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An Easy Synthesis of Two Steroid-Dihydropyrimidine Derivatives Using Three Components System

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In this study two new steroid-dihydropyrimidine derivatives were synthesized. In the first stage the route involved preparation of 6-(3-hydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[a]-phenanthren-17-yl)-4-phenyl-3,4-dihydro-1*H*-pyrimidin-2-one (**4**) using estrone, benzaldehyde and urea in the presence of hydrochloric acid. The following stage was achieved by the reaction between pregnenolone, thiourea and benzaldehyde using as catalyst, hydrochloric acid to form the compound 6-[1-(3-hydroxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthen-17-yl)-ethyl]-4-phenyl-3,4-dihydro-1*H*-pyrimidine-2-thione (**7**). The structure of all compounds was confirmed by spectroscopy and spectrometry data. In conclusion, in this study we report an efficient method for synthesis of two steroid-dihydropyrimidine derivatives using three components system. It is important to mention that the method used is highly versatile and the yield is good.

Key Words: Steroid, Dihydropyrimidine, Benzaldehyde, Thiourea.

INTRODUCTION

Combinatorial chemistry is a powerful tool for development of new drugs. In this context, over the past decade, several dihydropyrimidine-derivatives weresynthesized with a wide spectrum of biological actions[1,2], as antibacterials[3,4], antivirals[5] as well as antitumor agents. There are several reports of multi-component reactions for synthesis of dihydropyrimidines. The works reported by Hantzsch[6] described preparation of 1,4-dihydropyridine using three components system (acetoacetic ester, benzaldehyde and ammonia or ammonium salts) in ethanol. Other reports made by Bignelli[7] showed the synthesis of dihydropyrimidines derivatives using ethyl acetoacetate, benzaldheyde and urea. Recently the dihydropyrimidin-2(1*H*)-one was synthesized using the three component system (urea/thiourea, ethylacetoacetate/acetyl acetone) in presence of phosphorus pentoxide[8]. Another works showed the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones under solvent-free conditions using ruthenium(III) chloride-catalyzed[9]. In addition, Kappe and coworkers[10] showed a highly versatile solid-phase synthesis of biofunctional 4-aryl-3,4-dihydropyrimidines using resin-bound isothiourea building blocks and multidirectional resin cleavage. In addition, Shirini and coworkers[11] display that $Fe(HSO_4)_3$ as an efficient catalyst for the preparation of 3,4-dihydropyrimidin-2(1*H*)-ones using the three component system (β-keto ester, benzaldheyde and thiourea). Another studies made by Salehia and coworkers[12] showed the synthesis of dihydropyrimidinones using aldheyde-derivatives, dicarbonyl compounds and urea orthiourea in presence of diammonium hydrogen phosphate. All these experimental data show several protocols for synthesis of dihydropyrimidine-derivatives, nevertheless, the use of expansive reagents requires of specialconditions. In this work our initial design included an easy synthesis of two steroid-dihydropyrimidine derivatives using the three components system (pregnenolone or estrone, benzaldehyde and urea or thiourea) in presence of hydrochloric acid.

EXPERIMENTAL

The compounds evaluated in this study were purchased from Sigma-Aldrich Co., Ltd. The melting points for the different compounds were determined on an Electrothermal (900 model). Infrared spectra were recorded using KBr pellets on a Perkin Elmer Lambda 40 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR-300/5 FT NMR spectrometer at 300 and 75.4 MHz in $CDCl_3$/acetone-d_6 using TMS

as internal standard. EIMS spectra were obtained with a Finnigan Trace GCPolaris Q. spectrometer. Elementary analysis data were acquired from a Perkin Elmer Ser. II CHNS/0 2400 elemental analyzer.

6-(3-Hydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[a]-phenanthren-17-yl)-4-phenyl-3,4-dihydro-1*H*-pyrimidin-2-one (4) (Fig. 1): A solution of estrone (100 mg, 0.37 mmol), benzaldehyde (51 µL, 0.50 mmol) and urea (50 mg, 0.83 mmol) in 10 mL of ethanol was stirring for 10 min. After 0.5 mL of hydrochloric acid was added, the mixture was stirring for 72 h to room temperature. The reaction mixture was evaporated to a smaller volume. After the mixture was diluted with water and extracted with chloroform. The organic phase was evaporated to dryness under reduced pressure, the residue was purified by crystallization from methanol:water (3:1), yielding 75 % of product, m.p. 160-162 ºC; IR (KBr, ν_{max}, cm^{-1}): 3450, 3330, 1720; ^{1}H NMR (300 MHz, $CDCl_3$/acetone-d_6) ^{1}H NMR (300 MHz, $CDCl_3$/acetone-d_6) δ_H: 0.73 (s, 3H, C18-CH_3), 1.60-2.06 (m, 8H), 2.28-2.56 (m, 3H), 3.22 (m, 1H), 4.56 (d, 1H, *J* = 5.0 Hz), 5.07 (d, *J* = 5.0 Hz), 5.86 (d, 1H, *J* = 9.65 Hz), 6.30 (d, 1H, *J* = 9.65 Hz), 6.47 (s, 1H), 6.58(d, 1H, *J* = 2.70), 6.65 (d, 1H, *J* = 2.70 Hz), 7.02(d, 1H, *J* = 8.0), 7.18 (m, 2 H), 7.38(m, 2H), 7.50 (m, 1H), 8.02 (s, 1H), 9.62 (broad) ppm. ^{13}C NMR (75.4 Hz, $CDCl_3$/acetone-d_6) δ_C: 14.23 (C-31), 25.71 (C-21), 27.02 (C-19), 28.01 (C-22), 38.46 (C-17), 39.22(C-20), 43.63 (C-14), 44.58 (C-18), 44.79 (C-15), 49.44 (C-16), 58.37 (C-4), 102.25 (C-5, C-30), 113.22 (C-28), 115.56 (C-27), 124.44 (C-13, C-9), 126.06 (C-26), 126.73 (C-12, C-10), 127.61 (C-11), 127.70 (C-24), 132.31 (C-23), 138.18 (C-25), 140.92 (C-8), 144.23 (C-6), 155.02 (C-29), 155.71 (C-2) ppm. EI-MS m/z ($I_{rel.}$ %): 426.06 (M^+), 351.21, 313.47, 271.43, 253.39, 213.10, 173.19, 105.14. Anal. calcd. (%) for $C_{28}H_{30}N_2O_2$: C, 78.84; H, 7.09; N, 6.57; O, 7.50. Found (%): C, 78.80; H, 7.06.

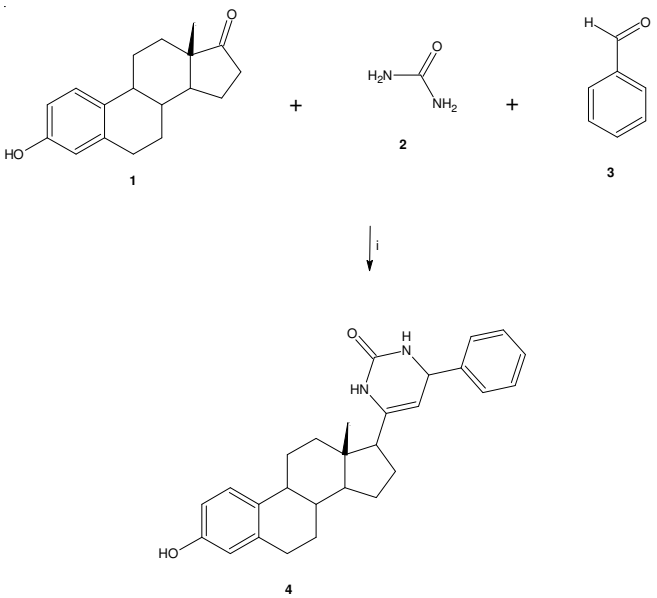

Fig. 1. Synthesis of 6-(3-hydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[a]-phenanthren-17-yl)-4-phenyl-3,4-dihydro-1*H*-pyrimidin-2-one (**4**). Reaction between estrone (**1**), urea (**2**) and benzaldehyde (**3**) to form **4**. i = hydrochloric acid/ethanol/rt

6-[1-(3-Hydroxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]-phenanthen-17-yl)-ethyl]-4-phenyl-3,4-dihydro-1*H*-pyrimidine-2-thione (7) (Fig. 2): A solution of pregnenolone (100 mg, 0.32 mmol), benzaldehyde (51 µL, 0.50 mmol) and thiourea (50 mg, 0.66 mmol) in 10 mL of ethanol was stirring for 10 min. After 0.5 mL of hydrochloric acid was added, the mixture was stirring for 72 h to room temperature. The reaction mixture was evaporated to a smaller volume. After the mixture was diluted with water and extracted with chloroform. The organic phase was evaporated to dryness under reduced pressure, the residue was purified by crystallization from methanol:water (3:1), yielding 66 % of product, m.p. 156 ºC; IR (KBr, ν_{max}, cm^{-1}): 3452, 3322, 1650; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 0.72 (S, 3H), 0.91 (m, 1H), 0.93 (s, 3H), 1.01 (d, 3H, *J* = 7.0), 1.05-1.92 (m, 17H), 2.08 (m, 1H), 2.28 (m, 2H), 3.54 (m, 1H), 4.76 (d, 1H, *J* = 5.0),5.14 (d, 1H, *J* = 5.0), 5.33 (m, 1H), 6.77 (broad, 3H)7.22-7.50 (m, 5H) ppm. ^{13}C NMR (75.4 Hz, $CDCl_3$/acetone-d_6) δ_C: 12.25(C-33), 16.59 (C-32), 19.34 (C-34), 20.91 (C-20), 24.05 (C-23), 29.42 (C-22), 31.71 (C-29), 31.75 (C-24), 31.84 (C-18), 36.47 (C-28), 37.43 (C-27), 38.41 (C-16), 39.50 (C-21), 40.39 (C-14), 42.27 (C-31), 50.16 (C-19), 54.19 (C-15), 56.65 (C-17), 63.24 (C-4), 71.55 (C-30), 108.22 (C-5), 121.33 (C-25), 127.54 (C-11), 127.89 (C-13,C-9), 128.65 (C-12, C-10), 140.75 (C-26), 145.83 (C-8), 151.20 (C-6), 177.82 (C-2) ppm. EI-MS m/z ($I_{rel.}$ %): 489.97 (M^+, 7), 217.18, (100), 174.24 (60), 105.17 (45), 78.05 (58). Calcd. (%) for $C_{31}H_{42}N_2OS$: C, 75.87; H, 8.63; N, 5.71; S, 6.53. Found (%): C, 75.85; H, 8.64.

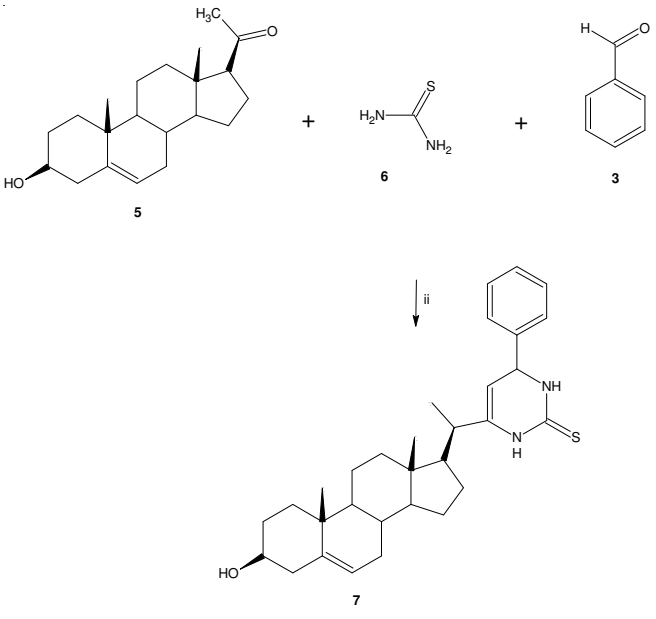

Fig. 2. Synthesis of 6-[1-(3-hydroxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthen-17-yl)-ethyl]-4-phenyl-3,4-dihy-dro-1H-pyrimidine-2-thione (**7**). Reaction between pregnenolone (**1**), thiourea (**6**) and benzaldehyde (**3**) to form **7**. i = hydrochloric acid/ethanol/rt

RESULTS AND DISCUSSION

In this study two steroid-dihydropyrimidine derivatives were synthesized using the three component system. It is

important to mention that many procedures for the formation of dihydropyrimidine derivatives are known in the literature. The most widely practiced method employs boric acid[13], silica sulphuric acid[14], poly(4-vinylpyridinecodivynylbenzene)-Cu(II) complex[15], H_2SO_4[16], silica triflate[17] and phosphorus pentoxide[18]. Nevertheless, despite its wide scope, the former protocols suffer from several drawbacks. Some reagents have a limited stability and its preparation can be dangerous. Therefore, in this study in the first stage, estrone (**1**) was made reacting with thiourea (**2**) and benzaldehyde (**3**) using hydrochloric acid as catalyst to form the compound **4**. The results indicate that the ^{1}H NMR spectrum of **4** showed signals at 0.73 ppm for methyl group present in the steroid-rings; at 1.60-3.22, 5.07-6.30, 6.58-6.65 and 7.02 ppm for methylenes involved in steroid nucleus; at 6.47 ppm for -NH group (pyrimidine-ring). Finally, spectra display several chemical shifts at 7.70 and 8.02 ppm for -NH groups (pyrimidine-ring); at 7.18-7.50 ppm for phenyl groups; at 9.62 for hydroxyl group.

On the other hand, ^{13}C NMR spectra displays chemical shifts at 14.23 ppm for methyl group present in the steroid-rings; at 25.71-49.44, 102.25-115.56, 126.06,127.70-138.18 and 155.02 ppm for steroid nucleus; at 58.37, 102.25 and 144.23 ppm for pyrimidine ring. Finally, a signal at 155.71 ppm for carbon bound to oxygen atom involved on pyrimidine-ring. Additionally, the mass spectra display a molecular ion of m/z 426.06 (M^+, 17) which confirm the structure of **4**.

The second stage was achieved by the reaction between pregnenolone (**5**), thiourea (**6**) and benzaldehyde (**3**) using hydrochloric acid as catalyst to form the compound **7**. The ^{1}H NMR spectrum of **7** showed signals at 0.72, 0.93 and 1.01 ppm for methyl groups; at 0.91and 1.05-1.92, 2.28-3.54 and 5.33 ppm for methylenes involved in steroid nucleus; at 2.10 for methylene bound to pyrimidine-ring; at 4.76-5.14 ppm for protons involved in pyrimidine-ring; at 6.77 ppm for both amino and hydroxyl groups; at 7.22-7.50 ppm for phenyl groups.

On the other hand, ^{13}C NMR spectra displays chemical shifts at 12.25 and 19.34 ppm for methyl groups; at 16.59, 20.91-39.50, 42.27-56.65, 71.55, 121.33 and 140.75 ppm for steroid nucleus; at 40.39 ppm for carbon bound to pyrimidine-ring; at 63.24, 108.22 and151.20 ppm for methylenes involved in the pyrimidine-ring; at 127.54 and 127.89-145.83 for phenyl group. Finally, a signal at 177.82 ppm for carbon bound to sulphur atom. In addition, the mass spectra display a molecular ion of m/z 489.97 (M^+, 17) which confirm the structure of **7**.

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