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Synthesis of some Acetylenic Amines Derivatives by Mannich Reaction

Haiffaa Y. Hussin
Department of Chemistry
College of Science
Mosul University

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ABSTRACT

Some acetylenic amine derivatives containing nitrogen bases (cytosine, uracil) were synthesized through Mannich reaction which involved reaction of N-propargyl cytosine or uracil with paraformaldehyde and secondary amines. The structure of synthesized compounds have been confirmed depending on the physical and spectral data.

Key words: Acetylenic amines derivatives, Mannich reaction.

تحضير عدد من مشتقات الأمينات الأستيلينية بواسطة تفاعل مانخ

الملخص

حضرت عدد من مشتقات الأمينات الأستيلينية الحاوية على قواعد نايتروجينية (السايتوسين، اليوراسيل) من خلال تفاعل مانخ الذي تضمن مفاعلة N-بروبرجيل السايتوسين أو اليوراسيل مع البارافورمالديهايد والأمينات الثانوية، وشخصت المركبات المحضرة اعتماداً على المعلومات الفيزياوية والطيفية.

الكلمات المفتاحية: مشتقات الأمينات الاستيلينية، تفاعل مانخ.

INTRODUCTION

Mannich-reaction have been employed in the organic synthesis of natural compounds such as peptides, nucleotides, antibiotics, and alkaloids (e.g. tropinone), other applications were in agro chemicals such as plant growth regulators (da Rosa *et al.*, 2003), also used in the synthesis of medicinal compounds e.g. rolitetracycline, flaoxetine and tolmetin (anti-inflammatory drugs) (Mitsumori *et al.*, 2006).

In general, acetylenic compounds were found to be of high significant in medical science, since the medical compounds of triple bond have higher activity and lower toxicity (Al-Ajely *et al.*, 2003), besides they are easier to be absorbed by living bodies as compared with alkenes (Rultledge, 1968). Some acetylenic compounds were used as antispasmodics (Dahlbom, 1964), hypertensive (Wilson *et al.*, 1975), anticholinergic agents (Muhi-Eldeen, 1981), anticancer agents (Khuthier and Al-Abachi, 1993) and antibacterial agents (Sheat and Dawood, 2004).

On the other hand, many compounds containing cytosine nucleus were found to possess human anti-tumor activity (Creasy *et al.*, 2006), other compounds containing uracil group were found to be as a new type of anticancer agents (Yamamoto, 1981). Accordingly, we described here an approach to synthesize some aminoacetylenic compounds containing Cytosine(4-amino-2-hydroxypyrimidine) and Uracil (2,4-dihydroxypyrimidine) moieties to improve the expected biological activities of such compounds.

EXPERIMENTAL

Melting point were determined using electrothermal 9300 melting point apparatus and are uncorrected. IR. spectra were recorded by Pye-Unicam SP1100 Spectrophotometer as (KBr) disc. UV. Spectra were recorded on shimadzu (UV-160) UV-visible spectrophotometer using absolute ethanol as a solvent.

Preparation of N-propargyl cytosine [4-(N-propargylamino)-2-hydroxy pyrimidine] (I) (Redha *et al.*, 2002):

Propargyl bromide (1.18 gm, 0.01 mole) was added dropwise to a solution of cytosine (1.11 gm, 0.01 mole) in ethanol (50 ml) with stirring. The mixture was refluxed for 5 hrs, then it was concentrated by heating and cooled. The white solid product was filtered, washed with ethanol and recrystallized from benzene to afford compound (I) as a white crystals of (89%) yield and m.p. (294-296 ^{o}C).Compound (I) showed the following spectral data:

3169cm^{-1} (br) $\upsilon \equiv C-H$, 2120cm^{-1} (w) $\upsilon C\equiv C$, 1650 cm^{-1} (s) υ **C=O**, 1620 cm^{-1} (s) υ **C=N** & υ **C=C**, λmax (abs. EtOH) 268 nm.

Preparation of N-(4-substitutedaminobut-2-ynyl) cytosine (Ia-e):
General method (Mannich Reaction) (Afaf *et al.*, 2000):

A mixture of paraformaldehyde (0.9 gm, 0.001 mole) and appropriate secondary amine (0.015 mole) in absolute ethanol (10 ml) was refluxed till clear solution was obtained. Compound (I) (0.59 gm, 0.004 mole) was heated in absolute ethanol (10 ml), then added to the first reaction mixture and refluxed for (2 hrs). The mixture was concentrated by heating and the separated product was filtered off and recrystallized form chloroform – petroleum ether (80-100 ^{o}C) to give the desired compounds (Ia-e). The physical and spectral data of compounds (Ia-e) were listed in Table (1).

Preparation of 3-(N-propargyl) uracil (II) (Sheat and Dawood, 2004):

A cooled solution of sodium hydroxide (1.36 gm, 0.034 mole) in ethanol (50 ml) was added to a cooled solution of uracil (3.8 gm, 0.034 mole) in ethanol (50 ml) with stirring and cooling at 0^{o}C. Propargyl bromide (4 gm, 0.034 mole) was added dropwise with stirring. After the addition is completed, the reaction mixture was refluxed for (3 hrs) with continuous stirring , then extracted with chloroform (2 × 50 ml). The chloroform extracts were dried with anhydrous magnesium sulphate, then filtered and the solvent was removed in vacuum. The precipitate was recrystallized from benzene-petroleum ether

(80-100 ^{o}C) to afford compound (II) as white crystals of (75%) yield and m.p. (132-133 ^{o}C).

Compound (II) showed the following spectral data:

3236 cm^{-1} (s) υ ≡C–H, 2118 cm^{-1} (w) υ C≡C, 1717 cm^{-1} (s) υ **C=O** asym, 1689 cm^{-1} (s) υ **C=O** sym (for imidic group), 1622 cm^{-1} (m) υ **C=C,** 3418 cm^{-1} (br) υN-H, λmax (abs. EtOH) 250 nm.

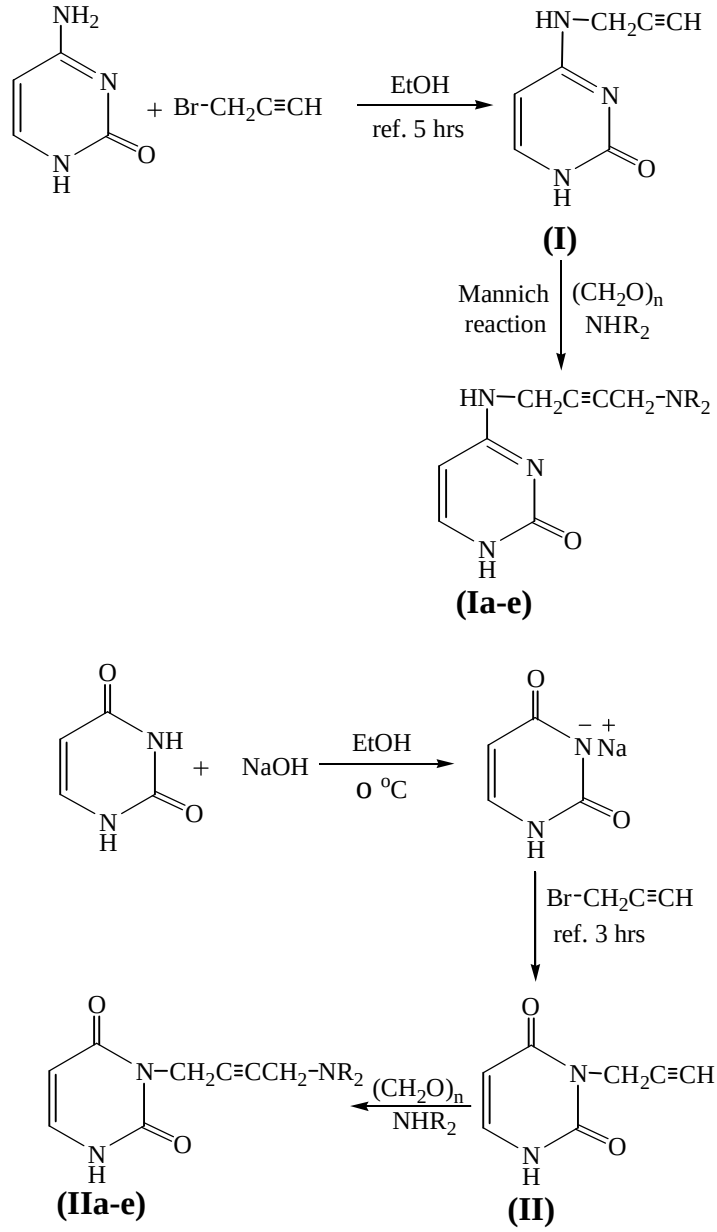
Preparation of N-(4-aminobut-2-ynyl)uracil (IIa-e) (Redha et al, 2002):

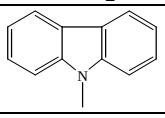
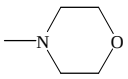
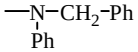
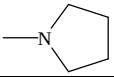
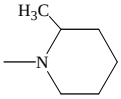
The compounds (IIa-e) were prepared by following the above mentioned procedure for compound (Ia-e) and recrystallized from benzene. The physical and spectral data of compounds (Ia-e , IIa-e) were listed in Table (1).

Table 1: physical and spectral data of the synthesized compounds (Ia-e , IIa-e)

Compd. NO.	**Yield %**	**m.p. ^{o}C**	**IR. (cm^{-1}) (KBr)**				**UV (EtOH) λmax (nm)**
			υ C=O (s)	**υ C=N (s)**	**υC=C (s)**	**υN-H (br)**	
Ia	60	242-244	1647	1636		3446	280
Ib	63	158-161	1646	1614		3418	260
Ic	50	188-190	1655	1625		3443	286
Id	55	239-241	1653	1626		3421	282
Ie	40	80-82	1652	1617		3421	280
IIa	53	323-325	1735 1655	-	1625	3455	290
IIb	60	313-315	1716 1669	-	1620	3446	276
IIc	45	148-150	1714 1663	-	1618	3446	264
IId	48	131-133	1711 1667	-	1622	3433	258
IIe	42	145-147	1716 1656	-	1625	3441	276

* All the compounds were of white color.



Compd. No.	-NR_2	Compd. No.	-NR_2
Ia , IIa		Id , IId	
Ib , IIb		Ie , IIe	
Ic , IIc			

Scheme (1)

RESULTS AND DISCUSSION

It is well known that many acetylenic amines derivatives are pharmaceutically active compounds. This fact was confirmed from the mentioned previous studies in the introduction. Accordingly, the synthesis of acetylenic amines derivatives containing cytosine and uracil moieties may show characteristic biological activity.

Therefore, two series of acetylenic amines derivatives have been synthesized using cytosine and uracil as a starting material in the Mannich synthesis as shown in scheme (1).

The synthesized acetylenic amines derivatives (Ia-e & IIa-e) have been investigated according to their physical and spectroscopic data (IR and UV) (Parikh, 1974). Other supporting evidence is the positive Tollen test for the acetylenic hydrogen in proporgyl compounds (I ,II) which became negative test in Mannich products.

The IR. spectra of compounds (Ia-e) showed strong absorption bands at (1646-1655) cm^{-1} for the amidic carbonyls frequencies, another strong absorption bands for the two bands (C=N & C=C) which overlapped at the region (1614-1636) cm^{-1}.While the broad absorption bands at (3418-3446) cm^{-1} is due to υN-H. The broad band at 3169 cm^{-1} which appeared for the acetylenic hydrogen in compound (I) is disappeared in Mannich products (Ia-e) as shown in Table (1).

The IR. Spectra of compounds (IIa-e) showed two strong absorption bands at the regions (1711-1735) cm^{-1} and (1656-1669) cm^{-1} due to the asymmetric and symmetric stretching vibrations of the imidic carbonyl groups, strong absorption bands appeared at (1618-1625) cm^{-1} for υC=C, a broad absorption band appeared at (3433-3455) cm^{-1} for the amidic hydrogen. Also the strong band at 3236 cm^{-1} which appeared for the acetylenic hydrogen in compound (II) is disappeared in Mannich products (IIa-e) as shown in Table (1).

The UV. spectra of compounds (Ia-e and IIa-e) showed higher λmax. values as compounds with those of compounds (I and II). This is due to the appearance of conjugation effect which increase λmax values and cause bathochromic shift in the $n \longrightarrow \pi^*$ transition of these compounds.

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