Synthesis and Study of Some New Histidine Derivatives

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Abstract

In this work: Oxazole derivative (1) were prepared from reaction histidine with acetic anhydride ,which on treatment with thiosemicarbazide afford Schiff bases (2),and then two methods are used for Schiff bases fusion ,one of them fusion to obtained imidazole derivative (3) ,while the other method treatet with chloro ethyl acetate to obtained oxoimidazole derivative (4).Imidazole derivative(5) were prepared by fusion oxazole derivtive (1) with o-phenylene diamine. Finally oxazole dreivative (1) treated with hydrazine hydrate gave imidazole derivative (6),which on treatment with aldehyde afford Schiff bases (7a,7b). The structure of the newly synthesized compounds was confirmed by M.p, elemental analysis, IR spectral data. All these synthesized compounds showed in Scheme (1).

Keywords: histidine, thiosemicarbazide , imidazole .

تخليق ودراسة بعض مشتقات الهيستدين الجديدة

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الخلاصة

في هذا البحث حضرت مشتقات الاوكسازول (1) بمفاعلة الهيستدين مع انهدريد حامض الخليك, والتي تم تفاعلها مع الثايوسيميكاربازايد للحصول على قواعد شيف (2) , بعد ذلك تم صهر الاخير بطريقتين , اولا الصهر للحصول على مشتق الاميدازول (3) وثانيا الصهر بوجود كلورو اثيل اسيتات للحصول على مشتق اوكسواميدازول (4). تم تحضير مشتق الاميدازول (5) من خلال صهر المركب (1) مع اورثو فنيلين ثنائي امين. واخيرا تمت مفاعلة مشتق الاوكسازول (1) مع الهيدرازين المائي للحصول على مشتق الاميدازول (6) , حيث تم الاستفادة من مجموعة الامين الحرة بتفاعلها مع الديهايدات مختلفة للحصول على قواعد شيف (7a , 7b). شخصت جميع المركبات المحضرة باستخدام الطرق الطيفية IR , تحليل العناصر ,بالاضافة الى قياس درجة الانصهار ,وقد تم تدوين جميع المركبات المحضرة بالمخطط (1).

الكلمات المفتاحية: هستيدين , ثايوسيمياربازايد , ايميدازول

Introduction

In recent years, the chemistry of nitrogen heterocyclic compounds especially imidazoles has attracted attention due to their reactivity and biological activities. Compounds bearing imidazole nucleus are known to show unique anti-edema and anti-inflammatory activities (1-2) ,differently subs .imidazole have also as anathematic (3,4) ,analgesic (5) ,anti-bacterial (6) ,anti fungal (7) ,antiviral (8) ,anti tubercular (9) , anti –cancer (10) and Cox -2 / lox inhibitor (11,12) and they are also know as melanocortin-4– receptor (MC4-R) antagonists (13) .Besides their pharmacological actions they also function as dyestuffs catalysts and polymerizing agents (14). Histidine derivatives are often core constituents in biologically active compounds (15).

Experimental

Melting points of the newly synthesized compounds were determined in open capillary tubes on a Galle Kamp melting point apparatus. IR spectra were recorded on apye-unicom SP-300 spectrometer in KBr pellets.

1- Synthesis of 4(4-methyl imidazole)-2- methyl- oxazol – 5- (4H) one (1)

A mixture of amino acid (histidine) (5gm) and acetic anhydride (15ml) was refluxed for 3 hrs. Excess of acetic anhydride was evaporated and the residue was purified by column chromatography silica gel (ethanol: water) (7:3) as eluant (yield 68 %), IR (υ , cm^{-1}) 1740 (C=O) , 2975 , 2880 (C-H alph.) , 1070-1050 (C-O),(C.H.N) analysis for (1) ($C_7H_9N_3O_2$) calculated C% = 62.222, H%=6.656, N% =31.111, found C% = 62.305, H% =6.073, N% =31.039.

2- Synthesis of 4 -(4-methyl imidazole)-2-methyl-4-thiosemicarbazide–oxazole (2)

A mixture of compound (1) (0.01 mol) and thiosemicarbazide (0.01 mol) in absolute ethanol was refluxed to (5) hrs., and drops of ACOH was added, the residue after the solvent evaporated was purified by column chromatography silica gel (ethanol) as eluant. (yield 78%) M.p (81-82C^{0}), IR(υ, cm^{-1}) 3300 (NH), 2902,2850 (C-H alph.), 1600(C=N), 3300- 3200 (NH_2), 1349 (C=S). (C.H.N) analysis for (2) ($C_8H_{12}N_5O_5$) calculated C% = 42.499, H% = 5.3097,N% = 30.973 found C% = 42.666, H% =5.869,N% = 30.111.

3- Synthesis of (2- thioxo-2, 3-dihydro-(1, 2- 4) triazole (1, 4-C) imidazolyl -4-methyl imidazole (3)

Compound (2) was heated up to fusion in an oil bath for 2 hrs. After cooling water was added and the solid was obtained filtered off and crystallized from xylene to give compound (3), yield 80%, M.p = 98-99, IR(υ, cm^{-1}) 3300 (NH) 2920-2850 (C-H alph.) and 1337 cm^{-1} (C-S).

4- Synthesis of 4-(-4-oxo-imidazollidin-2-thione)5-imidazolyl-4-methylimidazole (4)

Amixture of compound (2) (0.01 mol) and chloro ethyl acetate (0.01 mol) in methanol (50 ml) in presence of fused sodium acetate (0.03 mol) was heated under reflux for 6 hr.Then washed with hot water , dried and purified by suitable solvent to give (4) yield , 83 % , m.p = 220-222. IR(υ,cm^{-1}) 3260 (NH), 2920 -2850(C-H alph.), 1705(C=O) 1587(C=N) and 1325 (C=S) .

5- Synthesis of 1-benzo (4, 5) imidazo(1,2-b)imidazo-5-yl)-4-methyl imidazole (5)

Compound (1) and o-phenylene diamine was heated up to fusion in an oil bath for 2 hrs. After cooling water was added and the solid obtained filtered off and crystallized from xylene to give compound (5) , yield 87% , M.p = 87-89 , IR(υ,cm^{-1})2920,2850 (C-H of acetyl) , 1610 cm^{-1} (C=N), (C.H.N) analysis for (4) ($C_{13}H_{12}N_5$) Calculated C% =56.548 , H%= 1. 2618, N% = 29. 4117 found C% = 56.489, H% = 1.009, N% = 29.109.

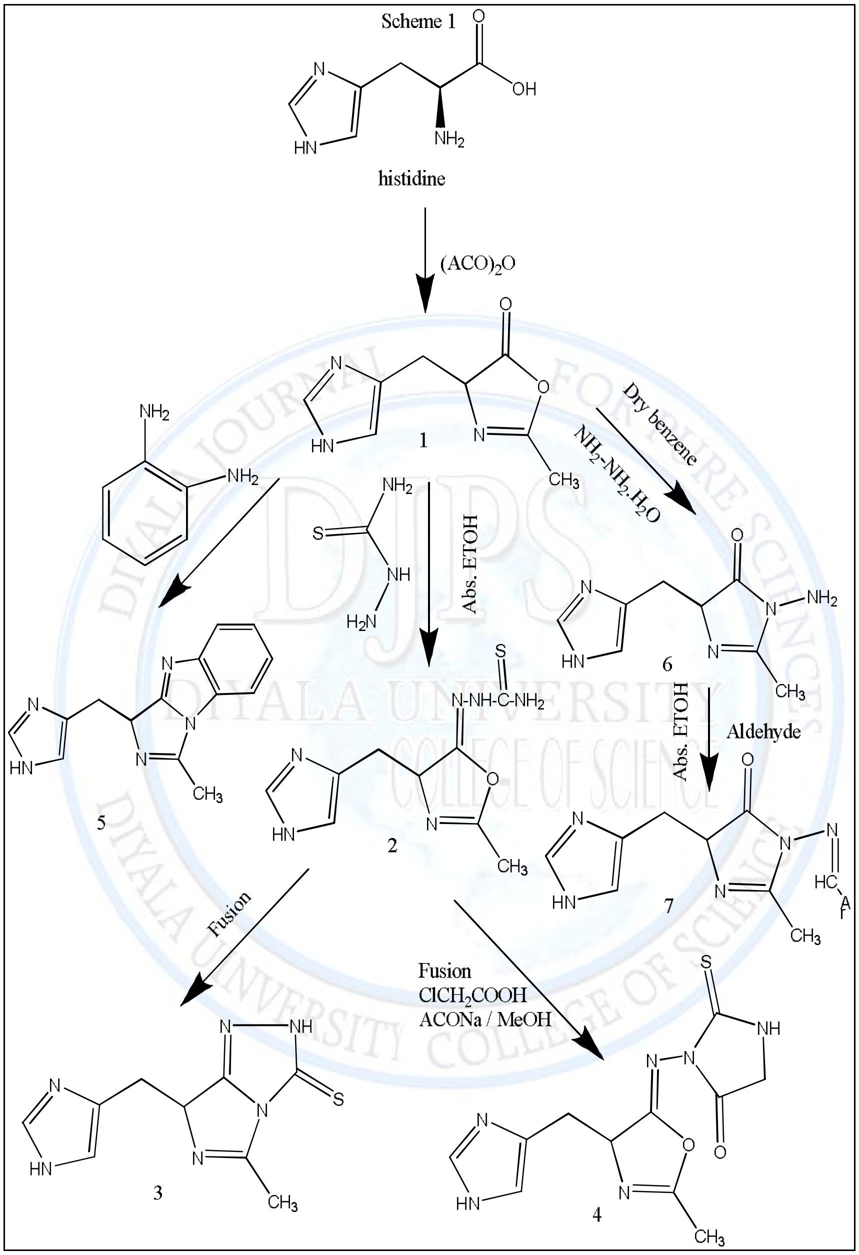
6- Synthesis of 1- amino -4-(4-(--methyl imidazolyl) -1-4-imidazole 5(4H)-one (6)

Asolution of (6mmole) in dry benzene (30 ml) and hydrazine hydrate (5mmole) was heated under reflux for 4hr. Then the mixture was poured upon water. The precipitated solid was filtered off, dried and crystallized from ethanol to give (6) yield, 82%, m.p = 86-88, IR (υ,cm^{-1}) 3300-3200 NH_2, 2920, 2850 (C-H alph.) and 1677(C=O).

7- Synthesis of Schiff bases (7a, 7b)

The corresponding aryl aldehyde (0.05 mol) was added to a stirred solution of compound (6) (0.05 mole) in absolute ethanol 30 ml and the mixture was refluxed for 2hr. After cooling the solvent was filtered off and the solid was creystallized form methanol (purified by columnon silica gel).For compound 7a: yield 77% ,m.p 263-265 c , IR(υ, cm^{-1}) 1685 C=O ,1630(C=N) ,3050 (Ar-H) ,2980,2850 (C-H alph),1580-1490 (C=C) . (C.H.N) analysis for (7a) Calculated ($C1_5H_{14}N_5O$) found C% 64.285, H%5.000, N%25.000 C%64.438, H%4.889, N%25.132, For compound 7b yield 82% ,m.p 185-187,IR(υ, cm^{-1}) 1700(C=O) ,1620 (C=N) ,3100(Ar-H) , 3400 (O-H),2900,2850 (C-H alph) , 1590 ,1480 (C=C) .

Scheme 1


histidine
(ACO)2O
1
Dry benzene
NH2-NH2.H2O
6
Abs. ETOH
Aldehyde
7
Abs. ETOH
2
5
Fusion
3
Fusion
ClCH2COOH
ACONa / MeOH
4

Result and discussion

Compound 4(-4-methyl – imidazol)-2-methyl oxazol-5(4H) one (1) was obtained by reaction of histidine with acetic anhydride, and was confirmed by IR spectra, appearance bands at 1740 cm^{-1} for C=O and at 2975-2880 cm^{-1} due to C-H alph. when 4(-4-methyl- imidazole) -2-methyl oxazol-5-(4H) one (1) was reacted with thiosemicarbazide in absolute ethanol, afforded Schiff bases (2), the formation of compound (2) was indicated by their IR spectra of the azomethine CH=N stretching band at 1600 cm^{-1} , combined the disappearance of C=O stretching band .

Compound (3) was synthesized by cyclization compound (2) by fusion above its melting point to obtained compound (3), the product was confirmed by IR spectra, disappearance of bands over 3310 cm^{-1} of NH_2 and disappearance a strong band at 1070-1050 cm^{-1} attributed of oxazole ring. .

The data (C.H.N) analysis show the found data was so close from calculated data for above compounds. The reaction of compound (2) with chloro ethyl acetate in presence of fused sodium acetate in methanol under reflux, afforded the corresponding compound (4), was obtained in 83 % yield and was confirmed by IR spectra, the IR spectra for compound (4) which displaced band at 3300-3250 cm^{-1} for (NH_2) stretching. While fusion of compound (1) with O-phenylene diamine above its melting point in an oil bath yielded bridgehead nitrogen compound (5), it was confirmed by IR spectra and analysis (C.H.N), the IR spectra appearance bands at 1610 cm^{-1} to azomethine CH=N stretching, combined the disappearance of C=O stretching band. Finally oxazole dreivative (1) treated with hydrazine hydrate gave imidazole derivative (6), The product was confirmed by IR spectra, disappearance of bands over 3310 cm^{-1} of NH_2 and disappearance a strong band at 1070-1050 cm^{-1} attributed of oxazole ring,which on treatment with aldehyde afford Schiff bases (7a,7b), The product was confirmed by IR spectra, disappearance of bands over 3310 cm^{-1} of NH_2.

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