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Preparation of an oxetan-phenyltetrahydropyridazine-3,6-dione derivative using some chemistry tools

Paat-Estrella Josefa[a], Figueroa-Valverde Lauro*[a], López-Ramos Maria[a], Hau-Heredia Lenin[a], Díaz-Cedillo Francisco[b], García-Cervera Elodia[a], Pool-Gómez Eduardo[a], Rosas-Nexticapa Marcela[c]. Mateu-Armad Maria Virginia[c]

[a]*Laboratory of Pharmaco-Chemistry, Faculty of Chemical Biological Sciences, University, University Autonomous of Campeche, Av. Agustín Melgar s/n, Col Buenavista C.P. 24039 Campeche, Camp.,México*

[b]*Escuela Nacional de Ciencias Biológicas del Instituto Politécnico Nacional. Prol. Carpio y Plan de Ayala s/n Col. Santo Tomas, México, D.F. C.P. 11340*

[c]*Facultad de Nutrición, Universidad Veracruzana, Médicos y Odontologos s/n C.P. 91010, Unidad del Bosque Xalapa Veracruz, México*

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Abstract

The aim of this study was to synthesize a new oxetan-phenyltetrahydropyridazine-3,6-dione derivative (compound **6**) using different techniques. The first method was achieved by the preparation of a phenylhydrazine derivative (**2**) using three-components system (3,17-aldol-estradiol, phenylhydrazine, 5-hexyn-3-ol) in the presence of Copper(II). Then, **2** was reacted with *tert*-butyldimethylsilyl chloride to form the compound **3** (trimethylbutan-silyloxy-steroid-hydrazine). Following, a pyridazine derivative (**4**) was prepared by the reaction of **3** with succinic acid using boric as catalyst. The compound **4** was reacted with hydrofluoric acid to form the tetrahydropyridazine-3,6-dione (**5**). Finally, the preparation of **6** was carried out by the reaction of **5** with CopperII. Spectroscopy analyses NMR was used to confirm the chemical structure of compounds. In conclusion, a facile method to synthesize an oxetan-phenyltetrahydropyridazine-3,6-dione is reported.

Keywords: Steroid; derivative; phenylhydrazine; tetrahydropyridazine; oxetan.

Introduction

There are several reports for preparation of pyridazinone derivatives; for example, the synthesis of 4-Chloro-5-[4-(2-furoyl)pipera- zin-1-yl]pyridazin-3(2H)-one by the reaction of 4,5-dichloropyridazin-3(2H)-one with 1-(2-furoyl)piperazine [1]. Other report showed the preparation of some 6-(substituted-phenyl)-2-(substitutedmethyl)-4,5-dihydro-pyridazin-3-(2*H*)-one derivatives by reacting 6-substituted-phenyl-4,5-dihydropyridazin-3(2*H*)-one with cyclic secondary amine under Mannich reaction [2]. In addition, the other one indicates the synthesis of 6-(4-Chlorophenyl)-2-allyl-2H-pyridazin-3-one using the three-system (pyridazone, 2-bromo-alkyl ester and propargyl chloride) as exposed to ultrasound [3]. Also, a report showed

*Corresponding author: Figueroa-Valverde Lauro
Tel: +55 (981) 81198001, Fax: +55 (981) 8119800
E-mail: lauro_1999@yahoo.com

the reaction of hydrazine monohydrate-acetic acid with quinazolinyl-oxobutyrate derivative to form a quinazolinyl-pyridazinone analog [4]. Other data indicated the synthesis of 6-Phenyl(3'-imino-benzylidene)-2,3,4,5-tetrahydropyri- dazin-3-one from aminobenzoyl propionic acid and hydrazine [5]. Additionally, indolyl,6-(substituted-phenyl)-2-(substituted-methyl)-4,5-dihydropyridazine-3(2H)-one was prepared using Friedal-Craft acylation of aromatic hydocabons with succinic anhydride [6]. Other report showed the synthesis of some pyridazinone derivatives via the reaction of phosphonium ylides with different hydrazines [7]. Moreover, a study showed the process for the preparation of 6-phenyl-3(2H)-pyridazinone from acetophenone and glyoxylic acid [8]. All these experimental results show several procedures which are available for synthesis of some pyridazinone derivatives; nevertheless, expensive reagents and special conditions are required. Therefore, the aim of study involved the synthesis of an oxetan-phenyltetrahydro- pyridazine-3,6-dione derivative using the 3,17-aldol-estradiol reagent as chemical tool.

Experimental

General

Compound **1** (3,17-aldol-estradiol) was pre-pared by a previously reported reported [9]. Additionally, the other compounds used in this work were purchased from Sigma-Aldrich Co. Ltd. The melting points for the different compounds were determined on an Electrothermal (900 model). 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 in $CDCl_3$ 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.

7-{3-[5-Hydoxy-1-(*N´*-pheyl-hydrazino)-hept-2-ynyl]-13-methyl-7,8,9,11,12,13,14, 15,16,17-decahydro-6*H*-cyclopenta[*a*]phe-nanthren-17-yl}-7-(*N´*-phenyl-hydrazino)-hept-5-yn-3-ol (2)

A solution of **1** (200 mg, 0.67 mmol), phenylhydrazine (150 µl, 1.52 mmol), 5-hexyn-3-ol (160 µl, 1.44 mmol), Copper(II) chloride anhydrous (200 mg, 1.44 mmol), in 5 mL of methanol was stirred for 72 h at room temperature. The reaction mixture was evaporated to dryness under reduced pressure. Afterwards, the residue was purified by crystallization from methanol:water (4:1) yielding 55 % of product, m.p. 130-132 ^{o}C; IR (V_{max}, cm^{-1}): 3430 and 3400; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 0.70 (s, 3H), 1.00 (s, 6H), 1.14-1.32 (m, 3H), 1.40 (m, 2H), 1.44-1.50 (m, 2H), 1.60 (m, 2H), 1.66-2.16 (m, 7H), 2.32-2.34 (m, 2H), 2.35-2.50 (m, 2H), 2.52-2.53 (m, 2H), 2.78-2.80 (m, 2H), 3.68 (m, 2H), 3.74 (m, 1H), 4.34 (m, 1H), 4.42 (broad, 6H), 6.80-6.92 (m, 6H), 6.94 (m, 1H), 7.10-7.14 (m, 4H), 7.40-7.52 (m, 2H) ppm. ^{13}C NMR (75.4 Hz, $CDCl_3$) δ_C: 10.70 (C-48, C-50), 15.30 (C-18), 25.88 (C-9), 26.32 (C-5), 27.10 (C-8), 27.74 (C-10), 27.76 C-39), 27.90 (C-44), 29.30 (C-11), 29.41 (C-47, C-49), 38.52 (C-3), 40.00 (C-1), 40.22 (C-6), 44.52 (C-4), 47.98 (C-19), 52.39 (C-28), 52.54 (C-7), 55.40 (C-2), 63.82 (C-42), 74.00 (C-40, C-45), 86.04 (C-38), 88.10 (C-43), 88.62 (C-37), 111.40 (C-23, C-27), 111.85 (C-32, C-36), 121.54 (C-25, C-34), 124.06 (C-17), 125.18 (C-15), 125.80 (C-33, C-35),

126.00 (C-24, C-26), 128.42 (C-14), 137.82 (C-13), 138.10 (C-16), 139.42 (C-12), 150.72 (C-22), 151.90 (C-31) ppm. EI-MS *m/z:* 672.44 Anal. Calcd. for $C_{44}H_{56}N_4O_{22}$: C, 78.53; H, 8.39; N, 8.33; O, 4.76. Found: C, 78.48 H, 8.30.

1-(2-Phenylhydrazinyl)-2-((1*S*)-5-((dime- thyl(2,3,3-trimethylbutan-2-yl)silyl)oxy)-1-((13*S*,17*S*)-3-(5-((dimethyl(2,3,3-trimethyl- butan-2-yl)silyl)oxy)-1-(2-phenylhydrazyn- yl)hept-2-yn-1-yl]-13-methyl-7,8,9,11,12, 13,14,15,16,17-decahydro-6*H*-cyclopenta [*a*]phenanthren-17-yl)hept-2-yn-1-yl)hy- drazine (3)

A solution of **2** (200 mg, 0.29 mmol), *tert*-Butyldimethylsilyl chloride (200 µl, 1.07 mmol) in 5 mL of chloroform was stirred for 12 h at room temperature. The reaction mixture was evaporated to dryness under reduced pressure. Then, the residue was purified by crystallization from methanol:water (4:1) yielding 67 % of product, m.p. 108-110 ^oC; IR (V_{max}, cm^{-1}): 3432 and 1245; ^1H NMR (300 MHz, $CDCl_3$) δ_H: -0.09 (s, 12H), 0.72 (s, 3H), 0.84 (s, 18H), 0.88 (s, 6H), 1.08 (s, 18H), 1.14-1.32 (m, 3H), 1.36 (m, 2H), 1.44-1.50 (m, 2H), 1.56 (m, 2H), 1.66-2.50 (m, 9H), 2.64-2.65 (m, 2H), 2.70 (m, 2H), 2.78-2.80 (m, 2H), 3.70 (m, 1H), 3.80 (m, 2H), 4.34 (m, 1H), 5.90 (broad, 4H), 6.80-6.92 (m, 6H), 6.94 (m, 1H), 7.10-7.14 (m, 4H), 7.40-7.52 (m, 2H) ppm. ^{13}C NMR (75.4 Hz, $CDCl_3$) δ_C: -3.60 (C-43, C-50, C-53, C-59), 10.60 (C-52, C-58), 15.30 (C-18), 19.30 (C-63, C-64, C-67, C-68), 25.86 (C-9), 25.92 (C-39), 26.02 (C-46), 26.29 (C-5), 27.12 (C-8), 27.76 (C-10), 28.10 (C-54, C-60), 28.84 (C-56, C-62, C-65, C-66, C-69, C-70), 29.30 (C-11), 29.72 (C-51, C-57), 38.54 (C-3), 39.98 (C-1), 40.22 (C-6), 41.20 (C-55, C-61), 44.60 (C-4), 47.98 (C-19), 52.40 (C-28), 52.54 (C-7), 55.40 (C-2), 63.82 (C-44), 74.00 (C-40, C-47), 86.08 (C-38), 88.10 (C-45), 88.6 (C-37), 111.40 (C-23, C-27), 111.89 (C-32, C-36), 121.52 (C-25, C-34), 124.06 (C-17), 125.18 (C-15), 125.78 (C-33, C-35), 126.00 (C-24, C-26), 128.44 (C-14), 137.82 (C-13), 138.08 (C-16), 139.38 (C-12), 150.72 (C-22), 151.90 (C-31) ppm. EI-MS *m/z:* 984.70 Anal. Calcd. for $C_{62}H_{96}N_4O_2Si_2$: C, 75.55; H, 9.82; N, 5.68; O, 3.25; Si, 5.70. Found: C, 75.48 H, 9.74.

1-(5-((Tert-butyldimethylsilyl)oxy)-1-((13S, 17S)-17-((1S)-5-((terbutyldimethylsilyl)- oxy-1-(3,6-dioxo-2-phenyltetrahydropyri- dazin-1(2H)-yl)hept-2-yn-1-yl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl)hept-2-yn-1-yl)-2-phenyltetrahydropyridazine-3,6-dione (4)

A solution of **3** (200 mg, 0.20 mmol), succinic acid (50 mg, 0.42 mmol) and boric acid (50 mg, 0.80 mmol) in 5 mL of methanol was stirred for 12 h at room temperature. The reaction mixture was evaporated to dryness under reduced pressure. Finally, the residue was purified by crystallization from methanol:water (4:1) yielding 44 % of product, m.p. 122-124 ^oC; IR (V_{max}, cm^{-1}): 2190, 1702 and 1246; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 0.04 (s, 12H), 0.68 (s, 3H), 0.86 (s, 6H), 0.88 (s, 18H), 1.08 (s, 18H), 1.14 (m, 1H), 1.36 (m, 2H), 1.44-1.50 (m, 3H), 1.56 (m, 2H), 1.66-2.50 (m, 10H), 2.66 (m, 2H), 2.68 (m, 2H), 2.70 (m, 2H), 2.72-2.76 (m, 3H), 2.77-2.79 (m, 2H), 2.82-2.90 (m, 3H), 3.60 (m, 2H), 4.86 (m, 1H), 5.40 (m, 1H), 6.96 (m, 1H), 7.13 (m, 1H) 7.14-7.25 (m, 6H) 7.28 (m, 1H), 7.76-7.82 (m, 4H) ppm. ^{13}C NMR (75.4 Hz, $CDCl_3$) δ_C: -4.20 (C-39, C-50, C-59, C-72), 10.60 (C-49, C-71), 15.70

(C-40), 17.90 (C-51, C-73), 23.44 (C-22), 23.46 (C-35), 23.60 (C-55), 23.92 (C-21), 25.84 (C-52, C-68, C-69, C-74, C-75, C-76), 26.29 (C-19), 27.76 (C-23), 29.30 (C-24), 29.72 (C-48, C-70), 30.60 (C-5, C-45), 30.68 (C-4), 30.84 (C-46), 37.80 (C-20), 38.58 (C-17), 44.60 (C-18), 50.50 (C-15), 52.48 (C-16), 53.34 (C-13), 55.44 (C-14), 57.50 (C-41), 60.42 (C-53), 75.10 (C-36, C-56), 85.28 (C-33), 89.22 (C-34), 91.30 (C-54), 121.10 (C-8, C-12), 121.62 (C-61, C-65), 123.56 (C-30), 124.66 (C-28), 127.22 (C-10, C-63), 127.44 (C-27), 128.30 (C-62, C-64), 128.54 (C-9, C-11), 129.00 (C-29), 136.74 (C-26), 138.48 (C-25), 138.98 (C-7), 140.16 (C-60), 161.00 (C-44), 161.12 (C-6), 163.54 (C-47), 163.56 (C-3) ppm. EI-MS *m/z:* 1064.62 Anal. Calcd. for $C_{64}H_{88}N_4O_6Si_2$: C, 72.14; H, 8.32; N, 5.26; O, 9.01; Si, 5.27. Found: C, 72.06; H, 8.24.

1-(2-Phenylhydrazinyl)-2-((1*S*)-1-((13S, 17S)-3-(1-(3,6-dioxo-2-phenylhydrazyny-l- (2H)-yl)-5-hydroxyhept-2-yn-1-yl]-13-me- thyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-yl)-5-hydroxyhept-2-yn-1-yl)tetrahydropyrida- zine-3,6-dione (5)

Hydrofluoric acid (5 mL) was added to a flask containing compound **4** (200 mg, 19 mmol), after being stirred for 72 h at room temperature. The reaction mixture was evaporated to dryness under reduced pressure. Then, the residue was purified by crystallization from methanol:water (4:1) yielding 45 % of product, m.p. 68-70 ºC; IR (V_{max}, cm^{-1}): 3400 and 3400, 2190, 1704 ans 1210; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 0.68 (s, 3H), 1.00 (s, 6H), 1.14 (m, 1H), 1.40 (m, 2H), 1.42 (broad, 2H), 1.44-1.52 (m, 3H), 1.60 (m, 2H), 1.66-2.26 (m, 9H), 2.32-2.33 (m, 2H), 2.50 (m, 1H), 2.51-2.52 (m, 2H), 2.66-2.76 (m, 5H), 2.78-2.80 (m, 2H), 2.82-2.90 (m, 3H), 3.70 (m, 2H), 4.84 (m, 1H), 5.40 (m, 4H), 6.98 (m, 1H), 7.13 (m, 1H), 7.14-7.24-7.25 (m, 4H), 7.28 (m, 1H), 7.80-7.84 (m, 4H) ppm. ^{13}C NMR (75.4 Hz, $CDCl_3$) δ_C: 10.70 (C-47, C-62), 15.68 (C-38), 23.42 (C-22), 23.94 (C-21), 25.30 (C-35), 25.47 (C-50), 26.32 (C-19), 27.78 (C-23), 29.33 (C-24), 29.40 (C-46, C-61), 30.60 (C-5, C-43), 30.68 (C-4), 30.84 (C-44), 37.74 (C-20), 38.56 (C-17), 44.57 (C-18), 50.51 (C-15), 52.44 (C-16), 53.37 (C-13), 55.46 (C-14), 57.52 (C-39), 60.44 (C-48), 74.02 (C-36, C-51), 85.25 (C-33), 89.26 (C-34), 91.30 (C-49), 121.12 (C-8, C-12), 121.57 (C-54, C-58), 123.56 (C-30), 124.66 (C-28), 127.23 (C-10, C-56), 127.44 (C-27), 128.31 (C-55, C-57), 128.55 (C-9, C-11), 128.98 (C-29), 136.78 (C-26), 138.44 (C-25), 138.94 (C-7), 140.20 (C-53), 160.98 (C-42), 161.12 (C-6), 163.52 (C-45), 163.56 (C-3) ppm. EI-MS *m/z:* 836.45 Anal. Calcd. for $C_{52}H_{60}N_4O_6$: C, 74.61; H, 7.22; N, 6.69; O, 11.47. Found: C, 74.54, H, 7.18.

Preparation of 1-((1S,Z)-1-((13*S*,17*S*)-3-((E)-1-(3,6-dioxo-2-phenyltetrahyropyri- dazin-1(2H)-yl)-2-(4-ethyloxetan-2-ylide-ne)ethyl)-13-methyl-7,8,9,11,12,13,14,15, 16,17-decahydro-6H-cyclopenta[a] phenan thren-17-yl)-2-(4-ethyloxetan-2-ylidene) ethyl)-2-phenyltetrahydropyridazine-3,6-dione (6)

A solution of **5** (200 mg, 0.24 mmol) and Copper(II) chloride anhydrous (100 mg, 0.74 mml) in 5 mL of methanol was stirred for 72 h at room temperature. The reaction mixture was evaporated to dryness under reduced pressure. After that the residue was

purified by crystallization from methanol:water (4:1) yielding 55 % of product, m.p. 234-236 ^{o}C; IR (V_{max}, cm^{-1}): 1702, 1248 and 1210; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 0.76 (s, 3H), 0.98 (s, 6H), 1.14-1.44 (m, 4H), 1.45-1.48 (m, 4H), 1.70-2.50 (m, 10H), 2.54 (m, 1H), 2.60 (m, 1H), 2.62-2.66 (m, 4H), 2.68 (m, 1H), 2.70-2.76 (m, 3H), 2.77 (m, 1H), 2.79 (m, 1H), 2.80 (m, 1H), 2.88-4.26 (m, 3H), 4.28 (m, 1H), 4.92 (d, 1H, J = 3.10 Hz), 5.10 (m, 1H), 6.18 (d, 1H, J 1.58 = Hz), 6.92-7.08 (m, 3H), 7.14-7.88 (m, 10H) ppm. ^{13}C NMR (75.4 Hz, $CDCl_3$) δ_C: 9.70 (C-6, C-62), 15.40 (C-40), 23.62 (C-29), 24.30 (C-30), 26.29 (C-24), 27.10 (C-3), 27.59 (C-19), 27.90 (C-5, C-61), 29.33 (C-18), 29.80 (C-46), 29.92 (C-13), 30.60 (C-12, C-45), 33.36 (C-52), 37.22 (C-23), 38.56 (C-20), 44.58 (C-25), 50.92 (C-22), 51.82 (C-21), 52.90 (C-31), 57.98 (C-41), 60.94 (C-8), 74.07 (C-2, C-51), 102.55 (C-7), 103.20 (C-48), 121.30 (C-54, C-58), 121. 76 (C-33, C-37), 123.88 (C-16), 125.06 (C-28), 125.52 (C-27), 127.23 (C-35, C-56), 128.32 (C-34, C-36), 128.54 (C-55, C-57), 133.08 (C-15), 136.52 (C-17), 136.94 (C-26), 137.01 (C-53), 138.25 (C-32), 156.58 (C-49), 158.05 (C-4), 164.32 (C-11), 164.53 (C-44), 166.62 (C-14), 166.70 (C-47) ppm. EI-MS *m/z:* 836.45 Anal. Calcd. for $C_{52}H_{60}N_4O_6$: C, 74.61; H, 7.22; N, 6.69; O, 11.47. Found: C, 74.58, H, 7.17.

Results and discussion

In this study an oxetan-phenyltetra-hydropyridazine-3,6-dione derivative was prepared using different strategies; the first stage was achieved (Figure 1) by the synthesis of a phenylhydrazine derivative (**2**). It is noteworthy that there are procedures for preparation of hydrazine derivatives suing several reagents such as thiosemicarbazide/acetic acid [10], palladium [11], acetylenic ester [12], 1-oxo-1,2,3,4-tetrahydrocarbazole [13] and others; however, despite its wide scope, it met some drawbacks; for example, several used agents have limited stability and their preparation requires special conditions. In this study, the phenylhydrazine derivative was prepared using three-components system (compound **1**, phenylhydrazine, 5-hexyn-3-ol) in presence of Copper(II) (Figure 1). The ^{1}H NMR spectrum of compound **2** showed several signals at 0.70 ppm for methyl group bound to steroid nucleus; at 1.00 ppm for methyl group involved in the hexynol fragment; at 1.14-1.32, 1.44-1.50, 1.66-2.16, 2.35-2.50, 2.78-2.80, 6.94 and 7.40-7.54 ppm for steroid moiety; at 1.40, 1.60, 2.32-2.34, 2.52-2.53 and 3.68 ppm for hexynol fragment; at 3.74 ppm for methylene group bound to both amino group and cyclopentene ring; at 4.34 ppm for methylene group bound to both amino and alkyne groups; at 6.80-6.92 and 7.10-7.14 ppm for phenyl groups. The ^{13}C NMR spectrum display peaks at 10.70 ppm for methyl group involved in the hexynol fragment; at 15.30 ppm for methyl group bound to steroid nucleus; at 25.88-27.74, 29.30, 38.52-44.52, 52.54-55.40, 124.06-125.18 and 128.42-139.42 ppm for steroid moiety; at 27.76-27.90, 29.41 and 74.00 ppm for the hexynol fragment; at 47.98 ppm for methylene bound to both alkyne and amino groups; at 52.39 ppm for methylene group bound to alkyne and cyclopentene ring; ata 63.82 and 86.04-86.62 ppm for alkyne groups; at 11.40-121.54, 125.80-126.00 and 50.72-151.90 ppm for phenyl groups. In addition, **2** showed a molecular ion at *m/z* 672.44.

The second stage was achieved by protection of hydroxyl groups involved

in the chemical structure of **2**. Several triorganosilyl groups have been employed for protection of hydroxyl groups such as *tert*-butyldime- thylsilyl and *tert*-butyldiphenylsilyl [14,15]; in this study, the compound **2** reacted with *tert*-butyldimethylsilyl chloride to form the compound **3** (Figure 1); It is important to mention that the yielding was good. The ^{1}H NMR spectrum of compound **3** showed several signals at 0.09, 0.84 and 1.08 ppm for tert-butyldimethylsilane fragment; at 0.72 ppm for methyl group bound to steroid nucleus; at 0.88 ppm for methyl group involved in the hexynol fragment; at 1.14-1.32, 1.44-1.50, 1.66-2.50, 2.78-2.80, 6.94, 7.40-7.52 ppm for steroid nucleus; at 1.36, 1.56, 2.64-2.70 and 3.80 ppm for hexynol fragment; at 3.70 ppm for methylene group bound to both amino group and cyclopentene ring; at 4.34 ppm for methylene group bound to both amino and alkyne groups; at 5.90 ppm for amino groups; at 6.80-6.92 and 7.10-7.14 ppm for phenyl groups. The ^{13}C NMR spectrum displays peaks at -3.62, 19.30, 28.10-29.84 and 41.20 ppm for tert-butyldimethylsilane fragment; at 15.30 ppm for methyl group bound to steroid nucleus; at 10.60 ppm for methyl group involved in the hexynol fragment; at 25.86, 26.29-27.76, 29.30, 38.54-40.22, 44.60, 52.54-55.40 and 128.44-139.38 ppm for steroid nucleus; 25.92-26.02, 29.92 and 74.00 ppm for hexynol fragment; at 47.98 ppm for methylene group bound to both amino group and cyclopentene ring; at 52.40 ppm for methylene group bound to both amino and alkyne groups; at 63.82 and 86.08-88.60 ppm for alkyne groups; at 11.40-124.06, 125.78-126.00 and 150.72-151.90 ppm for phenyl groups. Finally, **3** showed a molecular ion at *m/z* 984.70.

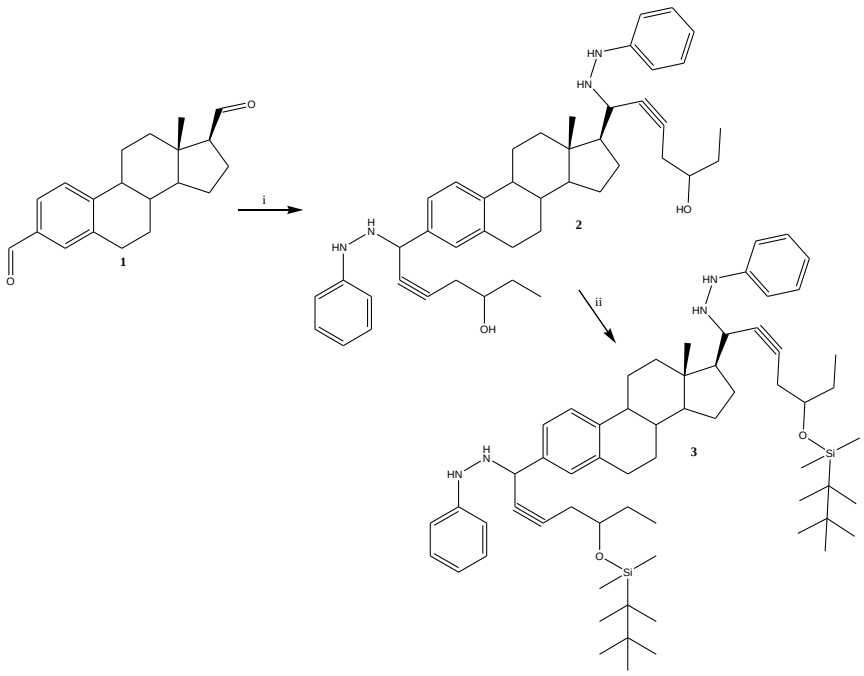

Figure 1. Preparation of trimethylbutan-silyloxy-steroid-hydrazine (**3**). The first stage was achieved by the synthesis of a phenylhydrazine derivative (**2**) using the three-components system (3,17-aldol-estradiol, phenylhydrazine, 5-hexyn-3-ol) in the presence of Copper(II) (i). Then, **2** was reacted with *tert*-butyldimethylsilyl chloride (ii) to form the compound **3**.

The third stage was achieved by preparaing a pyridazine derivative (**4**); here it is important to mention that there are reports on the synthesis of several pyridazine derivatives using some reagents such as; phosphorus chloride [16], enzenediazo- nium chloride [17], haloazodiene derivatives [18] hydrochloric acid [19] and others; however, handling requires special conditions. Therefore, in this study, the synthesis of **4** was carried out by the reaction of **3** with succinic acid using boric as catalyst to form the pyridazine-3,6-dione ring (Figure 2).The ^{1}H NMR spectrum of compound **4** showed several signals at 0.04 and 0.88 ppm for terbutyldimethylsylane fragment; at 0.68 ppm for methyl group bound to steroid nucleus; at 0.86 ppm for methyl group involved in the hexynol fragment; at 1.14, 1.44-1.50, 1.66-2.50, 2.77-2.79, 6.96 and 7.13 ppm for steroid nucleus; at 1.36, 1.56, 2.66, 2.70 and 3.60 ppm for methylene groups bound to both ether and alkyne groups; at 2.68, 2.76 and 2.82-2.90 ppm for pyridazine-3,6-dione rings; at 4.86 ppm for methylene bound to both amino group and cyclopentene ring; at 5.40 ppm for methylene group bound to both amino and phenyl groups; at 7.14-7.25 and 7.76-7.82 ppm for phenyl groups. The ^{13}C NMR spectrum display peaks at -4.20, 17.90 and 25.84 ppm for terbuthyldimethylsylane fragment; at 10.60 ppm for methyl group involved in the arm bound to both ether and alkyne groups; at 15.70 ppm for methyl bound to steroid nucleus; at 23.44, 23.92, 26.29-29.30, 37.80-52.48, 55.44, 123.56-124.66, 127.44 and 129.00-138.44 ppm for steroid moiety; at 23.46-23.60, 29.72 and 75.10 ppm for arm bound to pyridazine-3,6-dione rings; at 30.60-30.84 ppm for pyridazine-3,6-dione rings; at 53.34 ppm for methylene group bound to both amino group and cyclopentene ring; at 57.50 ppm for methylene group bound to both amino and alkyne group; at 60.42 and 85.28-91.30 ppm for alkyne groups; at 121.10-12.62, 127.22, 128.30-128.54 and 138.98-140.61 ppm for phenyl groups. In addition, **4** showed a molecular ion at *m/z* 1064.62. The following stage was achieved by the removal of silyl-protecting group of the compound **4**. It is worth mentioning that several reagents have been used for the removal of silyl protecting groups from hydroxyl such as ammonium fluoride [20, 21], tris(dimethyl-amino)sulfonium/difluorotrimethylsilic ate [22], hydrofluoric acid [23] and others. Therefore, in this study, hydrofluoric acid was used to remove silyl-protecting group from hydroxyl of **4** (Figure 2) to form the compound **5**.

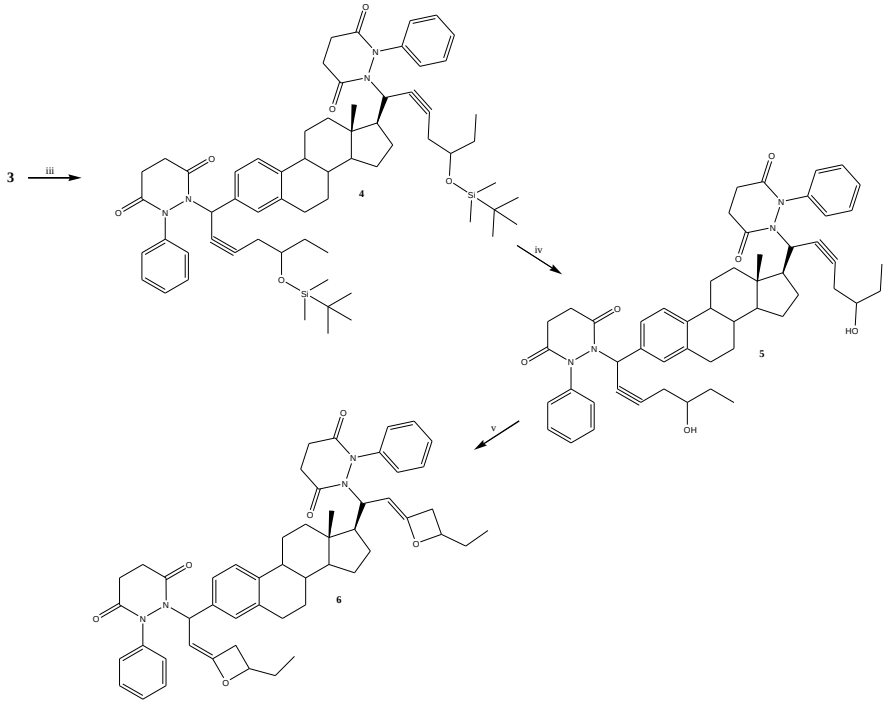

Figure 2. Preparation of an oxetan-phenyltetrahydropyridazine-3,6-dione derivative (**6**). The first satage was achieved by the reaction of **3** with succinic acid (iii) to form a pyridazine derivative (**4**). Then, **4** was reacted with hydrofluoric acid (iv) to synthesis of a tetrahydropyridazine-3,6-dione (**5**). Finally, **6** was carried out by the reaction of **5** with CopperII (v).

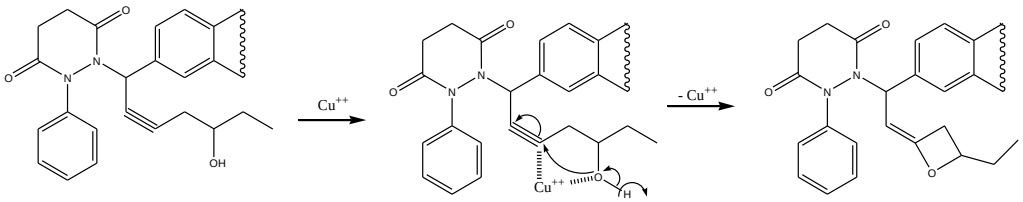

Figure 3. Mechanism of reaction involved in the synthesis for the compound **6**

The ^{1}H NMR spectrum of compound **5** showed several signals at 0.68 ppm for methyl bound to steroid nucleus; at 1.00 ppm for methyl group involved in the hexynol fragment; at 1.14, 1.44-1.52, 1.66-2.26, 2.50, 2.78-2.80, 6.98, 7.14 and 7.28 ppm for steroid moiety; at 1.40, 1.60, 2.32-2.33, 2.52-2.52 and 3.70 ppm for the hexynol fragment; at 1.42 for hydroxyl groups; at 2.66-2.76 and 2.82-2.90 ppm for pyridazine-3,6-dione ring; at 4.84 ppm for methylene group bound to both alkyne and cyclopentane ring; at 5.40 ppm for methylene group bound to both alkyne group and pyridazine-3,6-dione ring; at 7.13, 7.24 and 7.80-7.84 ppm for phenyl groups. The ^{13}C NMR spectrum displays peaks at 10.70 ppm for methyl group of the hexynol fragment; at 15.68 ppm for methyl group bound to steroid nucleus; at 23.42, 26.32-29.33, 37.44-52.44, 55.46, 126.56-124.66, 127.44 and 136.78-138.44 ppm for steroid moiety; at 25.30-25.47, 29.40 and 74.02 ppm for hexynol fragment; at 30.60-30.84 ppm for pyridazine-3,6-dione ring; at 53.37 for methylene group bound to both alkyne group and cyclopentane ring; at 57.52 ppm for methylene group bound to alkyne and phenyl groups; at 60.44, 82.25-91.30

ppm for alkyne groups; at 121.12-121.57, 127.23, 128.31-128.55 and 138.94-140.20 ppm for phenyl groups; at 160.98-163.56 ppm for ketone groups. Finally, **5** showed a molecular ion at *m/z* 836.45.

Finally, the oxetan-phenyltetrahydropyrida- zine-3,6-dione derivative (**6**) was synthezised; it is important to mention that there are some reports for the synthesis of oxetane derivatives which the use of several reagents such as tetrabutylammonium bromide [24], Rhodium [25], dimethyl- oxosulfonium Methylide [26] and others. In this study, the compound 5 was reacted with Cooper(II) to form oxetane-steroid derivative (Figure 2 and 3). The ^{1}H NMR spectrum of compound **6** showed several signals at 0.76 ppm for methyl bound to steroid nucleus; at 0.98 ppm for methyl group involved in the hexynol fragment; at 1.14-1.44, 1.70-2.50, 2.77, 2.80, 6.92-7.08 ppm for steroid moiety; at 1.45-1.48 ppm for hexynol fragment; at 2.54, 2.60-2.66, 2.70-2.76 ppm for pyridazine-3,6-dione ring; at 2.60, 2.68, 2.79 and 2.88-4.26 ppm for oxetane ring; at 4.28 ppm for methylene bound to both alkene groups and pyridazine-3,6-dione rings; at 4.92 and 6.18 ppm for alkene groups: at 7.14-7.88 ppm for phenyl groups. The ^{13}C NMR spectrum display peaks at 9.70 ppm for methyl group of the hexynol fragment; at 15.40 ppm for methyl group bound to steroid nucleus; at 23.62-26.29, 27.59, 29.33, 37.22-52.90, 123.88-125.52 and 133.08-136.94 ppm for steroid moiety; at 27.10, 33.36, 74.07 and 156.58-158.05 ppm for oxetane ring; at 27.90 ppm for methylene group bound to both oxetane ring and methyl group; at 29.80-30.60 ppm for pyridazine-3,6-dione ring; at 57.98 ppm for methylene group bound to both cyclopentane ring and pyridazine-3,6-dione ring; at 60.94 ppm for methylene group bound to both alkene group and pyridazine-3,6-dione ring; at 102.55-103.20 ppm for alkene groups; at 121.30-123.76, 127.23-128.54 and 137.01-138.25 ppm for phenyl groups; at 164.32-166.70 ppm for ketone groups. Finally, **6** showed a molecular ion at *m/z* 836.45.

Conclusion

In this study, a facile synthesis of an oxetan-phenyltetrahydropyridazine-3,6-dione derivative was reported using some chemistry tools.

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