Synthesis and Characterization of Some *O*-[2-{"2-Substituted Aryl ("1,"3,"4 thia diazolyl) ['3,'4-b]-'1,'2,'4-Triazolyl]-Ethyl]-p- chlorobenzald oxime Derivatives.

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Received in : 12January 2014, Accepted in : 14 April 2014

Abstract

In this study new derivatives of *O*-[2-{"2-Substituted Aryl ("1,"3,"4 thia diazolyl) ['3,'4-b]-'1,'2,'4- Triazolyl]-Ethyl]-p- chlorobenzald oxime (6-11) have been synthesized from the starting material p-chloro – E- benzaldoxime 1.

Compound 2 was synthesized by the reaction of p-chloro – E- benzaldoxime with ethyl acrylate in basic medium. Refluxing compound 2 with hydrazine hydrate in ethanol absolute afforded 3. Derivative 4 was prepared by the reaction of 3 with carbon disulphide, treated of compound 4 with hydrazine hydrate gave 5. The derivatives (6-11) were prepared by the reaction of 5 with different substitutes of aromatic acids. The structures of these compounds were characterized from their melting points, infrared spectroscopy, elemental analysis and ^{1}HNMR (some of them). Compounds (6-11) were exhibited biological activity against *E- coli bacteria*. Compound 9 exhibited higher degree of activity than the other.

Key words: Synthesis of new derivatives of thiaduazol and triazol compounds.

Introduction

Heterocyclics bearing a triazole or 1,3,4- thiadiazole moiety are reported to show biological properties such as antibacterial, anti- inflammatory, anticonvalsant, anticonvulsant, analgesic and antitumoral [1,2]. Banday and Rouf [13] have prepared some new 1, 2, 4-triazole derivative with antimicrobial activity.

Neslihan [14] has synthesized compounds incorporating both 1, 2, 4-triazole and 1,3,4 thia diazole due to their possible diverse pharmacological properties.

Cherkupally et al [15] synthesized a new series of triazoloe and thiadiazole derivatives. All the symthesized compounds were tested for *in vitro* activities against certain strains of bacteria such as *staphylococcus aureus*, *Baccillus subtills*, *Escherichia coil* and fungi such as *Aspergillus niger* Aspergillus nodulans , Alternaria alternate some of these derivatives showed marked inhibition of bacterial and fungal growth. The other new compounds also showed appreciable activity against the test bacteria and fungi.

Gowramma et al [16] synthesized a series of 1, 3, 4- thiadiazole derivatives .All the compounds were evaluated for antibacterial and antifungal activities. Most of the compounds have shown significant antibacterial and antifungal activity when compared with the standard drugs.

In this study, we decided to synthesize new derivatives of thiadiazole and triazole for their biological activity.

Experimental

Materials:

All chemical used were supplied from Riedel-De Hean AG, BDH chemicals, Acros Organics, Janssen chemical, Merk chemicals Fluka AG Hopkin and wiliams. Elemental analyzer were carried out by using carlo Erba/Mod 1106, Infrared spectra were recorded using Shimadzu-408 (KBr disc), ^{1}HNMR spectra were recorded in Hitachi Perkin Elmer, R-24 B at 60MHz and melting points were recorded using Electrothermal melting point apparatus. The biometerials were obtained from Biomerieux Ltd.

Synthesis of *O*-[2-Ethoxy carbonyl) ethyl –p-chloro- bemzaldoxime] [18]. 2

A mixture of (0.01 mole) of ethyl acrylate and 1.2 ml of 2N KOH solution in EtOH was added dropwise into a solution of (0.01 mole) of p-chloro- E-benzaldoxime 1 in EtOH (8ml). The mixture was heated at 38 C$^\circ$ for 15 hrs. and the solvent was removed under reduced pressure. The residue was dissolved in diethyl ether, treated with 10% NaOH solution and H_2O. The organic layer was dried and removed to give 2 as solid. Compound 2 was recrystallized from ethyl acetate.

Synthesis of O-(ethyl hydrazide) –p-chloro benzaldoxime. 3

A mixture of (0.005 mole) of compound 2 and (1ml) of hydrazine hydrate 98% in 10 ml of EtOH absolute was refluxed for 2hrs. After cooling the precipitate was fromed, filtered and recrystallized from EtOH to give derivative 3 as solid.

Synthesis of *O*-2-[´5 thiol- ´1, ´3, ´4- oxadiazole-´2- yl) - ethyl] –p- chloro benzaldoxime. 4

Compound 3 was dissolved in (20ml) of EtOH, a solution of (0.5g) KOH in (5ml) water and (0.03 mole) of CS_2 was added. The reaction mixture was heated under reflux until the evaluation of hydrogen sulphide ceased. The reaction mixture was cooled, diluted with cold water (30ml) and acidified with HCL 10%. The precipitate was formed, collected by filtration, washed with water and recrystallized from (ethanol- DMF 9:1) mixture.

Synthesis of *O*-[2-´4 N-amino -´5 – thiol -´1, ´2, ´4- triazole- ´3-yl) ethyl] –p- chloro benzaldoxime. 5

A mixture of compound 4 (0.01 mole) and hydrazine hydrate 98% (0.01 mole) in dry pyridine (15ml) was refluxed for 2hrs. Reaction mixture was cool and neutralized with dilute HCL. The precipitate was formed filtered and recrystallized from DMF. ^{1}HNMR ($CDCl_3$) δ 3.4 (1H, s, CH=NO); 7.4 (2H, d, Aromatic); 7.8 (2H, d, Aromatic); 4.4 (2H, t, O*CH_2 CH_2); 3.3 (2H, t, OCH_2 $^*CH_2$)

Synthesis of *O*-[2 {"2-p-Substituted –phenyl ("1, "3, "4- thiadiazoly) ['3,'4] - "1, "2, "4-triazolyl} ethyl] p-chloro benzaldoximc. 6-11

General procedure:

A mixture of compound 5 (0.01) mole, substituted benzoic acid (0.01 mole) and $POCL_3$ (15ml) was refluxed for 6hrs, cooled and poured in to crushed ice with stirring. The solid which separated, filtered, washed successively with aqueous Na_2CO_3 solution and cold water. The product was dried and recrystallized from methanol.

^{1}HNMR ($CDCl_3$) for derivative 6:δ3.2 (1H, s, CHNO) 7.3-7.8 (9H, m, aromatic), 4.5(2H, t, O $^*CH_2$ CH_2); 3.4 (2H, t, OCH_2 $^*CH_2$), 5.2 (2H, s, NH_2); 5.5(1H, s, 5H).

Results and discussion

The synthesis of the compounds [2-11] is depicted in the scheme 1 we used E-isomer of the oxime 1 as starting material. Compound 1 was synthesized according to known procedure [17]. Compound 2 was synthesized by the reaction of 1 with ethyl acrylate by Michale- type addition [18]. The IR spectrum of 2 showed a strong stretching band at 1725cm^{-1} due to (C=O) of the ester group, another stretching band was observed at 1195cm^{-1} for (OC_2H_5). Tables (1) and (2) showed the characteristic IR absorption and physical properties for all new derivatives. Gatterman method [19] was used for the synthesis of derivative 3. The derivative

3 was indicated by its melting point and infrared spectrum which showed displacement of (CO) group to low frequency at 1650 cm^{-1} with appearance of stretching band at 3355 cm^{-1} for (NH_2) group. The cyclization of compound 3 with Carbone disulphide in alkaline medium gave the oxadiazole derivative 4. Derivative 4 was characterized from its melting point and IR spectrum. The IR spectrum of 4 showed two distinct peaks, the first stretching band at 1050 cm^{-1} due (C=S) [20] and the second weak band at 3410 cm^{-1} due to (NH) stretching [21], another stretching band at (1650 cm^{-1}) was also obtained for (C=N) of the oxadiazole ring. Treatment of compound 4 with hydrazine hydrate 98% gave the triazole 5which was characterized from its melting point, IR spectrum and ^{1}HNMR . The IR spectrum showed stretching bands at 3390 cm^{-1}, 3280 cm^{-1} due to (NH_2) group, other bands at 2800 [22] cm^{-1} for (SH) and 1610 cm^{-1} for (C=N). The ^{1}HNMR of compounds 5 exhibited a singlet at δ 3.4 due to (CH=NO) proton, two doublets at δ (7.4 and 7.8) integrating for four aromatic protons; triplet at δ 4.4 for (O *CH_2 CH_2) protons and triplet at δ 3.3 for (O CH_2 *CH_2) protons. Scheme 2 explains the suggested mechanism for derivative 5. The derivatives (6-11) were synthesized from the reaction of compound 5 with different substituted aromatic carboxylic acids in $POCl_3$. Derivatives 6-11 were characterized from their m.p., IR and CHN-analysis, IR spectra showed the disappearance of the (NH_2) and (SH) stretching bands for triazole with appearance of a weak bands in the range (1600-1640) cm^{-1} attribute to the (C=N) group. A strong bands were appeared in the range (1490-1498) cm^{-1} attributed to the (S-C=N) stretching in thiadiazole ring [23]. Compound 6 was also characterized by ^{1}HNMR. The ^{1}HNMR of 6 exhibited a singlet at δ 3.2 due to (CH=NO) proton, multiplet at δ (7.3 - 7.8) integrating for nine aromatic protons, triplet at δ 4.5 for (O *CH_2 CH_2) and triplet at δ 3.4 (O CH_2*CH_2) protons. Scheme 3 explains the suggested mechanism for compounds (6-11). Compounds 6-11 exhibited a biological activity against E-Coli bacteria. Compound 9 exhibited higher degree of activity than the others table (3).

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Table (1): Characteristic IR absorption bands of the new derivatives

Compound No.	Infrared data ($\mu_{max} cm^{-1}$) KBR (disc)
2	(C=O) 1725; (CH aliphatic) 2910, 2930; (C-O) 1195; (C=C) 1610; (C=C) out of plan (C-H) aromatic 820.
3	(C=O) 1650; (NH)3150; (NH_2) 3300; (C=C) 1610; (C=C)) out of plan (C-H) aromatic 815.
4	(NH) 3310; (C=N) 1605; (C=S) 1050; (-N.C=S) 1495; (C=C) 1595; (C=C) bending 820.
5	(NH_2) 3370; (SH) 2800; (C=N) 1610; (C=N)1610, (C=C) 1590; (C=C)) out of plan (C-H) aromatic 815; (-N.C=S1)1490.
6	(C=N) 1600; (C=C) 1595; (C=C)) out of plan (C-H) aromatic 835.
7	(C=N) 1620; (C=C) 1590; (C=C)) out of plan (C-H) aromatic 850; (-OCH3) 2830
8	(C=N) 1640; (C=C) 1600; (C=C)) out of plan (C-H) aromatic 830.
9	(C=N) 1625; (C=C) 1610; (C=C)) out of plan (C-H) aromatic 820.
10	(OH) 3630; (C=N) 1630; (C=C) 1600; (C=C)) out of plan (C-H) aromatic 810.
11	(-NO_2) (1345 and 1515); (C=N) 1615; (C=C) 1610: (C=C)) out of plan (C-H) aromatic 820.

Table (2): Physical properties for all new derivatives

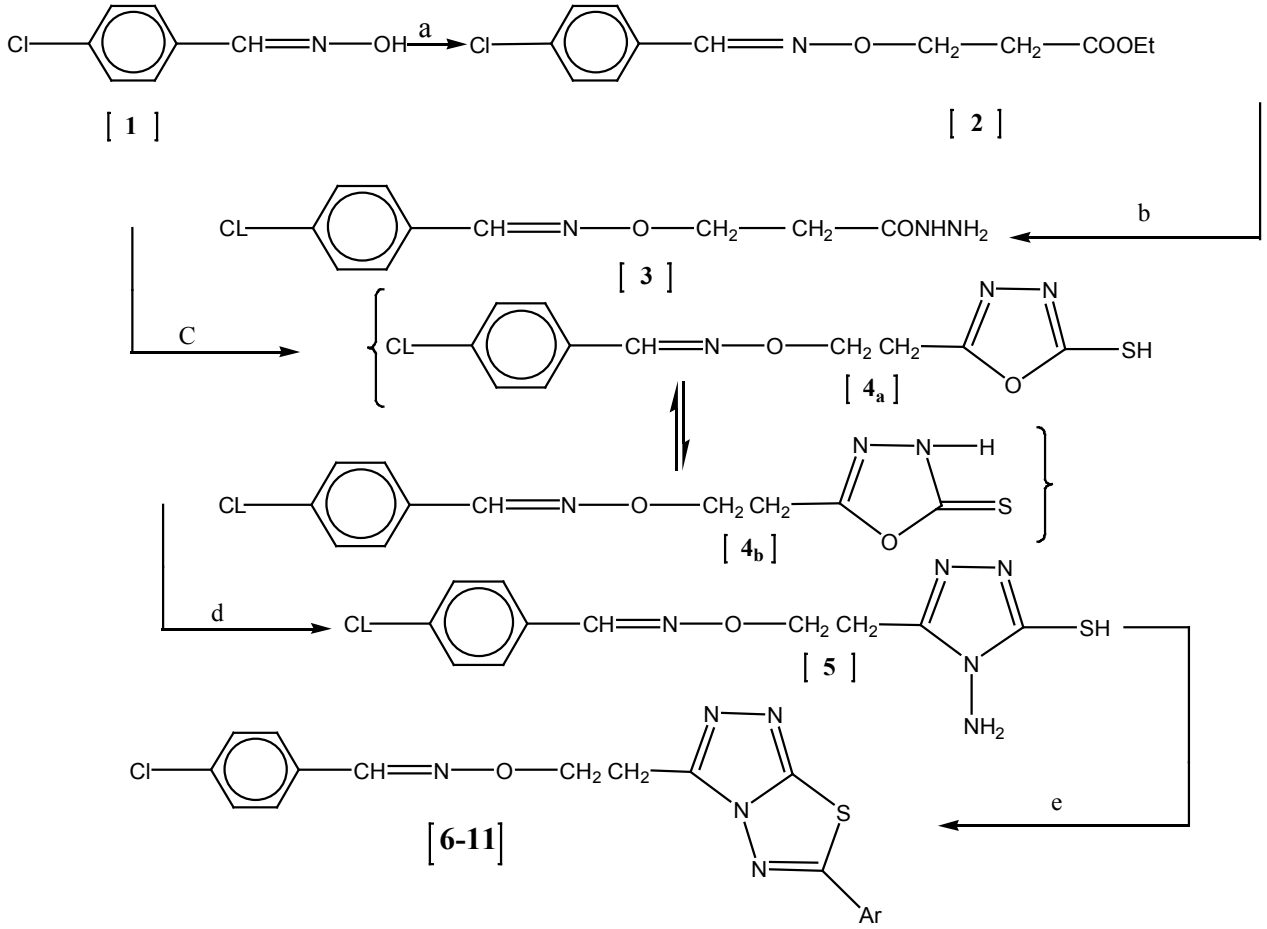
Compound No.	Formula	Melting point °C	Elemental analysis calculated (found)			Yield %
			C%	H%	N%	
2	$C_{12}H_{14}NO_3Cl$	179	56.47 (56.27)	5.49 (5.41)	5.49 (5.53)	60
3	$C_{10}H_{12}N_3O_2Cl$	195	49.79 (49.68)	4.97 (5.00)	17.42 (17.33)	55
4	$C_{11}H_{10}N_3O_2ClS$	225	46.64 (46.62)	3.53 (3.61)	14.84 (14.90)	75
5	$C_{11}H_{12}N_5OClS$	284	44.44 (44.60)	4.04 (3.91)	23.56 23.73	86
6	$C_{18}H_{15}N_5OClS$	228	59.01 (59.11)	4.29 (4.02)	19.12 (19.11)	65
7	$C_{19}H_{17}N_5O_2ClS$	222	57.57 (57.21)	3.66 (3.31)	17.67 (17.15)	70
8	$C_{18}H_{14}N_5OCl_2S$	219	56.54 (56.21)	3.66 (3.31)	18.32 (18.11)	68
9	$C_{18}H_{14}N_5OClSBr$	221	48.64 (48.41)	3.15 (3.01)	15.76 (15.51)	62
10	$C_{18}H_{14}N_5O_2ClS$	252	56.54 (56.32)	3.92 (3.81)	18.32 (18.21)	67
11	$C_{18}H_{14}N_6O_3ClS$	231	52.55 (52.42)	3.40 (3.21)	20.43 (20.22)	58

Table (3): Effect of antimicrobial agents on Escherichia Coli

No. compound	Effect of new derivatives on the growth of *E-Coli bacteria*											
	1	0.9	0.8	0.7	0.6	0.5	0.4	0.3	0.2	0.1	0.09	Concentration gm/ml
6	_	_	_	_	_	_	+					
7	_	_	_	_	_	+						
8	_	_	_	_	_	_	_	+				
9	_	_	_	_	_	_	_	_	_	_	+	
10	_	_	_	_	_	_	_	_	+			
11	_	_	_	_	_	_	_	_	_	+		
Blank	+											

(-) No growth
(+) Growth

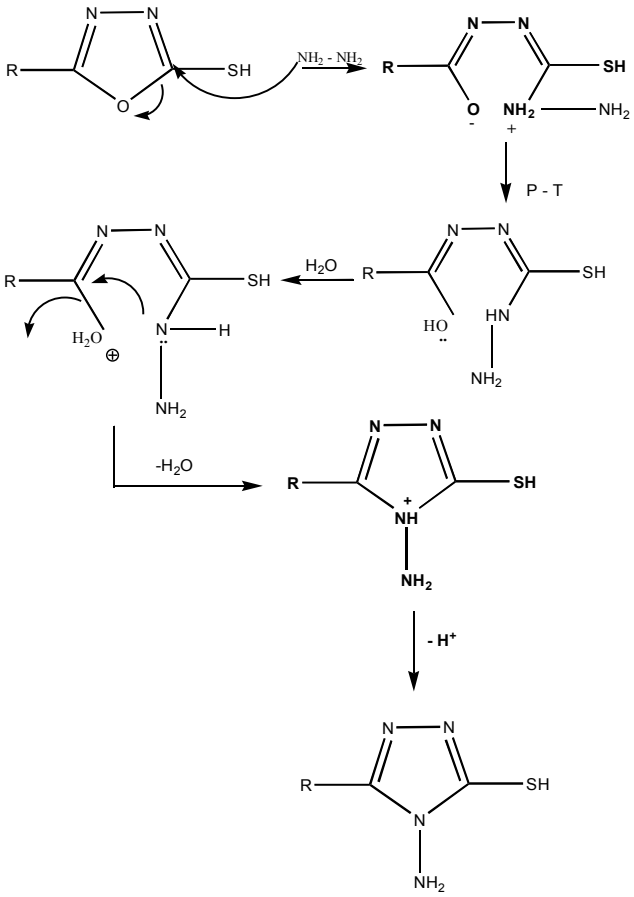
(Scheme 1)



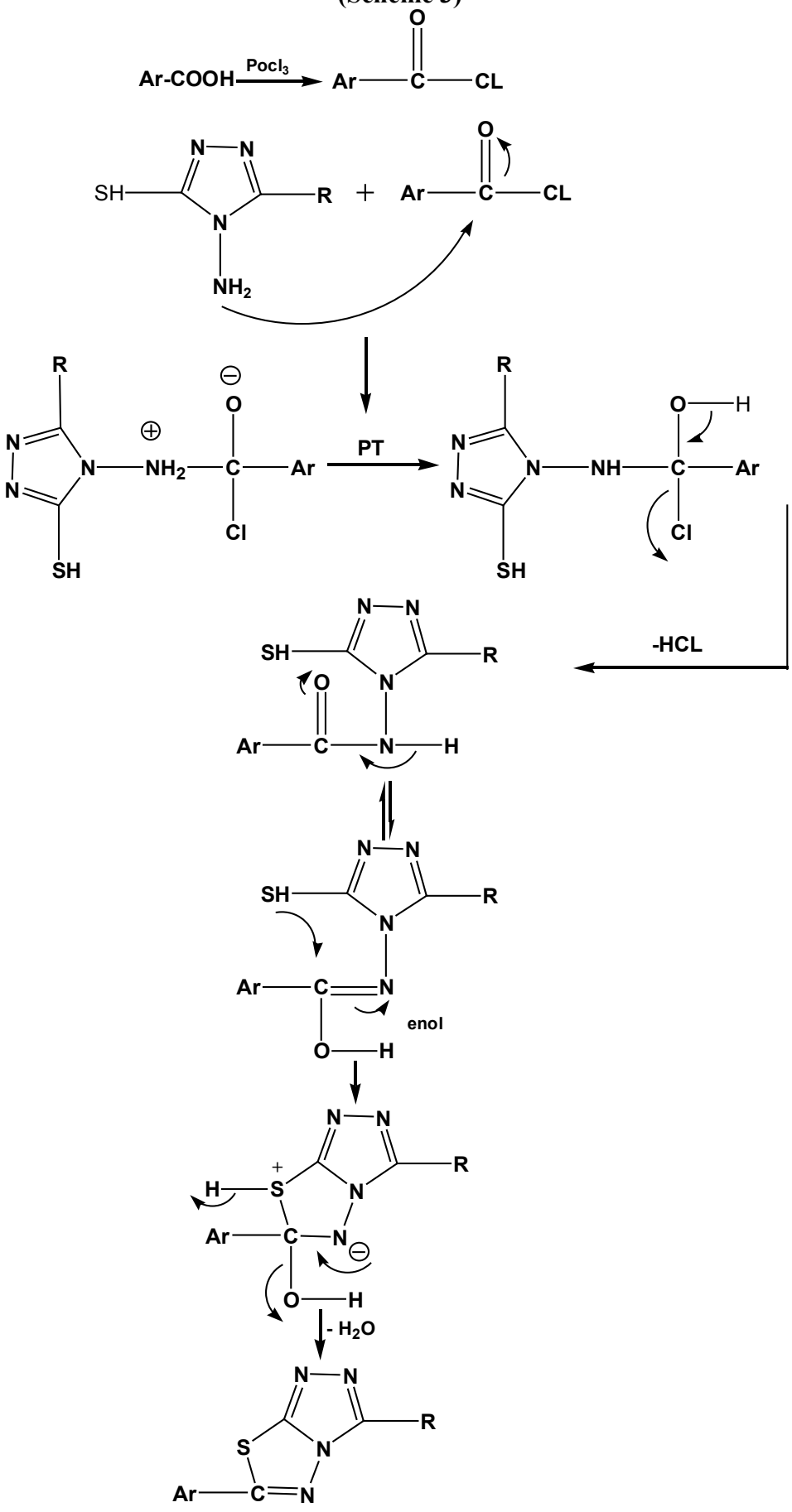
Where Ar =	Phenyl	p-methoxy phenyl	p-chloro phenyl	p-bromo phenyl	p- hydroxy phenyl	p- nitro phenyl
Compound No.	6	7	8	9	10	11

a: KOH, CH_2=CH—C(=O)—OEt

b: NH_2NH_2, EtOH
c: CS_2, KOH
d: NH_2NH_2, Pyridine
e: ArCOOH, $POCl_3$


NH2 - NH2
P - T
H2O
-H2O
- H+

(Scheme 3)



تحضير ودراسة بعض مشتقاتO-[2 {2'' – معوض اريل (1'',3'', 4''-ثايادايزوليل) [4,'3]-b]-1' ,2,'4- ترايزوليل}- اثيل] باراكلورو بنزالدوكزيم

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استلم البحث في :12 كانون الثاني 2014 ،قبل البحث في : 14 نيسان 2014

الخلاصة

تم في هذا البحث تحضير مشتقات جديدة من O-[2 {2'' – معوض اريل (1'',3'', 4''- ثايادايزوليل) -1' ,2,'4 [4,'3-b] - ترايزوليل}- اثيل] باراكلورو بنزالدوكزيم 6-11. وقد استعمل المركب بارا- كلورو-E- بنزالدوكزيم 1 مادة اولية في التحضير. المركب 2 حضر من تفاعل المركب 1 مع الاثيل اكريليت في وسط قاعدي. مفاعلة المركب 2 مع الهيدرازين اعطى المشتق 3. تم مفاعلة المركب 3 مع ثنائي كبريتيد الكاربون، اعطى المركب الحلقي 4. معاملة المشتق 4 مع الهيدرازين بوجود البريدين اعطى المشتق 5. المشتقات 6-11 حضرت من تفاعل المشتق 5 مع حوامض اورماتية مختلفة التعويض. شخصت المشتقات الجديدة من درجة انصهارها وباستخدام طيف IR وتحليل العناصر.كما شخص المركب 6,5 وباستخدام ^{1}HNMR. درست الفعالية البايولوجية للمشتقات من 6-11 ضد بكتريا القولون وكان اكثرها فاعلية المشتق 9.

الكلمات المفتاحية :تحضير مشتقات جديدة لمركبات الثاياديازول و الترايازول