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SYNTHESIS OF SOME NEW 2,4,6-TRISUBSTITUTEDTHIAZOLO-[5,4-d] PYRIMIDINE-5,7(4H,6H)-DIONES.

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ABSTRACT : Reaction of 2,6-disubstitutedthiazolo[5,4-d]pyrimidin-7(6H)-ones **2** with ethyl chloroformate/ethanol mixture afforded 5-(ethoxycarbonylamino) -2-(substitutedthio) thiazole-4-(N-substituted)-carboxamides **4a-c**. Thermal fusion of **4** followed by treatment with dimethyl sulfate gave the corresponding trisubstituted thiazolo[5,4-d]-pyrimidinediones **6**. When the thiazole esters **7a,b** were reacted with ethyl chloroformate, the corresponding ethyl 5-(ethoxycarbonyl)-aminothiazole-4-carboxylates **8** were obtained. Reaction of **8b** with benzylamine gave the 2-benzylthio-5-(3-benzylureido)thiazole-4-(N-benzyl)carboxamide **9**.

INTRODUCTION

Previously, ethyl chloroformate has been reported [1] as a reagent for adding a carbonic acid-type carbon, fully oxidized, in the ring closure of some o-aminonicotinamides to their pyrido [2,3-d]-pyrimidine -2,4- (1H,3H)-diones. Also, the same compound was employed [2] in the presence of pyridine, for stepwise synthesis of some thiazolo [5,4-d]-pyrimidine - 5,7 (4H,6H)-diones.

Moreover, ethyl chloroformate/DMF mixture has been reported as a reagent for a facile ring closure of different o-aminocarboxamide heterocyclic derivatives to afford their condensed pyrimidines [3-5] and pyrimidotriazolone [6] derivatives. On the other hand, ethyl chloroformate/ethanol mixture has been reported as a ring fission reagent [7] for thiazolopyrimidinone derivatives.

In continuation of our studies [3-7] , on the chemistry of ethyl chloroformate here we wish to report the behaviour of ethyl chloroformate/ethanol mixture towards 2,6-disubstituted thiazolo [5,4-d]pyrimidine -7 (6H)-ones.

EXPERIMENTAL

Melting points are uncorrected. Microanalyses were carried out by the Microanalytical Center, Cairo University. IR spectra were recorded (KBr-disc) by using Pye-Unicam SP-1100 spectrophotometer. ^{1}H-NMR spectra were measured in $CDCl_3$ (or DMSO-d_6 whenever reported) by using Hitachi Perkin-Elmer R-600 and Jeol GLM Ex Ft NMR systems with chemical shifts in δ (from Me_4Si). Mass spectra were recorded by using MS 5988 mass spectrometer.

Compounds **1a** [8], **1b**, **2c** and **7** [9-11] were prepared according to reported procedures.

Reaction of products 1 and 5 with dimethyl sulfate

To a solution of **1** or **5** (1.0g) in sodium hydroxide solution (100 ml, 10%), dimethyl sulfate (5 ml) was added and the mixture was stirred for 1 hr. at room temperature (for products **5** the reaction mixture was left over night). The solid product separated out (product **6a** was obtained by extracting the reaction mixture with chloroform and then, the solvent was removed under reduced pressure) was filtered off, washed with water, dried and crystallized to give **2** and **6** , respectively.

6-Methyl-2-methylthiothiazolo[5,4-d] pyrimidin-7 (6H)-one 2a: 71% yield (1hr), m.p. 229-30°C (n-butanol). IR ν /cm^{-1}: 1692 (C=O). ^{1}H-NMR (DMSO-d_6) δ 2.40 (s,3H, SCH_3); 3.50 (s, 3H, N-CH_3); 8.45 (s, 1H, H-5). MS m/e (M^+): 213. **Anal. Calcd.** for $C_7H_7N_3OS_2$: C, 39.44; H, 3.29; N, 19.72. **Found:** C, 39.40; H, 3.20; N, 19.90%.

2-Benzylthio-6-methylthiazolo[5,4-d]pyrimidin-7(6H)-one 2b: 86% yield (1hr), m.p. 165-6°C (EtOH); IR ν/cm^{-1}: 1685 (C=O), ^{1}H-NMR δ: 3.60 (s, 3H, CH_3); 4.55 (s, 2H, CH_2); 7.23 (m, 5H, C_6H_5); 7.85 (s, 1H, H-5). **Anal. Calcd.** for $C_{13}H_{11}N_3OS_2$: C, 53.98; H, 3.81; N, 14.53. **Found:** C, 53.80; H, 4.00; N, 14.40%.

4,6-Dimethyl-2-methylthiothiazolo[5,4-d]pyrimidine-5,7(4H,6H)-dione 6a: 85% yield (24hr), m.p. 186-7°C (EtOH). IR ν /cm^{-1}: 1719, 1678 (C=O). ^{1}H-NMR δ: 2.75 (s, 3H, SCH_3); 3.55 (d, 6H, $2NCH_3$). MS m/e (M^+) : 243. **Anal. Calcd.** for $C_8H_9N_3O_2S_2$: C, 39.51; H, 3.70; N, 17.28. **Found:** C, 39.30; H, 3.60; N, 17.50%.

2-Benzylthio-4,6-dimethylthiazolo[5,4-d]pyrimidie-5,7(4H,6H)-dione 6b: 90% yield (24hr), m.p. 190-1°C (EtOH). IR ν /cm^{-1}: 1717, 1663 (C=O). ^{1}H-NMR δ : 3.50 (d, 6H, $2NCH_3$); 4.50 (s, 2H, CH_2); 7.35 (m, 5H, C_6H_5). MS m/e (M^+): 319. **Anal. Calcd.** for $C_{14}H_{13}N_3O_2S_2$: C, 52.66; H, 4.08; N, 13.17. **Found:** C, 52.90; H, 4.10; N, 13.30%.

6-Benzyl-2-benzylthio-4-methylthiazolo[5,4-d]-pyrimidine-5,7(4H,6H)-dione 6c: 86% yield (24hr), m.p. 160-1°C (EtOH). IR ν/cm^{-1}: 1706, 1662 (C=O).

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^{1}H-NMR δ : 3.44 (s, 3H, CH_3); 4.53 (s, 2H, SCH_2); 5.09 (s, 2H, NCH_2), 7.40 (m, 10H, $2C_6H_5$). MS m/e (M^+) : 395. **Anal. Calcd.:** for $C_{20}H_{17}N_3O_2S_2$: C, 60.76; H, 4.30; N, 10.63. **Found:** C, 61.00; H, 4.50; N, 10.50%.

5 - (Ethoxycarbonylamino)-2-(substitutedthio)thiazole-4-(N-substituted)carboxamides 4a-c:

To a mixture of ethyl chloroformate and ethanol (30 ml, 1:5 ratio), compound **2a,b** or **c** (0.01 mol) was added. The reaction mixture was heated under reflux for 3hr. and then concentrated. After cooling, the solid product obtained was filtered off, dried and crystallized from methanol to give **4a-c.**

5-Ethoxycarbonylamino-2-methylthiothiazole-4-(N-methyl)-carboxamide 4a: 70% yield; m.p. 111-2°C. IR ν /cm^{-1}: 3408, 3157 (NH); 1720, 1635 (C=O). ^{1}H-NMR δ : 1.25 (t, 3H, CH_3-ethyl); 2.60 (s, 3H, SCH_3); 2.95 (d, 3H, NCH_3); 4.25 (q, 2H, CH_2); 7.10 (b, 1H, NH); 10.00 (b, 1H, NH-ester). MS m/e (M^+): 275. **Anal. Calcd.** for $C_9H_{13}N_3O_3S_2$: C, 39.27; H, 4.73; N, 15.27. **Found:** C, 39.40; H, 4.50; N, 15.40%.

2-Benzylthio-5-(ethoxycarbonyl)aminothiazole-4-(N-methyl)-carboxamide 4b: 93% yield; m.p. 61-2°C. IR ν /cm^{-1}: 3392, 3230 (NH); 1714, 1638 (C=O). ^{1}H-NMR δ : 1.20 (t, 3H, CH_3-ethyl); 2.80 (d, 3H, NCH_3); 4.15 (m, 4H, $2CH_2$); 6.85 (b, 1H, NH); 7.05 (s, 5H, C_6H_5); 10.20 (b, 1H, NH-ester). MS m/e (M^+): 351. **Anal. Calcd.** for $C_{15}H_{17}N_3O_3S_2$: C, 51.28; H, 4.84; N, 11.97. **Found:** C, 51.20; H, 4.90; N, 12.10%.

2-Benzylthio-5-(ethoxycarbonyl)aminothiazole-4-(N-benzyl)-carboxamide 4c: 75% yield, m.p. 65-6°C. IR ν/cm^{-1}: 3414, 3223 (NH); 1711, 1644 (C=O). ^{1}H-NMR δ : 1.30 (t, 3H, CH_3-ethyl); 4.20 (m, 4H, SCH_2, CH_2-ethyl); 4.60 (d, 2H, NCH_2); 7.30 (m, 6H, C_6H_5 , NH); 10.50 (b,1H, NH-ester). MS m/e (M^+): 427. **Anal. Calcd.** for $C_{21}H_{21}N_3O_3S_2$: C, 59.02; H, 4.92; N, 9.84. **Found:** C, 58.80; H, 4.90; N, 9.90%.

6-(Substituted)-2-(substitutedthio)thiazolo[5,4-d]- pyrimidine -5,7 (4H, 6H)-diones 5a-c:

When the thiazole-(N-substituted)carboxamide **4** (1g) was heated in a thermal decomposition tube at 200°C (oil-bath temperature) for 45 min., it melted and then solidified again. The solid was treated with methanol, filtered off, dried and crystallized to give **5a-c.**

6-Methyl-2-(methylthio)thiazolo[5,4-d]pyrimidine-5,7 (4H, 6H)-dione 5a: 67% yield, m.p. 295-7°C (n-butanol). IR ν /cm^{-1}: 3237 (NH); 1728, 1638 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 2.55 (s, 3H, SCH_3); 3.5 (s, 3H, NCH_3); 11.80 (b, 1H, NH). MS m/e (M^+): 229. **Anal. Calcd.** for $C_7H_7N_3O_2S_2$: C, 36.68; H, 3.06; N, 18.34 **Found:** C, 36.60; H, 3.10; N, 18.70%.

2-Benzylthio-6-methylthiazolo[5,4-d]pyrimidine-5,7(4H,6H)-dione 5b: 65% yield, m.p. 246-8°C (ethanol). IR ν /cm^{-1}: 3240 (NH); 1737, 1638 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 3.20 (s, 3H, CH_3); 4.50 (s, 2H, CH_2); 7.40 (m, 5H, C_6H_5); 12.15 (b, 1H, NH). MS m/e (M^+): 305. **Anal. Calcd.** for $C_{13}H_{11}N_3O_2S_2$: C, 51.15; H, 3.61; N, 13.77. **Found:** C, 51.40; H, 3.60; N, 13.50%.

6-Benzyl-2-(benzylthio)thiazolo[5,4-d]pyrimidine-5,7(4H,6H)-dione 5c: 72% yield, m.p. 216-8°C (ethanol). IR ν /cm^{-1}: 3276 (NH); 1734, 1658 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 4.50 (s, 2H, SCH_2); 5.00 (s, 2H, NCH_2); 7.40 (m, 5H, C_6H_5); 12.25 (b, 1H, NH). MS m/e (M^+): 381. **Anal. Calcd.** for $C_{19}H_{15}N_3O_2S_2$ C, 59.84; H, 3.94; N, 11.02. **Found:** C, 60.00; H, 3.90; N, 11.30%.

Ethyl 5- (ethoxycarbonylamino) -2- (substitutedthio)-thiazole -4- carboxylates 8 :

To a suspension of **7a** or **b** (0.01 mol) in ethyl chloroformate (30 ml), pyridine (0.5 ml) was added and the mixture was heated under reflux for 1hr, concentrated and left to cool. The solid product obtained was filtered off, dried and crystallized from methanol to give **8.**

Ethyl-5-(ethoxycarbonylamino)-2-(methylthio)-thiazole-4-carboxylate 8a: 84% yield, m.p. 88-9°C. IR ν /cm^{-1}: 3279 (NH); 1717, 1663 (C=O). ^{1}H-NMR δ : 1.35 (m, 6H, $2CH_3$); 4.20 (m, 4H, $2CH_2$); 9.73 (b, 1H, NH). MS m/e (M^+): 290. **Anal. Calcd.** for $C_{10}H_{14}N_2O_4S_2$: C, 41.38; H, 4.83; N, 9.66. **Found:** C, 41.60; H, 4.60; N, 9.80%.

2-(Benzylthio)-5-(ethoxycarbonylamino)thiazole-4-carboxylate 8b: 85% yield, m.p. 79-80°C. IR ν / cm-^{1}: 3278 (NH); 1718, 1664 (C=O). ^{1}H-NMR δ 1.30 (m, 6H, $2CH_3$); 4.20 (m, 6H, $3CH_2$); 7.10 (m, 5H, C_6H_5); 9.75 (b, 1H, NH). MS m/e (M^+): 366. **Anal. Calcd.** for $C_{16}H_{18}N_2O_4S_2$: C, 52.46; H, 4.92; N, 7.65. **Found:** C, 52.40; H, 4.70; N, 7.60%.

2-Benzylthio-5-(3-benzylureido)thiazole-4-(N-benzyl)-carboxamide 9:

A mixture of **8b** (2g) and benzylamine (4 ml) was heated at 180°C (oil-bath temperature) for 2 hr. After cooling, the reaction mixture was treated with methanol. The solid product obtained was filtered off and

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crystallized from methanol to give **9** (85%), m.p. 300-1°C; IR ν /cm^{-1}: 3311 (NH); 1668, 1624 (C=O). ^{1}H-NMR δ: 4.00 (s, 2H, SCH_2); 4.20 (m, 4H, $2NCH_2$); 5.75 (b, 1H, -NCONH-C); 7.00 (m, 16H, $3C_6H_5$, CONH-C); 10.30 (b, 1H, NHCO-N). MS m/e (M^+): 488. **Anal. Calcd.** For $C_{26}H_{24}N_4O_2S_2$: C, 63.93; H, 4.92; N, 11.48. Found: C, 63.70; H, 5.00; N, 11.80%.

RESULTS AND DISCUSSION

Reaction of the 2-(substitutedthio)thiazolo [5,4-d] pyrimidin-7(6H)-ones **1** with dimethyl sulfate in sodium hydroxide solution, afforded the corresponding 6-methyl-2-(substitutedthio)thiazolo[5,4-d]pyrimidin-7-(6H)-ones **2a,b** rather than the ether derivatives **3**. **(Scheme 1)**. Structure of products **2a** and **b** was elucidated by careful studying of their IR spectra, which revealed the presence of carbonyl absorptions at 1692 and 1685 cm^{-1}, respectively.

When products **2** were heated under reflux with a mixture of ethyl chloroformate/ethanol, the ring fission products,5-(ethoxycarbonyl-amino)-2- (substitutedthio)-thiazole-4- (N-substituted) carboxamide derivatives **4a-c** were smoothly obtained **(Scheme 1)**.

Formation of products **4** from the 6- substituted-thiazolo[5,4-d]-pyrimidinones **2** can be explained according to the mechanism shown in scheme 2. Thus, the N-4 of the thiazolopyrimidinones 2 are attacked by the ethyl chloroformate and quarternized to the unstable intermediate **(A)**, which in the presence of ethanol undergo ethanolysis to form **(B)**. The latter intermediates undergo ring fission of the pyrimidine ring to the thiazole derivative intermediates **(C)**, which in turn add EtO^- group to afford **(D)**. The latter eliminates a formate residue to afford the thiazoles **4. (Scheme 2).**

Structure of compounds **4a-c** was elucidated by carefull studying of their spectral determinations. The IR spectra showed ν NH at 3414-3392 cm^{-1} and 3230-3157 cm^{-1} regions, the spectra showed also ν CO (ester) at 1720-1711 cm^{-1} and ν CO (amide) [12] at 1643-1635 cm^{-1} regions. ^{1}H-NMR spectra of products **4a-c** were characterized by the presence of ethyl proton signals at δ: 1.20-1.30 ppm (triplet) and 4.15-4.25 ppm (quartet) regions, this is beside the NH proton signals (D_2O exchangeable). Also, the structure of products **4a-c** was accorded by mass spectra which revealed m/e (M^+) at 275, 351 and 427 respectively.

On the other hand, when the thiazole derivatives **4a-c** were heated above their melting points for a short time,the corresponding 6-substituted-2- (substitutedthio) thiazolo[5,4-d]-pyrimidine-5,7(4H,-6H)-diones**5a-c** were smoothly obtained in good yields.

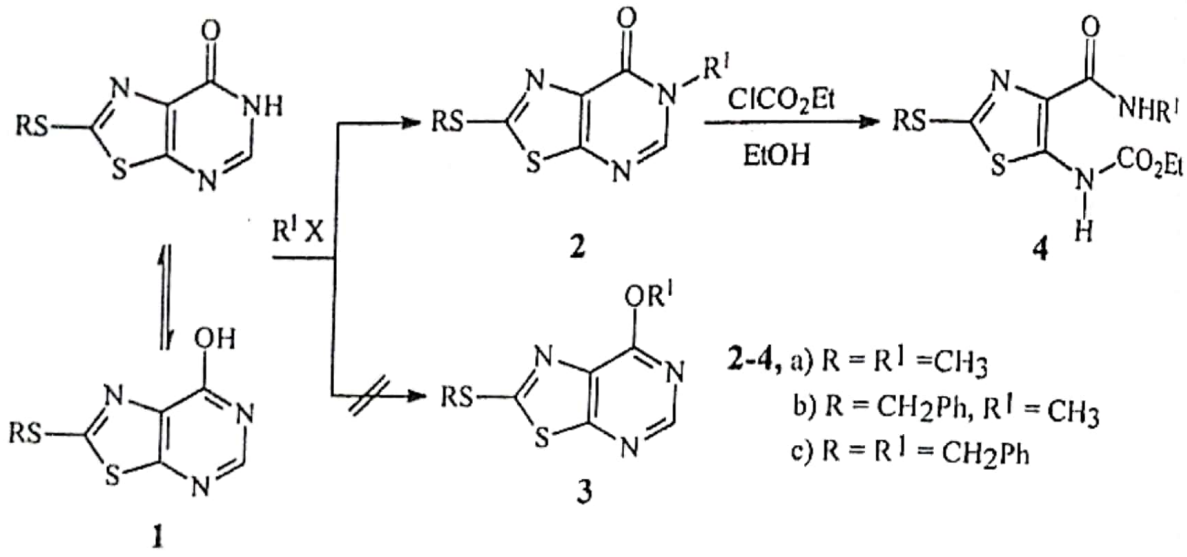
IR spectra of products **5a-c** showed ν NH at 3276-3237 cm^{-1} region and ν CO (two bands) at 1737-1728 cm^{-1} (NHCONH) and 1658-1635 cm^{-1} (-C=C-CON-R) regions [8] . The ^{1}H-NMR spectra of **5a-c** revealed the stability of the amide substituent through the thermolysis.

Methylation of products **5a-c** was also carried out by treating **5** with dimethyl sulfate in sodium hydroxide solution at room temperature to afford the corresponding 4-methyl-2,6-di(substituted)-thiazolo[5,4-d] - pyrimidine - 5,7 (4H,6H)-diones **6a-c (Scheme 3).**

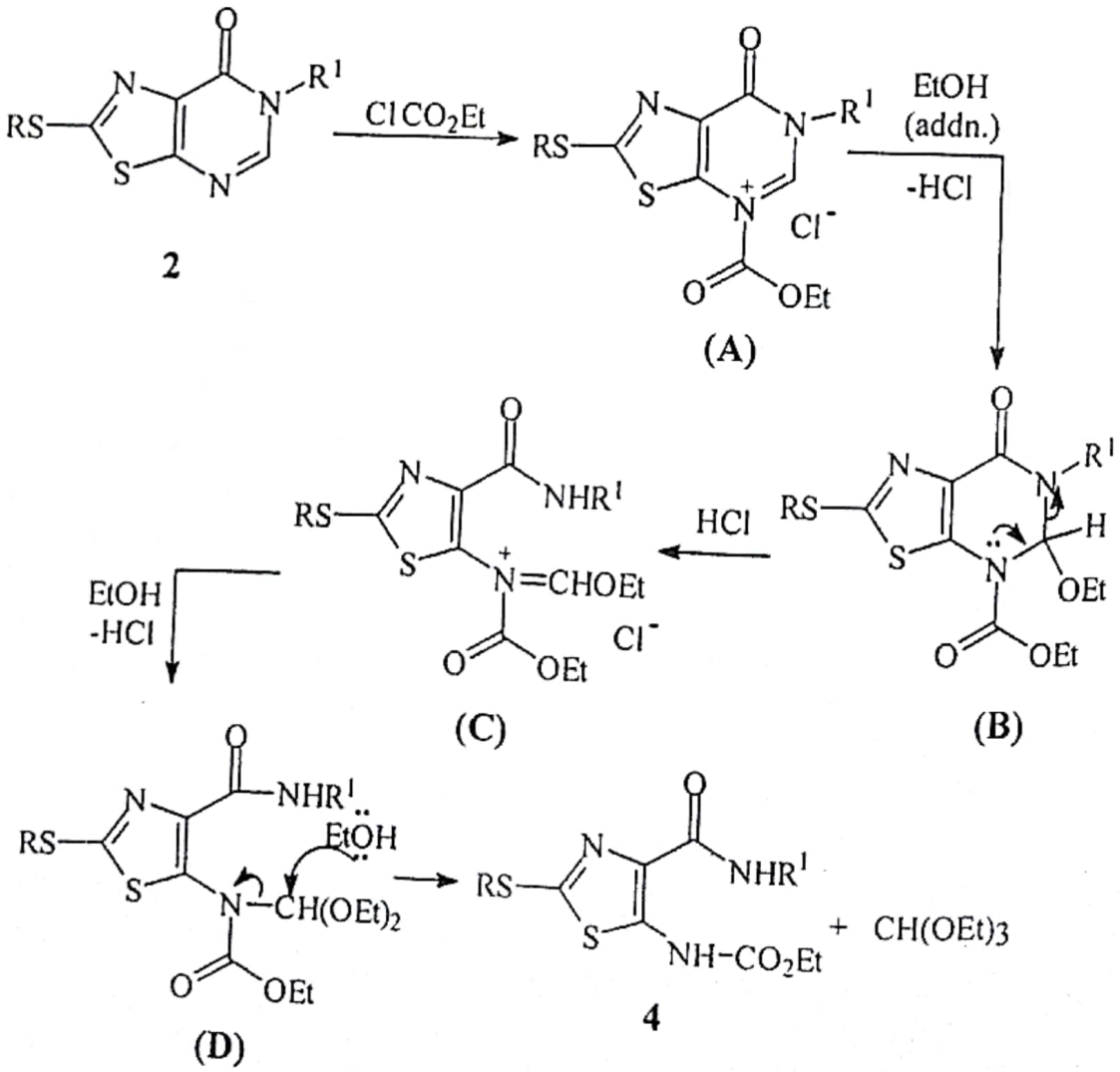
^{1}H-NMR spectra of products **6a-c** were characterized by the presence of methyl proton signals at position-4 at δ: 3.44-3.55 ppm beside the other characteristic signals. Also, the mass spectra of **6a-c** accorded their structures and revealed m/e (M^+) at 243, 319 and 395, respectively.

Attempts to prepare products **5a-c** from the ethyl 5-(ethoxy-carbonylamino)thiazole-4-carboxylates **8** (which obtained from reacting the ethyl 5-aminothiazole-4-carboxylates **7a,b** [9-11] with ethyl chloroformate in the presence of pyridine as catalyst) by reaction with the corresponding primary amine have been failed. Thus, in case of reacting of **8** with aqueous methylamine, the ethyl 5-aminothiazole-4-carboxylates **7** were obtained[13]. Whereas, when **8b** was reacted with benzylamine, the corresponding 2-benzylthio-5-(3-benzylureido)thiazole- 4-(N-benzyl)carboxamide **9** was obtained.

Infrared absorption spectra of products **8a** and **b** showed the presence of carbonyl ester moiety. Also, ^{1}H-NMR spectra revealed the presence of two ethyl proton signals at δ: 1.30-1.33 (CH_3) and 4.20 (CH_2) ppm, this is beside the NH proton signals at δ: 9.73-9.75 ppm (D_2O-exchangeable) region.



(Scheme 1)



(Scheme 2)

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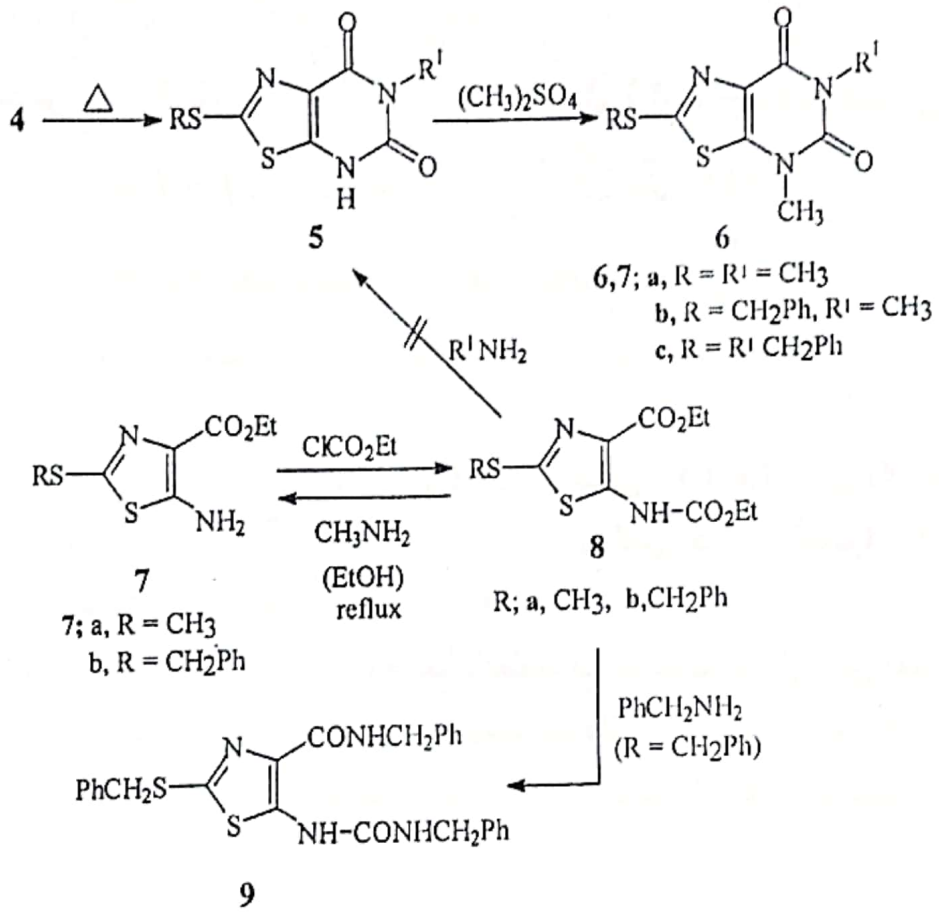

(Scheme 3)

Structure of product **9** was confirmed by IR spectrum which lack carbonyl ester absorption, instead it showed ν (C=O (amide) at 1668 and 1624 cm^{-1}. Also, its 1H-NMR spectrum accorded the proposed structure which revealed the presence of three benzyl protons signals. Furthermore, the mass spectrum of **9** revealed an ion peak at m/e 488 which corresponded to M^+.

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تشييد بعض من ٢، ٤، ٦- ثلاثى مشتق الثيازولو (٥، ٤ – د) بيريميدين ٥، ٧ – (٤ هـ، ٦ هـ) ثنائى أونات الجديدة

وحيد محمد بسيونى ، هناء محمد حسنى

قسم مبيدات الآفات - المركز القومى للبحوث - الدقى - الجيزة -مصر

بتفاعل ٢ ,٦ - ثنائى مشتق الثيازولو (٥ ، ٤ -د) بيريميدين -٧ (٦هـ) - اون (٢) مع خليط من الأيثيل كلورفورمات -كحول ايثيلى نتجت مشتقات ٥- (ايثوكسى كربونيل أمينو) -٢- مشتق ثيوثيازول -٤- (ن - مشتق كاربوكساميدات (٤أ-جـ)

وقد أسفر الإنصهار الحرارى للمركبات (٤) متبعاً بالمعاملة مع كبريتات الميثيل عن أعطاء ثلاثِى مشتق ثيازولو {٥، ٤-د} البيرميدينونات المقابلة (٦) وعند مفاعلة استر الثيازولات (٧أ ، ب) مع الايثيل كلورفورمات تم الحصول على ٥- (ايثوكسى كربونيل) أمينو ـ ثيازول -٤- كربوكسيلات (٨).