Sci. J. Fac. Sci. Monoufia Univ. Vol. VII (1993). 97 - 113

STUDIES WITH POLYFUNCTIONALLY SUBSTITUTED HETEROAROMATICS : SYNTHESIS AND CHEMICAL REACTIVITY OF 4-ARYLAZO- 2-ISOPROPYL MERCAPTO-2-OXAZOLIN-5-ONES AND OF 4-ARYLIDEN-2-ISOPROPYL-MERCAPTO- 2-OXAZOLIN-5-ONES.

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ABSTRACT

O-Isopropylethylxanthate (1) reacts with glycine to yield the glycine thiocarboxylate (4). Compound 4 afforded the 2-oxazolin-5-one (5) on heating in acetic anhydride which could be trapped as 4-arylhydrazones 7a,b and 4-arylidene derivatives 8a,c. Compounds 7a,b rearranged into 5-oxo-1,24-triazolin-3- carboxylic acid derivatives on treatment with nucleophilic reagents. The arylidene 8b rearranged by action of amines into the imidazolidines 25.

Polyfunctionally substituted heteroaromatics are biologically interesting molecules and their chemistry has in the past received

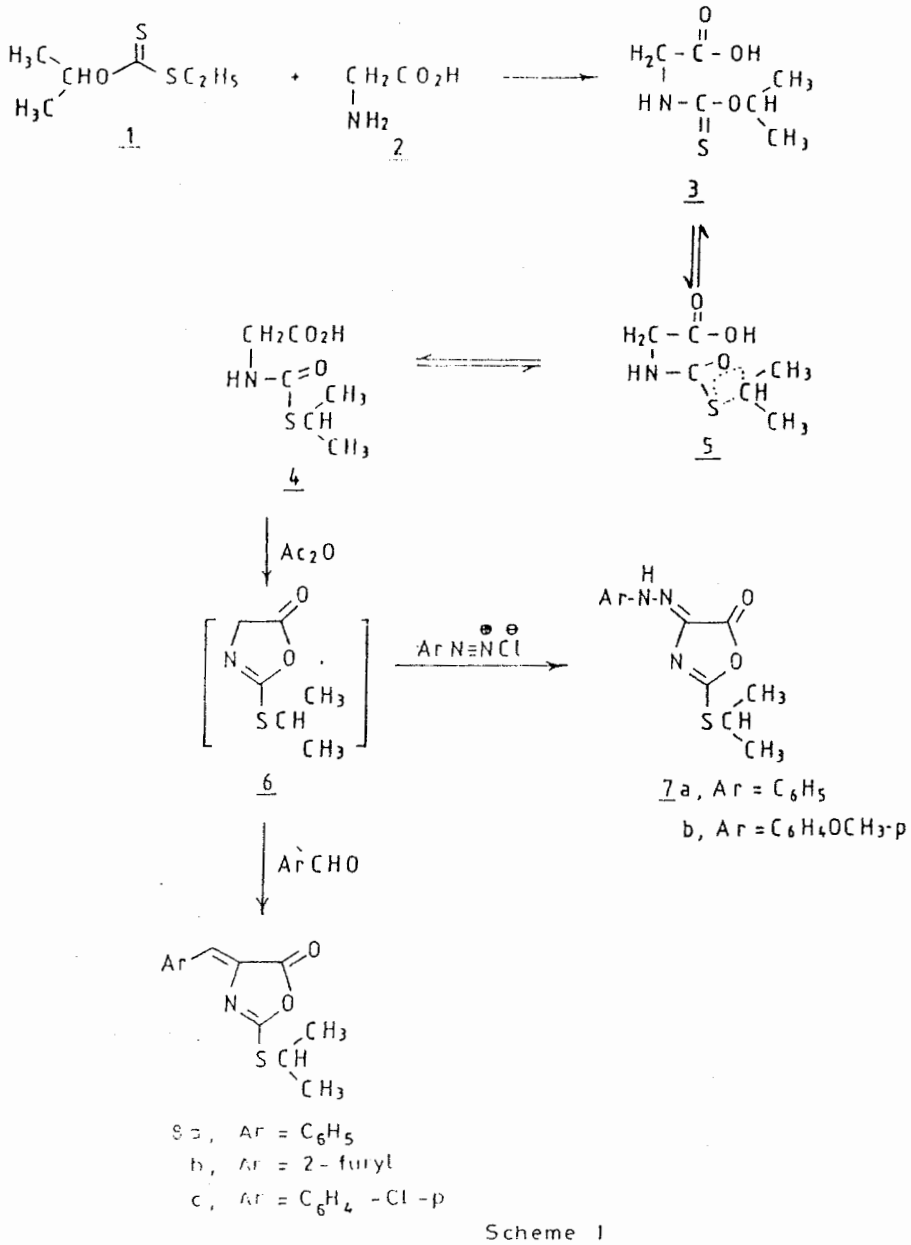
considersble interest[1-3]. In the last few years we were involved in a program aimed at designing simple and efficient approaches to polyfunctionally substituted heterocycles utilizing inexpensive, readily obtainable starting materials. During this phase of our research novel syntheses of thiophenes[4,5], thiazoles[6], oxadiazoles[7], thiadiazoles[8], pyridazines[9,10], pyridines[11], and condensed heterocycles[12,14] could be developed. In conjunction of this work we report the synthesis of new class of functionally substituted 2-oxazoline-5-ones and enabled their rearrangement into several other new functionally substituted azoles. Thus, we have found that O-isopropylethylxanthate (1) reacts with glycine (2) in refluxing aqueous, potassium hydroxide to yield a condensation product that may be formulated as 3 or isomeric 4, Structure 4 was preferred over possible isomeric 3 based on ^{1}H-NMR which revealed the isopropyl CH proton at δ = 5.60 ppm. If the reaction product was 3 this proton should has appeared at much higher field (Ca δ = 4.5 ppm). Reaction of 1 with glycine (2) yield firstly 3 which rearranges into 4 via isopropyl group-transfer into the more electronegative sulphur atom as in intermediate 5. It is of value to report here that the reaction of 1 and 2 in aqueous ethanolic potassium hydroxide has previously been reported to yield 15,16. The difference in behavior may be rationalized for in terms of higher temperature employed now as in absence of ethanol reaction temperature of > 100°C is reached.

Compound 4 readily cyclized on heating with acetic anhydride into the 2-oxazolin-5-one derivative 6. This should never be isolated in pure from but could be trapped as the arylhydrazone derivatives 7a,b and the arylidenes 8 a-c by coupling with aryldiazonium salts and

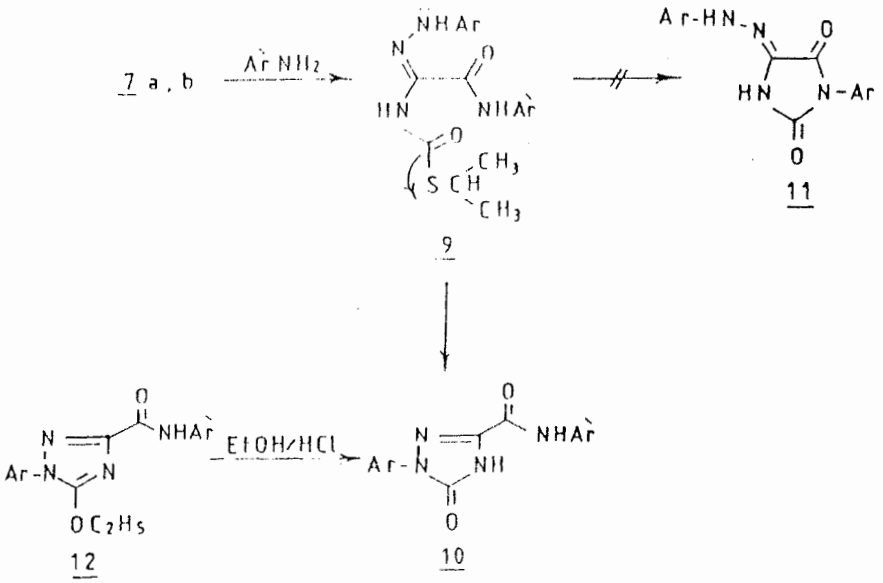
condensation with aromatic aldehydes respectively.

Compounds 7a,b reacted with aromatic amines to yield products of addition of aromatic amines and isopropyl mercaptan elimination. Two structures were considered (cf. structures 10 and 11). The imidazolidine structure 11 could be readily ruled out based on the fact that the reaction products were all colourless. Moreover, the same products 10a could be also obtained via refluxing the known compound 12a[17] with ethanolic hydrochloric acid, The formation of 10a-c is assumed to occur via acyclic intermediate 9 which rearranges into final products via loss of isopropyl mercaptan. The behavior of 7a,b towards aromatic amines finds parallelism to the reported rearrangement of 4-arylhrazono-2-oxazolin-5-ones[18,21] and of 4-arylhydrazono-2-thiazolin-5-ones towards aromatic amines 15, 16, 22- 24. Simiarly, treatment of 7a,b with aminoheterocyclic compound yield 1,2,4- triazolin-3-carboxamides 10d-g.

In previous work[17] it was shown that 4-arylhydrazono-2-ethoxy- 2-thiazolin- 5-one (13) rearranges by action of aromatic amines into 1,2,4- triazol-3-carboxylic acid anilides 17 via loss of hydrogen sulphide while morpholine and piperidine afforded 5-oxotriazolin-3-carboxamide (19) via loss of ethyl mercaptan. The mechanism of reaction is summarized in Scheme 3. We have found that 13 (Ar = C_6H_4 - p - CH_3) rearranges on treatment with 5-amino-1,2,4-triazole and with 3-phenyl-5- aminopyrazole into the 5-ethoxy-1,2,4-triazoles 20 and 21 respectively. The reaction proceeds via loss of hydrogen sulphide. The behavior of 13 towards heterocyclic amines is thus similar to their behavior towards aromatic amines.


1
2
3
4
5
6
Ac2O
ArN≡NCl
ArCHO
7a, Ar = C6H5
b, Ar = C6H4OCH3-p
8a, Ar = C6H5
b, Ar = 2-furyl
c, Ar = C6H4-Cl-p

Scheme 1



a, Ar = Ar` = C_6H_5

b, Ar = C_6H_4 -p- OCH_3 ; Ar` = C_6H_5

c, Ar = Ar` = C_6H_4 - p- OCH_3

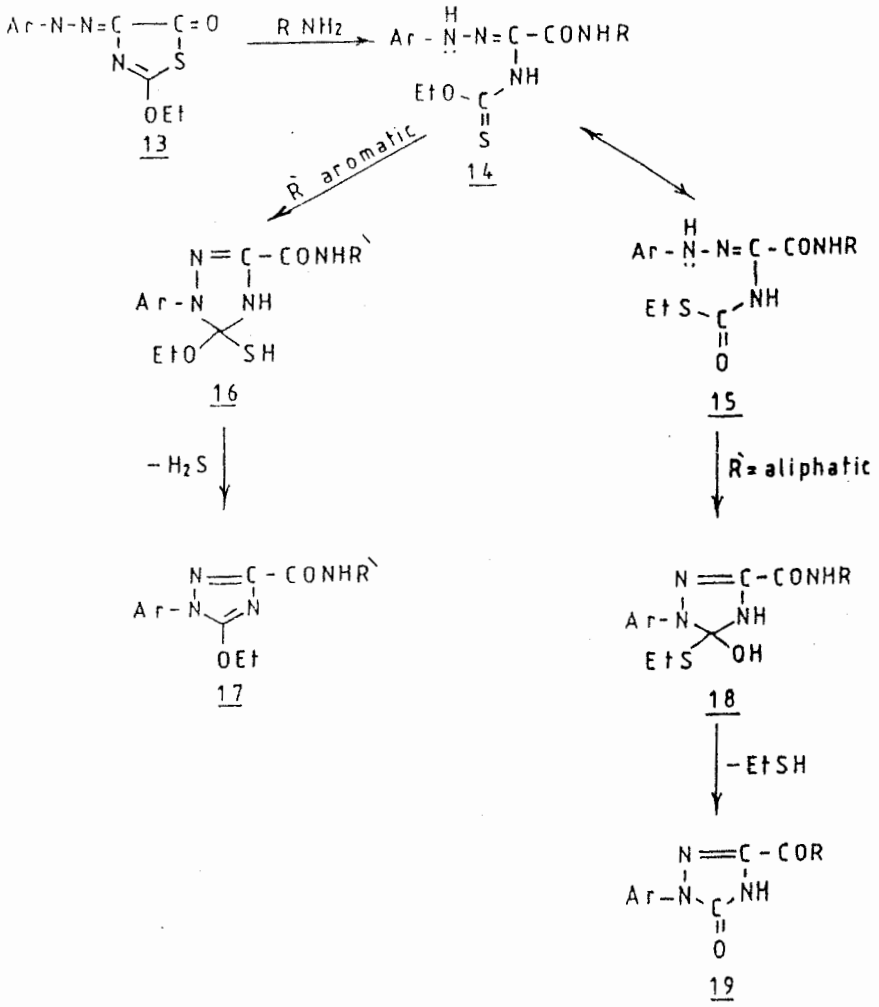
d, Ar = C_6H_5, Ar` = 4-phenylthiazole - 2- yl

e, Ar = C_6H_5, Ar` = 1-phenyl -2,3- dimethyl pyrazoline - 5- one 4 - yl

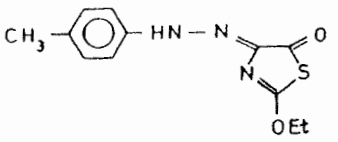
f, Ar = C_6H_4 -p- OCH_3, Ar` = 4 - phenyl -5- methyl pyrazol - 3 - yl

g, Ar = C_6H_4 -p- OCH_3, Ar` = pyrid - 2 - yl

Scheme 2



Scheme 3



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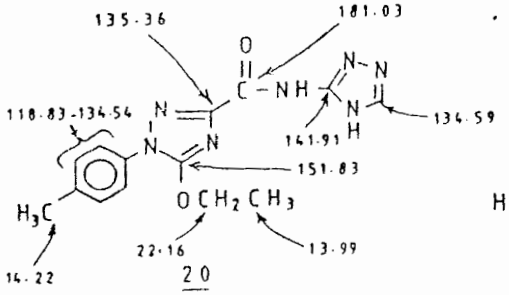

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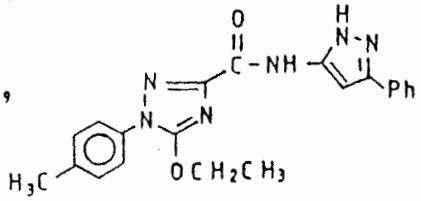

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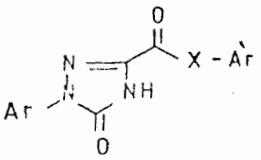

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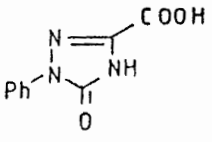
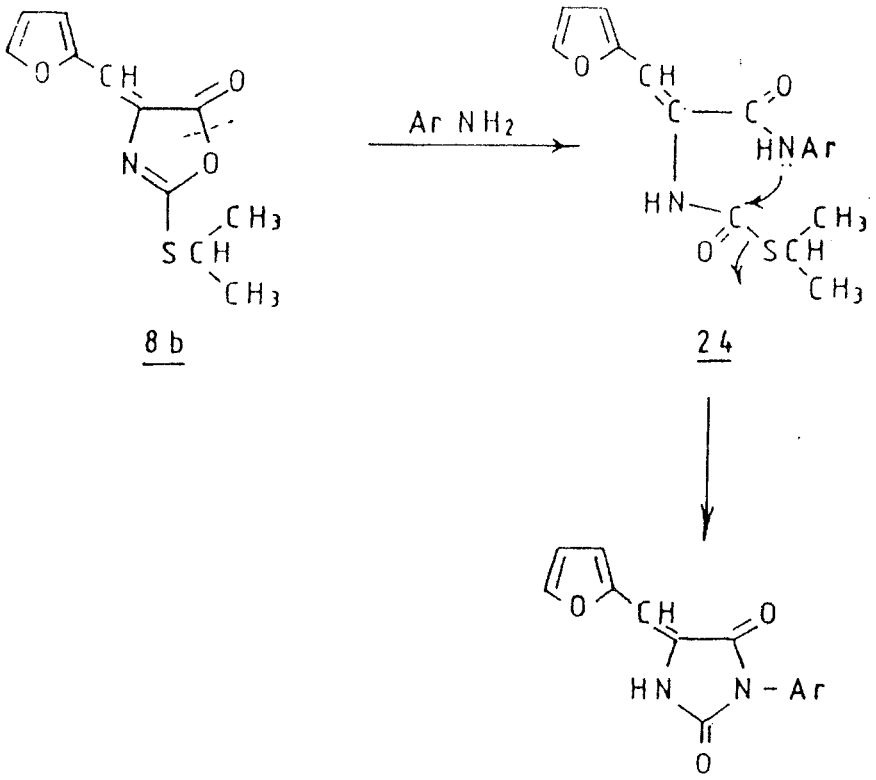


23

22 a, Ar = C_6H_5, X = O , Ar` = 2-naphthyl
b, Ar = C_6H_5, X = S , Ar` = 2-naphtyl
c, Ar = C_6H_4 -p-OCH_3, X = O , Ar` = C H
d, Ar = C_6H_4 -p-OCH_3, X = O , Ar` = C H -p-Br

Scheme 4



Scheme 5

Compounds 7a,b react with phenols to yield 1,2,4-triazole-3-carboxylic easters 22a-d. Compound 22a could be converted into 1,2,4-triazolin-3-carboxylic acid 23.

Compound 8 could be also converted into imidazolidines 25. Thus, when treated with aniline or 4-phenylthiazol-2-amines, the hydantoin derivatives 25a,b were formed via intermediacy 24 with loss of iso-propyl mercaptan.

EXPERIMENTAL

All melting points are uncorrected. Analytical data were obtained from the Microanalytical Data Unit at Cairo University. The IR spectra were carried out on a Pye-Unicam Sp-1000 Spectrophotometer. ^{1}H-NMR spectra were measured in DMSO on a Varian Em-360-60 MHz, using TMS as internal standard and chemical shifts are expressed as δ ppm. ^{13}C-NMR was measured in DMSO on a Bruker AC 250 Spectrometer using TMS. Mass spectra were recorded on Varian MAT 311A spectrometer.

Glycine, N-(S-ispropylthiocarboxylate) (4) :

A mixture of O-isopropylethylxanthate (0.01 mol) and glycine (0.01 mol) was refluxed in aqueous potassium hydroxide (20 ml; 10%) for two hours. The reaction mixture was neutralized and the solid, so formed, was filtered, washed with water, then crystallized from dilute ethanol.

Compound 4 : Yield 56%, m.p. 125°C. -IR(KBr): 3480-3320 (COOH and NH): 2950 (CH_3) 1700 (C=O). -^{1}H-NMR: δ=1.35 (d, 6H, $2CH_3$); 4.42 (s, 2H,CH_2); 5.60 (m, 1H, CH); 6.22 (s, 1H, NH); 10.70

(s, 1H, COOH). MS: m/z=177M^+ (Found; C, 40.7; H, 6.2; N, 7.9; S, 18.2. Calc. for $C_6H_{11}NO_3S$: C. 40.6; H, 6.2; N, 7.9; S, 18.0%).

4-Arylazo-2-isopropylmercapto-2- oxazolin-5-ones 7a,b:

Glycine, N-(O-isopropylthiocarboxylate)3[23] was heated with acetic anhydride, then treated with the appropriate aromatic diazonium chloride as previously described[16] for the preparation of 4-arylazo- 2-benzyloxy-2-thiazolin-5-ones.

Compound 7a: Yellow crystals, yield 76%, m.p. 165°C. -IR (KBr): 3380 (NH), 2970 (CH3); 1710 (C=O). -^{1}H-NMR: δ=1.50 (d, 6H, $2CH_3$); 5.59 (m, 1H, CH); 7.20-7.45 (m, 3H, ArH); 7.61-7.89 (m, 2H, ArH); 10.30 (br, 1H, NH). MS: m/z = 263 M^+. (Found : C, 54.8; H, 5.1; N, 15.8; S, 12.1. Calc. for $C_{12}H_{13}N_3O_2$ S: C, 54.8; H, 5.0; N, 16.0; S, 12.2%)

Compound 7b : Yellow crystals, yield 57%, m.p. 153°C. - IR (KBr) : 3385 (NH); 2975 (CH_3); 1710 (C=O). (Found, C, 53.1; H, 5.1; N. 14.3; S, 10.8. Calc. for $C_{13}H_{15}N_3O_3$ S : C, 53.2; H, 5.1; N, 14.3; S, 11.0%).

4-Aryliden-2- isopropylmercapto -2-oxazolin -5-ones 8a-c :

They were prepared by the action of the appreprate aldehyde on glycine N-(O- isopropylthiocarboxylate) 3 in acetic anhydirde after the procedure described by Cook *et al.* [24].

Compound 8a : Colourless crystals, yield 79%, m.p. 50°C. -IR (KBr): 2990 (CH_3); 1700 (C=O). -^{1}H-NMR; δ=1.50 (d, 6H, $2CH_3$); 5.55 (m, 1H, CH); 7.0 (s, 1H, styryl- H); 7.45-7.52 (m, 3H, Ar-H);

8.12-8.29 (m, 2H, Ar-H). (Found: C, 63.2; H, 5.2; N, 5.8; S, 12.9%. Calc. for $C_{13}H_{13}NO_2S$: C, 63.2; H, 5.3; N. 5.7; S, 13%).

Compound 8b : Brown crystals , yield 75%, m.p. 65°C. IR (KBr): 2990 (CH3); 1700 (C=O). (Found: C, 55.7; H, 4.3; N, 4.8; S, 11.4. Calc. for $C_{13}H_{12}ClNO_2S$: C.55.4; H, 4.5; N, 5.9; S, 13.5%).

Compound 8c : Colourless crystals, yield 70%, m.p. 102°C. -IR (KBr): 2998 CH_3); 1695 (C=O). (Found: C, 55.4; H, 4.3; N, 5.0; S, 11.4. Calc. for $C_{13}H_{12}ClNO_2S$: C, 55.4, H, 4.3; N, 5.0; S, 11.4%).

1-Aryl-3-(N-substituted carboxamido) 1,2,4-triazolin- 5-ones 10a-g :

Method (A) : Amixture of 7a,b (0.01 mol) and the appropriate aromatic or heterocyclic amine (o.o1 mol) was heated on a boiling water-bath for two hours. The reaction mixture was triturated with ethanol and the resulting solid was crystallized from ethanol.

Method (B) : 1-phenyl-3-(N-phenylcarboxamido)-5- ethoxy-1,2,4-triazole 12a[17] (0.01 mol) was refluxed in 50 ml ethanolic hydrochloric acid (20%) for two hours. Ethanol was evaporated and the solid was triurated with water, collected by filtration, then crystallized from ethanol.

Compound 10a : Yield 60%, m.p. 280°C. -IR (KBr): 3380-3330 (NH), 1690, 1675 (C=O). -^{1}H-NMR: δ=7.12 -7.51 (m, 5H, Ar-H), 7.85-8.19 (m, 5H, Ar-H), 10.31 (br, 1H, NH), 13.20 (br, 1H, NH). MS: m/z = 280 M^+. (Found: C, 64.3; H, 4.2; N, 19.8. Calc. for $C_{15}H_{12}N_4O_2$: 64.3; H, 4.3; N, 20.0%).

Compound 10b : Yield 65%, m.p. 283°C. -IR (KBr): 3390-

3330 (NH); 1680, 1665 (C=O). (Found: C, 61.8; H, 4.4; N, 18.0. Calc. for $C_{16}H_{14}N_4O_3$: C, 61.9; H, 4.5; N, 18.1%).

Compound 10c : Yield 65%, m.p. 262°C,- IR (KBr): 3385-3330 (NH); 1700, 1670 (C=O). (Found: C, 56.9;H, 4,7; N, 15.5. Calc. for $C_{17}H_{16}N_4O_4$: C, 60.0; H, 4.7; N,15.6%).

Compound 10d : Yield 55%, m.p. > 280°C. - IR (KBr): 3380-3330 (NH); 1690,1670 (C=O). - 1H-NMR: δ = 5.25-7.60 (m, 5H. Ar-H); 7.78 (s, 1H, thiazole-H); 7.92 (m, 3H, Ar-H); 10.21 (br, 1H, NH). (Found: C, 59. 5;H, 3.6; N, 19.4; S,89. Calc. for $C_{18}H_{13}N_5O_2S$: C, 59.5; H,3.6; N, 19,3; S, 8.8%).

Compound 10e : Yield 45%, m.p. 270°C. - IR (KBr): 3380-3330 (NH);1700, 1680 (C=O). (Found: C, 61.4; H, 4..8; N, 21.5. Calc. for $C_{20}H_{18}N_6O_3$: C, 61.5; H, 4.6; N, 21.5%).

Compound 10 f : Yield 46%, M.p. > 280°C. - IR (KBr) : 3380-3335 (NH); 1685, 1670 (C=O). (Found: C, 61.5; H, 4.7; N, 21.6. Calc. for $C_{20}H_{18}N_6O_3$: C, 61.5; H, 4.6; N, 21.5%).

Compound 10g : Yield 63%, m.p. 217°C. - IR(KBr): 3370-3330 (NH); 1990, 1665 (C=O). -^{1}H-NMR: δ = 3.83 (s, 3H, CH_3), 6.95-7.55 (m, 4H, pyridine-H), 7.80-8.21 (m, 5H, Ar-H), 8..20 (br, 1H,NH). MS: m/z = 311 M^+. (Found: C, 58.2; H, 3.8; N, 22.4. Calc. for $C_{15}H_{13}N_5O_3$: C, 58.6; H, 3.9; N, 22.6%).

1-Aryl-3-(N-substituted carboxamido)-5-ethoxy-1,2,4- triazoles 20,21:

Amixture of 4-tolylhydrazono-2-ethoxy-2- thiazolin-5- one(13)[17]

(0.01 mol) and the appropriate heterocyclic amine (0.01 mol) was heated on aboiling water-bath for two hours. The reaction mixture was triturated with ethanol and the resulting solid was crystallized from ethanol. All formed compounds are colourless.

Compound 20 : Yield 60%, m.p. > 280°C. -IR (KBr): 3380-3350 (NH), 1685 (C=O), -^{1}H-NMR: δ = 1.30 (t, 3H, CH_3); 3.32 (q, 2H, CH_2); 7.10-8.89 (m, 5H, Ar-H); 8.50 (s, 1H, NH); 13.00 (br, 1H, NH). MS: m/z = 313 M^+. (Found: C, 53.6; H, 4.8; N, 31.3. Calc. for $C_{14}H_{15}N_7O_2$: C, 53.7; H, 4.8; N, 31.3%).

Compound 21 : Yield 65%, m.p. > 280°C. -IR (KBr): 3390 - 3345 (NH), 1670 (C=O). (Found : C, 64.9; H, 5.2; N,22.0. Clac. $C_{21}H_{18}N_6O_2$: C, 64.9; H, 5.2; N, 21.6%).

5-Oxo-1-phenyl-1,2,4-triazol-3-carboxylic acid ester 22a-d:

Amixture of 7a,b (0.01 mol) and the appropritate phenol (0.01 mol) was heated on a boiling water-bath for two hours. The reaction mixture was triturated with ethanol and the reaulting solid was crystallized from ethanol. All formed compounds are colourless.

Compound 22a : Yield 45%, m.p. 240°C. -IR (KBr): 3350 (NH): 1785 (C=O ester);1710 (C=O). ^{1}H-NMR: δ = 7.0-8.29(m,, 12H, Ar-H), 10.75 (s, 1H, NH). (Found: C, 68.9; H, 3.8; N, 12.6. Calc. for $C_{19}H_{13}N_3O_3$: C, 68.9; H, 3.9; N, 12.7%).

Compound 22b : Yield 51%, m.p. 263°C.- IR(KBr): 3400 (NH); 1795 (C=O thioester); 1710 (C=O). MS: m/z = 347 M^+. (Found: C, 65.7; H, 3.8; N, 12.2; S, 9.4 Calc. for $C_{19}H_{13}N_3O_2S$: C, 65.7; H,3.7; N, 12.11; S, 92%).

Compound 22c : Yield 42%, m.p. 213°C. -IR(KBr): 3370 (NH); 1785, 1705 (C=O). ^{1}H-NMR: δ = 3.06 (3H, OCH_3); 6.92-7.59 (m, 9H, Ar-H), 10.75 (s, 1H, NH), (Found: C, 61.8; H, 4.2; N, 13.4. Calc. for $C_{16}H_{13}N_3O_4$: C, 61.7; H, 4.2; N, 13.5%).

Compound 22d : Yield 42%, m.p. 139°C. -IR(KBr): 3330 (NH); 1725, 1685 (C=O). (Found: C, 49.3; H, 3.2; N, 10.9. Calc. for $C_{16}H_{12}BrN_3O_4$: C, 49.2; H, 3.1; N,10.8%) .

5-Ox0-1-phenyl-1,2,4-triazol-3- carboxylic acid 23:

A suspension of 22a (0.01 mol) in ethanolic potassium hydroxide (50 ml; 10%) was refluxed for three hours. The resulting reaction mixture was filtered and the filtrate was acidifted with cold hydrochloric acid. The resulting solid prodcts was crystallized from benzene as colourless crystals.

C0mpound 23 : Yield 25%, m.p. 152°C, -IR(KBr): 3600-3450 (COOH); 3330 (NH), 1680 (C=O). -^{1}H-NMR: δ = 7.22-7.65 (m, 5H,Ar-H); 9.55 (s, 1H,COOH); 10.75 (s, 1H, NH). (Found: C, 52.7; H, 3.4; N, 20.6 Calc. for $C_9H_7N_9O_9$: C, 52.7; H, 3.4; N, 20.5%).

1-Aryl-4-furfuryliden-2- hydantoin 25 a,b :

A mixture of 8b (0.01 mol) and the appropriate amine (o.o1 mol) was heated on oil bath (120°C) for one hour. The rection mixture was diluted with water, acidified with hydrochloric acid. The solid products, so formed, were crystallized from ethanol as colourless crystals.

Compound 25a : Yield 30%, m.p. > 280°C. -IR (KBr): 3300

(NH); 1705, 1675 (C=O). (Found: C, 66.2; H, 3.7; N, 11.3. Calc. for $C_{14}H_{10}N_2O_3$: C, 66.1; H, 3.9; N, 11.0%).

Compound 25b : yield 35%, m.p. > 280°C.- IR (KBr): 3350 (NH); 1710, 1680 (C=O). -^{1}H-NMR: δ = 6.61-7.19 (M, 4H, styryl, furyl-H); 7.28-7.60 (m, 4H, Ar, thiazol -H), 11.19 (br, 1H, NH) (Found: C, 60.4; H, 3.2; N, 12.5; S, 9.5. Calc. for $C_{17}H_{11}N_9O_3S$: C, 60.5; H, 3.3; N, 12.5; S, 9.5%).

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الملخص العربى

دراسات على الأروميتات غير المتجانسة عديدة المستبدلات الوظيفية، التخليق والنشاط الكيميائي لمشتقات ٤ - أريل أزو -٢- أيزوبروبيل مركابتو -٢ - أوكسازولينون و ٤ - أريليدين - ٢ - أيزوبروبيل مركابتو - ٢ - أوكسازولينون

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يتفاعل زنثات أيزوبروبيل الإيثيل (١) مع الجليسين لينتج ثيوكربوكسيلات الجليسين (٤) . عند غليان المركب ٤ في أنهدريد حمض الخليك يتكون المركب ٢- أوكسازولينون (٥) والذي يتم الحصول عليه علي هيئة مشتقات ٤ - أريليدين هيدرازون ٧ أ،ب و ٤ - أريليدين ٨ أ-ج .

عندما تتفاعل المركبات ٧ أ،ب مع النيوكليوفيلات يعاد تنظيم تركيبها فتنتج مشتقات ٥ -أوكسو - ١و٢و٤ - ترايازولين - ٣ -حمض الكربوكسيليك . وتفاعل المركبات ٨ ب مع الأمينات يؤدي الي إعادة تنظيم التركيب فتتكون مركبات الإميدازولينات (٢٥).