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Synthesis and design of a progesterone-alkyne derivative

L. Figueroa-Valverde[1], F. Díaz-Cedillo[2], M. López-Ramos[1], E. García- Cervera[1], E. Pool-Hernandez[1]

[1]*Laboratorio de Farmacoquímica, Facultad de Ciencias Químico-Biológicas, Universidad Autónoma de Campeche, Av. Agustín Melgar, Col Buenavista C.P.24039 Campeche Cam., México.*
[2]*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.*

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In this work a progesterone-alkyne derivative was synthesized. The first stage involves preparation of a progesterone-ethylenediamine derivative (**2**) by the reaction of progesterone with ethylenediamine using Mannich reaction. The second stage involves the formation of ethylenediamine-progesterone oxime (**4**) by the reaction of **2** with hydroxylamine hydrochloride (Method A). Additionally, **4** was also synthesized by the reaction of pregn-4-ene-3E,20E-dioxime (**3**) with ethylenediamine using Mannich reaction (method B). Finally, the route for synthesis of progesterone-alkyne derivative (**5**) was followed using a three-component system (compound **4,** benzaldehyde and 1-hexyne) in the presence of anhydrous cupric chloride.

Key words: Progesterone, oxime, three-component system.

1. INTRODUCTION

There are several reports of multi-component reactions for the synthesis of several compounds [1-3]; for example, some studies [4] described the preparation of propargylamines using a three-component system (aldehyde, amine, and alkyne) in water or copper iodide [5] as catalyst. In other studies an enantioselective, copper(I)-catalyzed three-component reaction is used for the preparation of propargylamines [6]. In ref. [7] the diastereoselective synthesis of α-oxyamines using a three-component system (α-oxyaldehyde, amine and alkyne) in presence of gold, silver and copper in water is used. In other studies [8] the synthesis of tertiary propargylamine using a three-component system which involves aldehyde, alkyne and 4-piperidone hydrochloride in presence of cupric bromide is developed. In the report of Yadav and coworkers [9] the synthesis of propargylamines by reaction of aldehydes, amines and alkyne derivatives using copper (I) bromide as catalyst in ionic liquids is described. Recently a carbamazepine-alkyne derivative was synthesized using a three-component system (carbamazepine, benzaldehyde and 1-hexyne) in presence of cupric chloride as catalyst [10]. All these studies report the synthesis of several compounds using a three-component system; nevertheless, various protocols and special conditions are required for its development. In this study, our initial design included a facile synthesis of a new steroid-alkyne derivative; the route involves preparation of progesterone-alkyne derivative using a three-component system such as 4-[(2-amino-ethylamino)-methyl]-pregnen-4-en-3E,20E-dioxime, benzaldehyde and 1-alkyne in the presence of cupric chloride as catalyst.

2 EXPERIMENTAL

General methods

Pregn-4-ene-3E,20E-dioxime was prepared according to a previously reported method [11]. Progesterone and the other compounds used in this study were purchased from Sigma-Aldrich Co., Ltd. The melting points of the compounds were determined on an Electrothermal (900 model) apparatus. Infrared (IR) spectra were recorded in 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 DMSO-d_6 using TMS as internal standard. EIMS spectra were obtained on a Finnigan Trace GCPolaris Q. spectrometer. Elemental analysis data were acquired from a Perkin Elmer Ser. II CHNS/0 2400 elemental analyzer.

* To whom all correspondence should be sent:
e-mail: lauro_1999@yahoo.com

4-[(2-Amino-ethylamino)-methyl]-17-(1-hydroxyimino-ethyl)-10,13-dimethyl-1,2,6,7,8, 9,10,11,12,13,14,15,16,17-tetradecahydro-cyclo-penta[a]phenanthren-3-one oxime (2).

A solution of pregn-4-en-3,20-dione (100 mg, 0.32 mmol), ethylenediamine (35 µL, 0.52 mmol), and methanol (3 mL) in formaldehyde (10 mL) was gently refluxed for 24 h and then cooled to 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 (4:1) yielding 75 % of product, m.p. 92-94ºC; IR (V_{max}, cm^{-1}): 3384, 3354, 1716; ^{1}HNMR (300 HMz, DMSO-d_6) δ_H: 0.65 (s, 3H), 0.89-0.98 (m, 2H), 1.08 (s, 3H), 1.17-1.44 (m, 3H), 1.46-1.64 (m, 4H), 1.67-1.78 (m, 3H), 2.03-2.11 (m, 4H), 2.14 (s, 3H), 2.18 (m, 1H), 2.52 (broad , 3H), 2.54-2.60 (m, 3H), 2.66 (t, 2H, J = 6 Hz), 2.82 (t, 2H, J = 6 Hz), 3.36 (m, 2H) ppm. ^{13}C NMR (74.5 MHz, DMSO-d_6) δ_C: 13.26 (**C**-18), 17.20 (**C**-27), 20.78 (**C**-5), 23.30 (**C**-11), 23.80 (**C**-9), 26.64 (**C**-8), 29.90 (**C**-28), 30.97 (**C**-10), 34.88 (**C**-3), 35.02 (**C**-15), 35.58 (**C**-16), 38.10 (**C**-6), 38.88 (**C**-17), 41.17 (**C**-24), 43.80 (**C**-1), 44.60 (**C**-21), 52.10 (**C**-23), 56.12 (**C**-2), 57.64 (**C**-4), 63.40 (**C**-7), 132.70 (**C**-13), 159.44 (**C**-12), 196.76 (**C**-14), 206.60 (**C**-19) ppm. MS (70 ev): *m/z* 386.20 [M^+]; Anal. calcd. for $C_{24}H_{38}N_2O_2$: C, 74.57; H, 9.91; N, 7.25; 0, 8.28. Found: C, 74.50; H, 9.90.

4-[(2-Amino-ethylamino)-methyl]-17-(1-hydroxyimino-ethyl)-10,13-dimethyl-1,2,6,7,8, 9,10,11,12,13,14,15,16,17-tetradecahydro-cyclo-penta[a]phenanthren-3-one oxime (4).

Method A. A solution of **2** (100 mg, 0.29 mmol), ethylenediamine (35 µL, 0.52 mmol) and ethanol (3 mL) in formaldehyde (10 mL) was gently refluxed for 24 h and then cooled to 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 60 % of product, m.p. 118-120 ºC; IR (V_{max}, cm^{-1}): 3380, 3352, 3300;^{1}HNMR (300 HMz, DMSO-d_6) δ_H: 0.87 (s, 3H), 0.89-0.98 (m, 2H), 1.01 (s, 3H), 1.23-1.44 (m, 3H), 1.46-1.64 (m, 3H), 1.67-1.69 (m, 2H), 1.74 (s, 3H), 1.78-2.16 (m, 6H), 2.28-2.45 (m, 2H), 2.62 (m, 1H), 2.68 (t, 2H, J = 6 Hz), 2.82 (t, 2H, J = 6 Hz), 2.83 (m, 1H), 3.50 (s, 2H), 4.40 (broad, 5H) ppm. ^{13}CNMR (74.5 MHz, DMSO-d_6) δ_C: 12.70 (**C**-30), 13.25 (**C**-18), 19.25 (**C**-29), 21.17 (**C**-5), 21.31(**C**-15), 22.53 (**C**-11), 25.84 (**C**-9), 26.64 (**C**-8), 30.81 (**C**-16), 30.97 (**C**-10), 34.88 (**C**-3), 37.88 (**C**-17), 37.95 (**C**-6), 41.17 (**C**-25), 44.06 (**C**-22), 44.89 (**C**-1), 52.10 (**C**-24), 54.91 (**C**-4), 56.70 (**C**-2), 57.14 (**C**-7), 137.70 (**C**-13), 152.06 (**C**-12), 156.76 (**C**-14), 161.12 (**C**-19) ppm. MS (70 ev): *m/z* 416.40 [M^+]; Anal. calcd. for $C_{24}H_{40}N_4O_2$: C, 69.19; H, 9.68; N, 13.45; 0, 7.68. Found: C, 69.15; H, 9.71.

Method B. A solution of **2** (100 mg, 0.26 mmol), hydroxylamine hydrochloride (54 mg, 0.77 mmol) and sodium hydroxide (5%) in 10 mL of ethanol was refluxed for 24 h. The reaction mixture was evaporated to a smaller volume. The residue was dissolved in 10 mL of distilled water. The solution was adjusted to pH 2 with conc. hydrochloric acid and extracted with 20 mL of ethyl acetate: chloroform (2:1). The organic solution was dried with Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was extracted with chloroform and chromatographed on a silica gel column (10 × 75 mm). The product was purified by crystallization from methanol:water yielding 25 % of product. The ^{1}H NMR and ^{13}C NMR data were similar to those of the product obtained by Method A.

4-{[2-(Hex-1-ynil-phenyl-amino)-ethylamino]-methyl}-17-(1-hydro-xyimino-ethyl)-10,13-dimethyl-1,2,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-cipenta[a]phenan-thren-3one oxime (5).

A solution of **4** (100 mg, 0.29 mmol), benzaldehyde (60 µL, 0.59 mmol) 1-hexyne (50 µL, 0.43 mmol) and ethanol (10 mL) was stirred for 10 min at room temperature. Then anhydrous cupric chloride (113 mg, 0.84 mmol) 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 70 % of product, m.p. 162-164 ºC; IR (Vmax, cm^{-1}) 3350, 3304 2140 cm^{-1}: ^{1}HNMR (300 HMz, DMSO-d_6) δ_H: 0.87 (s, 3H), 0.89 (m, 1H), 0.91 (t, 3H, J = 7.0 Hz), 0.94 (m, 1H),1.05 (s, 3H), 1.20-1.40 (m, 3H), 1.44-1.48 (m, 4H), 1.49-1.70 (m, 5H), 1.74 (s, 3H), 1.78-2.28 (m, 7H), 2.35 (m, 2H), 2.42-2.85 (m, 3H), 2.94 (t, 2H, J = 7.0 Hz), 3.19 (t, 2H, J = 7.0 Hz), 3.50 (s, 2H), 6.08 (broad, 3H), 6.58-7.16 (m, 5H) ppm. ^{13}CNMR (74.5 MHz, DMSO-d_6) δ_C: 12.71 (**C**-36),

13.24 (**C**-18), 15.63 (**C**-42), 16.95 (**C**-39), 19.55 (**C**-35), 21.17 (**C**-5), 21.31 (**C**-15), 21.98 (**C**-41), 22.51 (**C**-11), 25.84 (**C**-5), 26.62 (**C**-8), 30.67 (**C**-16), 30.96 (**C**-10), 32.01 (**C**-40), 34.88 (**C**-3), 37.68 (**C**-17), 37.95 (**C**-6), 44.06 (**C**-22), 44.89 (**C**-1), 49.18 (**C**-24), 52.73 (**C**-4), 54.91 (**C**-2), 57.73 (**C**-7), 58.02 (**C**-25), 59.25 (**C**-38), 82.56 (**C**-37), 114.67 (**C**-32, **C**-28), 120.72 (**C**-30), 129.63 (**C**-31, **C**-29), 137.77 (**C**-13), 146.23 (**C**-27), 151.40 (**C**-12), 156.96 (**C**-14), 161.29 (**C**-19) ppm. MS (70 ev): *m/z* 572.70 [M^+]; Anal. calcd. for $C_{36}H_{52}N_4O_2$: C, 75.48; H, 9.15; N, 9.78; 0, 5.59. Found: C, 75.44; H, 9.17.

5. RESULTS AND DISCUSSION

In this study, a straightforward route is reported for the synthesis of a progesterone-alkyne derivative (**5**). The first stage was carried out by reacting pregnen-4-en-3,20-dione (**1**) with ethylenediamine and formaldehyde to form an amino-progesterone derivative (**2**) using the Mannich method (Figure 1).

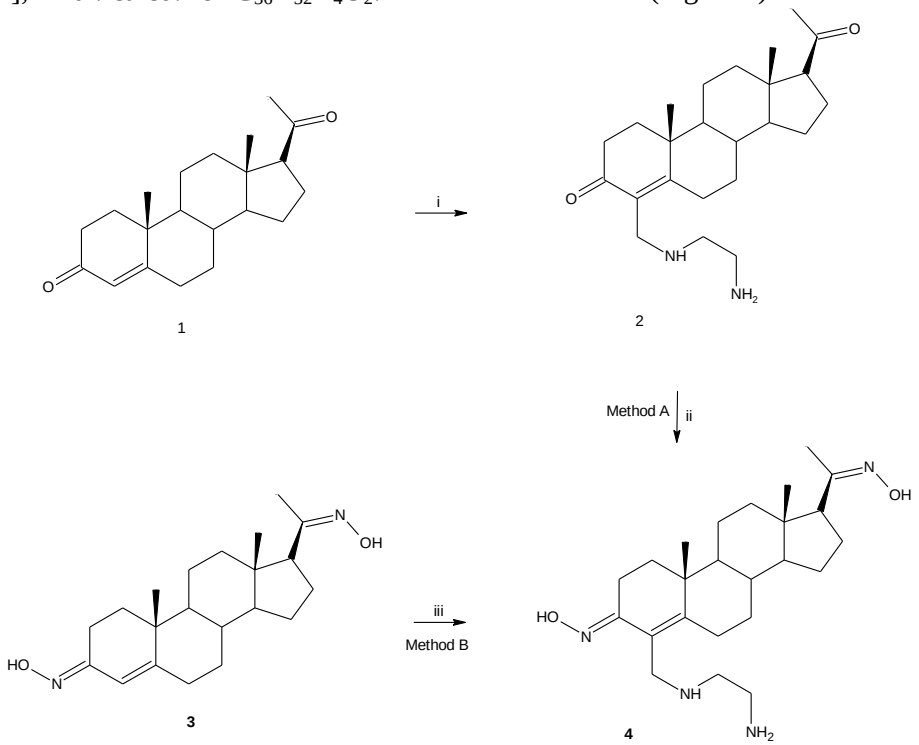

Fig. 1. Synthesis of an ethylenediamine-progesterone oxime derivative (**4**). The first stage involves the preparation of a progesterone-ethylenediamine derivative (**2**) by the reaction of progesterone with ethylenediamine, followed by formation of the compound (**4)** by oximation of (**2)** (method A). The second stage (method B) involves the synthesis of (**4)** by the reaction of progesterone-oxime (**3**) with ethylenediamine. i = formaldehyde/methanol; ii = hydroxylamine hydrochloride; iii = formaldehyde/methanol.

It is important to mention that several amino-steroid derivatives have been obtained using the Mannich reaction; the structural chemistry of these compounds [12] involves an activated methyl group in ring A. Therefore, in this work a study of the reactivity of the hydrogen atom involved in ring A of compound 1 was undertaken by means of Mannich reaction. The ^{1}H NMR spectrum of 2 showed several signals at 0.65, 1.08 and 2.14 ppm corresponding to methyls presents in the steroid nucleus and at 0.89-0.98 and 1.17-2.60 ppm for protons involved in the steroid nucleus. Several signals at 2.52 ppm for protons of amino groups; at 2.66-3.36 ppm for methylene groups involved in the arm bound to A-ring of steroid nucleus were found. The ^{13}C NMR spectra displayed chemical shifts at 13.26, 17.20 and 29.90 ppm for the carbons of methyl groups present in the steroid nucleus. The chemical shifts of the methylenes involved in the steroid nucleus were found at 20.78-26.64, 30.97-38.78, 43.80 and 56.12-196.76 ppm. Additionally, several chemical shifts at 41.17, 44.60 and 52.10 ppm for methylenes present in the arm bound to the A-ring of the steroid nucleus were displayed. A signal at 206.60 ppm for a ketone group was found. The presence of the compound 2 was further confirmed by the mass spectrum which showed a molecular ion at m/z 386.20.

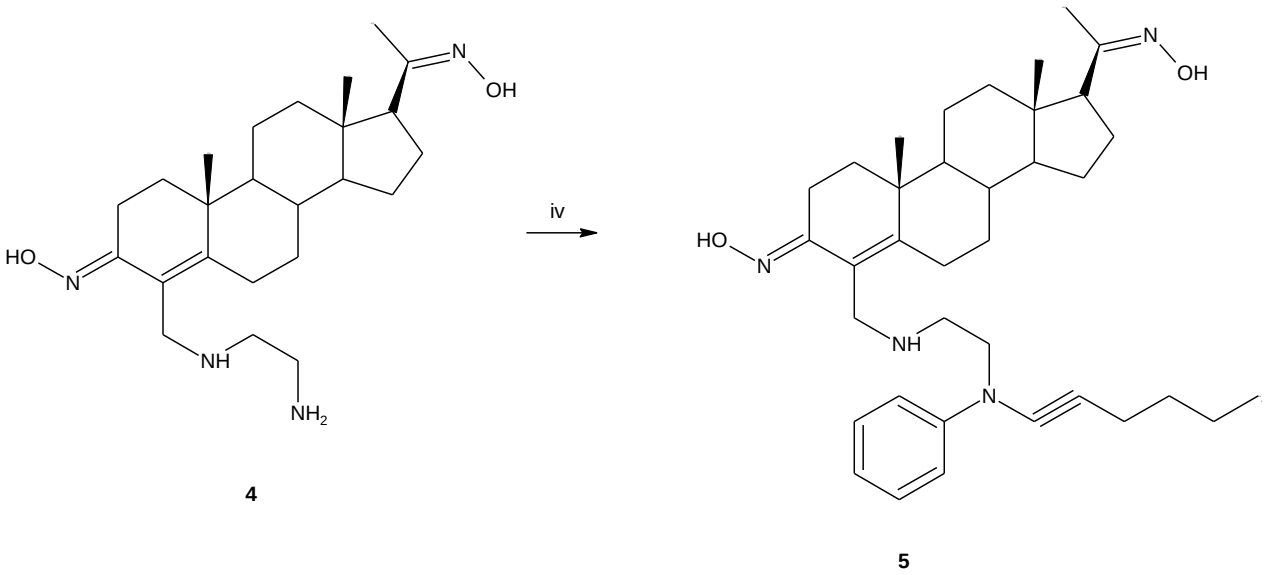

Fig. 2. Synthesis of a progesterone-alkyne derivative (**5**) using a three-component system (compound (**4**), benzaldhehyde and 1-hexyne). iv = anhydrous cupric chloride /ethanol

The second stage was performed by the synthesis of 4 using two different methods; in method A, the pregnen-4-en-3E,20E-dioxime (3) was reacted with ethylenediamine to form 4 using the Mannich reaction. The ^{1}H NMR spectrum of 4 showed several signals at 0.87, 1.01 and 1.74 ppm corresponding to methyls present in the steroid nucleus; at 0.89-0.98, 1.23-1.69, 1.78-2.62 and 2.83 ppm for protons involved in the steroid nucleus were found. In addition, signals at 2.68, 2.82 and 3.50 ppm for hydrogens involved in the arm bound to the A-ring of the steroid nucleus were registered. A signal at 4.40 ppm for both hydroxyl and amino groups was found as well. The ^{13}C NMR spectra displayed chemical shifts at 12.72, 13.25 and 19.45 ppm for the carbons of methyl groups present in the steroid nucleus. The chemical shifts of the methylenes involved in the steroid nucleus were found at 21.17-37.95, 44.89, 54.91-151.40 ppm. In addition, several chemical shifts at 41.17, 44.06 and 52.12 ppm for the arm bound to the A-ring of the steroid nucleus were displayed. Signals at 156.96 and 161.29 ppm carbons bound to hydroxyl amino group were found as well. The presence of compound 4 was further confirmed by the mass spectrum which showed a molecular ion at m/z 416.40. In the method B the compound 2 was reacted with hydroxylamine hydrochloride to form 4. The ^{1}H NMR and ^{13}C NMR data were similar to those of the product obtained by method A. It is important to mention that method A gives higher yields of compound 4 than method B.

The third stage was performed using the three-component system for the synthesis of 5 (see Figure 2). There are many procedures which use a three component system for the synthesis of several compounds. The most widely practiced method employs boric acid [13], silica sulfuric acid [14], poly(4-vinylpyridine-codivynylbenzene)-Cu(II) complex [15], H_2SO_4[16], silica triflate [17] and phosphorus pentoxide [18]. Nevertheless, despite their wide scope, the protocols mentioned suffer from several drawbacks owing to the limited stability of some reagents. Analyzing these data and the reports which indicate that the copper (I) reagent has been found to be an efficient catalyst for an enantioselective one-pot three-component synthesis using aldehydes, amines, and alkynes [19,20], in this study we report a straightforward route for the synthesis of 5 using a three-component system consisting of compound 4, benzaldehyde and 1-alkyne in presence of cupric chloride as catalyst (see Figure 2). The ^{1}H NMR spectrum of 5 showed several signals at 0.87, 1.05 and 1.74 ppm for methyl groups present in the steroid nucleus; at 0.91 ppm for a methyl group involved in the arm of alkyne; at 0.89-0.94, 1.20-1.40, 1.49-1.70, 1.78-2.28 and 2.43-2.85 ppm for protons involved in the

steroid nucleus. Several chemical shifts at 1.44-1.48 and 2.35 ppm for methylenes involved in the arm of alkyne; at 2.94, 3.19 and 3.50 ppm for an arm bound to the A-ring of the steroid nucleus were displayed. Signals at 6.08 ppm for both hydroxyl and amino groups and at 6.58-7.16 ppm for protons involved in the phenyl group were found. The presence of the compound 5 was further confirmed by the mass spectrum which showed a molecular ion at m/z 572.70.

6. CONCLUSIONS

In this study, we report an easy methodology to synthesize a progesterone-alkyne derivative (**5**).

REFERENCES

1. P. Appukkuttan, W. Dehaen, V. Fokin, E. Eycken. *Org. Lett.*, **6**, 4223 (2004).
2. B. Ranu, A. Hajra, J. Umasish. *J. Org. Chem.*, **65**, 6270 (2000).
3. J. McNally, M. Youngman, S. Dax. *Tetrahedron Lett.*, **29**, 967 (1998).
4. V. Kar-Yan, Y. Liu, W. Man-Kin, C. Chi-Ming. *Org. Lett.*, **8**,1529 (2006).
5. P. Sreedhar, S. Reddy, V. Prakash, A. Ravindra. *Tetraedron Lett.*, **46**, 7019 (2005) .
6. N. Gommermann, C. Koradin, K. Polborn, P. Knochel. *Angew. Chem*., **42**, 5763 (2003).
7. H. Baosheng, Y. Xiaoquan, L. Chao. *Adv. Synth. Cat.*, **348**, 1528 (2006).
8. P. Aschwanden, C. Stephenson, E. Carreira. *Org. Lett*., **8**, 2437 (2006).
9. J. Yadav, B. Reddy, V. Naveenkumar, R. Rao, K. Nagaiah. *New J. Chem.*, **28**, 335 (2004).
10. L. Figueroa-Valverde, F. Díaz-cedillo, A. Camacho-Luis, M. López-Ramos, E. García-Cervera. *Asian J. Chem*., **22**, 7057 (2009).
11. L. Figueroa-Valverde, F. Díaz-Cedillo, M. Lopez-Ramos, E. Garcia-Cevera. *Int. J. Pharm. Tech. Res.*, **2**, 334 (2010).
12. N. Khoury, A. Usubillaga, S. Cedillo. *J. Pharm. Sci*., **80**, 661 (1991).
13. S. Tu, F. Fang, C. Miao, H. Jiang, Y. Feng, D. Shi. *Tetrahedron Lett.*, **44**, 6153 (2003).
14. P. Salehi, N. Fard. Tetrahedron Lett., **44**, 2889 (2003).
15. R. Yarapathi, S. Kurva, S. Tammishetti. *Catal. Commun*., **5**, 511 (2004).
16. J. Bussolari, P. McDonnell. *J. Org.Chem*., **65**, 6777 (2005).
17. F. Shirini, K. Marjani, H. Nahzomi. *Arkivoc*, 51 (2007).
18. R. Crossland, K. Servis. *J. Org. Chem*., **35**, 3195 (1970).
19. N. Gommermann, C. Koradin, K. Polborn, P. Knochel. *Angew. Chem.*, **115**, 5401 (2003).
20. M. Anary, H. Anaraki. *Monatsh. Chem*., **140**, 3497 (2009).

СИНТЕЗ И ДИЗАЙН НА ПРОГЕСТЕРОН-АЛКИНОВИ ПРОИЗВОДНИ

Л. Фигероа-Валверде[1], Ф. Диас-Седильо[2], М. Лопес-Рамос[1], Е.Гарсиа-Сервера[1], Е. Поол-Ернандес[1]

[1]Лаборатория по фармацевтична химия, Факултет по химико-биологични науки, Автономен университет на Кампече, Мексико

[2]Висше училище по биологични науки, Национален политехнически институт, Санто Томас, Мексико

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(Резюме)

В настоящата работа се съобщава за синтезирането на прогестерон-алкинови производни. Първият етап включва проготвяне на прогестерон-етилендиаминово производно (**2**) използвайки реакцията на Mannich. Вторият етап включва получаването на оксима на етилендиамина-прогестерона (**4**) чрез реакцията на **2** с хидроксиламин-хидрохлорид (метод А). Освен това **4** е също синтезирано чрез реакцията на прегно-4-ен-3E,20E-диоксим (**3**) с етиленсиамин по реакцията на Маних (метод В). Накрая се следва маршрута за синтезата на прогестерон-алкиновите производни (**5**) в три