Preparation and Characterization of Amino Acetylene Derivative by Mannich Reaction .

TAREQ .A. MANDEEL , MANAF.A. GUMA.

jm@yahoo.com. , manafalhiti@yahoo.com.

Department Of Chemistry ,College Of Science , University of ANBAR.

Received 19 May 2013 ; Accepted 15 September 2013

Abstract

A short procedure for preparation of {4-[17-(1,5-Dimethyl-hexyl)-10,13-dimethyl-hexadecahydro-cyclopenta[a]phenanthren-3-yloxy] –but -2-ynylamino}-acetaldehyde)(3) from reaction of terminal acetylene with N-(diphenylmethylene) glycinates (2) is described. The reaction of terminal acetylene with compound (2) promoted by amino acid gave the dehydroamino acids containing secondary amine in good yield with aldehyde in presence of CuCl via microwave technique according to Mannich reaction .The compound(2) was prepared by refluxing cholesterol with propargyl bromide in dilute ethanolic potassium hydroxide solution at 70 ^{o}C .All compounds were characterized by means of their FT.IR spectra data and melting points.

Key words: Mannich reaction , Terminal acetylene , S_N2 mechanism, cholesterol.

(1) ischolesterol:17-(1,5-Dimethyl-hexyl)-10,13-dimethyl-,3,4,7,8,9,10,11,12,13,14,15,16,17-tetra -decahydro-1H-cyclo penta[a]phenanthren-3-ol.

(2) is 17-(1,5-Dimethyl-hexyl)-10,13-dimethyl-3-prop-2-ynyloxy-hexadecahydro–cyclopenta [a] phena -nthrene.

(3) is{4-[17-(1,5-Dimethyl-hexyl)-10,13-dimethyl-hexadecahydro-cyclopenta[a]phenanthren-3-yloxy]-but-2-ynylamino}-acetaldehyde.

Preparation and Characterization of Amino Acetylene Derivative by Mannich Reaction .

TAREQ .A. MANDEEL , MANAF.A. GUMA

تحضير وتشخيص مشتق اميني استليني بتفاعل مانخ

طارق عبد الجليل منديل – مناف عبد الرحمن جمعة

قسم الكيمياء - كلية العلوم – جامعة الانبار .

الخلاصة

تم في هذا البحث تحضير مشتق اميني استليني بطريقة مختصرة جدا حيث ان المركب الناتج هو (4-17 ثنائي مثيل سداسي – 10 – 13- ثنائي مثيل سداسي عشر – خماسي الحلقة فينانثرولين)(3), الذي حضر بتفاعل مركب الاستلين الطرفي المحضر مع الكولسترول (مركب حيوي) مع الكلايسين (حامض اميني) وذلك بتفاعل مانخ . وقد تم اولا تحضير المركب الاستليني الطرفي بتفاعل الكولسترول من موقع مجموعة الهيدروكسيل مع بروميد البروبارجيل لتكوين مركب ايثري، وذلك بتصعيد الكولسترول بوجود هيدروكسيد البوتاسيوم الكحولي في 70 مْ ، ثم تم تفاعل المركب الاستليني الطرفي مع الكلايسين بميكانيكية S_N2 بتفاعل مانخ بتقنية المايكروويف . تم تشخيص المركبات بطيف الاشعة تحت الحمراء ونقاط الانصهار حيث جاءت جميع النتائج لهذه الدراسة مطابقة للجانب النظري مؤكدة صحة التفاعلات والتحضير.

الكلمات الدالة: تفاعل مانخ ,استلين طرفي ,ميكانيكية S_N2 ، كولسترول

Introduction

Aryl alkyneamines are important compounds for medicinal chemistry[1], The most important and widely used aminoalkylation of CH-acidic compounds is the Mannich reaction[2] . The Mannich Reaction has been suggested in many biosynthetic pathways, especially for alkaloids Mannich [3].The most active uses as Anticholinergic Agents[4] , Hypertensive Agents [5] , CNS Stimulant Agents[6], Antispasmodic Agents ,Local Anesthetic and Anticancer Agents[7]. Mannich type reactions are among the most important carbon-carbon bond forming reactions an organic preparation [8]. They provide amino carbonyl compounds which are important synthetic intermediates for various pharmaceuticals and natural products [9,10] and can be readily converted to derivatives that possess useful applications in paint and polymer chemistry, plant protection, and particularly medicine and

the pharmaceutical industry [11] . By this wide applicability, unlike the parent aldol reaction, modern asymmetric Mannich-type reactions have emerged only in the pre mentioned fields. These reaction typically involve the addition of preformed enolate equivalents to preformed imines, and both are stoichiometric[12].

The diffusion of the Mannich reaction has been fueled by the ubiquitous nature of nitrogen containing compounds in drugs and natural products [13]. In 1933 Mannich and Charg tested alkyne compound by reaction of phenyl acetone with formaldehyde presence of secondary amine via using dioxane at (100 ^{0}C)[14]. An important Catalyst that used in Mannich reaction was copperous and its salts [15]. The general reaction of Mannich was shown (eq…1) [16] ; The mechanical reaction was found in tow media ,acid and base media .

Experimental

Materials and Procedures :

Chemicals and reagents: All the reagents and solvents was purchased ; cholesterol, glycine , Ethanol (absolute), sodium hydroxide , CuCl , Dioxane , Diethyl ether , formaldehyde and Propargyl bromide from Flulka Co. All solvents were purified prior to use according to standard literature methods[17].

Instrumentation: The products were characterized by FT-IR spectra were recorded on infrared FTIR Nicoletir 100 – spectrophotometer, And Melting points were obtained from a an electric heated block apparatus (Gallen Kamp.).

A: Preparation of terminal acetylene ;(17-(1,5-Dimethyl-hexyl)-10,13-dimethyl-3-prop-2-ynyloxy-hexadecahydro-cyclopenta[a]phenanthrene): Cholesterol was reacted with unsaturated alkyl halide (RX) by substitution reaction via S_N2 mechanism to produce a terminal acetylene . as shown in scheme-1.

General Procedure[17] : Three-neck round bottomed flask equipped with a reflux condenser, dropping funnel and thermometer ; (3g, 0.007 mmol) of cholesterol was dissolved in (25ml alcohol) and stirred for 15 minutes, A (2ml, 0.016 mmol) of Propargyl bromide was then added drop-wise to the well stirred reaction mixture. The which was heated to 60-70 ºC fore 2.5 hour. The Reaction was stopped and the mixture was cooled to room temperature. An Ice water was added to the reaction mixture and the crude product was extracted twice by ethylene dichloride. The organic layer was evaporated and crystals product was obtained. Crystals was dried by an oven for 2 hour at (50 ºC) .

B: Preparation of Mannich reaction from acetylene(2):

(17-(1,5-Dimethyl-hexyl)-10,13-dimethyl-3-prop-2-ynyloxy-hexadecahydro-cyclopenta [a] phena -nthrene) (0.5 gm) was reacted with (0.006mol) of formaldehyde and (0.006 mol) (glycine) as an amine in presence of (0.2 g)CuCl as catalyst in (20 ml) of dioxane by Microwave technique for 5 minute. The product was extracted by ethanol. The organic layer was evaporated and crystals product was obtained. Crystals was dried by an oven for 2 hour at (50 C^0) . and the reaction can be shown in schemes -1,2.

RESULTS AND DISCUSSION:

A :Preparation of the Terminated acetylene(2):

Terminated acetylene wes Prepared getting 100 % yield using cholesterol as bio compound and propargyl bromide in the presence of alcoholic potassium hydroxide. The mechanism of reaction Shown in Scheme. (2).The reaction was concluded to occoure via S_N2 mechanism. Terminal alkyne was Prepared by condensing cholesterol with propargyl bromide in dilute ethanolic potassium hydroxide solution at 70ºC according to neuochlophile substitution reaction.

Characterization of the Terminated acetylene(2):

Melting point (119-121°C). The FT.IR [19,20] for the Terminated acetylene gives bands (fig-1) in : 1431cm^{-1} for a R-O-R, and 2371 cm^{-1} for C≡C stretch; 2868 cm^{-1} that signify C-H

stretch , C-H Cyclic in 3086 cm^{-1}; 3436 cm^{-1} for ≡C-H hydrogen of alkyne, 1463 cm^{-1} C=C stretch for cholesterol crude, peak of OH for the first compound couldn't found in 3624 cm^{-1}[18] .

B :Preparation of (3) an amino acetylene derivative by Mannich reaction :

This is nucleophils addition reaction of an aldehyde to a secondary amine to produce a Schiff base by protonation and elimination of a water molecule. The addition of a carbanaion called the Mannich base. The Mannich base formed can readily eliminate the secondary amine to give the synthetic usefulness of the reaction[19].

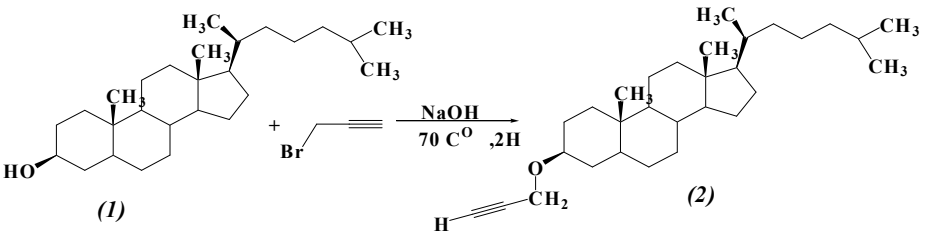
The exact mechanism of the reaction is not known with certainty. It has been suggested that the reaction may involve the intermediate formation of a methyloiamine , which was under the influence of acids. That is converted to a reactive methylene-ammonium salt. The latter condenses either with the ketone itself , or with the enol form of the ketone; that was formed catalytically by the acid present[20].

Characterization of the Mannich derivative (3):

Melting point was recorded for the synthetic Mannich derivative it was (140-142°C. The FT.IR shown in (fig-2) : the new groups of amine was found in 3351-3448 cm^{-1} for NH_2 .C-H for aldehyde group was converted from carboxylic acid via catalyst .another groups found as similar as to (fig-1) , but ≡C-H hydrogen of alkyne was disappeared , and the reaction can be shown in

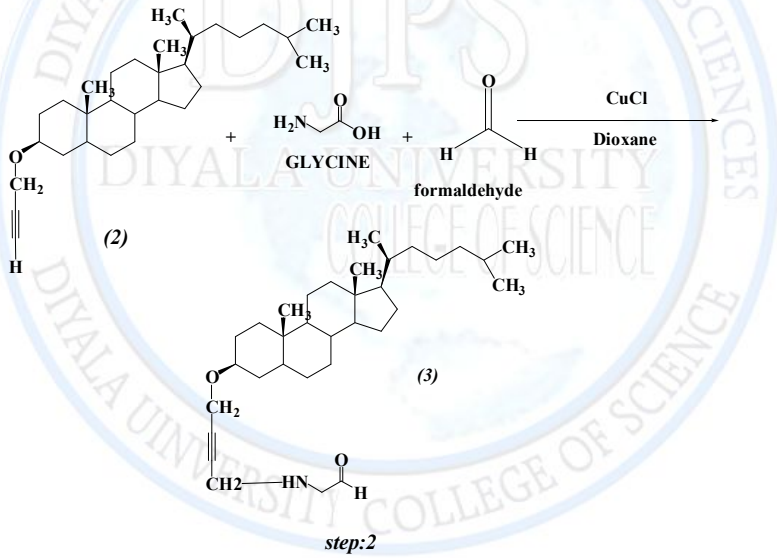
Preparation and Characterization of Amino Acetylene Derivative by Mannich Reaction .

TAREQ .A. MANDEEL , MANAF.A. GUMA



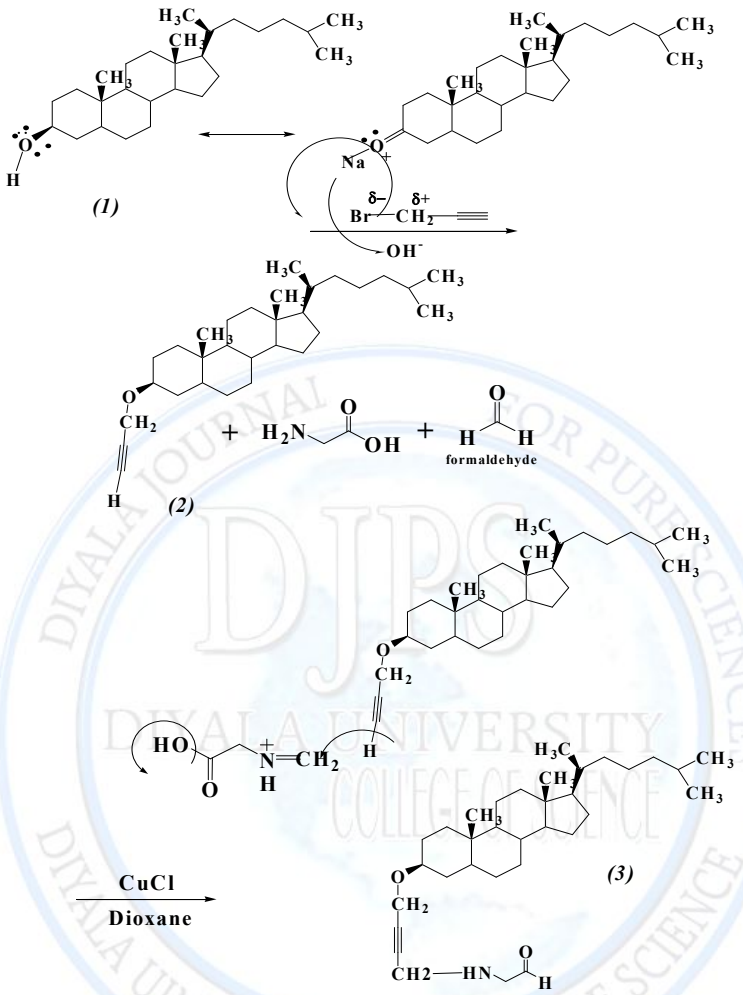
step : 1

Scheme (1): Reaction of cholesterol with propargyl bromide .



step:2

Scheme (1): The reaction of compound(2) with glycine and formaldehyde .



Scheme (3): The mechanism of Preparation of cholesterol with propargyl bromide and reaction of compound(2) with glycine and formaldehyde.

CONCLUSIONS

The acetylenic compounds are very easy to use glycine as an amino acids (secondary amine) for reaction with an aldehyde in presence of CuCl via microwave technique according to Mannich reaction getting good yield . and the products may be used as a medical compounds in future.

Preparation and Characterization of Amino Acetylene Derivative by Mannich Reaction .

TAREQ .A. MANDEEL , MANAF.A. GUMA

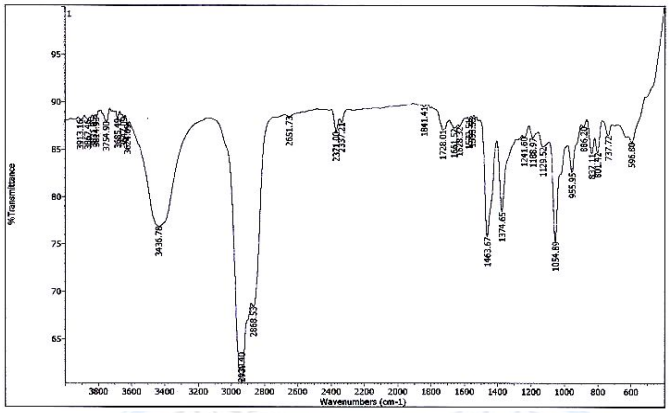


Fig.1. FT-IR spectra of terminated acetylene prepared using the KBr-disc method.

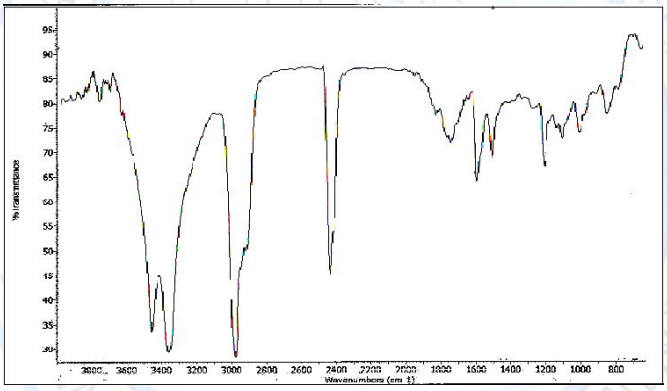


Fig.2. FT-IR spectra of amino acetylene derivative prepared by Mannich reaction using the KBr-disc method.

References

1. a) Sonogashira, K. In Metal-Catalyzed Cross-Coupling Reactions; Diedrich, F., de Meijere, A., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 1, p 319; (b) Sonogashira, K. In Handbook of Organopalladium Chemistry for Organic Preparation ; Negishi, E., de Meijere, A., Eds.; Wiley-Interscience: New York, 2002; p 493. and references therein.
2. Arend, M.; Westermann, B.; Risch, N. Angew. Chem., Int. Ed 1998, 37, 1044.
3. Azizi ,N., Ebrahimi, F.and. Saidi, M.R; Sharif University of Technology, December 2009, Vol. 16, No. 2, pp. 94-98.
4. Svensson, U.; Ringdahl, B.; Lindgren, S. and Dahlbom, R., Acta. Pharm. Suec., 1975; 12:290.
5. Wilson, A. Sclhd, H.O. and Modell, W. “Applied Pharmacology”, Churchill Livingstone, 11th ed., 1975, 133.
6. L.-W. Xu, C.-G. Xia, L. Li, J. Org. Chem., 2004, 69, 8482-8484.
7. Muhi-Eldeen, Z.; Ghantous, H. and Garabet, M., Iraqi J. Sci, 1981; 22(2): 155.
8. Dulude, H.; Gallant, G. and Salvador, T., Anticancer Res., 1993; 13(11):133.
9. Arend, M., Westermann, B. and Risch, N. \Modernvariants of the Mannich reaction", Angew. Chem. Int.Ed., 1998, 37(8), pp. 1044-1070.
10. Muller, R., Goesmann, H. and Waldmann, H. \N,NPhthaloylaminoacids as chiral auxiliaries in asymmetricMannich-type reactions", Angew. Chem. Int. Ed., 1999,38(2), pp. 184-187.
11. (a) Robinson’s landmark preparation of tropinone; see: Robinson, R. J. Chem. Soc. 1917, 111, 762. (b) Corey’s preparation of porantherine; see: Corey, E. J.; Balanson, R. D. J. Am. Chem. Soc. 1974, 96, 6516. (c) Overman’s preparation of strychnine; see: Knight, S. D.; Overman, L. E.; Pairaudeau, G. J. Am. Chem. Soc. 1993, 115, 9293.
12. Kano, T.; Yamaguchi, Y.; Tokuda, O.; Maruoka, K. J. Am. Chem. Soc. 2005, 127, 16408-1640.
13. Notz, W., Tanaka, F., Watanabe, S.-I., Chowdari,N.S., Turner, J.M., Thayumanavan, R. and Barbas,C.F. \The direct organocatalytic asymmetric Mannich reaction: Unmodi_ed aldehydes as nucleophiles", J.Org. Chem., 2003,68(25), pp. 9624-9634 ().

14. C.Mannich ,F.T.chang,chem Ber,1933,66,419,.
15. M.Tramntini,preparation.,1973,12,703.
16. Ali S., Mojtaba M. and Reza Naimi-Jamalb. M, . JOURNAL OF CHEMICAL RESEARCH ,2007 , 129–132 , 129.
17. Manaf A. G. ; Thesis For Master Degree in Chemistry, " Preparation and Characterization of New Alkynic Dimers and polymers and the study Of Some of Its Physical Properties and Industrial Applications "; 2010 ,Al-Anbar University.
18. Organicheskie reaktsii, collection 1. Moscow, 1948. P 399.
19. Vogels , Textbook of "Practical Organic Chemistry" 5ed, New York., 1989,ISBN 0.582-46236-3.
20. Manish .M.P.; Joseph .I.A. ; international journal of Dairy technology, 2002 ,Vol 55,No 3 ,august , p127.