

# Synthesis and Spectral Identification of Novel Stable Triazene: As Raw Material for the Synthesis Biocompatible Surfactants-Pyrazole-Isoxazole-Dihydropyrimidine-Tetrahydropyridine Derivatives

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## Abstract

The chemical reactivity of novel stable triazene 3 toward some nucleophilic and electrophilic reagents was investigated. Traizene 3 was used as a key precursor for the synthesis of some novel important heterocyclic compounds such as Pyrazole, Isoxazole, Dihydropyrimidine, Tetrahydropyridine derivatives with expected antimicrobial activity. The synthesized compounds were obtained in good yields. The structures of the newly synthesized compounds were confirmed by elemental analysis, IR, <sup>1</sup>H-NMR and Ms spectral data.

## Keywords

Biocompatible Surfactants, Pyrazole, Isoxazole, Dihydropyrimidine Tetrahydropyridine Derivatives, Spectral Characteristics

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## 1. Introduction

Surfactants are organic compounds that have the ability to decrease the surface tension of water and consisting of two moieties: a non-polar hydrophobic group (referred to as the tail) which is usually a straight or branched long hydrocarbon chain which is attached to a polar hydrophilic group (referred to as the head) [1]. Surfactants are widely used in the food, pharmaceutical, cosmetic, textile, paint and coating industries, as emulsifying, wetting

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and foaming agents, solubilizers and suspension stabilizers [2] [3]. Amino acid-based surfactants are characterized by low toxicity, good biocompatibility and fast biodegradation. Some of these compounds also show anti-bacterial activity [4]-[8]. Simple nitrogen-containing heterocycles receive a large amount of attention in the literature, as a consequence of their exciting biological properties and their role as pharmacophores of considerable historical importance. Pyrazolones nucleus have attracted much attention due to their interesting biological activities [9] [10]. Pyrazolone derivatives are widely used in medical practice (antipyrene, amidopyrene, analgin, etc.) [11]. A large number of thienopyrimidines were reported in the literature as virucides, bactericides, fungicides, acaricides, insecticides [12]. In this paper, we have reported a variety of syntheses of heteroaromatics developed using functionally substituted triazene as readily obtainable building blocks possessing multiple electrophilic and nucleophilic moieties of expected biological interest.

## 2. Material and Methods

### 2.1. Experimental

All melting points were measured using Akofler Block instrument and are uncorrected. IR spectra (KBr) were recorded on a FTIR 5300 spectrometer ( $\nu$ ,  $\text{cm}^{-1}$ ). The  $^1\text{H-NMR}$  spectra were recorded in  $\text{DMSO-d}_6$  and  $\text{CDCl}_3$  at 300 MHz and 400 MHz on a Varian Gemini NMR. 1000 EX mass spectrometer at 70 eV. The purity of synthesized compounds was checked by thin layer chromatography TLC (aluminum sheets) using n-hexane, ethyl acetate (9:1, V/V) eluent. Elemental analyses were carried out by the Microanalytical Research Center, Faculty of Science, and Microanalytical Unit, Faculty of Pharmacy, Cairo University, Egypt.

### 2.2. General Procedure for the Preparation of Compounds (3a-c)

The aromatic amines (0.01 mole) were dissolved in (2 M) hydrochloric acid (10 ml), diluted with water (30 ml) and diazotized at  $0^\circ\text{C}$  with sodium nitrite (0.01 mole) in a minimum volume of water. A solution of glycine ethyl ester hydrochloride in water was added slowly to the diazonium salt solution. The mixture was stirred for 1 hr at  $0^\circ\text{C}$ , where upon the solution was normally clear. The clear solution was treated with a large excess of sodium acetate (5 gm) with continuous stirring for 2 hr. The resulting reaction product was filtered off, washed with water and crystallized from the proper solvent to give compounds (3a-c).

#### 1) Ethyl-2-(3-(4-chlorophenyl)triaz-2-enyl)acetate (3a)

Formed as brown crystals from n-hexane; yield (67%); M.P.  $60^\circ\text{C}$  -  $62^\circ\text{C}$ ; IR (KBr)  $\nu_{\text{cm}^{-1}}$  = 3389 (NH), 3113 (CH-arom), 2974 - 2933 (CH-aliph), 1734 (C=O);  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$  (ppm) = 1.17 (t, 3H,  $\text{CH}_3$ ,  $J = 3$  Hz), 4.13 (q, 2H,  $\text{CH}_2\text{-O}$ ,  $J = 6$  Hz), 5.02 (br s, 2H,  $\text{CH}_2\text{-N}$ ), 6.53 - 8.22 (m, 4H, Ar-H), 12.62 (s, 1H, NH); MS:  $m/z$  (%) 241 ( $\text{M}^+$ ); Anal. Calcd. For  $\text{C}_{10}\text{H}_{12}\text{ClN}_3\text{O}_2$  (241); C, 49.70; H, 5.00; N, 17.39; found C, 49.72; H, 5.01; N, 17.40.

#### 2) Ethyl-2-(3-p-tolyltriaz-2-enyl)acetate (3b)

Formed as brown crystals from n-hexane; yield (71%); M.P.  $74^\circ\text{C}$  -  $76^\circ\text{C}$ ; IR (KBr)  $\nu_{\text{cm}^{-1}}$  = 3200 (NH), 3020 (CH-arom), 2918 - 2850 (CH-aliph), 1740 (C=O);  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$  (ppm) = 1.32 (t, 3H,  $\text{CH}_3$ ,  $J = 6$  Hz), 1.90 (s, 3H,  $\text{CH}_3$ ), 4.10 (q, 2H,  $\text{CH}_2\text{-O}$ ,  $J = 6$  Hz), 4.42 (br s, 2H,  $\text{CH}_2\text{-N}$ ), 7.36 - 8.57 (m, 4H, Ar-H), 12.60 (s, 1H, NH); MS:  $m/z$  (%) 221 ( $\text{M}^+$ ); Anal. Calcd. For  $\text{C}_{11}\text{H}_{15}\text{N}_3\text{O}_2$  (221); C, 59.71; H, 6.83; N, 18.99; found C, 59.70; H, 6.84; N, 19.01.

#### 3) Methyl-4-(3-(2-ethoxy-2-oxoethyl)triaz-1-enyl)benzoate (3c)

The starting compound (3c) was prepared under the same experimental conditions according to a literature procedure [16].

### 2.3. 4-(3-(2-Ethoxy-2-Oxoethyl)-Triaz-1-Enyl)-2-Hydroxynaphthalene-1-Sulphonic Acid (3d)

The aromatic amines (0.06 mole) were treated with (3.18 gm) of anhydrous  $\text{Na}_2\text{CO}_3$  dissolved in 10 ml of distilled water. The mixture was stirred for 15 min at  $40^\circ\text{C}$ . Where upon the solution was normally clear, cooled mixture at  $0^\circ\text{C}$ . The clear solution was treated with 2.0 gm of  $\text{NaNO}_2$  dissolved in a minimum volume of water. The solution was cooled in ice water, a mechanical stirrer being used, by the slow addition of (0.2 mole) of HCl from a separatory funnel. A solution of glycine ethyl ester hydrochloride in water was added slowly to the diazonium salt solution. The mixture was stirred for 1 hr at  $0^\circ\text{C}$ . The clear solution was treated with a large excess

of NaOH (40 mL, 10%) and the triazene precipitated slowly from the reaction mixture. Precipitation was normally evident after 30 min, and was usually complete within 3 hr. The resulting reaction product was filtered off, washed with water, and crystallized from ethanol to give brown crystals; yield (77%); M.P. 250°C - 252°C; IR (KBr)  $\nu_{\text{cm}^{-1}}$  = 3400 (NH/OH), 3136 (CH-arom), 2950 - 2850 (CH-aliph), 1700 (C=O);  $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$  (ppm) = 1.05 (t, 3H, CH<sub>3</sub>, J = 6 Hz), 4.62 (q, 2H, CH<sub>2</sub>-O, J = 6 Hz), 5.74 (br s, 2H, CH<sub>2</sub>-N), 7.08 - 9.02 (m, 6H, Ar-H and SO<sub>3</sub>H), 10.56 (s, 1H, OH), 12.16 (br, 1H, NH); MS: m/z (%) 355 (M<sup>+</sup>+2); Anal. Calcd. For C<sub>14</sub>H<sub>15</sub>N<sub>3</sub>O<sub>6</sub>S (353); C, 47.59; H, 4.28; N, 11.89; found C, 47.61; H, 4.37; N, 11.90.

## 2.4. General Procedure for the Preparation of Compounds (5a-c)

A mixture of compounds **3a-c** (0.01 mol) and ammonium acetate (2 gm) were fused without solvent for 20 min. The solid precipitate so formed was treated with ethanol and filtered out and crystallized from the proper solvent to give (**5a-c**).

### 1) 1-(4-Chlorophenyl)-1H-1,2,3-triazol-5-ol (5a)

Formed as pale yellow crystals from n-hexane; yield (68%); M.P. 70°C - 72°C; IR (KBr)  $\nu_{\text{cm}^{-1}}$  = 3454 (OH), 3063 (CH-arom);  $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$  (ppm) = 6.93 - 8.06 (m, 5H, Ar-H + CH-triazole), 12.06 (s, 1H, OH); MS: m/z (%) 197 (M<sup>+</sup>+2); Anal. Calcd. For C<sub>8</sub>H<sub>6</sub>ClN<sub>3</sub>O (195); C, 49.12; H, 3.09; N, 21.48; found C, 49.14; H, 3.10; N, 21.47.

### 2) 1-p-Tolyl-1H-1,2,3-triazol-5-ol (5b)

Formed as pale yellow crystals from n-hexane; yield (68%); M.P. 60°C - 62°C; IR (KBr)  $\nu_{\text{cm}^{-1}}$  = 3434 (OH), 3060 (CH-arom), 2916 (CH-aliph);  $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$  (ppm) = 1.89 (s, 3H, CH<sub>3</sub>), 6.70 - 8.49 (m, 5H, Ar-H + CH-triazole), 12.40 (s, 1H, OH); MS: m/z (%) 177 (M<sup>+</sup>+2); Anal. Calcd. For C<sub>9</sub>H<sub>9</sub>N<sub>3</sub>O (175); C, 61.70; H, 5.18; N, 23.99; found C, 61.71; H, 5.19; N, 23.98.

### 3) Methyl-4-(5-hydroxy-1H-1,2,3-triazol-1-yl)benzoate (5c)

Formed as pale yellow crystals from n-hexane; yield (68%); M.P. 86°C - 88°C; IR (KBr)  $\nu_{\text{cm}^{-1}}$  = 3448 (OH), 3057 (CH-arom), 2926 (CH-aliph);  $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$  (ppm) = 1.64 (s, 3H, COOCH<sub>3</sub>), 7.22 - 8.62 (m, 5H, Ar-H + CH-triazole), 12.66 (s, 1H, OH); MS: m/z (%) 219 (M<sup>+</sup>); Anal. Calcd. For C<sub>10</sub>H<sub>9</sub>N<sub>3</sub>O<sub>3</sub> (219); C, 54.79; H, 4.14; N, 19.17; found C, 54.80; H, 4.15; N, 19.16.

## 2.5. General Procedure for the Synthesis of Palmitoyl Chloride from Palmitic Acid

Palmitoyl chloride was prepared by gently refluxing a mixture of palmitic acid (26.6 gm, 0.01 mol) and thionyl chloride (23.7 ml, 0.01 mol) on water bath maintained at 35°C - 40°C with shaking. The reaction mixture was refluxed in the water bath for 6 hr. The excess of thionyl chloride was removed by washing successively with water and the residue was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> to collect the liquid palmitoyl chloride.

## 2.6. General Procedure for the Preparation of Compounds (7a-d)

A mixture of **3a-d** (0.01 mol), and palmitoyl chloride **6** (0.01 mol) in CH<sub>2</sub>Cl<sub>2</sub> (30 ml), pyridine (5 ml) was added to this solution slowly and heated under reflux for 8 hr. The reaction mixture allowed to cool, poured into crushed ice and acidified with HCl. The solid product was filtered off and crystallized from the proper solvent to give (**7a-d**).

### 1) Ethyl-2-(3-(4-chlorophenyl)triaz-2-enyl)-3-oxooctadecanoate (7a)

Formed as pale yellow crystals from n-hexane; yield (68%); M.P. 86°C - 88°C; IR (KBr)  $\nu_{\text{cm}^{-1}}$  = 3310 (NH), 3102 (CH-arom), 2919 - 2850 (CH-aliph), 1659 (C=O);  $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$  (ppm) = 0.84 (t, 3H, CH<sub>3</sub>, J = 3 Hz), 1.22 - 1.28 (m, 24H, 12CH<sub>2</sub>), 1.56 (t, 3H, CH<sub>3</sub>, J = 6 Hz), 2.27 (t, 2H,  $\beta$ -CH<sub>2</sub>, J = 6 Hz), 2.48 (t, 2H,  $\alpha$ -CH<sub>2</sub>, J = 3 Hz), 2.49 (s, 1H, CH), 3.29 (q, 2H, CH<sub>2</sub>-O, J = 12 Hz), 7.29 - 7.61 (m, 4H, Ar-H), 9.94 (s, 1H, NH); MS: m/z (%) 479 (M<sup>+</sup>); Anal. Calcd. For C<sub>26</sub>H<sub>42</sub>ClN<sub>3</sub>O<sub>3</sub> (479); C, 65.05; H, 8.82; N, 8.75; found C, 65.07; H, 8.84; N, 8.76.

### 2) Ethyl-3-oxo-2-(3-p-tolyltriaz-2-enyl)octadecanoate (7b)

Formed as brown crystals from n-hexane; yield (75%); M.P. 63°C - 65°C; IR (KBr)  $\nu_{\text{cm}^{-1}}$  = 3313 (NH), 3050 (CH-arom), 2953 - 2849 (CH-aliph), 1700, 1661 (2C=O);  $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$  (ppm) = 0.83 (t, 3H, CH<sub>3</sub>, J = 9 Hz), 1.18 - 1.36 (m, 24H, 12CH<sub>2</sub>), 1.50 (t, 3H, CH<sub>3</sub>, J = 6 Hz), 2.13 (s, 3H, CH<sub>3</sub>), 2.16 (t, 2H,  $\beta$ -CH<sub>2</sub>, J = 6 Hz), 2.21 (t, 2H,  $\alpha$ -CH<sub>2</sub>, J = 9 Hz), 2.47 (s, 1H, CH), 3.29 (br s, 2H, CH<sub>2</sub>-O), 7.04 - 7.45 (m, 4H, Ar-H),

9.69 (s, 1H, NH); MS: m/z (%) 461 ( $M^+ + 2$ ); Anal. Calcd. For  $C_{27}H_{45}N_3O_3$  (459); C, 70.55; H, 9.87; N, 9.14; found C, 70.58; H, 9.88; N, 9.14.

3) Methyl 4-(3-(1-ethoxy-1,3-dioxooctadecan-2-yl)triaz-1-enyl)benzoate (7c)

Formed as yellow crystals from n-hexane; yield (69%); M.P. 53°C - 55°C; IR (KBr)  $\nu_{cm^{-1}}$  = 3459 (NH), 2954 - 2848 (CH-aliph), 1701, 1640 (C=O);  $^1H$ -NMR ( $CDCl_3$ )  $\delta$  (ppm) = 0.72 (t, 3H,  $CH_3$ , J = 8 Hz), 1.28 - 1.30 (m, 24H, 12 $CH_2$ ), 1.32 (s, 3H,  $CH_3$ ), 1.63 (t, 3H,  $CH_3$ , J = 8 Hz), 2.18 (s, 1H, CH), 2.20 (t, 2H,  $\beta$ - $CH_2$ , J = 8 Hz), 2.37 (t, 2H,  $\alpha$ - $CH_2$ , J = 8 Hz), 3.95 (q, 2H,  $CH_2$ -O, J = 12 Hz), 6.81 - 8.05 (m, 4H, Ar-H), 11.26 (s, 1H, NH); MS: m/z (%) 503 ( $M^+$ ); Anal. Calcd. For  $C_{28}H_{45}N_3O_2$  (503); C, 66.77; H, 9.01; N, 8.34; found C, 66.78; H, 9.02; N, 8.35.

4) 4-(3-(1-ethoxy-1,3-dioxooctadecan-2-yl)triaz-1-enyl)-2-hydroxynaphthalene-1-sulphonic acid (7d)

Formed as pale yellow crystals from n-hexane; yield (75%); M.P. 46°C - 48°C; IR (KBr)  $\nu_{cm^{-1}}$  = 3462 (NH/OH), 2956 - 2849 (CH-aliph), 1702 (C=O);  $^1H$ -NMR ( $CDCl_3$ )  $\delta$  (ppm) = 0.89 (t, 3H,  $CH_3$ , J = 8 Hz), 1.27 - 1.30 (m, 24H, 12 $CH_2$ ), 1.32 (t, 3H,  $CH_3$ , J = 8 Hz), 1.60 (s, 1H, CH), 1.64 (t, 2H,  $\beta$ - $CH_2$ , J = 8 Hz), 2.35 (t, 2H,  $\alpha$ - $CH_2$ , J = 8 Hz), 4.30 (q, 2H,  $CH_2$ , J = 8 Hz), 7.28 - 8.39 (m, 8H, Ar-H +  $SO_3H$  + OH and NH); MS: m/z (%) 591 ( $M^+$ ); Anal. Calcd. For  $C_{30}H_{45}N_3O_7S$  (591) C, 60.89; H, 7.66; N, 7.10; found C, 60.91; H, 7.65; N, 7.09%.

## 2.7. Ethyl-2-(3-(4-chlorophenyl)triaz-2-enyl)-3-(dimethylamino)acrylate (8)

A mixture of **3a** (0.01 mol) and DMF-DMA (0.01 mol) in dioxane (30 mL) was heated under reflux for 6 hrs. The reaction mixture was allowed to cool. The separated solid was filtered, washed with ethanol and crystallized from ethanol to give brown crystals; yield (78%); M.p. 100°C - 102°C; IR (KBr)  $\nu_{cm^{-1}}$  = 3378 (NH), 3063 (CH-arom), 2924 - 2853 (CH-aliph), 1667 (CO);  $^1H$ -NMR ( $DMSO-d_6$ )  $\delta$  = 1.33 (t, 3H,  $CH_3$ , J = 4 Hz) 3.35 (s, 6H, 2 $CH_3$ ), 4.37 (q, 2H,  $CH_2$ , J = 8 Hz), 7.22 - 8.03 (m, 5H, Ar-H + CH-oliffinic), 12.65 (s, 1H, NH); MS: m/z (%) 296 ( $M^+$ ), Anal. Calcd. For  $C_{13}H_{17}ClN_4O_2$  (296); C, 52.62; H, 5.77; N, 18.88; Found: C, 52.63; H, 5.78; N, 18.87 %.

## 2.8. General Procedure for the Preparation of Compound (9a-c)

A mixture of compound **3a** (0.01 mol), appropriate aromatic aldehydes (0.01 mol) in ethanol (30 ml) with catalytic amount of piperidine was heated under reflux for 3 hrs. The reaction mixture was allowed to cool and poured into crushed ice then acidified with HCl. The separated solid was filtered, washed with water and crystallized from the proper solvent to give **9a-c**.

1) Ethyl 2-(3-(4-chlorophenyl)triaz-2-enyl)-3-phenylacrylate (9a)

Formed as yellow crystals from n-hexane; yield (69%); M.P. 80°C - 82°C; IR (KBr)  $\nu_{cm^{-1}}$  = 3387 (NH), 3096 (CH-arom), 2975 (CH-aliph), 1692 (C=O);  $^1H$ -NMR ( $CDCl_3$ )  $\delta$  (ppm) = 1.35 (t, 3H,  $CH_3$ , J = 3 Hz), 4.37 (q, 2H,  $CH_2$ , J = 3 Hz), 7.09 - 7.94 (m, 10H, Ar-H + CH-oliffinic), 12.69 (s, 1H, NH); MS: m/z (%) 329 ( $M^+$ ); Anal. Calcd. For  $C_{17}H_{16}ClN_3O_2$  (329); C, 61.91; H, 4.89; N, 12.74; found C, 61.92; H, 4.90; N, 12.73.

2) Ethyl-2-(3-(4-chlorophenyl)triaz-2-enyl)-3-(4-methoxyphenyl)acrylate (9b)

Formed as yellow crystals from n-hexane; yield (69%); M.P. 60°C - 62°C; IR (KBr)  $\nu_{cm^{-1}}$  = 3447 (NH), 3097 (CH-arom), 2932 (CH-aliph), 1676 (C=O);  $^1H$ -NMR ( $DMSO-d_6$ )  $\delta$  (ppm) = 1.22 (t, 3H,  $CH_3$ , J = 8 Hz), 3.83 (s, 3H,  $OCH_3$ ), 4.44 (q, 2H,  $CH_2$ , J = 16 Hz), 7.38 - 8.76 (m, 9H, Ar-H + CH-oliffinic), 12.50 (s, 1H, NH); MS: m/z (%) 361 ( $M^+ + 2$ ); Anal. Calcd. For  $C_{18}H_{18}ClN_3O_3$  (359); C, 60.09; H, 5.04; N, 11.68; found C, 60.10; H, 5.05; N, 11.67.

3) Ethyl-3-(4-chlorophenyl)-2-(3-(4-chlorophenyl)triaz-2-enyl)acrylate (9c)

Formed as yellow crystals from n-hexane; yield (69%); M.P. 60°C - 62°C; IR (KBr)  $\nu_{cm^{-1}}$  = 3447 (NH), 3098 (CH-arom), 2935 (CH-aliph), 1688 (C=O);  $^1H$ -NMR ( $DMSO-d_6$ )  $\delta$  (ppm) = 1.09 (t, 3H,  $CH_3$ , J = 12 Hz), 4.36 (q, 2H,  $CH_2$ , J = 8 Hz), 6.78-8.04 (m, 9H, Ar-H + CH-oliffinic), 10.77 (s, 1H, NH); MS: m/z (%) 365 ( $M^+ + 2$ ); Anal. Calcd. For  $C_{17}H_{15}Cl_2N_3O_2$  (363); C, 56.06; H, 4.15; N, 11.54; found C, 56.07; H, 4.16; N, 11.53.

## 2.9. General Procedure for the Preparation of Compound (13 a,b)

A mixture of **8** (0.01 mol) and hydrazine hydrate, phenyl hydrazine (0.01 mol) in ethanol (30 mL) was heated under reflux for 12 hrs. The reaction mixture was allowed to cool and poured into crushed ice. The separated solid was filtered, washed with water and crystallized from the proper solvent to give **13a,b**.

## 1) 4-(3-(4-Chlorophenyl)triaz-2-enyl)-1H-pyrazol-3-(2H)-one (13a)

Formed as yellow crystals from n-hexane; yield (69%); M.P. 122°C - 124°C; IR (KBr)  $\nu_{\text{cm}^{-1}}$  = 3326, 3195, 3118 (3NH), 3066 (CH-arom), 1664 (C=O);  $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$  (ppm) = 5.19 (s, 1H, CH-pyrazole), 6.21 - 8.23 (m, 4H, Ar-H), 10.47 (s, 1H, NH), 10.53 (s, 1H, NH), 10.77 (s, 1H, NH); MS: m/z (%) 239 ( $M^+$ +2); Anal. Calcd. For  $\text{C}_9\text{H}_8\text{ClN}_5\text{O}$  (237); C, 45.49; H, 3.39; N, 29.47; found C, 45.50; H, 3.38; N, 29.48.

## 2) 4-(3-(4-Chlorophenyl)triaz-2-enyl)-2-phenyl-1H-pyrazol-3-(2H)-one (13b)

Formed as yellow crystals from n-hexane; yield (69%); M.P. 100°C - 102°C; IR (KBr)  $\nu_{\text{cm}^{-1}}$  = 3275, 3186 (2NH), 3060 (CH-arom), 1669 (C=O);  $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$  (ppm) = 5.74 (s, 1H, CH-pyrazole), 7.06 - 7.89 (m, 9H, Ar-H), 10.30 (s, 1H, NH), 11.40 (s, 1H, NH); MS: m/z (%) 313 ( $M^+$ ); Anal. Calcd. For  $\text{C}_{15}\text{H}_{12}\text{ClN}_5\text{O}$  (313); C, 57.42; H, 3.86; N, 22.32; found C, 57.43; H, 3.87; N, 22.31.

**2.10. 4-(3-(4-Chlorophenyl)triaz-2-enyl)isoxazol-5-(2H)-one (17)**

A mixture of **8** (0.01 mol), hydroxylamine hydrochloride in glacial acetic acid (30 mL) containing anhydrous sodium acetate (1 g) was heated under reflux for 24 hrs. The reaction mixture was allowed to cool and poured into cold water (60 ml). The separated solid was filtered and crystallized from ethanol to give brown crystals; yield (68%); M.p. 120°C - 122°C; IR (KBr)  $\nu_{\text{cm}^{-1}}$  = 3446, 3149 (2NH), 2980 (CH-aliph), 1716 (C=O);  $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$  (ppm) = 6.90 - 7.92 (m, 7H, Ar-H, CH-isoxazole and 2NH); MS: m/z (%) 240 ( $M^+$ +2), Anal. Calcd. For  $\text{C}_9\text{H}_7\text{ClN}_4\text{O}_2$  (238): C, 45.30; H, 2.96; N, 23.48; Found: C, 45.31; H, 2.97; N, 23.47%.

**2.11. General Procedure for the Preparation of Compound (21 a,b)**

To boiling solution of compound **8** (0.01 mol), thiourea (0.01 mol) and guanidine hydrochloride in sodium ethoxide (30 ml). The reaction mixture was refluxed for 12 h, then allowed to cool and poured into crushed ice then acidified with HCl. The separated solid was filtered, washed with water and crystallized from the proper solvent to give **21 a,b**.

## 1) 5-(3-(4-Chlorophenyl)triaz-2-enyl)-2-thioxo-2,3-dihydropyrimidin-4-(1H)-one (21a)

Formed as yellow crystals from n-hexane; yield (69%); M.P. 102°C - 104°C; IR (KBr)  $\nu_{\text{cm}^{-1}}$  = 3436, 3195 (2NH), 3094 (CH-arom), 1721 (C=O);  $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$  (ppm) = 7.23-7.84 (m, 5H, Ar-H + CH-pyrimidine), 8.60 (s, 1H, NH), 10.20 (s, 1H, NH), 12.20 (s, 1H, NH); MS: m/z (%) 283 ( $M^+$ +2); Anal. Calcd. For  $\text{C}_{10}\text{H}_8\text{ClN}_5\text{OS}$  (281); C, 42.63; H, 2.86; N, 24.86; found C, 42.64; H, 2.87; N, 24.85.

## 2) 5-(3-(4-Chlorophenyl)triaz-2-enyl)-2-imino-2,3-dihydropyrimidin-4-(1H)-one (21b)

Formed as yellow crystals from n-hexane; yield (69%); M.P. 206°C - 208°C; IR (KBr)  $\nu_{\text{cm}^{-1}}$  = 3445, 3421, 3372 (3NH), 3106 (CH-arom), 2942 (CH-aliph), 1690 (C=O);  $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$  (ppm) = 7.29 - 7.95 (m, 5H, Ar-H + CH-pyrimidine), 8.63 (s, 1H, NH), 10.00 (s, 1H, NH), 10.56 (s, 1H, NH), 10.82 (s, 1H, NH); MS: m/z (%) 266 ( $M^+$ +2); Anal. Calcd. For  $\text{C}_{10}\text{H}_9\text{ClN}_6\text{O}$  (264); C, 45.38; H, 3.43; N, 31.75; found C, 45.39; H, 3.44; N, 31.74.

**2.12. 5-(3-(4-Chlorophenyl)triaz-2-enyl)-6-oxo-2-thioxo-1,2,3,6-tetrahydropyridine-3-carbonitrile (25)**

A mixture of **8** (0.01 mol) and cyanothioacetamide (0.01 mol) in pyridine was heated under reflux for 12 hrs. The reaction mixture was allowed to cool and poured into crushed ice then acidified with HCl. The separated solid was filtered, washed with water and crystallized from ethanol to give brown crystals; yield (86%); M.p. 130°C - 132°C; IR (KBr)  $\nu_{\text{cm}^{-1}}$  = 3447, 3419 (2NH), 3111 (CH-arom), 2202 (CN), 1718 (CO);  $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$  = 6.90 - 6.92 (d, 1H, CH-pyridine), 7.10 - 7.12 (d, 1H, =CH-pyridine), 7.23 - 8.52 (m, 4H, Ar-H), 10.30 (s, 1H, NH), 12.41 (s, 1H, NH); MS: m/z (%) 307 ( $M^+$ +2), Anal. Calcd. For  $\text{C}_{12}\text{H}_8\text{ClN}_5\text{OS}$  (305): C, 47.14; H, 2.64; N, 22.91; Found: C, 47.15; H, 2.65; N, 22.90%.

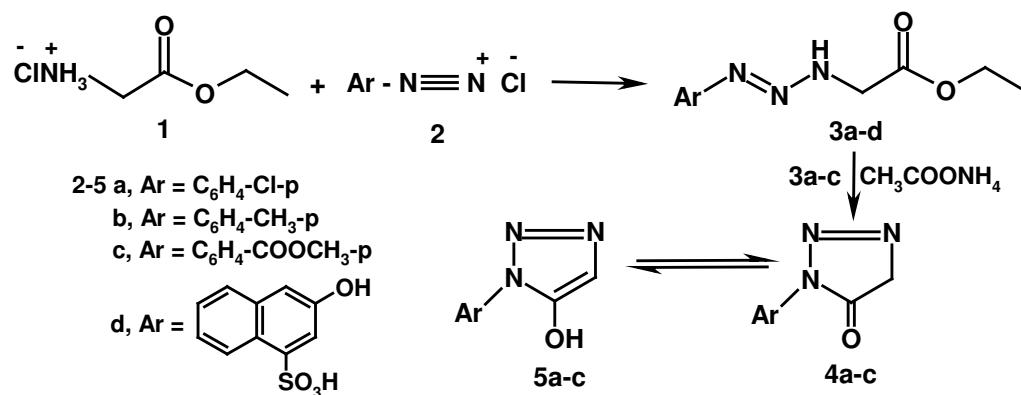
**3. Results and Discussion****3.1. Chemistry**

The reaction of diazonium salts with proteins has been extensively used as a structural probe, typically in the elucidation of the topography of the active sites of enzymes [13]. The azo-proteins formed in this way arise

largely from diazo-coupling with the activated aromatic rings of tyrosine and histidine residues and the  $\epsilon$ -amino group of lysines [14] [15]. Thus, the reaction of aryldiazonium salts **2a** with glycine ethyl ester hydrochloride in aqueous solution containing sodium acetate, the diazonium ion attacks at the  $\text{NH}_2$  moiety to afford stable triazene derivative **3a** and shows no tendency to attack at the activated  $\text{CH}_2$ , which would give rise to hydrozone formation [16]-[19], based on its spectral data. For example, the  $^1\text{H-NMR}$  spectrum of compound **3a** recorded in  $\text{DMSO-d}_6$  revealed the presence of a triplet signal at  $\delta = 1.17$  ppm corresponding to methyl group, a quartet signal at  $\delta = 4.13$  ppm corresponding to methylene group, a singlet signal at  $\delta = 5.02$  ppm corresponding to methylene group, a multiplet signal at  $\delta = 6.53 - 8.22$  ppm corresponding to aromatic protons and a singlet signal at  $\delta = 12.62$  ppm corresponding to  $\text{NH}$ . The mass spectrum of the same product is in accordance with the proposed structure. It shows a very intense molecular ion peaks at 241 and a number of fragments agree with the proposed structure. Similarly, glycine ethyl ester coupled readily with aryl diazonium chlorides **2b-d** in the same reaction conditions to give the corresponding triaza derivatives **3b-d**. Cyclization of triaza derivatives **3a-c** into triazol-5-ol derivatives **5a-c** took place by fusion of **3a-c** over melting point without solvent in the presence of ammonium acetate for 20 min. Establishing of the compounds **5a-c** were based on its elemental and spectral data. For example, the IR spectrum of compound **5a** revealed the disappearance of carbonyl group. The  $^1\text{H-NMR}$  spectrum revealed the presence of a signal at  $\delta = 6.93 - 8.06$  ppm corresponding to aromatic protons,  $\text{CH-triazole}$  and a singlet signal at  $\delta = 12.06$  ppm corresponding to  $\text{OH}$  group. The mass spectrum of the same product is in accordance with the proposed structure as demonstrated in (Scheme 1).

The foregoing results prompt us to investigate the synthetic potentiality of stable triazenes **3a-d** toward palmitoyl chloride. Thus, treatment of triazenes derivative **3a** with palmitoyl chloride **6** in refluxing methylene chloride containing a catalytic amount of pyridine afforded ethyl-2-(3-(4-chlorophenyl)triaz-2-enyl)-3-oxooctadecanoate **7a** [20]-[22]. The structure of **7a** was established as a sole reaction product based on its spectral data. For example, the  $^1\text{H-NMR}$  spectrum of compound **7a** recorded in  $\text{DMSO-d}_6$  revealed the presence of a triplet signal at  $\delta = 0.84$  ppm corresponding to terminal three protons of long chain fatty acid, a multiplet signal at  $\delta = 1.22 - 1.28$  ppm corresponding to  $(\text{CH}_2)_{12}$ , a triplet signal at  $\delta = 1.56$  ppm indicating methyl group, a triplet signal at  $\delta = 2.27$  ppm corresponding to  $\beta$ -methylene group, a triplet signal at  $\delta = 2.48$  ppm corresponding to  $\alpha$ -methylene group, a singlet signal at  $\delta = 2.49$  ppm corresponding to methine group, a quartet signal at  $\delta = 3.29$  ppm corresponding to methylene group, a multiplet signal at  $\delta = 7.29 - 7.61$  ppm corresponding to aromatic protons and a singlet signal at  $\delta = 9.94$  ppm corresponding to  $\text{NH}$ . The mass spectrum of compound **7a** revealed the molecular ion peak at  $m/z = 479$  ( $\text{M}^+$ ) corresponding to  $\text{C}_{26}\text{HCl}_2\text{N}_3\text{O}_3$ . Similarly, the triazenes derivatives **3b-d** was reacted with palmitoyl chloride in the same reaction conditions to afford **7b-d** as demonstrated in Scheme 2.

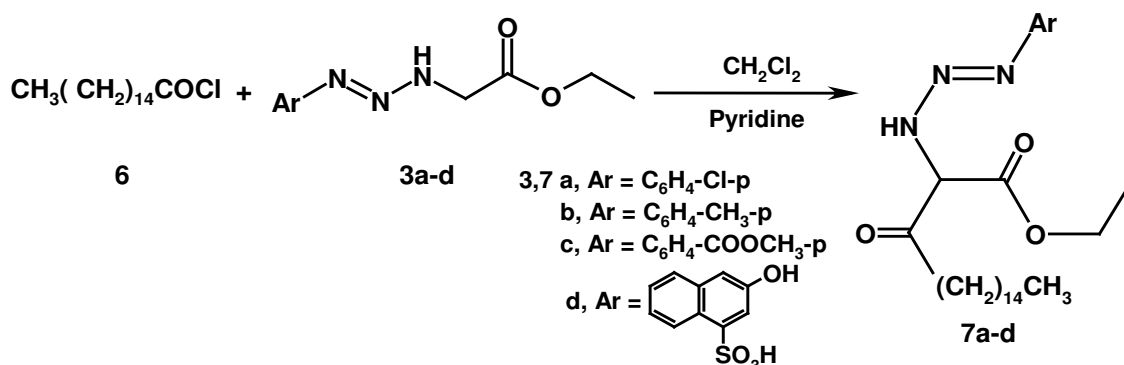
Ethyl-2-(3-(4-chlorophenyl)triaz-2-enyl)acetate **3a** was exploited as a key intermediate for the synthesis of hitherto unknown compounds through its reaction with some reagents. Thus, refluxing of compound **3a** with dimethylformamide-dimethylacetal in dry dioxane for about 6 hrs afforded ethyl-2-(3-(4-chlorophenyl)triaz-2-enyl)-3-(dimethylamino)acrylate **8**. Establishing structure **8** was based on its elemental analysis and spectral data. Thus,  $^1\text{H-NMR}$  spectrum of compound **8** revealed an intense singlet signal at  $\delta = 3.35$  corresponding to two methyl functions, the olefinic proton and  $\text{NH}$  group appeared as two singlet signals at  $\delta = 7.22$  and  $12.65$  ppm



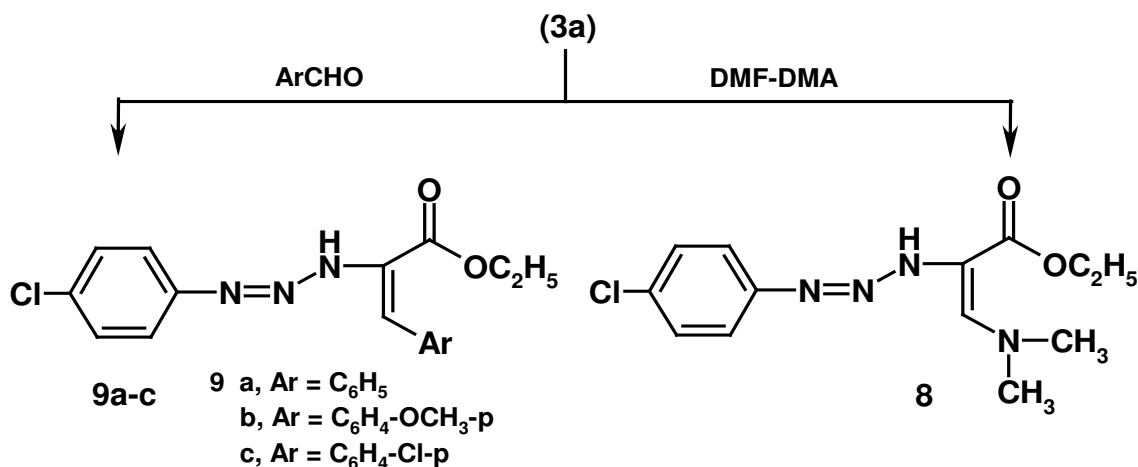
Scheme 1. Synthesis of compounds 1-5.

respectively. The mass spectrum of the same compound is in accordance with the proposed structure. Thus, it showed a very intense molecular ion peak at  $m/z = 296$  and a number of fragments agree with the proposed structure. Further support of the structure **3** by its condensation with aromatic aldehydes. Thus, it was condensed with aromatic aldehydes in refluxing ethanol and in the presence of a catalytic amount of piperidine to give **9a-c**. Establishing the structure of compound **9a-c**. were based on its elemental analysis and spectral data. Thus,  $^1\text{H-NMR}$  spectrum of compound **9a** as example revealed the absence of methylene function and revealed the presence of a singlet signal at  $\delta = 7.09$  ppm corresponding to olefinic proton (**Scheme 3**).

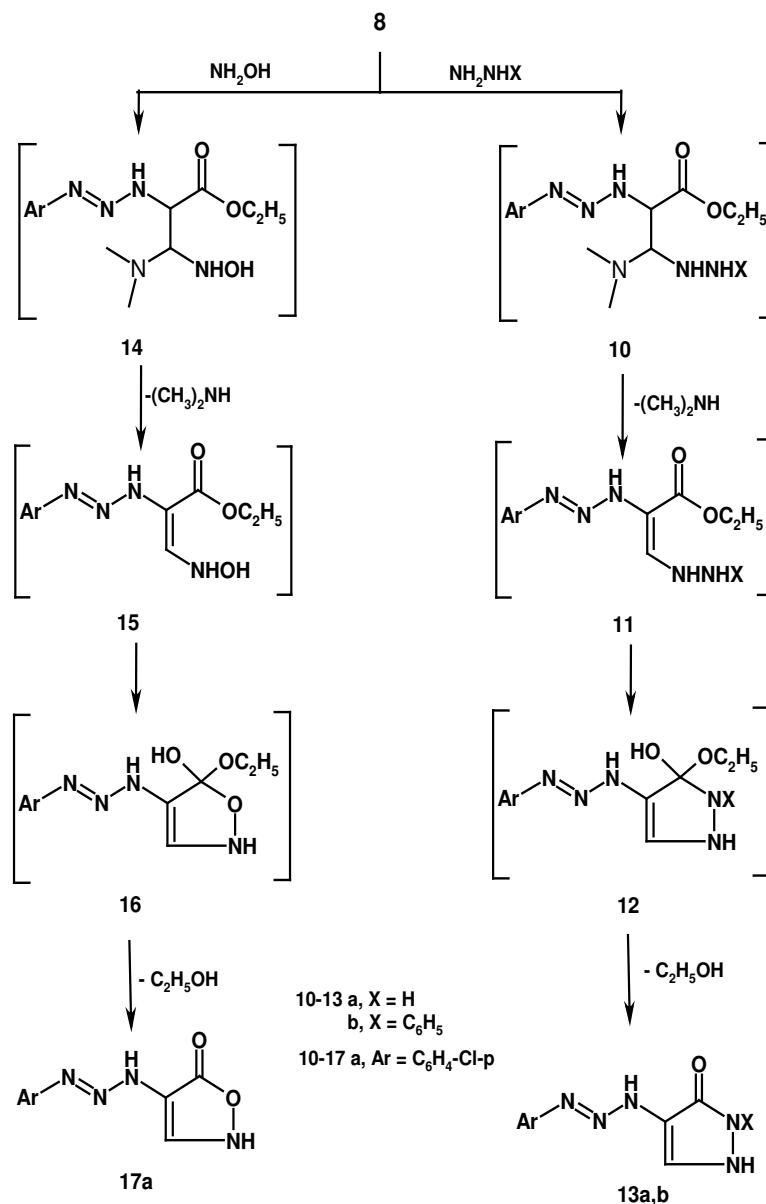
The enaminone **8** was examined as a key precursor toward a variety of nucleophilic reagents aiming at exploring its synthetic potentiality. Thus, when compound **8** is allowed to reflux with hydrazine and phenyl hydrazine in ethanol, pyrazolones **13a,b** derivatives were obtained via the intermediacy of **10-12**. Establishing structure **13a,b** was based on its elemental analysis and spectral data. For example, The  $^1\text{H-NMR}$  spectrum of **13a** revealed the presence of a singlet signal at  $\delta = 5.19$  ppm corresponding to CH-pyrazole, a multiplet signal at  $\delta = 6.21 - 8.23$  ppm corresponding to aromatic protons and the NH protons appeared as a singlet signal at  $\delta = 10.47, 10.53, 10.77$  ppm. The mass spectrum of the same product is in accordance with the proposed structure. Compound **13a,b** are assumed to be formed via the addition of the  $\text{NH}_2$  group of hydrazine, phenyl hydrazine to the double bond in compound **8** with subsequently elimination of dimethylamine molecule to give the non-isolable intermediate **11**. Which underwent intramolecular cyclization to form the final product **13a,b** through elimination of ethanol. When compound **8** was treated with hydroxylamine hydrochloride in refluxing glacial acetic acid, it afforded a single product identified as 4-(3-(4-chlorophenyl)triaz-2-enyl)isoxazol-5-(2H)-one **17**. Formation of **17** from the reaction of **8** and hydroxyl amine is believed to be formed via initial addition of  $\text{NH}_2$  group to the double bond system of **8** to give the intermediate **14-16** by loss dimethylamine and ethanol to give isoxazole **17** as demonstrated in (**Scheme 4**).



**Scheme 2.** Synthesis of compounds 6,7.



**Scheme 3.** Synthesis of compounds 8,9.

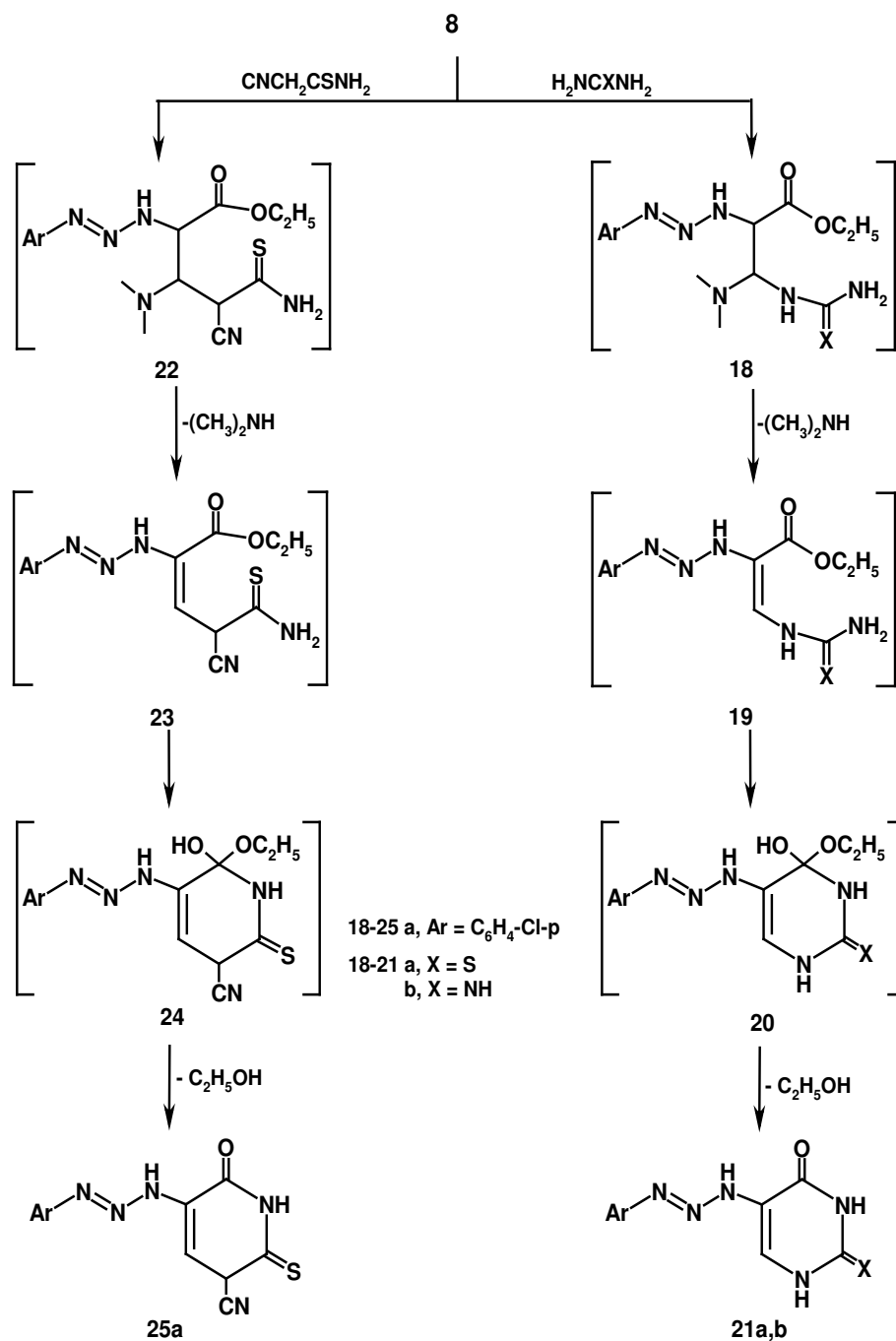


**Scheme 4.** Synthesis of compounds 10-17.

Treatment of compound **8** with thiourea in refluxing ethanol in the presence of sodium ethoxide, afforded 2-thio-2,3-dihydropyrimidin-4(1H)-one derivative **21a**. Compound **21a** is assumed to be formed via the addition of the NH<sub>2</sub> group of thiourea to the activated double bond in compound **8** with subsequent elimination of dimethylamine molecule to give the non-isolable intermediate **19**, which underwent intramolecular cyclization to form the final product **21a** via loss of ethanol molecule. Also, the reaction of **8** with guanidine hydrochloride resulted in the formation imino pyrimidine derivative via the intermediacy of **18-20** according to their spectral analysis. For example, the IR spectrum of compound **21b** revealed the presence of amino function at 3445, 3421, 3372 cm<sup>-1</sup> and carbonyl function at 1690 cm<sup>-1</sup>. The <sup>1</sup>H-NMR and mass spectrum of the same product are in accordance with proposed structure. Finally, compound **8** reacted also with cyanothioacetamide and gave the corresponding pyridinethione derivative **25**. The structure of compound **25** was deduced from their elemental analysis and spectral data. The IR spectroscopic investigation of **25** revealed characteristic bands at 3447, 3419 cm<sup>-1</sup> (2NH) and a pair of absorption band at 2202, 1718 cm<sup>-1</sup> for (CN) and carbonyl group respectively, in addition, <sup>1</sup>H-NMR of **25** revealed the presence of a doublet signal at δ = 6.90 - 6.92 ppm corresponding to CH-pyridine, a



doublet signal at  $\delta = 7.10 - 7.12$  ppm corresponding to =CH-pyridine, a pair of signals at  $\delta = 10.30, 12.41$  ppm corresponding to a pair of NH groups and a multiplet signal at  $\delta = 7.23 - 8.52$  ppm corresponding to aromatic protons. The mass spectrum of compound **25** is in accordance with the proposed structure. Thus, it showed a very intense molecular ion peak at 305 ( $M^+$ ) and a number of fragment agree with the proposed structure, Formation of **25** from the reaction of **8** and cyanothioacetamide is believed to be formed via initial addition of the active methylene group of cyanothioacetamide on the double bond system of **8** with subsequent elimination of dimethylamine to give non-isolable intermediate **23** which underwent intramolecular cyclization to form the final product **25** via loss of ethanol molecules as demonstrated in **Scheme 5**.



**Scheme 5.** Synthesis of compounds 18-25.

## 4. Conclusion

In conclusion, compounds 3a-d and 8 were used as efficient precursors for the synthesis of new heterocycles including triaz-2-enyl moiety with expected biological activities.

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