SYNTHESIS AND CYCLIZATION OF SOME THIOSEMICARBAZIDE DERIVATIVES

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Abstract

The thiosemicarbazide **3** was obtained from reaction between hydrazine **2** and heteroallene **1**. The condensed triazotriazole derivative **5** was obtained from the reaction of compound **3** with diethyl malonate. The cyclization of thiourea unit of compound **3** by heteroallene **1** furnished triazine **8**. Benzoylation of compound **3** using benzoyl chloride **9** formed triazole derivative **11**. Reaction of compound **3** and maleic anhydride **12** gave furothiadiazine **13**. cyclohexanopyrimidinthione **16** was obtained as a result of cyclocondensation of cyclohexanone **14** with compound **3**. Triazole **19** obtained from compound **3** and ammonium isothiocyanate **17** under thermal condition. Reaction of compound **3** with ethyl bromoacetate gave thiazole derivative **22**. [2+3] cyclocondensation of acetyl acetone **23** and compound **3** provided pyrazole **25**. Triazolotriazole **27** obtained from Formalin **26** and compound **3**. Compound **3** suffers intramolecular base mediated cyclization affording triazole **28**. Keeping compound **3** and propinaldehyde **29** under reflux provided triazolotriazole **31**. Compound **3** oxidized by iodine to oxadiazole **32**. Acylation of compound **3** by succinic acid formed triazolthione **34**.

Key words: Hydrazine derivatives, Thiosemicarbazide, Azoles, Azines

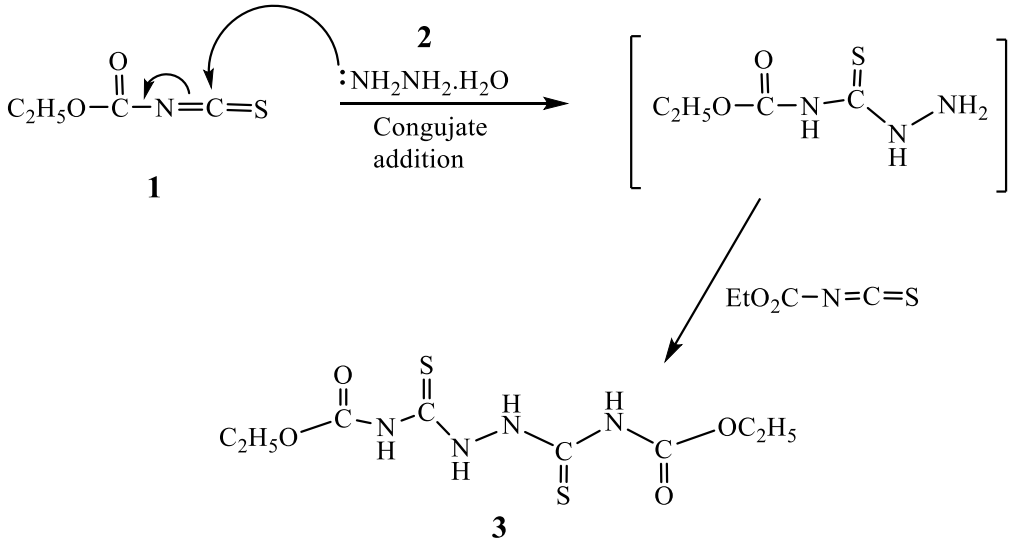
Introduction

Thiosemicarbazides possessing both electro- and nucleophilic reactivity can serve as versatile building blocks and have been extensively used in various carbon – carbons, carbon – heteroatom bond forming reactions using simple available laboratory reagents **[Greenbaum *et al.*, 2004]**, **[Sanack *et al.*, 2007]**, **[Nogachi *et al.*, 2003]**, **[Foroumadi *et al.*, 2003]**, **[Dobosz *et al.*, 1995/1996]** and **[Karakus** and **Rollas, 2002]**. Some

azoles and azines as important fine chemicals **[Bamsal** and **Bhagchandani, 1982]**, **[Ghoneim** and **Assy, 2015]** and **[Avanzo *et al*., 2012]** have been frequently found in many natural product and drugs and have exhibited a wide range of biological activities, such as antibacterial **[Bayrak *et al*., 2009]**, anticancer **[Chimenti *et al*., 2007]**, antiinflammatory properties **[Tozkoparan *et* al., 2002]**.

Results and discussion

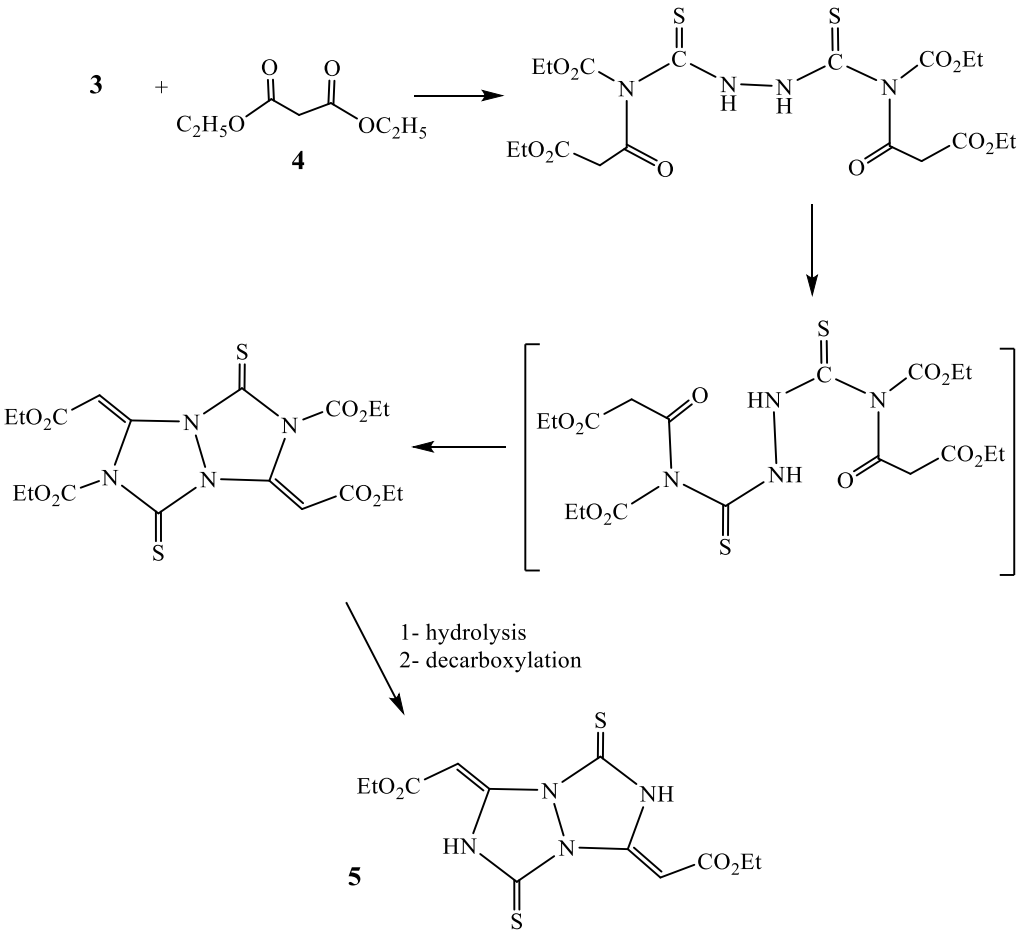
The thiosemicarbazide **3** was obtained from the attack of nucleophilic nitrogen of hydrazine **2** to the electrophilic carbon of heteroallene function of compound **1** (Scheme 1).



Scheme 1

The structure of thiosemicarbazide **3** was substantiated from its spectral and analytical data. Its IR spectrum displayed NH, C═O and C═S groups. Further support for the assigned structure was gained from its ^{1}H NMR spectrum that showed signals for NH, CH_3, and CH_2, also from mass spectrum showed a peak at m/z 294.34 (M^+, 68.67%) cross- ponding to its molecular ion with a base peak at m/z 157.25 (100%).

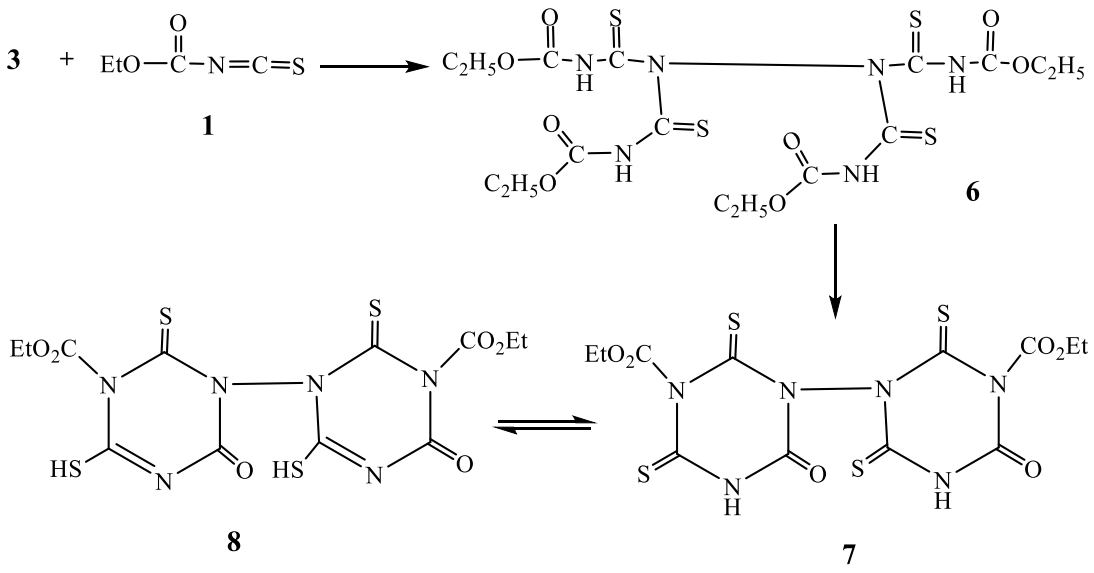
The condensed Triazolotriazole derivative **5** was obtained as the result of base mediated acylation of more acidic nitrogen using diethyl malonate **4** as acylating agent followed by intramolecular cyclodehydration and subsequent hydrolysis and decaroxylation of less stable ester group (Scheme 2).



Scheme 2

The structure assigned to the condensed system **5** was agreement with analytical and spectral data, thus IR spectrum shows NH group at 3140 cm^{-1} as medium band, carbonyl absorption frequency was detected at υ1711 cm^{-1} as sharp strong band, C═C was located at 1581 cm^{-1} in addition to C═S at that showed frequency at 1235 cm^{1}. ^{1}H NMR showed a deshielded signal at 11.73 ppm for NH function while olefinic proton was resonated at δ 6.7 ppm due to the electronic effect of C═O also the CH_2CH_3 was detected at the expected δ and multiplicity. Mass spectrum showed a peak at m/z 342.39(M^+, 6.08%) cross ponding to its molecular ion with a base peak at m/z 115.97(100%).

The cyclization of thiourea unit of compound **3** was performed via the initial formation of bis compound **6** followed by intramolecular triazine cyclization via losing of ethanol (Scheme 3).

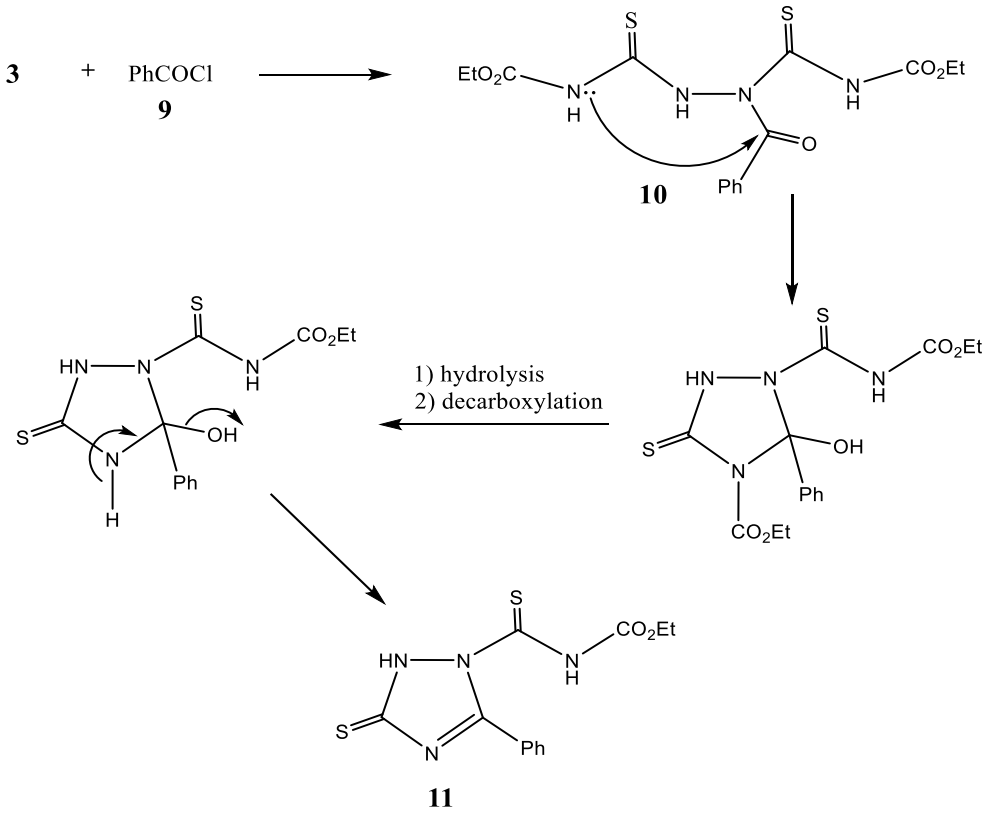


Scheme 3

The triazine cyclization was potentiated by spectral data which revealed a medium sharp peak at 3188 cm^{-1}, C═O absorption frequency at 1724 cm^{-1} in addition to C═S band at 1252 cm^{-1}. The triazine structure was also proved by ^{1}H NMR that showed down field signals of SH; NH at δ 13.05 ppm and 11.72 ppm, the aliphatic CH_2CH_3 was located at 4.2 ppm and 1.24 ppm as a quartet and triplet respectively. ^{13}C was also in an agreement with the assigned symmetric structure, thus signals at 171; 172 ppm was observed for SP^2 carbon of C═O and 153.4 ppm for SP^2 carbon of C═S while the SP^3carbon showed absorption signals at 62.46 ppm, 14.06 ppm respectively.

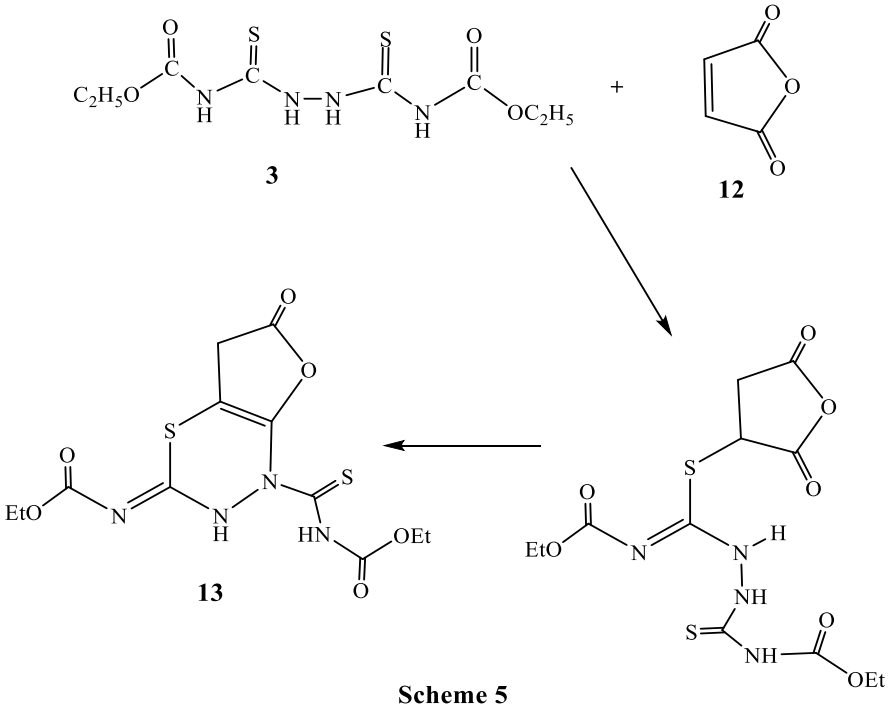
Benzoylation of thiosemicarbazide **3** using benzoyl chloride **9** resulted in triazole cyclization to furnish triazole derivative **11** via the initial acyclic compound **10** followed by heterocyclization, [hydrolysis and decarboxylation], subsequent dehydration (Scheme 4).

The triazole skeleton **11** was proved from analytical and spectral data. Which show absorption frequency at 3385 cm^{-1}, 1635 cm^{-1}, 1602 cm^{-1} and 1338 cm^{-1} for NH, C═O, C═N and C═S functions respectively. Also, ^{1}HNMR showed abroad signal at 11.73 ppm for NH's, and the deshielded aromatic proton was appeared in region 8.3 – 6.2 ppm together with the aliphatic protons that resonated up field region. ^{13}C of the same compound resonated at 172.02, 162.32, 156.3 and 153.84 ppm for SP^2 carbon of C═O, 2C═S, C═N in addition to aromatic SP^2 carbon and aliphatic SP^3 carbon.



Scheme 4

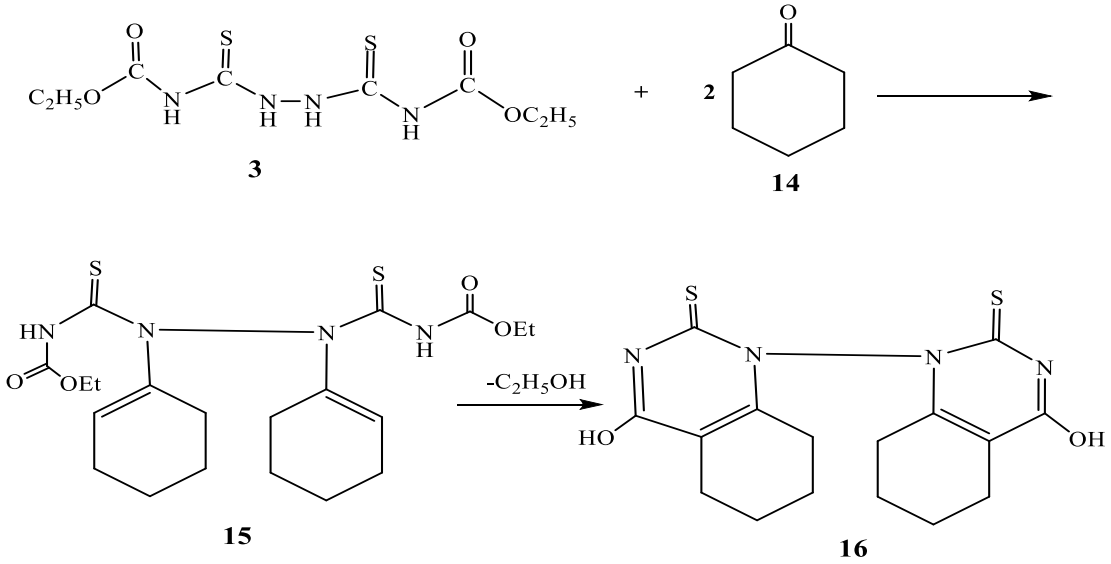
A one pot three component reaction of compound **3** and maleic anhydride **12** resulted in Michael addition, intramolecular thiadiazine cyclization to produce furothiadiazine as afinal product **13** (Scheme 5).



Scheme 5

The spectral data of furothiadiazine **13** showed absorption frequencies at 3142cm^{-1}, 1726cm^{-1}, 1712 cm-1 for NH and 2CO functions respectively. Also ^{1}H NMR potentiated the assigned structure **13**, thus abroad signal was observed in deshielded region at 11.75 ppm for NH, S, and aliphatic protons for CH_2CH_3 structure in addition to doublet of CH_2 at 2.8 ppm. ^{13}C revealed signals at 162.31ppm, 156.3ppm and 153.84ppm for SP^2 carbon of C═O, C═S and C═N in addition to SP^3 carbon signals that located at 61.96 ppm, 53.04 ppm, and 14.29 ppm.

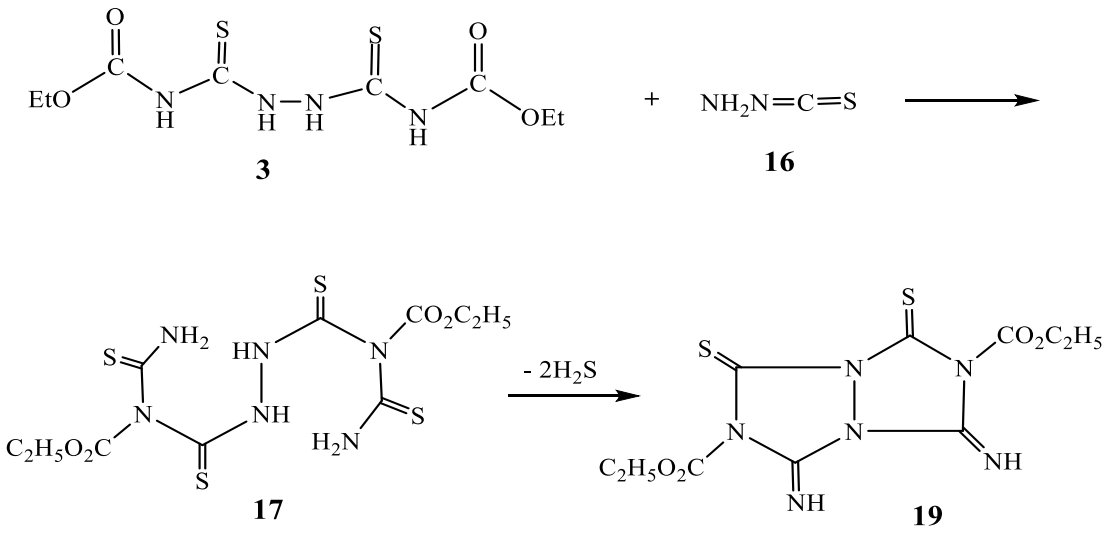
As depicted in scheme (6), cyclohexanopyrimidinthione **16** was obtained from cyclocondensation of two equivalent of cyclohexanone **14** with thiosemicarbazide **3**, that form non isolable cyclic enamine **15** followed by the pyrimidine cyclization via the attack of cyclic enaminic nucleophilic carbon to the electrophilic ester carbonyl carbon.



Scheme 6

The spectral data of the condensed skeleton **16** was in agreement with assigned structure, so IR spectrum showed OH, C═S frequency at υ 3180 cm^{-1}, υ 1227 cm^{-1} respectively. Also ^{1}H NMR potentiated of the structure, so OH signal was observed at δ 7.94 ppm in addition to cyclohexane protons that located in up field position. ^{13}C showed SP^2 carbons at δ 162.29 ppm, 156.29 ppm and 153.83 ppm while SP^3 carbons were located at 61.95 ppm, 35.76 ppm, 30.75 ppm and 14.29 ppm .

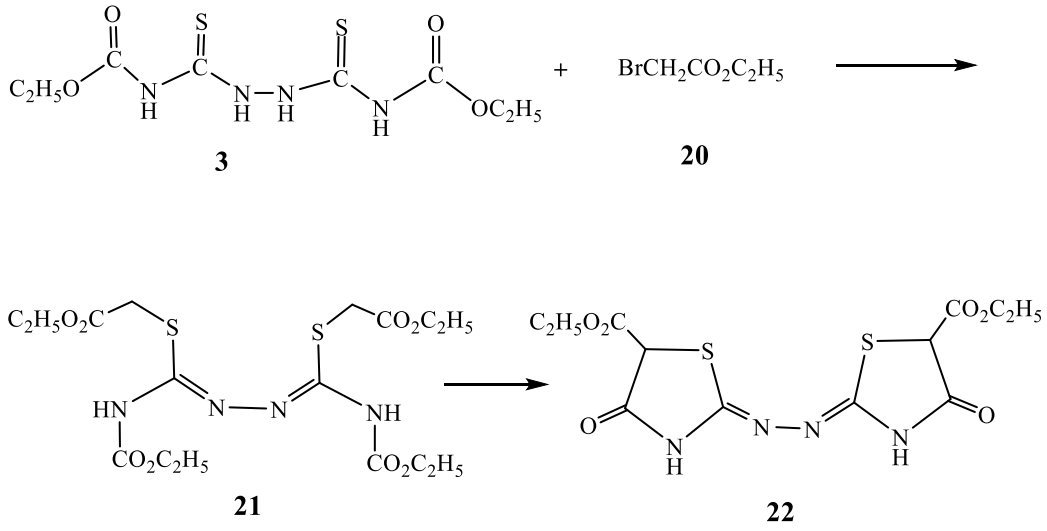
Triazole formation was achieved by keeping of thiosemicarbazide deri-veative **3** and ammonium isothiocyanate **17** under thermal condition via initial formation of non-isolable compound **18** that loss $2H_2S$ (Scheme 7).



Scheme 7

Compound **19** showed absorption bands at 3355 cm^{-1}, 1726 cm^{-1} and 1235 cm^{-1} for NH, C═O and C═S. ^{1}HNMR spectrum of compound **19** revealed signals at 11.73 ppm for NH proton also the quartet and triplet for CH_3CH_2– structure was observed at 4.197 ppm and 1.24 ppm respectively. Mass spectrum showed a peak at m/z 408.48(M^+, 6%) a corresponding to its molecular ion with a base peak at m/z 85.07(100%).

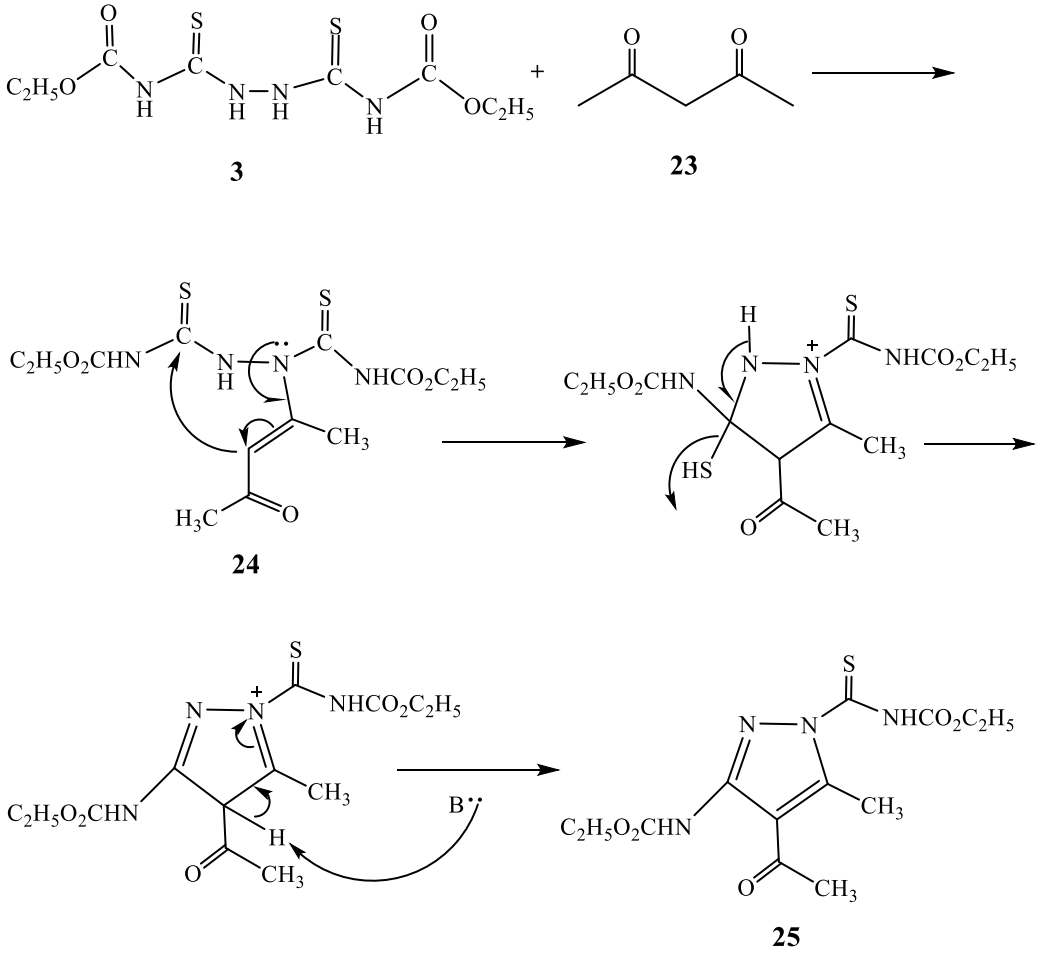
Base induced alkylation of thiosemicarbazide derivative **3** using ethyl bromoacetate **20** followed by the attack of nucleophilic carbonion to the ester electrophilic carbonyl carbon finished the thiazole derivative **22** (Scheme 8).



Scheme 8

The chemical structure of synthesized thiazole derivative **22** was elucidated by analysis of its spectroscopic data. In IR spectrum of compound **22** there are absorption bands at 3144 cm^{-1} and (1728- 1710 cm^{-1}) for NH and C═O respectively. Its ^1H NMR displayed a deshielded band at δ 11.73 ppm for NH,S the ester group and methenyl protons were located at expected δ and multiplicity. Mass spectrum showed a peak at m/z 374.04 (M^+, 51.76%) corresponding to its molecular ion with a base peak at m/z 291.12(100%).

[2+3] cyclocondensation of acetylacetone **23** and thiosemicarbazide derivative **3** provided pyrazole cyclization **25** via initial formation of enaminic system **24** followed by the attack of nucleophilic enaminic carbon to thioxo electrophilic carbon and subsequent loss of H_2S (Scheme 9).

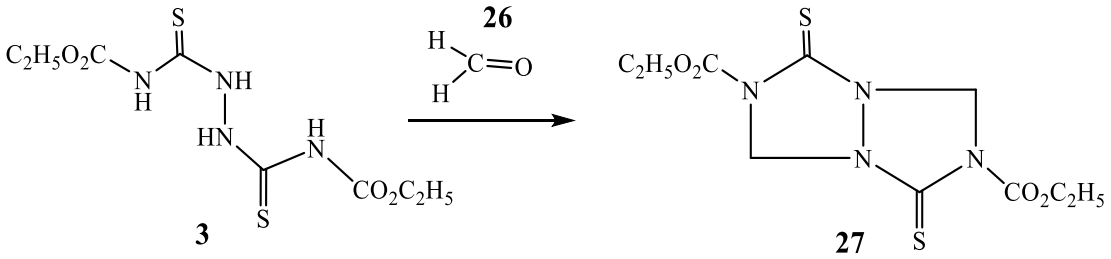


Scheme 9

The pyrazole structure **25** was confirmed by spectroscopic analysis. IR spectrum showed NH stretching frequency at 3140 cm^{-1} and C═O functions at 1724 cm^{-1} and 1712 cm^{-1}. ^1H NMR spectrum of compound

25 showed signal at δ 11.68 ppm for NH, NH of different electronic environment at δ 7.94 ppm, quarteteat δ 4.20, two methyl groups at δ 2.94 ppm and δ 2.88 ppm while the triplet at δ 1.24 ppm for ester CH_3. ^{13}C showed SP^2 carbons at δ 162.33 ppm, 156.32 ppm and 153.85 ppm while SP^3 carbons were located at 61.98 ppm, 35.80 ppm, 30.78 and 14.31ppm.

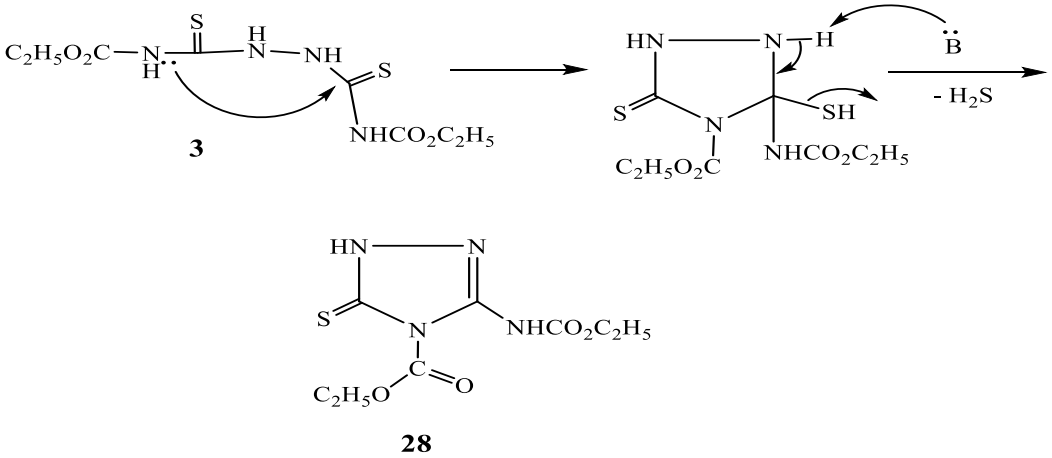
Formalin **26** and thiosemicarbazide **3** undergo thermal triazolotriazole cyclization as shown in (Scheme 10).



Scheme 10

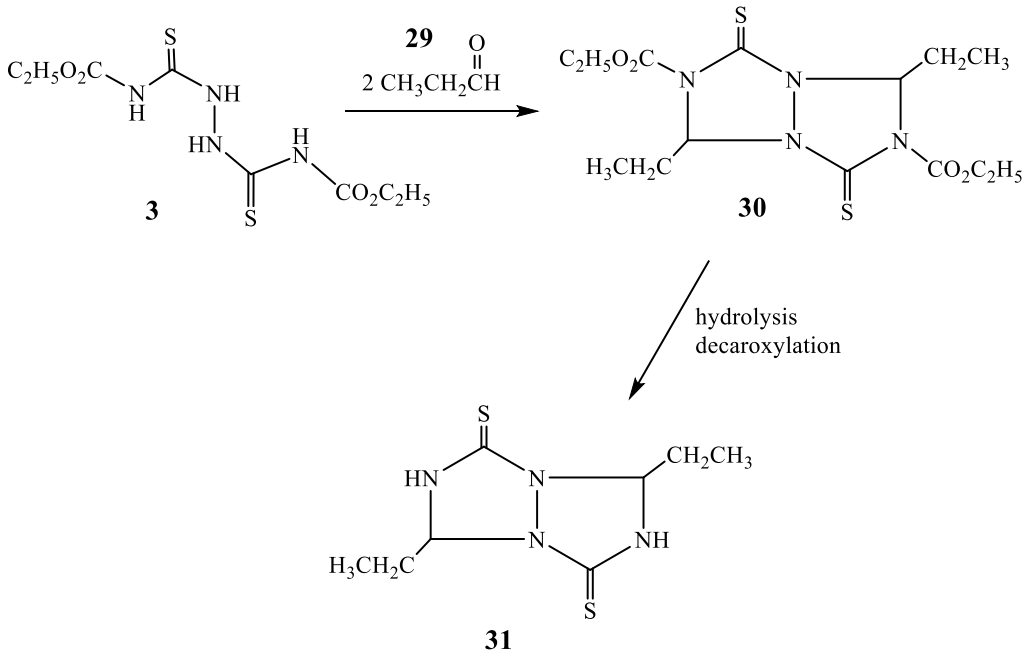
The structure of desired triazolotriazole **27** was elucidated from spectroscopic data. IR spectrum showed C═O, C═S frequency at 1710 cm^{-1}, 1226 cm^{-1} respectively. Also ^1H NMR showed quartet at δ 4.19 ppm for $C\underline{H}_2CH_3$, singlet at δ 3.74ppm for $–NCH_2N–$ while $C\underline{H}_3CH_2$ was observed as triplet at δ 1.24 ppm. Mass spectrum showed a peak at m/z 318.37 (M^+, 27.89%) corresponding to its molecular ion with a base peak at m/z 63.86(100%).

Thiosemicarbazide **3** suffers intramolecular base mediated cyclization affording triazole derivative **28** (Scheme 11).



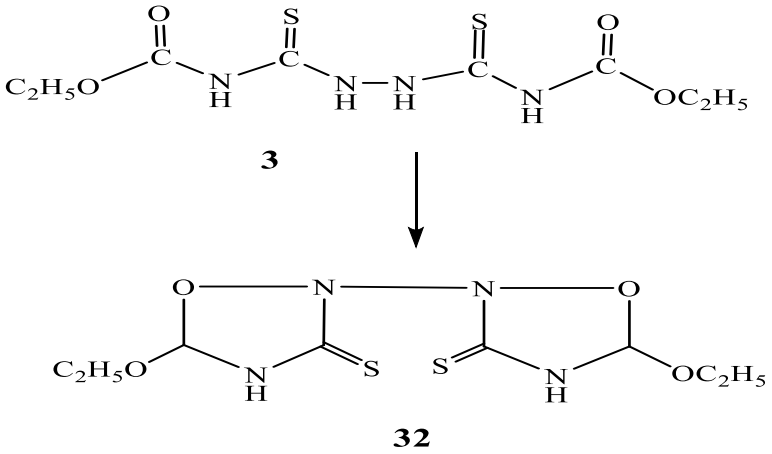
Scheme 11

The title compound was proved by analytical and spectral data, thus IR spectrum showed vibrational stretching band at 3150 cm^{-1}, 1649 cm^{-1} and 1228 cm^{-1} for NH, C═O and C═S function. ^1H NMR revealed broad signal at δ 11.66 ppm for cyclic NH while exocyclic NH was observed at δ 7.94 ppm in addition to CH_2CH_3 signals which observed at the expected δ and multiplicity. Mass spectrum showed a peak at m/z 260 (M^+, 6.01%) corresponding to its molecular ion with a base peak at m/z 59.99(100%).
Keeping thiosemicarbazide **3** and propinaldehyde **29** under reflux provided triazolotriazole **31** as showen in (scheme 12).



Scheme 12

The structure of triazolotriazole **31** was elucidated from spectroscopic data. IR spectrum showed NH, C═S frequency at 3140 cm^{-1}, 1236 cm^{-1} respectively. Also ^1H NMR showed δ 11.73 ppm for NH, quartet at δ 4.20 ppm for $C\underline{H}_2CH_3$, while $C\underline{H}_3CH_2$ was observed as a triplet at δ 1.24 ppm. Mass spectrum showed a peak at m/z 230.40(M^+, 2.43%) corresponding to its molecular ion with a base peak at m/z 59.97(100%).
Oxidative intramolecular cyclization of thiosemicarbazide **3** to oxadiazole **32** was achieved by the effect of iodine (scheme 13).



Scheme 13

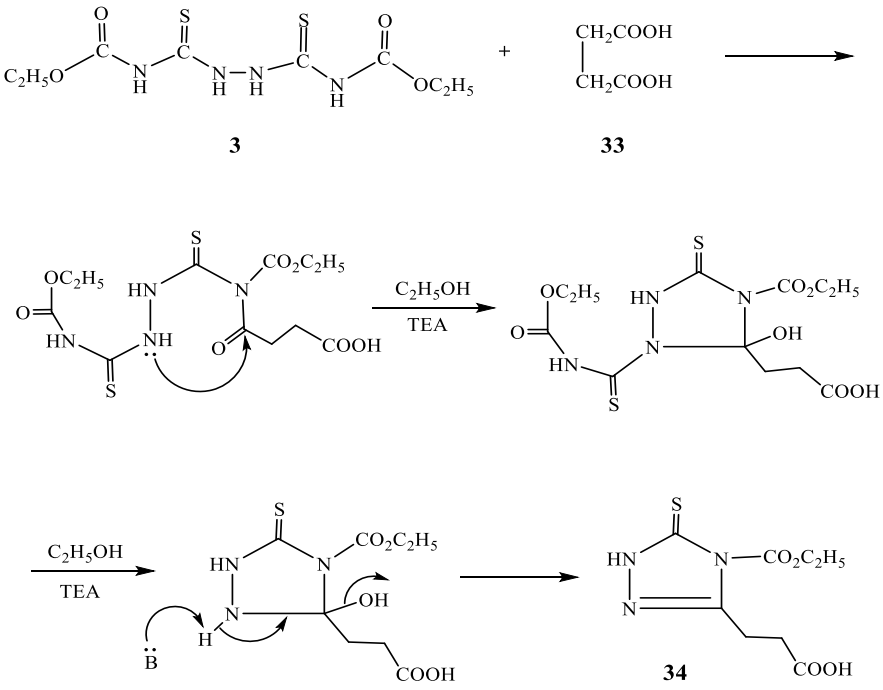
The structure of compound **32** was elucidated from spectroscopic data. IR spectrum showed NH, C═S frequency at 3140 cm^{-1}, 1230 cm^{-1} respectively. Also ^{1}H NMR showed δ 11.72 ppm for –CO– NH–CS–, δ 7.94 ppm for –CS–NH–N– and the CH_2CH_3 was detected at the expected δ and multiplicity. ^{13}C was in an agreement with the assigned symmetric structure, thus signals at 170.83 ppm was observed for SP^2 carbon of C═O and 156.28 ppm, 153.81 ppm for SP^2 carbon of 2C═S while the SP^3carbon showed absorption signals at 62.45 ppm, 14.29 ppm respectively.

Cyclization of thiosemicarbazide derivative **3** to triazolthione **34** was achieved by acylation using succinic acid, cyclization, hydrolysis and subsequent dehydration (scheme 14).

The spectral data of the triazolthione skeleton **34** was in agreement with assigned structure, so IR spectrum showed NH at 3138 cm^{-1}, 2C═O at 1726 cm^{-1}, 1710cm^{-1} and C═S at 1236 cm^{-1}. Also ^{1}H NMR potentiated of the structure, so COOH signal was observed at δ 12.19 ppm, NH at δ 11.8 ppm, quartet at δ 4.21 ppm for $C\underline{H}_2CH_3$, while $C\underline{H}_3CH_2$ was observed as a triplet at δ 1.24.

Experimental

Melting points were measured using an Electro thermal IA 9100 apparatus with open capillary tube and are uncorrected. All experiments were carried out using drying solvents. Products were purified by crystallization. The IR spectra (KBr disc) were recorded on a Pye-Unicam Sp-3-300 or a Shimadzu FT-IR 8101 PC infrared spectrophotometer. The ^{1}H NMR and ^{13}C NMR spectra were measured on a JEOL-JNM-LA 400 MHz spectrometer using DMSO-d_6 as a solvent.



Scheme 14

All chemical shifts were expressed on the δ (ppm) scale using TMS as an internal standard reference. The coupling constant (*J*) values are given in *Hz*. Mass spectra were measured on a GCMS-QP1000 EX spectrometer at 70 Ev. Analytical data were obtained from the Microanalysis Center at Cairo University, Giza, Egypt.

Ethyl (2-((((2λ^3-ethynyl)-λ^7-oxidanyl) carbonyl) carbamothioyl)hydrazine-1-carbonothioyl) carbamate (3)

A mixture of ammonium thiocyanate (0.04 mol) in dry aceton(60 mL) was warmed till complete dissolving then ethyl chloroformate (0.04 mol) was added dropwise and stirring in flask for 1h, after that hydrazine hydrate (0.04 mol) was added drop wise and stirring for 1h. The reaction mixture was poured into H_2O. The formed product was filtered off, dried and crystallized from ethanol (95%) to give compound **3** in 90% yield as pale yellow powder. Mp. 285-287 ^oC, IR (KBr, cm^{-1}): 3184 (NH), 1724 (C═O), 1212 (C═S); ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.24 (t, 6H, $\underline{2CH_3}CH_2$, J = 6.4 Hz), 4.2 (q, 4H, $\underline{2CH_2}CH_3$, J = 7.2 Hz), 11.7 (s, 2H, 2NH), 13.05 (s, 2H, NH–NH); Mass: m/z = M^+ 294 (68.67%) and 157 (100%); Anal. Calcd for $C_8H_{14}N_4O_4S_2$ (294.34): C, 32.64; H, 4.79; N, 19.03. Found: C, 32.58; H, 4.74; N, 19.05%.

Diethyl 2,2′-(3,7-dithioxotetrahydro-1H,5H-[1,2,4] triazolo[1,2-a] [1,2,4]triazole-1,5-diylidene)(2E,2E′)-diacetate (5)

A mixture of compound **3** (0.005 mol), diethylmalonate (0.005 mol) and few drops of triethylamine in ethanol absolute (20 mL) was heated under reflux for 6 h. The reaction mixture was cooled at room temperat-ure and poured into HCl/H_2O (1:10). The product was filtered off, washed with water and crystallized from ethanol to give compound **5** in 75% yields as white powder. Mp. over 360 ºC, IR (KBr, cm^{-1}): 3140 (NH), 1711(C═O), 1581(C═C), 1235 (C═S); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.24 (t, 6H, $\underline{2CH_3}CH_2$, J = 7.2 Hz), 4.2 (q, 4H, $\underline{2\ CH_2}CH_3$, J = 6.8 Hz), 6.7 (s,2H, olefinic proton), 11.7 (s, 2H, 2NH); Mass: m/z = M^+ 342 (6.08%) and 115 (100%); Anal. Calcd for $C_{12}H_{14}$-$N_4O_4S_2$ (342.39): C, 42.10; H, 4.12; N, 16.36. Found: C, 42.12; H, 4.10; N, 16.34%.

Diethyl 4′,6-dimercapto-4,6′-dioxo-2,2′-dithioxo-2*H*,2′*H*-[1,1′-bi(1,3,5-triazine)]-3,3′(4H,6′H)-dicarboxylate (8)

A mixture of ammonium thiocyanate (0.005 mol) in dry aceton(50 mL) was warmed till complete dissolving then ethyl chloroformate (0.005 mol) was added drop wise and stirring in flask for1h, after that compound **3** (0.005 mol) was added and few drops of triethylamine, then refluxed for 2 hr. The reaction mixture was cooled and poured into HCl/H_2O (1:10). The product was filtered off, washed with water and crystallized from ethanol to give compound **7** in 85% yields as yellow powder. Mp. over 360 ºC, IR (KBr, cm^{-1}): 3188 (NH), 1724 (C═O), 1213 (C═S); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.24 (t, 6H, $\underline{2CH_3}CH_2$, J = 7.2 Hz), 4.2 (q, 4H, $\underline{2CH_2}CH_3$, J = 7.2 Hz), 11.7 (s, 2H, 2NH), 13.05 (s, 2H, 2SH); ^{13}C-NMR: δ = 14.06 (CH_3), 62.46 (CH_2), 153.45 (C═S), 170.84, 171.85(C═O); Anal. Calcd for $C_{12}H_{12}N_6O_6S_4$ (464.5): C, 31.03; H, 2.60; N, 18.09. Found: C, 31.01; H, 2.50; N, 18.07%.

Ethyl (5-phenyl-3-thioxo-2,3-dihydro-1*H*-1,2,4-triazole-1-carbonothi-oyl) carbamate (11)

A mixture of compound **3** (0.005 mol**)** and benzoyl chloride (0.005 mol) in ethanol absolute (50 mL) was heated under reflux for 6 h. The reaction mixture was cooled at room temperature and poured into water. The product was filtered off, washed with water and crystallized from methanol and DMF to give compound **11** in 75% yields as yellow powder. Mp. over 360 ºC, IR (KBr, cm^{-1}): 3385 (NH), 1635 (C═O), 1602 (C═N), 1338 (C═S); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.24 (t, 3H, $\underline{CH_3}CH_2$, J = 6.8 Hz), 4.2 (q, 2H, $\underline{CH_2}CH_3$, J = 6.8 Hz), 6.2–8.3 (m, 5H, ArH's), 11.73 (br.s, H, NH's); ^{13}C-NMR: δ = 14.30, 21.05 (CH_3),

61.96 (CH_2O) 153.84 (C═N), 156.30, 162.32 (2C═S), 172.02 (C═O); Anal. Calcd for $C_{12}H_{12}N_4O_2S_2$ (308.37): C, 46.74; H, 3.92; N, 18.17. Found: C, 46.72; H, 3.89; N, 18.15%.

Ethyl (z)-(1-((ethoxycarbonyl)carbamothioyl)-6-oxo- 1,2,5, 6-tetrahydro-3*H*-furo[2,3-e][1,2,4]thiadiazin-3-ylidene)carbamate (13)

A mixture of compound **3** (0.005 mol), maleic anhydride (0.005 mol) and few drops of triethylamine in ethanol absolute (30 mL) was heated under reflux for 6 h. The reaction mixture was cooled at room temperature and poured into HCl/H_2O (1:10). The product was filtered off, washed with water and crystallized from methanol and DMF to give compound **13** in 80% yields as yellow powder. Mp. over 360 ^oC, IR (KBr, cm^{-1}): 3142 (NH), 1726 and 1712 (2C═O), 1581(C═C), 1541 (C═N), 1236 (C═S); ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.24 (t, 6H, $\underline{2CH_3}CH_2$, J = 6.8 Hz), 4.2 (q, 4H, $\underline{2CH_2}CH_3$, J = 6.8 Hz), 11.7 (br.s, H, NH); ^{13}C-NMR: δ = 14.29, 30.78 ($2CH_3$), 53.04, 61.96 ($2CH_2$), 153.84, 156.30 and 162.31 (C═N, C═S and C═O); Anal. Calcd for $C_{12}H_{14}N_4O_6S_2$ (374.39): C, 38.50; H, 3.77; N, 14.9. Found: C, 38.45; H, 3.72; N, 14.8%.

Diethyl (1,2-di(cyclohex-1-en-1-yl)hydrazine-1,2-dicarbonothioyl) dicarbamate (16)

A mixture of compound **3** (0.005 mol), cyclohexanone (0.005 mol) and few drops of triethylamine in ethanol absolute (50 mL) was heated under reflux for 4 h. The reaction mixture was cooled at room tempera-ture and poured into HCl/H_2O (1:10). The product was filtered off, washed with water and crystallized from methanol and DMF to give compound **16** in 85% yields as pale brown powder. Mp. over 360 ^oC, IR (KBr, cm^{-1}): 3180 (OH), 1226 (C═S); ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.88 (m, 8H, $4CH_2$ cyclohexane), 7.94 (s, 2H, OH); ^{13}C-NMR: δ = 14.29, 30.75 and 35.76 ($3CH_3$), 61.95 (CH_2), 153.83, 156.29 and 162.29 (C═N and 2C═S); Anal. Calcd for $C_{16}H_{18}N_4O_2S_2$ (362.47): C, 53.02; H, 5.01; N, 15.46. Found: C, 53.01; H, 4.98; N, 15.43%.

Diethyl 2,2'-(hydrazine-1,2-dicarbonothioyl)bis(2-carbamothioyl hydrazine-1-carboxylate) (19)

Ammonium thiocyanate (0.005 mol**)** in acetic acid (50 mL) was warmed till complete dissolving then compound **3** was added and ref-luxed for 4 h. The reaction mixture was cooled at room temperature and poured into water. The product was filtered off, washed with water and crystallized from methanol to give compound **19** in 63% yields as white powder. Mp. over 360 ^oC, IR (KBr, cm^{-1}): 3355 (NH), 1726 and1710 (2C═O),

1235(C═S); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.24 (t, 6H, $\underline{2CH_3}CH_2$, J = 7.2 Hz), 4.2 (q, 4H, $\underline{2CH_2}CH_3$, J = 7.2 Hz), 11.73 (s, 2H, 2NH); Mass: m/z = M^+ 408 (6.01%) and 85(100%); Anal. Calcd for $C_{10}H_{12}N_6O_4S_4$ (408.48): C, 29.40; H, 2.96; N, 20.57. Found: C, 29.37; H, 2.94; N, 20.53%.

Diethyl 2,2'-(hydrazine-1,2-diylidene)(2Z,2'Z)-bis(4-oxothiazolidine-5-carboxylate) (22)

A mixture of compound **3** (0.005 mol), ethyl bromoacetate (0.005 mol) and few drops of triethylamine in ethanol absolute (40 mL) was heated under reflux for 4 h. The reaction mixture was cooled at room temperature and poured into HCl/H_2O (1:10). The product was filtered off, washed with water and crystallized from methanol to give compound **22** in 83% yields as white powder. Mp. over 360 ºC, IR (KBr, cm^{-1}): 3144 (NH), 1728 and 1710 (C═O); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.24 (t, 6H, $\underline{2CH_3}CH_2$, J = 6.8 Hz), 4.2 (q, 4H, $\underline{2CH_2}CH_3$, J = 7.2 Hz), 11.73 (s, 2H, 2NH); Mass: m/z = M^+ 374 (51.76%) and 291 (100%); Anal. Calcd for $C_{12}H_{14}N_4O_6S_2$ (374.39): C, 38.50; H, 3.77; N, 14.97. Found: C, 38.47; H, 3.75; N, 14.96%.

Ethyl (4-acetyl-1-((ethoxycarbonyl)carbamothioyl)-5-methyl-1*H*-pyr-azol-3-yl)carbamate (25)

A mixture of compound **3** (0.005 mol), acetyl acetone (0.005 mol) and few drops of triethylamine in ethanol absolute (50 mL) was heated under reflux for 6 h. The reaction mixture was cooled at room temper-ature and poured into HCl/H_2O (1:10). The product was filtered off, washed with water and crystallized from methanol and DMF give compound **25** in 79% yields as yellow brown powder. Mp. over 360 ºC, IR (KBr, cm^{-1}): 3140 (NH), 1724 and 1712 (C═O), 1230 (C═S); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.24 (t, 6H, $\underline{2CH_3}CH_2$, J = 6.8 Hz), 2.88 and 2.94 (s, 6H, $2CH_3$), 4.2 (q, 4H, $\underline{2CH_2}CH_3$, J = 6.8 Hz), 7.94 (s, 2H, 2NH aliphatic), 11.68 (br.s, H, NH); ^{13}C-NMR: δ = 14.31, 30.78 and 35.80 ($4CH_3$), 61.98 ($2CH_2$), 153.85, 156.32 and 162.33 (C═S and 2C═O); Anal. Calcd for $C_{13}H_{18}N_4O_5S$ (342.37): C, 45.61; H, 5.30; N, 16.36. Found: C, 45.58; H, 5.28; N, 16.33 %.

Diethyl 1,5-dithioxo-1*H*,5*H*-[1,2,4]triazolo[1,2-a][1,2,4] triazole-2,6 (3*H*,7*H*)-dicarboxylate (27)

A mixture of compound **3** (0.005 mol), formalin (40%, 3 ml) and few drops of triethylamine in ethanol absolute (40 mL) was heated under reflux for 4 h. The reaction mixture was cooled at room temperature and

poured into HCl/H_2O (1:10). The product was filtered off, washed with water and crystallized from methanol and DMF to give compound **27** in 80% yields as pale orange powder. Mp. over 360 °C, IR (KBr, cm^{-1}): 1710 (C═O), 1226 (C═S); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.24 (t, 6H, $\underline{2CH_3}CH_2$, J = 7.2 Hz), 3.74 (s, 2H, –NCH_2N–), 4.2 (q, 4H, $\underline{2CH_2}CH_3$, J = 6.8 Hz); Mass: m/z = M^+ 318 (27.89%) and 63 (100%); Anal. Calcd for $C_{10}H_{14}N_4O_4S_2$ (318.37): C, 37.73; H, 4.43; N, 17.60. Found: C, 37.71; H, 4.42; N, 17.57%.

Ethyl 3-((ethoxycarbonyl)amino)-5-thioxo-1,5-dihydro-4*H*-1,2,4-triazole-4-carboxylate (28)

A mixture of compound **3** (0.005 mol) and few drops of triethyl-amine in ethanol absolute (50 mL) was heated under reflux for 4 h. The reaction mixture was cooled at room temperature and poured into HCl/H_2O (1:10). The product was filtered off, washed with water and crystallized from methanol to give compound **28** in 70% yields as pale brown powder. Mp. over 360 °C, IR (KBr, cm^{-1}): 3140 (NH), 1649 (C═O), 1228(C═S); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.24 (t, 6H, $\underline{2CH_3}CH_2$, J = 7.2 Hz), 4.2 (q, 4H, $\underline{2CH_2}CH_3$, J = 6.8 Hz), 7.94 (s, H, exocyclic NH), 11.66 (br.s, H, cyclic NH); Mass: m/z = M^+ 260 (8.71%) and 59 (100%); Anal. Calcd for $C_8H_{12}N_4O_4S$ (260.27): C, 36.92; H, 4.65; N, 21.53. Found: C, 36.89; H, 4.63; N, 21.51%.

3,7-Diethyl-1*H*,5*H*-[1,2,4]triazolo[1,2-a][1,2,4]triazole-1,5-dithione (31)

A mixture of compound **3** (0.005 mol), propinaldehyde (0.005 mol) and few drops of triethylamine in ethanol absolute (50 mL) was heated under reflux for 4 h. The reaction mixture was cooled at room temper-ature and poured into HCl/H_2O (1:10). The product was filtered off, washed with water and crystallized from methanol and DMF to give compound **31** in 90% yields white yellow powder. Mp. over 360 °C, IR (KBr, cm^{-1}): 3140 (NH), 1236 (C═S); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.24 (t, 6H, $\underline{2CH_3}CH_2$, J = 6.8 Hz), 4.2 (q, 4H, $\underline{2CH_2}CH_3$, J = 7.2 Hz), 11.73 (s, 2H, 2NH); Mass: m/z = M^+ 230 (2.43%) and 59 (100%); Anal. Calcd for $C_8H_{14}N_4S_2$ (230.35): C, 41.71; H, 6.13; N, 24.32. Found: C, 41.73; H, 6.11; N, 24.30%.

5,5'-Diethoxy-[2,2'-bi(1,2,4-oxadiazolidine)]-3,3'-dithione (32)

A mixture of compound **3** (0.005 mol) and iodine (30%, 5ml) in ethanol absolute (50 mL) was heated under reflux for 4 h. The reaction mixture was cooled at room temperature and poured into water. The pro-duct was

filtered off, washed with water and crystallized from methanol and DMF give compound **32** in70% yields as brown powder. Mp. over 360 °C, IR (KBr, cm^{-1}): 3140 (NH), 1230 (C═S); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.24 (t, 6H, $\underline{2CH_3}CH_2$, J = 2.4 Hz), 2.72 and 2.88 (s, 2H, 2CH cyclic), 4.2 (q, 4H, $\underline{2CH_2}CH_3$, J = 6.8 Hz), 11.72 (br.s, 2H, 2NH); ^{13}C-NMR: δ = 14.06 and 14.29 ($2CH_3$), 61.94 and 62.45 ($2CH_2$), 153.45, 153.81, 156.28 and 170.83 (2C═N and 2C═S); Anal. Calcd for $C_8H_{14}N_4O_4S_2$ (294.34): C, 32.64; H, 4.79; N, 19.03. Found: C, 32.61; H, 4.75; N, 19.01%.

3-(4-(Ethoxycarbonyl)-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl) propanoic acid (34)

A mixture of compound **3** (0.005 mol), succinic acid (0.005 mol) and few drops of triethylamine in toluene (50 mL) was heated under reflux for 6 h. The reaction mixture was cooled at room temperature and poured into HCl/H_2O (1:10). The product was filtered off, washed with water and crystallized from methanol to give compound **34** in 80% yields pale brown powder. Mp. over 360 °C, IR (KBr, cm^{-1}): 3138 (NH), 1726 and 1710(2 C═O), 1236 (C═S); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.24 (t, 3H, $\underline{CH_3}CH_2$, J = 6.8 Hz), 2.65 (m, 4H, $\underline{2CH_2}CH_2$, J = 6 Hz), 4.2 (q, 2H, $\underline{CH_2}CH_3$, J = 7.2 Hz), 11.8 (br.s, H, NH), 12.19 (br.s, H, COOH); Anal. Calcd for $C_8H_{11}N_3O_4S$ (245.25): C, 39.18; H, 4.52; N, 17.13. Found: C, 39.15; H, 4.43; N, 17.16%.

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تخليق وحولقة بعض مشتقات الثيوسيميكاربازيد

الملخص العربى

إضافة الهيدرازين المتهترت ٢ إلى الهيتيروآلين ١ (الإيثيل هيدرازين كاربونوثيويلكاربامات المحضر من تفاعل كلوروإسيتات الإيثيل مع ثيوسيانات الأمونيوم) ليعطى ثيوسيميكاربازيد ٣. تفاعل مالونات ثنائى الإيثيل ٤ مع المركب ٣ أعطى مشتق تريازوتريازول ٥. حولقة وحدة الثيويوريا للمركب ٣ بواسطة الهيتيروآلين ١ أعطت تريازين ٨. تفاعل كلوريد البنزويل ٩ مع المركب ٣ أعطت مشتق تريازول ١١. تفاعل المركب ٣ مع أنهيدريد ماليك ١٢ أعطت فيورو-ثياديازين ١٣. التكاثف الحلقى للهكسان الحلقى١٤مع المركب ٣ أعطت هكسانوحلقى بيريميدين-ثيون ١٦. إضافة إيزوثيوسيانات أمونيوم ١٧ إلى المركب ٣ أعطت تريازول ١٩. تفاعل المركب ٣ مع بروموإسيتات الإيثيل ٢٠ أعطت مشتق الثيازول ٢٢. التكاثف الحلقى للأسيتيل أسيتون ٢٣ مع المركب ٣ أعطت مشتق بيرازول ٢٥. إضافة الفورمالين ٢٦ إلى المركب ٣ أعطت تريازولوتريازول ٢٧. الحولقة القاعدية للمركب ٣ أعطت تريازول ٢٨. تفاعل المركب٣ مع بروبينالدهيد ٢٩ أعطت تريازولوتريازول ٣١. أكسدة المركب ٣ باليود أعطت أوكساديازول ٣٢. تفاعل المركب ٣ مع حمض السكسينيك ٣٣ أعطت تريازولثيون ٣٤.