Synthesis of Some Substituted Imidazole with Expected Biological Activity

A.Kh. Ahmed, N.S. Ezzat and H.S. Aziz
Chemistry Department, College of Education, Mosul University

(NJC)

(Received on 2/1 /2006) (Accepted for publication on 19/8/2006)

Abstract

Substituted imidazole are well known to have biological activity and have important uses in the industrial application, several compounds of this group were synthesized from 2-aminobenzothiazole, the structure of the new compounds were established on a base of physical and infrared data.

الخلاصة

تعد مركبات الاميدازول من المركبات المهمة والتي لها تاثيرات بايولوجية معروفة وكذلك تمتلك استخدامات مختلفة في المجال الصناعي مما دفع العديد من الباحثين الى تحضير ودراسة مشتقات عديدة لهذه المركبات. تم في هذا البحث تحضير عدد من معوضات الايميدازول وباستخدام 2-امينو بنزوثايازول كمادة اولية. شخصت المركبات الناتجة باستخدام طيف الاشعة تحت الحمراء والطرق الفيزيائية.

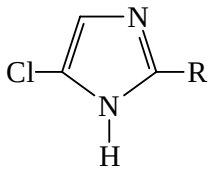
Introduction

Imidazole and benzimidazole ring aroused considerable, interest and a source of endless research pleasure but a key systems both in nature (such as amino acid, histidine, vitamine B12, a component of DNA base structure and purines, histamine, biotin), this obviously in pharmaceutical, veterinary and agrochemical products cimetidine (Tagamet), azomycine, metronidazole, misonidazole, chlotimazole, thibendiazole[1]. Also some imidazole derivatives have biological activity such as antibacterial toxices[2]. While some imidazole derivatives are used as anti-try-panosoma brucei agent[3], some imidazole derivatives are used as a catalyst in industrial uses[4,5].

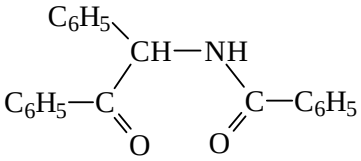
Since the discovery of the biological activities of these compounds, are the aim of many research projects to develop a new efficient general procedure for the synthesis of these imidazole derivatives. Cyclization of N,N-disubstituted oxamide (1) with phosphorous pentachloride gave 1-susbtituted-5-chloroimidazole[6] (2), while N-benzoyl-α-benzoyl benzyl amine (3) reacted with ammonium acetate in acetic acid gave the imidazole derivatives[7] (4). Also 2-phenyl-4-methyl imidazole (6) is formed by the reaction of α-halocarbonyl compound (5) with amidines in basic medium[8].

Finally, it is interesting to note that imidate reacts with aldehyde in microwave irradiation to produce imidazole derivatives[9].

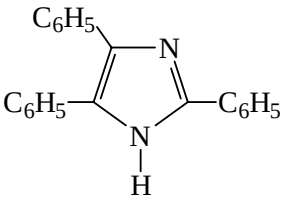
(1)



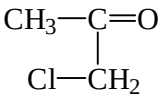
(2)



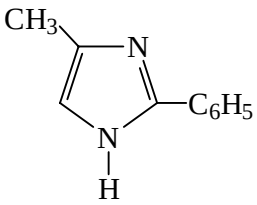
(3)



(4)



(5)



(6)

At the present paper, the aim is to synthesis some new substituted imidazole derivatives.

Experimental

Melting points were measured using Electrothermal 9300 and are uncorrected. The IR spectra were recorded on Bruker FT-IR Spectrophotometer, Tensor 27, using KBr Discs.

Synthesis of 2-amino benzothiazole (2):

It is synthesized by the reaction of (0.066 mole, 10 g) N-phenyl thiourea with bromine (6 ml) in (75 ml) chloroform, as mentioned in literature[10], yield 83%, 8.2 g, m.p. 128-130 °C (Lit. 129 °C).

Synthesis of substituted benzylidine (2-benzothiazolyl) amine (6a-b):

This were prepared from reaction of 2-amino-benzothiazole (0.01 mole, 1.5 g) with substituted aldehyde (0.01 mole) in (15 ml) absolute ethanol as mentioned in literature[11], yield (87, 81) %, m.p. (82, 102) °C (Lit. 82, 103 °C).

Synthesis of hypparic acid (1a-c):

These were prepared from the reaction of (0.1 mole) substituted benzoyl chloride with glycine (0.1 mole) in the presence of (10%) sodium hydroxide as mentioned in literature[12]. H: 186 °C, 3,5-diNO_2: 179 °C, 4-NO_2: 131°C, Lit. H: 183°C, 3,5-di-NO_2: 177-178°C, 4-NO_2: 130-131°C.

Synthesis of N-(2-benzothiazolyl) substituted hypparamide (3a-c)[13]:

To a solution of 2-aminobenzothiazole (2) (0.01 mole, 1.5 g) and triethylamine (0.01 mole, 1 g) in (20 ml) tetrahydrofurane, was added substituted hyppyl chloride (1a-c) (0.01 mole) in dry tetrahydrofurane dropwise with stirring. After the addition was completed, the mixture was refluxed for 2 hours, then cooled and filtered out. The precipitated was

washed with water, dried and recrystallized from ethanol afforded a crystal of (3a). The melting point and IR spectral data were listed in Table (1).

Synthesis of N-(2-benzothiazolyl)-2-substituted phenyl-5-chloroimidazole (4a-c)[(1)]:

A mixture of N-(benzothiazolyl) substituted hypparamide (3a-c) (0.01 mole), phosphorous pentachloride (0.02 mole, 4.12 g) and phosphorous oxychloride (4 ml) are spontaneously warmed after (3-5) minutes with formation of HCl gas, it is kept the temperature below 60 °C by using ice-water. Then the mixture was stirred at (20-25 °C) for (2 hrs.) and at (55-60 °C) for (3 hrs.). The excess of phosphoryl chloride was removed by distillation under reduced pressure. The cooled residue is treated with crushed ice, neutralized with aqueous ammonia (pH 8-9) and extracted with chloroform. The extract was washed with water, dried by using sodium sulfate and filtered, the solvent was removed and the product was recrystallized from ethanol. Melting point and IR spectral data were showed in Table (2).

Synthesis of dianil (7a-b)[(14)]:

To solution of compounds (6a-b) (0.01 mole) in dry dimethyl fromamide (15 ml), potassium cyanide (0.01 moles, 0.65 g) was added. The mixture was stirred for (72 hrs.), the precipitate was obtained by removing the solvent under reduced pressure, dried and was recrystallized from ethanol to afford dianil (7a-b). Melting points and IR spectral data were showed in Table (4).

Synthesis of 1,3-bis(2-benzothiazolyl)-4,5-diaryl imidazole-2-thione (8a-b)[(14)]:

To a solution of dianil (7a-b) (0.005 mole) in dry tetrahydrofurane (10 ml), pieces of sodium metal (0.044 mole, 1 g) in (60 ml) dry ether was added dropwise with stirring under nitrogen atmosphere. The mixture was refluxed with stirring for (4 hrs.), whereby it was cooled and filtered to remove unreacted sodium metal, and (2 ml) of carbon disulfide was added dropwise with stirring. The mixture was refluxed for (1 hr.), then was cooled and the solvent was evaporated, the compounds was dried and recrystallized from ethanol. The melting points and IR spectral data are indicated in Table (5).

Synthesis of 1,3-bis (2-benzothiazolyl)-4,5-diaryl imidazole-2-one (9a-b)[(14)]:

To solution of dianil (7a-b) (0.005 mole) in dry tetrahydrofurane (10 ml), pieces of sodium metal (0.044 mole, 1 g) in (60 ml) dry ether was added dropwise with stirring under nitrogen atmosphere. The mixture was refluxed with stirring for (4 hrs.), cooled and filtered to remove the unreacted sodium metal, then (2 ml) of ethylchloroformate was added to the reaction mixture dropwise with stirring. The product was refluxed for (1 hr.), cooled and the solvent was evaporated, dried and recrystallized from ethanol. The melting points and IR spectral data are indicated in Table (6).

Results and Discussion

The aim of synthesis of new 1,3-bis (2-benzothiazolyl)-4,5-diaryl imidazole-2-thione(one), may provide additional biologically active agents.

The N-(2-benzothiazoyl) substituted hypparamide (3a-c) were obtained by refluxing hyppyl chloride (1a-c) with 2-aminobenzothiazole (2) in tetrahydrofurane. These compounds (3a-c) were identified by spectroscopic evidence. The infrared spectrum appearance of the following bands at (1648-1702 cm^{-1}) for the carbonyl group stretching and also the (C=N) group at (1607-1630cm^{-1}). Two bands at (1542,1279cm^{-1}) for asymmetrical and symmetrical bands for (NO_2) group, band at (717-791cm^{-1}) for(C-S-C) group and also stretching band at (3093-3419cm^{-1}) for (N-H).

Compounds N-(2-benzothiazolyl)-2-substituted phenyl-5-chloro-imidazole (4a-c) were prepared by the reaction of the N-(2-benzothiazolyl) substituted hypparamide (3a-c) with phosphorous pentachloride in the presence of phosphorous oxychloride. These compounds were identified by the appearance of the following bands at (1590-1654 cm^{-1}) for the (C=N) stretching. Also the band for carbonyl group was absent in the spectrum, other bands appearance in the expected region as shown in Table (2).

Other rout started from the preparation of substituted benzylidine (2-benzothiazolyl) amine (6a-b) from the reaction of 2-aminobenzothiazole with substituted aldehyde in absolute ethanol in the presence of glacial acetic acid. These compounds were identified by IR spectrum through the appearance of the following bands in Table (3) (1650-1661 cm^{-1}) for (C=N str.) group, (1284-1261 cm^{-1}) for (C-N bend), (738-752 cm^{-1}) for (C-S-C) group, other bands were showed in Table (3). Reaction of compounds (6a-b) with potassium cyanide in dry dimethyl formamide yield the dianil (7a-b). Table (4) showed the IR spectrum shows absorption band at (1589-1661cm^{-1}) for (C=N) and band at (727-834cm^{-1}) for (C-S-C) group and also band at (525 cm^{-1}) for (C-Cl) and band at (1014 cm^{-1}) for (C-O-C) group. Cyclization of (7a-b) in the presence of carbon disulfide afforded the corresponding (8a-b). These compounds were identified by IR spectrum which shows the absorption band at (1619-1651 cm^{-1}) due to (C=N) group, (1371-1375 cm^{-1}) for thion group (C=S), (784-785 cm^{-1}) for (C-S-C) group, (597 cm^{-1}) for (C-Cl) and (1235 cm^{-1}) for (C-O-C) group.

Cyclization of compounds (7a-b) in the presence of ethyl chloroformate afforded the corresponding (9a-b), these compounds were identified by the following bands, (1650-1702 cm^{-1}) for carbonyl group (C=O), (1592-1606 cm^{-1}) for (C=N) group. Other bands appearance in expected region in Table (6).

Table (1): The melting points and IR spectral data for compounds (3a-c)

Comp. No.	X	m.p. °C	Yield %	IR, (KBr), ν cm^{-1}					
				C=O	C=N	NO_2		C-S-C	N-H
						Sym.	Asy.		
3a	H	170-172	68	1648	1608	-	-	791	3419
3b	4-NO_2	228-230	61	1693	1607	1279	1541	717	3116
3c	3,5-diNO_2	206-208	73	1702	1630	1286	1542	777	3093

Table (2): The melting points and IR spectral data for compounds (4a-c)

Comp. No.	X	m.p. °C	Yield %	IR, (KBr), ν cm^{-1}				
				C=N	NO_2		C-S-C	C-Cl
					Sym.	Asy.		
4a	H	125-127	83	1590	-	-	795	506
4b	4-NO_2	56-58	76	1608	1273	1524	788	537
4c	3,5-diNO_2	210-212	80	1654	1310	1541	749	518

Table (3): The melting points and IR spectral data for compounds (6a-b)

Comp. No.	X	m.p. °C	Yield %	IR, (KBr), ν cm^{-1}				
				C=N	C-N	C-S-C	C-O-C	C-Cl
6a	4-Cl	102	87	1661	1284	752	-	530
6b	4-CH_3O	82	81	1650	1261	738	1169	-

Table (4): The melting points and IR spectral data for compounds (7a-b)

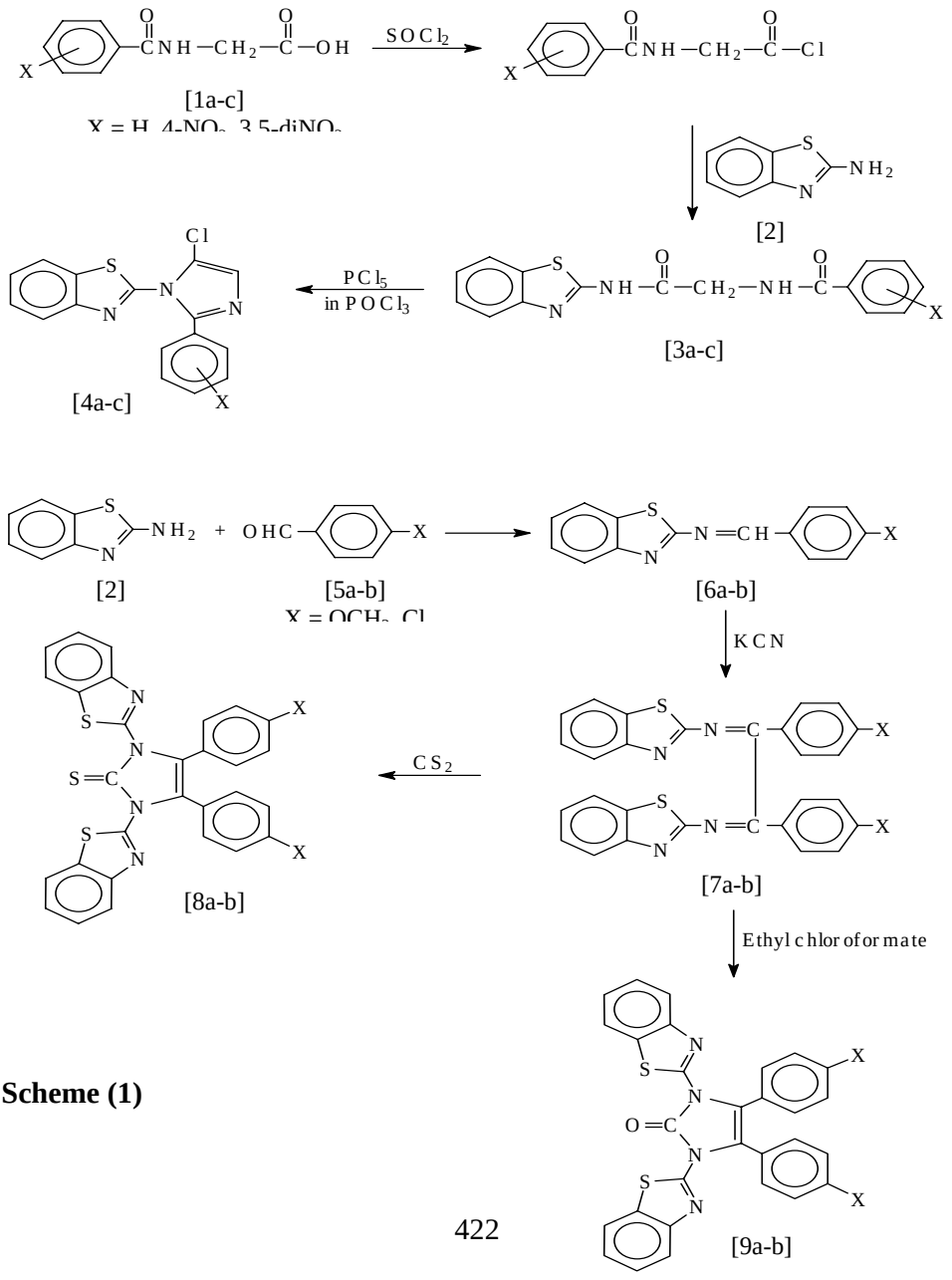
Comp. No.	X	m.p. °C	Yield %	IR, (KBr), ν cm^{-1}			
				C-S-C	C=N	C-Cl	C-O-C
7a	4-Cl	210-212	67	727, 834	1589, 1661	525	-
7b	4-CH_3O	94-96	71	752, 839	1582, 1605	-	1014

Table (5): The melting points and IR spectral data for compounds (8a-b)

Comp. No.	X	m.p. °C	Yield %	IR, (KBr), ν cm^{-1}				
				C=N	C=S	C-S-C	C-Cl	C-O-C
8a	4-Cl	256	79	1651	1375	784	597	-
8b	4-CH_3O	160	62	1619	1371	785	-	1235

Table (6): The melting points and IR spectral data for compounds (9a-b)

Comp. No.	X	m.p. °C	Yield %	IR, (KBr), ν cm^{-1}				
				C=O	C=N	C-S-C	C-Cl	C-O-C
9a	4-Cl	218-220	70	1650	1606	761	529	-
9b	4-CH_3O	Oily	79	1702	1592	794	-	1056



Scheme (1)

References

1. M. Ress Grimmett, "Imidazole and Benzimidazole Synthesis", (1997), Academic Press, Inc., London, p. 5.
2. A.H. El-Masry, H.H. Fahmy and S.H. Ali (2000), "Synthesis and antimicrobial activity of some new benzimidazole derivative", Molecule, 5, 1429-1438 (Internet).
3. "Design and synthesis of peptidomimetic protein farnesyl-transferase inhibitors as anti-trypanosma bruce agents", ***Journal of Medicinal Chemistry***, 2003, A-N (Internet).
4. J. Louie, J.E. Gibby, M.V. Fornuorth and T.N. Tekarec, ***J. Am. Chem. Soc.***, 2002, **124**, 15188 Internet.
5. H.A. Doung, M.J. Cross and J. Louie, ***Organic Letters***, 2004, **6**, 4679 Internet.
6. O. Wallach and E. Schatze, ***Ber. Dtsch. Chem. Ges***., 1881, **14**, 420.
7. D. Davidson, M. Weiss and M. Jelling, ***J. Org. Chem.***, 1938, **2**, 319.
8. J.W. Cornforth and H.T. Huang, ***J. Chem. Soc***., 1948, 1960.
9. G. Kerneur, J.M. Lerestif, J.P. Bazureau, ***J. Hamelin Synthesis***, 1997, 287-289 (Internet).
10. P.N. Bhargava and B.T. Baliga, "Studies on 2-aminobenzothiazole", ***J. Indian Chem. Soc.***, 1958, **35** (11), 807.
11. A.N.M. Al-Naib, M.Sc. Thesis, Mosul University, (2004).
12. H. Blatt, ***Organic Synthesis,*** Coll. Vol. 2, p. 328 (), John Wiley and Sons, Inc.
13. I.K. Jaber, M.Sc. Thesis, Mosul University, (2002).
14. K.N. Mehrotra, Geeta Singh, ***Synthesis***, 1980, 1001.