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ORIGINAL PAPER

Synthesis of a succinate–dihydrotestosterone–dihydropyrimidine conjugate

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Abstract In this work a new steroid–dihydropyrimidine derivative was synthesized. The route involved preparation of a dihydrotestosterone–dihydropyrimidine derivative using dihydrotestosterone, benzaldehyde, and thiourea in the presence of hydrochloric acid, followed by esterification of the dihydrotestosterone–dihydropyrimidine derivative with succinic acid to form a succinate–dihydrotestosterone–dihydropyrimidine conjugate.

Keywords Steroid–dihydropyrimidine derivative · Benzaldehyde · Thiourea

Introduction

In recent decades several dihydropyrimidine derivatives have been synthesized with a wide spectrum of biological actions [1], as antibacterials [2, 3], antivirals [4], and antitumor agents. In this sense, there are several reports of multi-component reactions for synthesis of dihydropyrimidines, for example the work reported by Hantzsch [5], which described preparation of 1,4-dihydropyridine using a three-component coupling reaction (acetoacetic ester, benzaldehyde, and ammonia or ammonium salts) in ethanol under reflux. Biginelli [6] has reported the synthesis of dihydropyrimidine derivatives using ethyl acetoacetate, benzaldehyde, and urea. In addition, dihydropyrimidin-2(1*H*)-one was recently synthesized by use of the three-component system urea/thiourea, ethyl acetoacetate, and acetyl acetone in the presence of phosphorus pentoxide [7]. Additionally, in other work Surya and coworkers [8] achieved the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones under solvent-free conditions using ruthenium(III) chloride as catalyst. In addition, Kappe and coworkers [9] have reported highly versatile solid-phase synthesis of biofunctional 4-aryl-3,4-dihydropyrimidines using resin-bound isothiourea building blocks and multidirectional resin cleavage.

Another study reported by Shirini and coworkers [10] showed that $Fe(HSO_4)_3$ can be an efficient catalyst for preparation of 3,4-dihydropyrimidin-2(1*H*)-ones using the three-component system β-keto ester, benzaldehyde, and thiourea. Additionally, Salehia and coworkers [11] have reported the synthesis of dihydropyrimidinones using aldehyde derivatives, dicarbonyl compounds, and urea or thiourea in the presence of diammonium hydrogen phosphate.

These experimental results show several procedures are available for synthesis of dihydropyrimidine derivatives by use of the Biginelli reaction; expensive reagents and special conditions are required, however. In this work, therefore, our initial design included a facile synthesis of a steroid–dihydropyrimidine derivative that contains, in the cyclopentane ring of the succinate–dihydrotestosterone–

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dihydropyrimidine conjugate nucleus, a spacer arm with both ester and acid functional groups. The route involves preparation of dihydrotestosterone–dihydropyrimidine derivative **4** using, first, the three-component system 5α-androstan-17β-ol-3-one, benzaldehyde, and thiourea in the presence of hydrochloric acid as catalyst, followed by esterification of the steroid–dihydropyrimidine derivative with succinic acid and 1,3-dicyclohexylcarbodiimide to form succinate–dihydrotestosterone–dihydropyrimidine conjugate **5**.

Results and discussion

It is important to mention that many procedures for formation of dihydropyrimidine derivatives are available in the literature. The most widely practiced methods employ boric acid [12], silica sulfuric acid [13], poly-(4-vinylpyridine-co-divinylbenzene)-Cu(II) complex [14], H_2SO_4 [15], silica triflate [16], and phosphorus pentoxide [7]. Nevertheless, despite their wide scope, these procedures suffer from several drawbacks; some reagents are of limited stability, and preparation can be dangerous.

Therefore, in this work we report a straightforward route for synthesis of a new steroid–dihydropyrimidine derivative. The first step involves preparation of dihydrotestosterone–dihydropyrimidine derivative **4** using the three-component system 5α-androstan-17β-ol-3-one, benzaldehyde, and thiourea in presence of hydrochloric acid as catalyst (Scheme 1). The ^{1}H NMR spectrum of the dihydrotestosterone–dihydropyrimidine derivative shows signals at 0.74 and 0.78 ppm for methyl groups present in the heterocyclic ring and at 4.83 ppm for CH involved in the pyrimidine ring; at low field there are several chemical shifts (7.21–7.29 and 7.46 ppm) corresponding to protons in the aromatic ring. Finally, the spectrum contains a signal at a chemical shift of 7.38 ppm for the NH (pyrimidine ring) and OH.

The ^{13}C NMR spectrum contains peaks at chemical shifts of 11.94 and 12.11 ppm for the carbons of the methyl groups present in the heterocyclic ring. The chemical shifts of methylene joined to the pyrimidine ring are at 109.01 (C–*C*=C) and 125.57 ppm (C=*C*–N). Downfield there are several signals (125.60, 127.38, 127.46, 128.33, and 139.31 ppm) corresponding to the carbons of the aromatic ring.

In the mass spectrum the molecular ion is at $m/z = 436.16$ ($[M + H]^+$), which confirms the structure of **4**.

The second step involves esterification of the hydroxyl group of the dihydrotestosterone–dihydropyrimidine derivative by reaction of **4** with succinic acid. It is important to mention that diverse reagents are available for producing ester derivatives [17, 18]; nevertheless, most conventional methods have found only limited use for this purpose. During recent years, carbodiimides and, especially, dicyclohexylcarbodiimide (DCC) have attracted increasing attention as condensing agents in ester synthesis [19, 20]. Nevertheless, it is important to mention that when dicyclohexylcarbodiimide is used as condensing agent in esters synthesis, yields of the esters are often unsatisfactory because of formation of the *N*-acylurea derivative as by-product. Some reports reveal that addition of a catalytic amount of a strong acid to the esterification reaction in the presence of dicyclohexylcarbodiimide considerably increases the yield of esters and reduces the formation of the *N*-acylurea compound [21]. For this reason, esterification of the hydroxyl group of dihydrotestosterone–dihydropyrimidine derivative **4** with succinic acid in the presence of dicyclohexylcarbodiimide and *p*-toluenesulfonic acid (Scheme 1) was used to increase the yield of the succinate–dihydrotestosterone–dihydropyrimidine conjugate **5**.

The ^{1}H NMR spectrum of **5** shows signals at 0.76 and 0.83 ppm for methyl groups present in the heterocyclic ring and at 4.81 ppm for CH in the pyrimidine ring. In addition, at low field there are several signals (7.24–7.43 ppm) corresponding to protons in the aromatic ring. Finally, the spectrum contains a signal with a chemical shift of 8.60 ppm for NH (pyrimidine ring) and CO_2H.

The ^{13}C NMR spectrum of **5** contains peaks at chemical shifts of 11.98 and 12.13 ppm for the carbons of the methyl groups present in the heterocyclic ring. The chemical shifts of methylene joined to the pyrimidine ring are at 108.02 (C–*C*=C) and 125.58 ppm (C=*C*–N). At low field there are several signals (125.60, 127.39, 127.42, 128.35, 139.32, and 142.02 ppm) corresponding to the carbons of the aromatic ring. Two chemical shifts at 172.81 (*C*O_2H) and 180.62 ppm (N–*C*=S, pyrimidine ring) are also found.

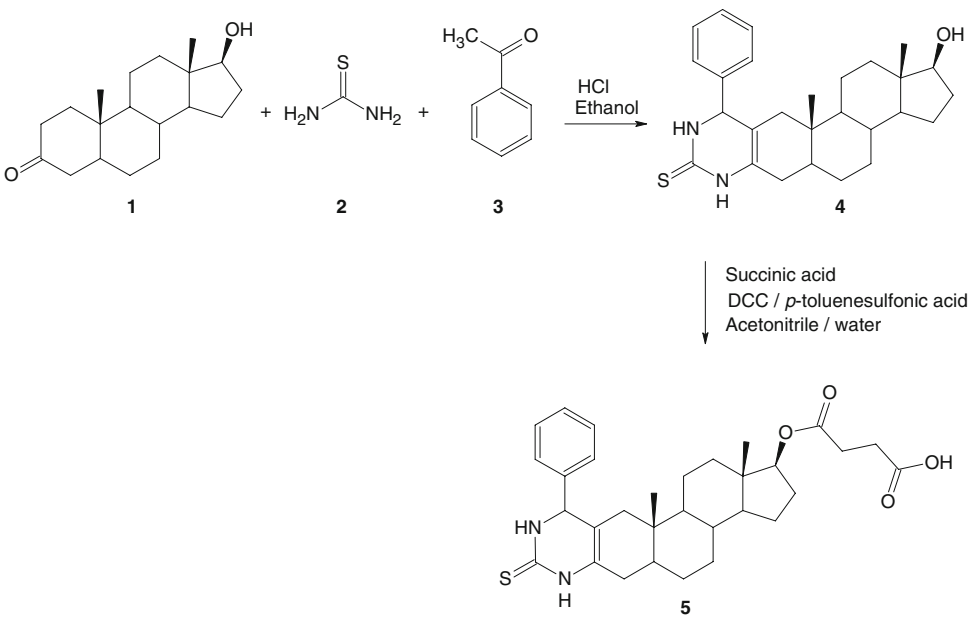
In the mass spectrum the molecular ion is at $m/z = 534.31$ ($[M + H]^+$), which confirms the structure of **5**.

In conclusion, in this work we report an efficient and simple method for synthesis of the new steroid–dihydropyrimidine derivative **4**, using a multi-component system in the presence of hydrochloric acid as catalyst. It is important to mention that this method is highly versatile and the yield is good. In addition, esterification of the dihydrotestos_terone–dihydropyrimidine derivative using succinic acid in the presence of 1,3-dicyclohexylcarbodiimide and *p*-toluenesulfonic acid is a good system for increasing the yield of **5**.

Experimental

Dihydrotestosterone (5α-androstan-17β-ol-3-one) and the other compounds evaluated in this study were purchased

Scheme 1



from Sigma–Aldrich. Melting points were determined on an Electrothermal model 900. Ultraviolet spectroscopy (UV) was carried out in dry methanol on a Perkin–Elmer model 552 spectrophotometer and infrared spectra (IR) 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, respectively, in $CDCl_3$, using TMS as internal standard. EI-MS spectra were obtained with a Finnigan Trace GCPolaris Q spectrometer. Elemental analysis data were obtained by use of a Perkin–Elmer Ser. II CHNS/0 2400 elemental analyzer.

3′,6′-Dihydro-17-hydroxy-6′-phenylandrost-2-eno[3,2-d] pyrimidine-2′(1′H)-thione (**4**, $C_{27}H_{36}N_2OS$)

A solution of 118 mg dihydrotestosterone (0.41 mmol), 123.70 mg thiourea (1.62 mmol), and 0.65 cm^3 benzaldehyde (1.62 mmol) in 10 cm^3 ethanol was stirred for 10 min at room temperature. Then 1 cm^3 hydrochloric acid was added and the mixture was stirred for 48 h 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 80% of product **4**. M.p.: 107 °C; UV (MeOH): λ_{max} (log ε) = 217 (0.18), 258 (0.09) nm; IR: $\bar{\nu}$ = 3,330, 1,620, 1,470 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.74 (s, 3H, CH_3), 0.78 (s, 3H, CH_3), 0.87 (m, 1H, H-7), 0.96–1.09 (m, 2H), 1.11–1.79 (m, 11H), 1.85–1.90 (m, 2H), 2.06–2.52 (m, 4H), 3.61 (m, 1H), 3.80 (m, 1H), 4.83 (s, 1H), 7.21–7.29 (m, 3H, ArH), 7.38 (m, NH pyrimidine ring and OH), 7.46 (m, 2H, ArH) ppm; ^{13}C NMR (74.5 MHz, $CDCl_3$): δ = 11.94 (CH_3), 12.11 (CH_3), 20.55, 23.56, 27.87, 27.89, 30.33, 34.93, 35.36, 35.38, 36.41, 42.66, 50.58, 50.77, 53.39, 53.43, 58.25, 61.32, 82.84 (*C*–OH), 109.01 (C–*C*=C), 125.57 (C=*C*–N), 125.60, 127.38, 127.46, 128.33, 139.31 (Ar), 179.30 (pyrimidine ring) ppm; EI-MS: *m/z* = 436.16 ([M + H]$^+$).

Succinic acid mono(1′,2′,3′,6′-tetrahydro-6′-phenyl-2′-thioxoandrost-2-eno[3,2-d]pyrimidin-17-yl)ester (**5**, $C_{31}H_{40}N_2O_4S$)

Dihydrotestosterone derivative **4** (100 mg, 0.23 mmol) was added to a solution of 85 mg succinic acid (0.72 mmol) and 100 mg 1,3-dicyclohexylcarbodiimide (0.48 mmol) in 15 cm^3 acetonitrile–water (3:1) and 69 mg *p*-toluenesulfonic acid monohydrate (0.36 mmol) was added and the mixture was stirred at room temperature for 72 h. The solvent was then removed under vacuum and the crude product was purified by crystallization from methanol–hexane–water (3:2:1) yielding 78% of product **5**. M.p.: 121 °C; UV (MeOH): λ_{max} (log ε) = 218 (0.19), 261 (0.20) nm; IR: $\bar{\nu}$ = 3,326, 1,615, 1,712 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.76 (s, 3H, CH_3), 0.83 (s, 3H, CH_3), 0.87 (m, 1H), 1.10 (m, 1H), 1.10–1.80 (m, 11H), 1.85–1.90 (m, 2H), 2.03–2.43 (m, 4H), 2.57 (m, 2H), 3.62 (m, 1H), 3.81 (m, 2H), 4.44 (m, 1H), 4.81 (s, 1H), 7.24–7.43 (m, 5H, ArH), 8.60 (1H, br s, NH pyrimidine ring and CO_2H) ppm; ^{13}C NMR (74.5 MHz, $CDCl_3$): δ = 11.98 (*C*H_3-22), 12.13 (*C*H_3-23), 20.55, 23.52, 27.85, 27.89, 29.73, 29.81, 30.31, 32.01, 34.96, 35.34, 35.36, 36.44, 42.69, 50.56, 50.71, 53.31, 53.45, 61.37, 82.83 (C–*C*–O, cyclopentane), 108.02 (C–*C*=C), 125.58 (N–*C*=C), 125.60, 127.39, 127.42, 128.35, 139.32, 142.02 (*C*–Ar), 172.81 *C*O_2H), 173.05 (*C*O_2), 180.62

(N–*C*=S, pyrimidine ring) ppm; EI-MS: $m/z = 534.31$ ($[M + H]^+$).

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References

1. Cheng CI (1969) Prog Med Chem 6:67
2. Mishra R, Mishra B, Moorthy H (2008) Trends Appl Sci Res 3:203
3. Padhy AK, Bardhan M, Panda CS (2003) Indian J Chem 42B:910
4. Vishnevskii SG, Pirozhenko VV, Chentsova NP, Antonenko SV, Barbasheva EV, Grin EV, Lyul'chuk MG, Sorochinskii AE, Remennikov GY, Puik AI, Kukhar VP (1994) Pharm Chem J 28:12
5. Hantzsch A (1892) Ann Chem 215:1
6. Kappe CO (2000) Acc Chem Res 33:879
7. Deshmukh MB, Prashant V, Anbhule PV, Jadhav SD, Mali AR, Jagtap SS, Deshmukh SA (2007) Indian J Chem 46B:1545
8. De SK, Gibbs RA (2005) Synthesis 1748
9. Kappe CO (2000) Bioorg Med Chem Lett 10:49
10. Shirinia F, Zolfigolb MA, Abria AR (2008) J Iran Chem Soc 5:96
11. Salehi P, Dabiri M, Khosropour AR, Roozbehniya P (2006) J Iran Chem Soc 3:98
12. Tu S, Fang F, Miao C, Jiang H, Feng Y, Shi D, Wang X (2003) Tetrahedron Lett 44:6153
13. Salehi P, Dabiri M, Zolfigol MA, Fard MB (2003) Tetrahedron Lett 44:2889
14. Yarapathi RV, Kurva S, Tammishetti S (2004) Cat Commun 5:511
15. Bussolari JC, McDonnell PA (2000) J Org Chem 65:6777
16. Shirini F, Marjani K, Nahzomi HT (2007) Arkivoc i:51
17. Crossland RK, Servis KL (1970) J Org Chem 35:3195
18. Zhu HP, Yang F, Tang J, He MY (2003) Green Chem 5:38
19. Kurzer F, Douraghi-Zadeh K (1967) Chem Rev 67:107
20. Felder E, Tiepolo U, Mengassini A (1973) J Chromatogr 82:291
21. Holmberg K, Hansen B (1979) Acta Chem Scand B33:410