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An easy synthesis of *progesterone-dihydropyrimidine derivative*

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Abstract: In this study, was synthesized a new *steroid-dihydropyrimidine derivative*; the route involved preparation of *progesterone-dihydropyrimidine derivative* (**4**) using the three components system (4-pregnene-3,20-dione (**1**), *benzaldheide* (**2**) and *thiourea* (**3**) in presence of *chloridric acid* such as catalyst.
Keywords. *Progesterone, dihydropyrimidine, benzaldheide*, derivative.

Introduction

Combinatorial chemistry is a powerful tool for development of new drugs. In this context, over the past decade, several *dihydropyrimidine-derivatives* were synthesized with a wide spectrum of biological actions[1], as antibacterials[2,3], antivirals[4] as well as antitumor agents. There are several reports of multi-component reactions for synthesis of *dihydropyrimidines*, for example the works reported by Hantzsch[5] which described preparation of 1,4-dihydropyridine using three components (*acetoacetic ester*, *benzaldheide* and *ammonia* or *ammoniumsalts*) coupling reaction in refluxin ethanol. Other reports made by Bignelli[6] showed the synthesis of *dihydropyrimidines derivatives* using ethyl *acetoacetate*, *benzaldheyde* and *urea*. Additionally, recently the *dihydropyrimidin-2(1H)-one* was synthesized using the three component system (*urea/thiourea*, *ethyl acetoacetate/acetyl acetone*) in presence of *phosphorus pentoxide*[7]. Another works showed the synthesis of 3,4-dihydropyrimidin-2-(1H)-ones under solvent-free conditions using ruthenium(III) chlorid-catalyzed[8]. In addition, Kappe[9] and coworkers showed a highly versatility 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[10] display that $Fe(HSO_4)_3$ as an efficient catalyst for the preparation of *3,4-dihydropyrimidin-2(1H)-ones* using the three component system *(β-keto ester*, *benzaldheyde* and *thiourea*). Another studies made by Salehia[11] and coworkers showed the synthesis of dihydropyrimidinones using aldheyde-derivatives, *dicarbonyl* compounds and urea or thiurea 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 special conditions. In this work our initial design included an easy synthesis of a *steroid-dihydropyrimidine derivative*. The route involve preparation of *progesterone-dihydropyrimidine derivative* (**4**) using the three components system (4-pregnene-3,20-dione, *benzaldheide* and *thiourea* in presence of *chloridric acid* such as catalyst.

Experimental

General methods

Progesterone (*4-pregnene-3,20-dione*) and the other 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). Ultraviolet spectroscopy (UV) was carried out in dry methanol on a Perkin-Elmer model 552 spectrophotometer and infrared spectra (IR) was 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 CDCl3 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.

Synthesis of 11a,13a-dimethyl-phenyl-1-[1-(6-phenyl-2-thioxo-1,2,3,6-tetrahydro-pyrimidin-4-yl)-ethyl]-1,2,3,3a,3b,4,5,5a,7,9,10,10a,11,11a,11b,12,13,13a-octadeca-hydro-1*H*-7,9-diaza-indeno[5,4-*a*]anthracene-8-thione.

A solution of *progesterone* 100 mg (0.31 mmol), *thiourea* 71 mg (0.93 mmol), *benzaldehyde* 60 µL (0.93 mmol) in *ethanol* 10 mL was stirring by 10 minutes at room temperature. After *chloridric acid* 1 mL was added and the mixture was stirring by 48 hours at room temperature. The reaction mixture was evaporated to a smaller volume, 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 70 % of product, mp 150 ^{o}C; UV (MeOH) λ_{max} (log ε) 219 (3.33), 278 (2.56) nm; IR V_{max} 3430, 1610 cm-1; ^{1}H RMN CDCl3 (300 MHz) δ_H; 0.61 (3H, s, 22-C**H**$_3$), 0.72-0.80 (2H, m), 0.86 (3H, s, 32-C**H**$_3$), 1.05 (3H, s, 23-C**H**$_3$), 1.08-1.16 (2H, m), 1.21-1.33 (2H, m), 1.44-1.66 (5H, m), 1.70-1.81 (2H, m), 1.97 (1H, m), 2.09 (1H, m), 2.20-230 (2H, m), 2.97-3.03 (2H, m), 4.48 (1H, m), 4.75 (1H, m), 5.14 (1H, d, -C**H**=C, *dihydropyridimidine-ring*), 6.27 (1H, d, -C**H**=C, *steroid-ring nucleus*), 7.23-7.33 (6H, m, *phenyl-rings*), 7.50-7.55 (4H, m, *phenyl-rings*), 7.70 (4H, m, -N**H**). ^{13}C RMN 13 $CDCl_3$ (75.4 MHz) δ_C; 12.26 (**C**-23), 14.70 (**C**-32), 15.56 (**C**-22), 24.25 (**C**-15), 25.35 (**C**-21), 28.28 (**C**-20), 28.53 (**C**-14), 34.33 (**C**-13), 37.37 (**C**-8), 37.90 (**C**-7), 37.90 (**C**-12), 39.94 (**C**-24), 40.05 (**C**-13), 40.15 (**C**-16), 48.47 (**C**-17), 53.96 (**C**-11), 55.53 (**C**-19), 57.25 (**C**-18), 63.24 (**C**-6), 63.69 (**C**-35), 108.22 (**C**-34, -**C**=C-, *dihydropyridimidine-ring*), 110.02 (**C**-10, **C**H=C, *steroid-ring nucleus*), 114.43 (C-1, **C**=C), 127.00 (**C**-42), 127.79 (C-40,C-44), 128.20 (**C**-28), 128.59 (C-41, C-43), 128.90 (C-27, C-29), 129.69 (C-26, C-30), 141.43 (C-25), 142.18 (C-2, **C**=C, d*ihydropyridimi- dine-ring*), 145.84 (C-39), 148.26 (C-9, *steroid-ring nucleus*), 151.25 (C-33, -HN-**C**=C), 165.02 (C-4, *dihydropyridimidine-ring*), 177.02 (C-37, *dihydropyridimidine-ring*). EI-MS, *m/s* 634.93 (M^{+}, 17), Anal. Calcd for C_{39}, H_{46}, N_4, S_2; C, 73.77, H, 7.30, N, 8.82, S, 10.10 Found: C, 73.51, H, 7.61, N, 8.78.

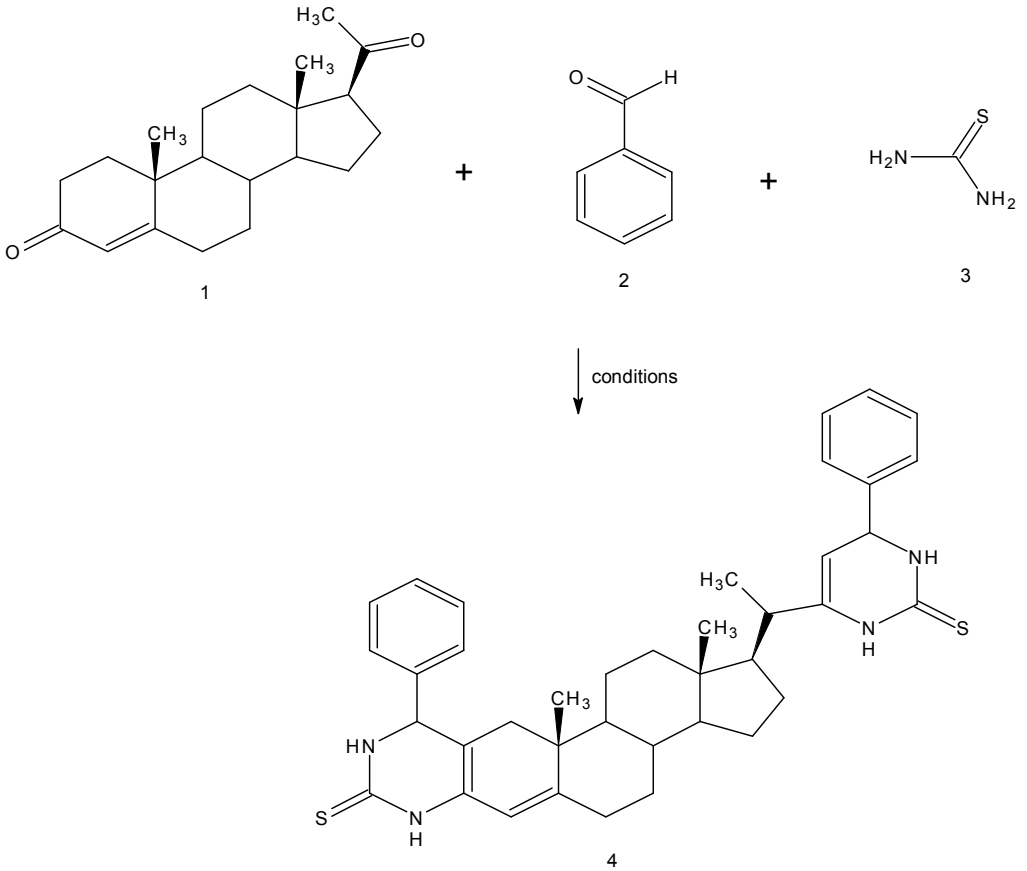

Figure 1. Synthesis of *progesterone-dihydropyrimidine derivative* (4) using the three components system (4-pregnene-3,20-dione (1), *benzaldheide* (2) and *thiourea* (3). Conditions: HCl/Ethanol

Results and Discussion

In this study the *progesterone-dihydropyrimidine* derivative was synthesized using the three component system (*4-pregnene-3,20-dione* [**1**], *benzaldheide* [**2**] and *thiourea* [**3**]) in presence of *chloridric acid* as catalyst. 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[12], silica sulfuric acid[13], poly(4-vinylpyridine-codivynylbenzene)-Cu(II) complex[14], H_2SO_4[15], silica triflate[16] and phosphorus pentoxide[17]. Nevertheless, despite its wide scope, the former protocols suffer from several drawbacks; some reagents have a limited stability and its preparation can be dangerous.

The results indicate that the ^{1}H NMR spectrum of *progesterone-dihydropyrimidine derivative* showed a signal at 0.61, 0.72 and 1.05 ppm for methyls present in the *steroid-rings nucleus*; at 5.14 and 6.27 ppm for methylens involved in *pyrimidine-ring and steroid-rings nucleus*. Additionally, there are several chemical shifts (723-733 and 750-7.55 ppm) corresponding to protons in *aromatic-rings*. Finally, spectra display a chemical shift similar at 7.70 ppm for -N**H** group (*pyrimidine-ring*).

On the other hand, ^{13}C NMR spectra displays chemical shifts at 12.26, 14.70 and 15.56 ppm for the carbons of the methyls groups presents in the *steroid-rings nucleus*. The chemical shift of the methylene joined to *pyrimidine-ring* at 108.22 ppm (-**C**=C-, *dihydropyridimidine-ring*) and 110.02 ppm (-**C**=C-, *steroid-ring nucleus*) were found. At down field there are several signals (127-141.43 and 145.84 ppm) corresponding to the carbons of *aromatic-rings*. Finally, several characteristic signals at 142.18 (-**C**=C-, *dihydropyridimidine-ring*), 148.26 for *steroid-ring nucleus* and 151.25 for carbon bound to nitrogen involved on *pyrimidine-ring* and at 165.02 and 177.02 for carbon bound to *sulphur atom involved* on *pyrimidine-ring*. Additionally, the mass spectra display a molecular ion of m/z 634.93 (M^+, 17) which confirm the structure of **4**. In conclusion in this work, we reported an easy procedure for the synthesis of *progesterone-dihydropyrimidine derivative.*

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