 (d, *J* 2.8 Hz), 6.69 (d, *J* 2.8 Hz), 6.82 (d, *J* 8 Hz), 6.83 (d, *J* 8 Hz), 7.11–7.16 (set of signals, 2H, Ar), 7.54–7.56 (m, 3H, Ph), 7.89–7.91 (m, 2H, Ph), 11.56, 11.58, 11.65, 11.67 [s, 1H, N(4)H]. ^{19}F NMR ([$^2H_6$]DMSO) δ: 93.80, 93.71, 93.66, 93.60. MS, *m/z* (FD/EI, 220 °C): 553 (M^+, 40), 456 (41), 283 (100), 270 (30), 187 (20.5), 97 (29). Found (%): C, 64.79; H, 5.26; N, 7.20. Calc. for $C_{30}H_{30}N_3O_4F_3$ (%): C, 65.09; H, 5.46; N, 7.59.

*2-(1-Trifluoroacetyl-5-oxo-3-*p*-tolyl-1,4,5,6-tetrahydro-1,2,4-triazin-6-yl)-3-methoxy-D-hydroxymethylestra-1,3,5(10)-trien-17-one* **3b**, **4b**: yield 87%, mp 284–286 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 0.91, 0.96 (br. s, 3H, Me), 1.61–2.14 (set of m, 12H, CH_2), 2.38 (br. s, 3H, Me), 2.54–2.67 (m, 3H, CH), 3.49, 3.50, 3.56, 3.58 (s, 3H, OMe), 5.84, 5.87 (set of singlets, 2H, $C^{triaz}_{sp^3}H$), 6.16, 6.68 (d, *J* 3.2 Hz), 6.82 (d, *J* 8 Hz), 6.83 (d, *J* 8 Hz), 7.13–7.16 (2H, Ar), 7.34, 7.33, 7.80, 7.78 (set of d, 4H, Tol, *J* 8.6 Hz), 11.49, 11.52, 11.59, 11.61 [s, 1H, N(4)H]. Found (%): C, 65.58; H, 5.70; N, 7.33. Calc. for $C_{31}H_{32}N_3O_4F_3$ (%): C, 65.61; H, 5.65; N, 7.41.

2-[1-Trifluoroacetyl-3-(4-chlorophenyl)-5-oxo-1,4,5,6-tetrahydro-1,2,4-triazin-6-yl]-3-methoxy-D-estra-1,3,5(10)-trien-17-one **3c**, **4c**: yield 52%, mp 244–246 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 0.93, 0.99 (br. s, 6H, Me), 1.27–1.33, 1.71–2.43, 2.68–2.72 (m, 12H, CH_2), 3.35–3.39 (m, 3H, CH), 3.54, 3.59 (br. s, 3H, OMe), 5.14 (br. s, 1H, $C^{triaz}_{sp^3}H$), 5.78 (d, *J* 2.8 Hz), 6.06 (br. s), 6.62–6.82 (m), 7.07–7.13 (m, 2H, Ar), 7.50 (d, *J* 8.5 Hz), 7.94 (d, 4H, ClC_6H_4, *J* 8.5 Hz), 11.53, 11.63 [br. s, 1H, N(4)H]. ^{19}F NMR ([$^2H_6$]DMSO) δ: 92.94, 92.95, 93.05, 93.08. MS, *m/z* (FD/EI, 220 °C): 588 (M^+, 11), 587 (32), 490 (32), 283 (100), 187 (28), 97 (34). Found (%): C, 61.23; H, 4.44; N, 7.14. Calc. for $C_{30}H_{29}N_3O_4F_3Cl$ (%): C, 61.28; H, 4.97; N, 7.15.

2-(1-Trifluoroacetyl-3-ethylthio-5-oxy-1,4,5,6-tetrahydro-1,2,4-triazin-6-yl)-3-methoxy-D-estra-1,3,5(10)-trien-17-one **3d**, **4d**: yield 61%, mp 232–234 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 0.93, 0.98 (br. s, 3H, Me), 1.38 (t, 3H, SCH_2Me), 2.47 (q, 2H, SCH_2Me), 1.27–1.47, 1.89–2.28, 2.77–2.98 (m, 12H, CH_2), 3.16–3.17 (m, 3H, CH), 3.70, 3.73 (br. s, 3H, OMe), 5.68 (br. s, 1H, $C^{triaz}_{sp^3}H$), 5.73 (br. s), 5.96 (br. s), 6.63–6.84 (m), 7.05–7.16 (m, 2H, Ar), 11.49 [br. s, 1H, N(4)H]. ^{19}F NMR ([$^2H_6$]DMSO) δ: 92.68, 92.63, 92.56, 92.54. MS, *m/z* (FD/EI, 190 °C): 537 (M^+, 25), 440 (18), 283 (100), 187 (31), 97 (38). Found (%): C, 57.87; H, 5.93; N, 7.64. Calc. for $C_{26}H_{30}N_3O_4F_3S$ (%): C, 58.09; H, 5.62; N, 7.82.



Scheme 2

‡ *General procedure for preparation of 3-substituted 2-acyl-1,2,4-triazin-5-ones* **5a**,**b**,**e**. A 3-substituted 1,2,4-triazin-5(2*H*)-one (1.7 mmol) was dissolved by heating in 1.5 ml of acetic anhydride. The reaction mixture was cooled and the precipitate was filtered off to give 3-substituted 2-acyl-1,2,4-triazin-5(2*H*)-one.

2-Acetyl-3-phenyl-1,2,4-triazin-5-one **5a**: yield 85%, mp 140–141 °C. Found (%): C, 61.66; H, 3.98; N, 19.88. Calc. for $C_{11}H_9N_3O_2$ (%): C, 61.40; H, 4.20; N, 19.53.

*2-Acetyl-3-(*p*-tolyl)-1,2,4-triazin-5-one* **5b**: yield 92%. Found (%): C, 63.12; H, 4.62; N, 18.16. Calc. for $C_{12}H_{11}N_3O_2$ (%): C, 62.87; H, 4.84; N, 18.33.

2-Acetyl-3-(2-pyridyl)-1,2,4-triazin-5-one **5e**: yield 78%. Found, %: C, 55.68; H, 4.01; N, 26.14. Calc. for $C_{10}H_8N_4O_2$ (%): C, 55.56; H, 3.71; N, 25.92.

§ *General procedure for the preparation of 3-substituted (1-acetyl-5-oxy-1,4,5,6-tetrahydro-1,2,4-triazin-6-yl)-3-methoxy-D-estra-1,3,5(10)-trien-17-ones* **6**, **7**. A 3-substituted 2-acyl-1,2,4-triazin-5-one (0.25 mmol) and 3-methoxyestra-1,3,5-trien-17-one (0.25 mmol) were dissolved in a mixture of 1.0 ml of trifluoracetic acid and 2.0 ml of dichloromethane. The reaction mixture was refluxed for 4 h. The solvent was removed *in vacuo*. The oily residue was mashed by Et_2O, the formed precipitate was filtered off and dried yielding 1:1 product of hetarylation of estrone 3-methyl ether.

2-(1-Acetyl-3-phenyl-5-oxy-1,4,5,6-tetrahydro-1,2,4-triazin-6-yl)-3-methoxy-D-estra-1,3,5(10)-trien-17-one **6a**, **7a**: yield 39%, mp > 255 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 0.89, 0.90 (s, 3H, Me), 1.55–1.61, 1.72–2.10 (m, 12H, CH_2), 2.23, 2.26 (s, 3H, Ac), 2.54–2.61, 2.73–2.77 (m, 3H, CH), 3.56, 3.58 (s, 3H, OMe), 5.95, 5.97 (s, 1H, $C^{triaz}_{sp^3}H$), 6.64, 7.03 (br. s, 2H, Ar), 7.51–7.53 (m, 3H, Ph), 7.88–7.92 (m, 2H, Ph), 11.36, 11.38 [s, 1H, N(4)H]. MS, *m*/*z* (FD/EI, 230 °C): 499 (M^+, 41), 456 (100), 310 (20), 174 (37), 104 (28), 97 (5). Found (%): C, 71.98; H, 6.93; N, 8.12. Calc. for $C_{30}H_{33}N_3O_4$ (%): C, 72.12; H, 6.66; N, 8.41.

*2-(1-Acetyl-5-oxy-3-*p*-tolyl-1,4,5,6-tetrahydro-1,2,4-triazin-6-yl)-3-methoxy-D-estra-1,3,5(10)-trien-17-one* **6b**, **7b**: yield 42%, mp 287–288 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 0.89, 0.90 (s, 3H, Me), 1.55–1.64, 1.76–1.83 (m, 12H, CH_2), 2.06–2.11 (m, 3H, CH), 2.20, 2.23 (s, 3H, Ac), 2.37 (br. s, 3H, Me), 2.55–2.56, 2.66–2.68 (m, 3H, CH), 3.55, 3.58 (s, 3H, OMe), 5.95, 5.97 (s, 1H, $C^{triaz}_{sp^3}H$), 6.63, 7.02 (br. s, 2H, Ar), 7.31, 7.41, 7.79, 7.80 (d, 4H, Tol, *J* 8 Hz), 11.30, 11.32 [s, 1H, N(4)H]. Found (%): C, 72.45; H, 7.17; N, 7.95. Calc. for $C_{31}H_{35}N_3O_4$ (%): C, 72.49; H, 6.87; N, 8.18.

4-[1-Acetyl-3-(2-pyridyl)-5-oxy-1,4,5,6-tetrahydro-1,2,4-triazin-6-yl)-3-methoxy-D-estra-1,3,5(10)-trien-17-one **6e**, **7e**: yield 63%, mp > 255 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 0.95, 0.96 (s, 3H, Me), 1.63–1.66, 1.84–2.08 (m, 12H, CH_2), 2.23, 2.26 (s, 3H, Ac), 2.45, 2.69, 3.13 (m, 3H, CH), 3.41, 3.43 (s, 3H, OMe), 6.10, 6.14 (s, 1H, $C^{triaz}_{sp^3}H$), 6.72, 6.76 (2d, 1H, Ar, *J* 8.8 Hz), 7.08, 7.09 (2d, 1H, Ar, *J* 8.8 Hz), 7.55–7.58 (m, 1H, Py), 7.97–8.01 (m, 1H, Py), 8.15–8.18 (m, 1H, Py), 8.67 (m, 1H, Py), 10.58 (br. s, 1H, NH). MS, *m*/*z* (FD/EI, 240 °C): 500 (M^+, 4), 457 (19), 310 (16), 283 (16), 218 (100), 175 (91), 105 (50), 97 (8). Found (%): C, 69.81; H, 6.82; N, 11.28. Calc. for $C_{29}H_{32}N_4O_4$ (%): C, 69.60; H, 6.42; N, 11.20.

to isolate an additional amount of parent 1,2,4-triazinone **2**. Attempts to separate **6** and **7** by column chromatography with a mixture of benzene and ethyl acetate as an eluent failed.

The diastereomeric composition of **6**–**7a**,**b**,**e** can be easily determined by ^{1}H NMR spectroscopy, according to the intensities of C(6) protons of the triazine ring and the protons of the aromatic estrone fragment. Thus, in the ^{1}H NMR spectra of the products of the regeoselective nucleophilic addition of estrone methyl ether to the unsubstituted C(6) atom of the triazine ring the H(6) signal is observed as a pair of singlets at the region 5.80–6.13 ppm, while the signal of the N(4) proton is located as a pair of singlets or as a broad singlet at 11.00 ppm. The aromatic protons of the estrone fragment appear as a pair of signals. Note that the structure of **6** and **7** depends on the nature of the substituent at the 3-position of the 1,2,4-triazinone ring. In the case of 3-phenyl- or 3-*p*-tolyl-1,2,4-triazin-5-one (**5a**,**b**), the reaction with **1** affords the 2-hetaryl-substituted estrone, but the introduction of 3-(2-pyridyl)-substituted triazinone **5e** into the reaction leads to the isomeric 4-hetaryl-substituted estrone.

In conclusion, for the first time, a direct C–C coupling of 1,2,4-triazin-5-ones and an estrone derivative without metal catalysts has been developed. Further, we hope, a new family of steroid sulfatase inhibitors can be synthesised using the elaborated methodology.

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