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Synthesis of novel heterocycles using 1,2,3-triazole-4-carbohydrazides as precursors

Hanan A. Mohamed^{1,2} | Rizk E. Khidre^{3,4} | Benson M. Kariuki⁵ | Gamal A. El-Hiti⁶ 

¹Applied Organic Chemistry Department, National Research Center, Dokki, Giza, Egypt

²Department of Chemistry, College of Science and Humanities, Shaqra University, Duwadimi, Saudi Arabia

³Chemical Industries Division, National Research Center, Dokki, Giza, Egypt

⁴Chemistry Department, Faculty of Science, Jazan University, Jazan, Saudi Arabia

⁵School of Chemistry, Cardiff University, Cardiff, UK

⁶Cornea Research Chair, Department of Optometry, College of Applied Medical Sciences, King Saud University, Riyadh, Saudi Arabia

Correspondence

Gamal A. El-Hiti, Cornea Research Chair, Department of Optometry, College of Applied Medical Sciences, King Saud University, P.O. Box 10219, Riyadh 11433, Saudi Arabia.
Email: gelhiti@ksu.edu.sa

Funding information

King Saud University

Abstract

Herein, we report the synthesis of various heterocyclic ring systems containing 1,2,3-triazole from the reactions of acid hydrazides and commercially available reagents, using efficient and simple procedures. Reactions of certain 1,2,3-triazole-4-carbohydrazides and α -bromoketones in boiling ethanol afforded the corresponding hydrazones rather than the expected triazines. The hydrazones could also be synthesized in 85–90% yield via an alternative pathway that involved the reaction of 1,2,3-triazole-4-carbohydrazides and 4-acetyl-1,2,3-triazoles in boiling ethanol containing glacial acetic acid. Reaction of one of the 4-carbohydrazides with carbon disulfide, followed by the reaction with hydrazine hydrate, gave 4H-1,2,4-triazole-3-thiol in 73% yield, which further reacted with other α -bromoketones in boiling ethanol to afford 7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazines in 82–84% yields. Additionally, reactions of certain carbohydrazides with ethyl 2-cyano-3,3-bis(methylthio)acrylate gave 1-aryl-1H-1,2,3-triazole-4-carbohydrazides rather than the expected 1H-pyrazole-4-carboxylates.

1 | INTRODUCTION

Designing novel heterocycles is one of the main challenges faced by chemists in the recent years. Many efficient methodologies have been developed to overcome some of the limitations associated with the traditional processes for the synthesis of heterocycles that have applications in pharmaceutical and other industries.^[1,2] Considerable efforts have been directed toward the synthesis of heterocycles using efficient, convenient, high yielding, cost-effective, and clean methods that involve few reaction steps. Acid hydrazides are widely used as

preservatives and as reagents for determining certain flavonoids and also for the production of pharmaceuticals and polymers.^[3,4] Indeed, acid hydrazides are efficient and common precursors in the production of various heterocycles^[5–8] that have enormous potential as antimicrobials,^[9–16] anticancer agents,^[17] pharmaceuticals,^[18] antidepressant,^[20] and anti-inflammatory agents.^[21] In addition, these heterocycles^{anticonvulsant,^[19]} act as herbicides^[22] and dyes.^[23,24] Acid hydrazides are generally produced from reaction of hydrazine and esters, cyclic anhydrides, acyl halides, and aldehydes,^[25] while [1,2,4]triazolo[3,4-b][1,3,4]thiadiazines can be produced through a two-step reaction that involves

hydrazides, carbon disulfide, hydrazine hydrate, and phenacyl bromides.^[26–28]

Heterocycles such as 1,2,3-triazoles have potentially important applications, and various processes have been developed for their synthesis.^[29–34] Recently, we have reported several procedures for the synthesis of various heterocycles.^[35–40] Herein, we report efficient and simple methods for the synthesis of heterocycles containing the 1,2,3-triazole moieties. These heterocycles, synthesized from 1,2,3-triazole-4-carbohydrazides, have important applications in many fields.

2 | RESULTS AND DISCUSSION

Reactions of carbohydrazides 1a-d (X = H, Me, Br, Cl)

and 2-bromo-1-(5-methyl-1-aryl-1H-1,2,3-triazol-4-yl) ethanones 2a,b (Y = Br, Cl) in boiling ethanol for 12 hours in the presence of sodium acetate and glacial acetic acid afforded hydrazones 3a-f (Scheme 1) in 46–58% yields (Table 1). No evidence was found for the expected products 1,2,4-triazines (4) under these conditions. The infrared (IR) spectra of 3a-f showed strong absorption bands corresponding to carbonyl stretching at 1679–1785 cm^{-1} . The ^1H NMR spectra of 3a-f showed exchangeable singlets at 10.19–10.28 ppm due to the presence of NH protons. In addition, the ^1H NMR spectra showed three singlets for the three different methyl groups in 3a,c-f and four singlets corresponding to the four different methyl groups in 3b (1.54–2.70 ppm). The ^{13}C NMR spectra of 3a-f suggested the presence of carbonyl carbons, as indicated by the chemical shift at about 157 ppm, along with all the other expected carbon atoms.

The molecular structures of 3a, 3b, and 3f obtained by X-ray diffraction are shown in Figure 1. The ethylidene-formohydrazide group at the center of the molecule is essentially planar in all the three compounds.

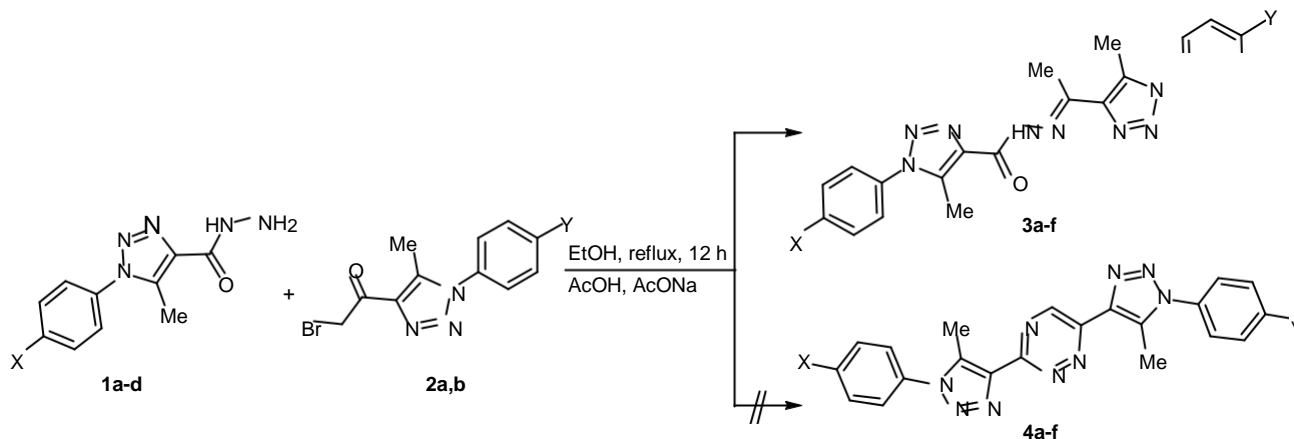
For 3a, the twist angle between the neighboring bromophenyl and methyltriazolyl groups is 45.1(1)°, and the angle between the phenyl group and the second methyltriazolyl group is 41.9(1)°. The corresponding angles in 3b are 43.5(1)° and 40.0(1)°, respectively. Compound 3f has two chlorophenyl groups and two triazolyl groups. The two twist angles between the groups are similar [50.1(1)° and 49.9(1)°].

It has been reported that reaction of bromoacetyl arenes and pyridine-2-carboxylic acid hydrazide or 2-thienylcarboxylic acid hydrazide gave the corresponding 3-pyridyl-1,2,4-triazines or 3-thienyl-1,2,4-triazines in low to moderate yields under similar reaction conditions to those used in Scheme 1.^[41] Clearly, different acid hydrazides were used, and this could be the reason for the formation of different products.

Formation of 3 involves reaction of hydrazides 1 and bromides 2 to produce the corresponding bromohydrazones A. Replacement of bromide of A in the presence of sodium acetate, which acts as a catalyst, gave intermediate B. It has been reported that debromination of α -bromoketones took place in the presence of acetic acid and sodium iodide.^[42] Treatment of B with acetic acid gave the corresponding hydrazones 3 (Scheme 2).

TABLE 1 Melting point and yield of Compounds 3 synthesized according to Scheme 1

Product	X	Y	Melting point (°C)	Yield (%)
3a	H	Br	248–250	46
3b	Me	Br	258–260	49
3c	H	Cl	246–248	51
3d	Br	Br	259–260	54
3e	Br	Cl	260–262	52
3f	Cl	Cl	244–246	58



SCHEME 1 Synthesis of hydrazones 3

Compounds **3** could also be produced in 79-87% yields via an alternative synthetic pathway wherein hydrazides **1** reacted with 4-acetyl-1,2,3-triazoles **5** to give hydrazides **3** (Scheme 3). The products were identical to those produced in the reactions shown in Scheme 1.

Reaction of **1c** (X = Br) and excess carbon disulfide (two molar equivalents) in the presence of potassium

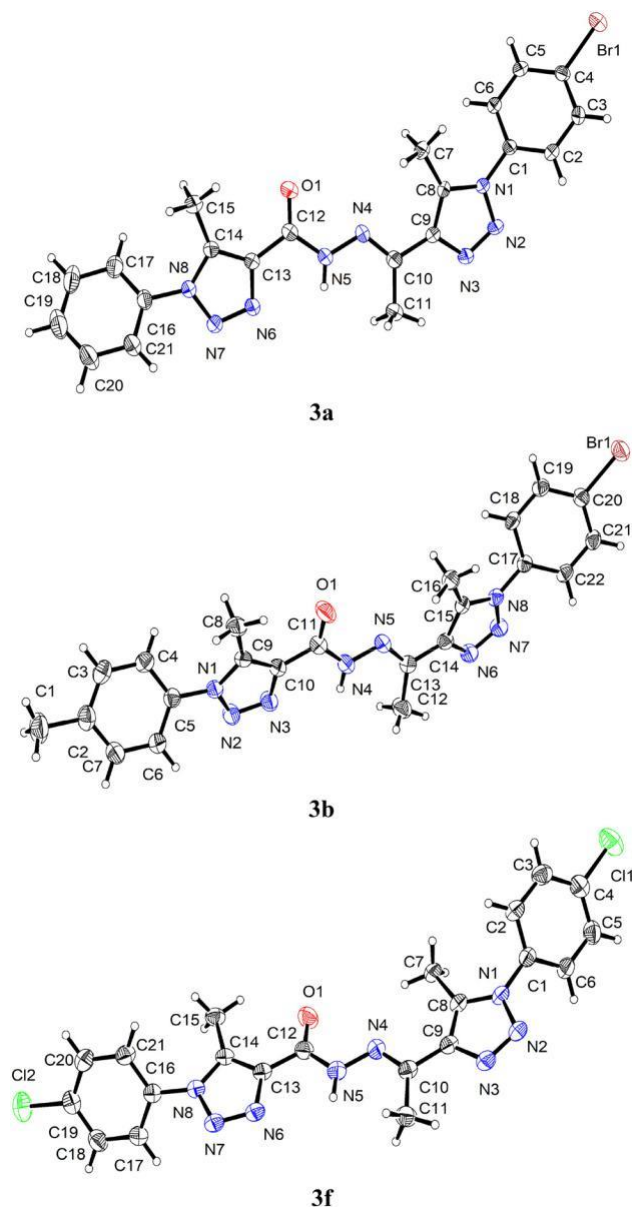
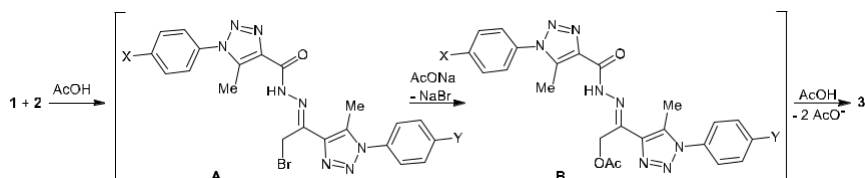


FIGURE 1 ORTEP representation of the molecular structure of **3a**, **3b**, and **3f** with 50% probability ellipsoids obtained by X-ray diffraction

SCHEME 2 Suggested mechanism for formation of **3**



ethoxide at 0 °C for 2 hours, followed by the treatment with excess hydrazine hydrate (two molar equivalents) under reflux for 5 hours, gave 4H-1,2,4-triazole-3-thiol **6** in 73% yield (Scheme 4). The ^1H NMR spectrum of **6** showed exchangeable singlets at 5.92 (2H) and 14.07 ppm (1H) due to the NH_2 and SH protons, respectively. Reactions of **6** and α -bromoketones **7a-c** in boiling ethanol in the presence of triethylamine as a base for 2 hours gave the corresponding 7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazines **8a-c** in 74-82% yields (Scheme 4).

The molecular structures of **8a** and **8c** obtained by X-ray diffraction are shown in Figure 2. In both **8a** and **8c**, the triazolothiadiazine groups are almost planar, while the methylene group deviates from planarity. The twist angles between the bromophenyl and methyltriazolyl groups are 40.4(1) and 47.4(1) for **8a** and **8c**, respectively.

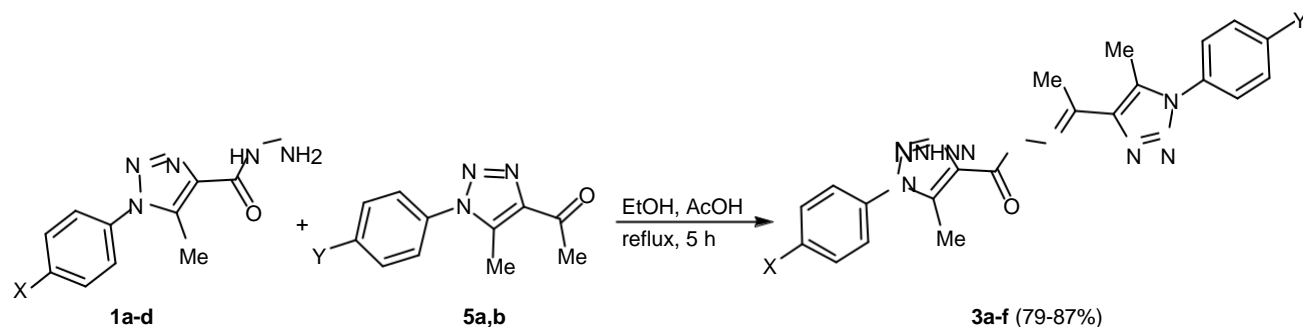
Finally, the reaction of acid hydrazides **1c,d** and ethyl 2-cyano-3,3-bis (methylthio)acrylate (**9**) in boiling ethanol for 3 hours gave the corresponding 1-aryl-1H-1,2,3-triazole-4-carbohydrazides **10a,b** (Scheme 5) in 55% (X = Cl) and 56% (X = Br) yields. None of the expected products, 1H-pyrazole-4-carboxylates **11a,b**, were formed under these conditions. Compounds **10a,b** have been synthesized previously from the reaction of acid hydrazides **1c,d** and 2-(methoxymethylene)malononitrile or ethyl 2-cyano-3-methoxyacrylate in boiling ethanol.^[24]

The structures of **10a** and **10b** obtained by X-ray diffraction are shown in Figure 3. In both **10a** and **10b**, the two halves of the molecule are related by pseudo-twofold symmetry through the hydrazine bond, with the formyl formohydrazide groups in gauche conformation. The twist angles between the bromophenyl and triazolyl groups are 38.0(1) and 46.9(1) for **10a** and 35.5(1) and 48.4(1) between chlorophenyl and triazolyl groups for **10b**.

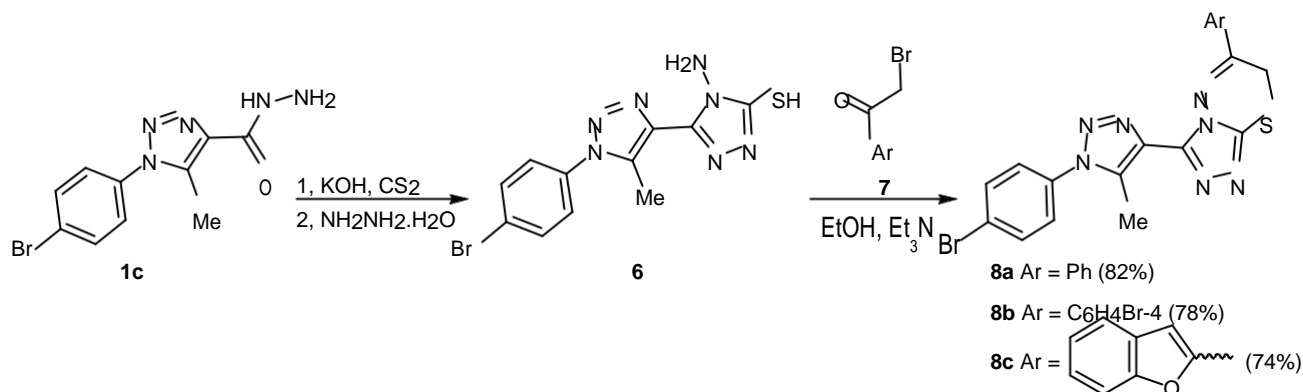
The formation of **10** involves the nucleophilic attack of NH_2 of the second mole of hydrazide **1** at the carbonyl carbon of intermediate **12**, which is formed from the reaction of **1** and **9**, to produce intermediate **13**. Diacylhydrazines **10** along with **9** were produced from the dissociation of **13** (Scheme 6).

3 | CONCLUSION

In summary, simple methods have been developed for the synthesis of novel heterocycles. For example, reaction



S C H E M E 3 Alternative route for the synthesis of hydrazones 3



S C H E M E 4 Synthesis of thiadiazines 8

of acid hydrazides containing the 1,2,3-triazole moiety and α -bromoketones gave the corresponding hydrazones rather than the expected 1,2,4-triazines, while reaction of acid hydrazides and carbon disulfide followed by hydrazine hydrate gave the corresponding 1,2,4-triazole-3-thiol which on reaction with α -bromoketones gave the corresponding 7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazines. In addition, reaction of acid hydrazides and ethyl 2-cyano-3,3-bis(methylthio)acrylate gave the corresponding (1,2,3-triazole-4-carbonyl)-1,2,3-triazole-4-carbohydrazides rather than the expected 1H-pyrazole-4-carboxylates. These compounds are expected to have important applications in many fields.

4 | EXPERIMENTAL

An Electrothermal IA 9000 melting point apparatus was used to determine the melting points. Elemental analyses were performed at Cairo University, Egypt. The IR spectra were recorded on a JASCO FT/IR-6100 spectrometer using KBr disks. A JOEL-ECA 600 MHz spectrometer was used to record the NMR spectra at 600 MHz for ^1H and 150 MHz for ^{13}C NMR in deuterated dimethyl sulfoxide using tetramethylsilane as the internal standard.

Single-crystal X-ray diffraction data were collected on an Agilent SuperNova Dual Atlas diffractometer with a mirror monochromator using either Cu ($\lambda = 1.5418 \text{ \AA}$) or Mo ($\lambda = 0.7107 \text{ \AA}$) radiation. Crystal structures were solved using SHELXS^[43] and refined using SHELXL.^[44] Nonhydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were inserted in idealized positions, and a riding model was used with $U_{\text{iso}}(\text{H})$ set at 1.2 or 1.5 times the value of $U_{\text{eq}}(\text{C/N})$. The crystallographic data for compounds 3a, 3b, 3f, 8a, 8c, 10a, and 10b have been deposited at the Cambridge Crystallographic Data Center with CCDC reference numbers 1861538-1861544.

4.1 | Synthesis

Compounds 1,^[19–21] 2,^[45] 5,^[46] 7,^[47] and 9^[48] were synthesized using the procedures reported in literature.

Synthesis of 5-methyl-N⁰-(1-(5-methyl-1-aryl-1H-1,2,3-triazol-4-yl)ethylidene)-1-aryl-1H-1,2,3-triazole-4-carbohydrazides 3: Method A. A mixture of 1 (2.0 mmol) and 2 (2.0 mmol) in EtOH (20 mL) containing glacial AcOH (2 mL) and $\text{MeCO}_2\text{Na} \cdot 3\text{H}_2\text{O}$ (0.27 g, 2.0 mmol) was refluxed for 5 hours. The solid obtained on cooling

was filtered and recrystallized from EtOH. Pure compound 3 was obtained in 46-58% yields (Table 1).

Synthesis of 3a-f: Method B: A mixture of 1 (2.0 mmol), 5 (2.0 mmol), and glacial acetic acid (2 mL) in EtOH

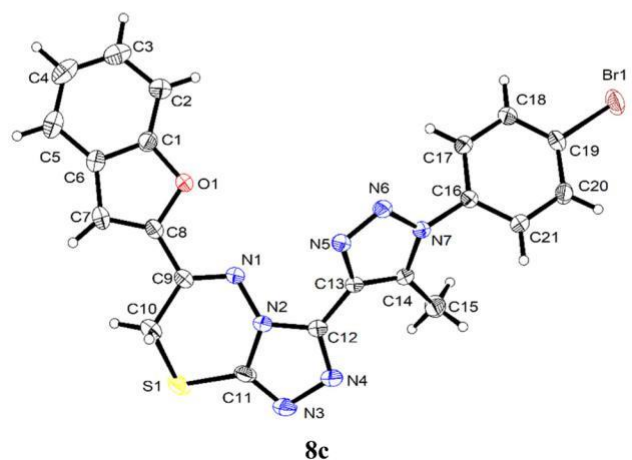
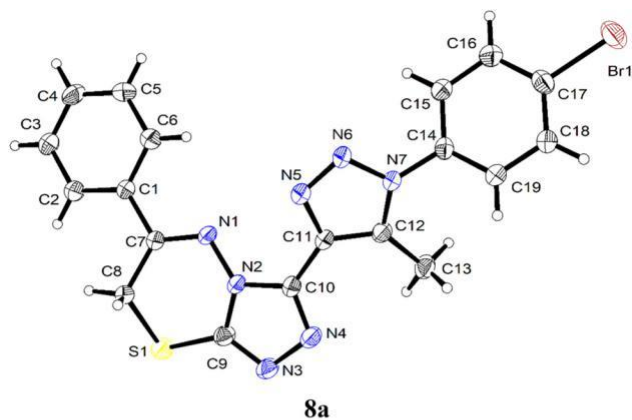


FIGURE 2 ORTEP representation of the molecular structures of 8a and 8c with 50% probability ellipsoids obtained by X-ray diffraction

(20 mL) was refluxed for 5 hours. The solid obtained on cooling was filtered and recrystallized from EtOH. Pure products were obtained in 79-85% yields.

N⁰-(1-(1-(4-bromophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)ethylidene)-5-methyl-1-phenyl-1H-1,2,3-triazole-4-carbohydrazide (3a): IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$: 1685 (C=O).

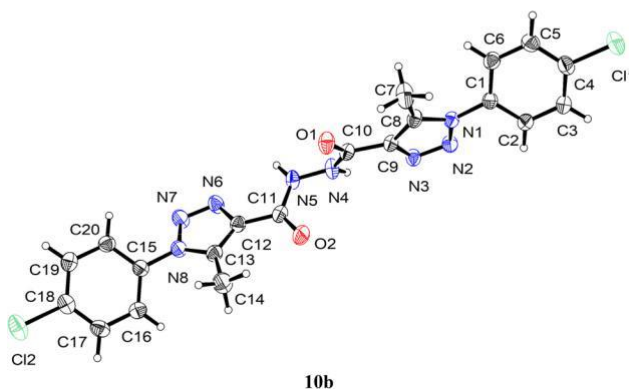
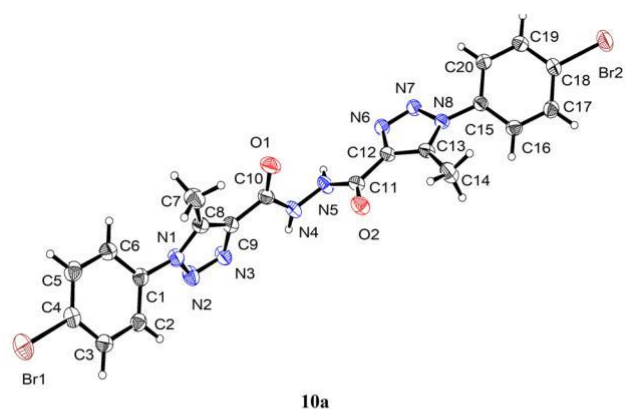
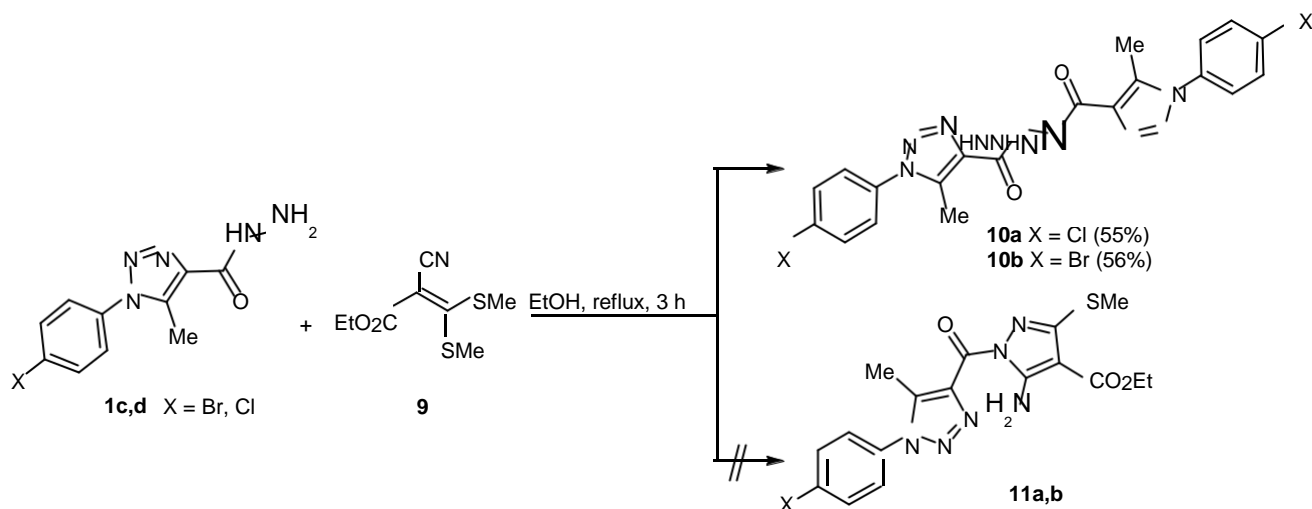
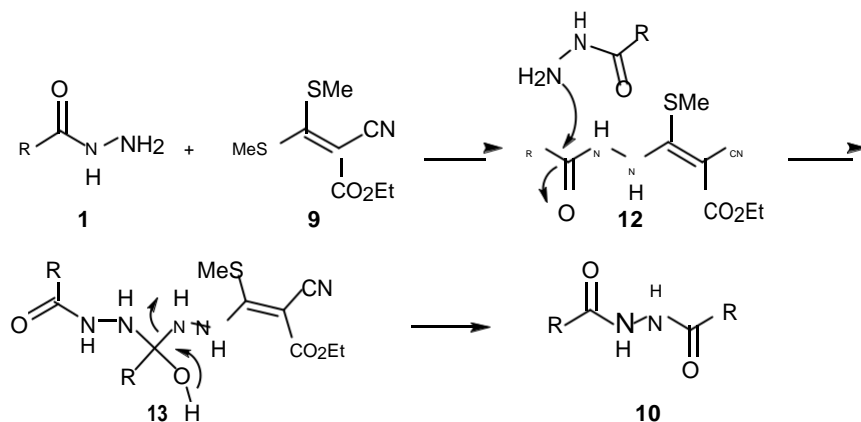


FIGURE 3 ORTEP representation of the molecular structure of 10a and 10b with 50% probability ellipsoids obtained by X-ray diffraction



SCHEME 5 Synthesis of carbohydrazides 10



S C H E M E 6 Proposed mechanism for the formation of carbohydrazides 10

¹H NMR: δ 1.56 (s, 3H, CH₃), 2.64 (s, 3H, CH₃), 2.70 (s, 3H, CH₃), 7.54-7.70 (m, 9H, Ar), 10.22 (s, exch., 1H, NH). ¹³C NMR: δ 9.8, 11.2, 13.0, 123.8, 125.2, 126.8, 129.7, 130.2, 132.8, 133.5, 134.9, 135.4, 137.6, 137.9, 142.97, 148.0, 157.2. Anal. Calcd. for C₂₁H₁₉BrN₈O (478.09): C, 52.62; H, 4.00; N, 23.38%. Found: C, 52.47; H, 4.19; N, 23.68%.

N⁰-(1-(1-(4-bromophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)ethylidene)-5-methyl-1-(4-tolyl)-1H-1,2,3-triazole-4-carbohydrazide (3b): IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$: 1681 (C = O). ¹H NMR: δ 1.55 (s, 3H, CH₃), 2.46 (s, 3H, CH₃), 2.64 (s, 3H, CH₃), 2.70 (s, 3H, CH₃), 7.51-7.70 (m, 8H, Ar), 10.21 (s, exch., 1H, NH). ¹³C NMR: δ 9.8, 11.2, 15.0, 21.3, 123.8, 125.1, 128.8, 129.0, 131.3, 132.8, 134.5, 135.0, 135.5, 138.6, 139.1, 139.7, 146.5, 157.3. Anal. Calcd. for C₂₂H₂₁BrN₈O (492.10): C, 53.56; H, 4.29; N, 22.71%. Found: C, 53.75; H, 4.37; N, 22.96%.

N⁰-(1-(1-(4-chlorophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)ethylidene)-5-methyl-1-phenyl-1H-1,2,3-triazole-4-carbohydrazide (3c): IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$: 1679 (C = O). ¹H NMR: δ 1.58 (s, 3H, CH₃), 2.67 (s, 3H, CH₃), 2.70 (s, 3H, CH₃), 7.46-7.61 (m, 9H, Ar), 10.24 (s, exch., 1H, NH). ¹³C NMR: δ 9.8, 11.2, 15.1, 125.0, 128.2, 128.5, 129.5, 129.8, 134.2, 134.6, 135.4, 135.6, 135.8, 139.6, 139.9, 148.0, 157.2. Anal. Calcd. for C₂₁H₁₉ClN₈O (434.14): C, 58.00; H, 4.40; N, 25.77%. Found: C, 58.15; H, 4.57; N, 25.88%.

1-(4-Bromophenyl)-N⁰-(1-(1-(4-bromophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)ethylidene)-5-methyl-1H-1,2,3-triazole-4-carbohydrazide (3d): IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$: 1683 (C = O). ¹H NMR: δ 1.55 (s, 3H, CH₃), 2.64 (s, 3H, CH₃), 2.70 (s, 3H, CH₃), 7.54-7.73 (m, 8H, Ar), 10.19 (s, exch., 1H, NH). ¹³C NMR: δ 9.8, 11.2, 15.0, 123.2, 123.8, 128.2, 128.6, 131.6, 132.0, 134.0, 134.8, 135.0, 135.0, 139.3, 139.5, 145.6, 157.6. Anal. Calcd. for C₂₁H₁₈Br₂N₈O (556.00): C, 45.18; H, 3.25; N, 20.07%. Found: C, 45.26; H, 3.45; N, 20.19%.

1-(4-Bromophenyl)-N⁰-(1-(1-(4-chlorophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)ethylidene)-5-methyl-1H-1,2,3-triazole-4-carbohydrazide (3e): IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$: 1682 (C = O).

¹H NMR: δ 1.54 (s, 3H, CH₃), 2.64 (s, 3H, CH₃), 2.68 (s, 3H, CH₃), 7.51-7.73 (m, 8H, Ar), 10.28 (s, exch., 1H, NH). ¹³C NMR: δ 9.7, 11.2, 14.9, 123.5, 128.4, 128.6, 129.8, 130.2, 133.6, 134.9, 135.0, 135.2, 135.9, 139.3, 139.6, 145.6, 157.6. Anal. Calcd. for C₂₁H₁₈BrClN₈O (512.05): C, 49.09; H, 3.53; N, 21.81%. Found: C, 49.23; H, 3.65; N, 22.01%.

1-(4-Chlorophenyl)-N⁰-(1-(1-(4-chlorophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)ethylidene)-5-methyl-1H-1,2,3-triazole-4-carbohydrazide (3f): IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$: 1680 (C = O). ¹H NMR: δ 1.61 (s, 3H, CH₃), 2.46 (s, 3H, CH₃), 2.49 (s, 3H, CH₃), 7.52-7.59 (m, 8H, Ar), 10.88 (s, exch., 1H, NH). ¹³C NMR: δ 9.9, 10.1, 14.9, 128.1, 128.9, 129.5, 131.7, 133.7, 133.9, 134.2, 134.7, 135.0, 135.5, 139.3, 139.5, 145.6, 157.6. Anal. Calcd. for C₂₁H₁₈Cl₂N₈O (468.10): C, 53.74; H, 3.87; N, 23.88%. Found: C, 53.86; H, 23.99; N, 23.65%.

Synthesis of 4-amino-5-(1-(4-bromophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)-4H-1,2,4-triazole-3-thiol (6): A mixture of 1c (1.50 g, 5.0 mmol), CS₂ (0.70 g, 10.0 mmol), and KOH (0.12 g, 2.0 mmol) in aqueous EtOH (20 mL, 80%) was stirred for 2 hours at 0-5 °C in an ice bath. Hydrazine hydrate (0.20 g, 4.0 mmol) was added, and the reaction mixture was refluxed for 5 hours. The mixture was allowed to cool to room temperature and poured into ice water (200 mL); dilute HCl was added till a pH of 7 was attained. The white solid obtained was collected by filtration to afford pure compound 6. Yield: 73%; Mp: 260-261 °C. IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$: 3321 (NH₂). ¹H NMR: δ 2.43 (s, 3H, CH₃), 5.92 (s, exch., 2H, NH₂), 7.61 (d, J = 9.2 Hz, 2H, Ar); 7.68 (d, J = 9.2 Hz, 2H, Ar), 14.07 (s, exch., 1H, SH). ¹³C NMR: δ 9.9, 123.1, 127.8, 132.1, 133.5, 135.1, 143.6, 145.6, 166.2. Anal. Calcd. for C₁₁H₁₀BrN₇S (350.99): C, 37.51; H, 2.86; N, 27.84%. Found: C, 37.66; H, 2.97; N, 28.07%.

Synthesis of 3-(1-(4-bromophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)-6-aryl-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazines 8: A mixture of 6 (0.35 g, 1.0 mmol) and α -bromoketones 7 (2.0 mmol) in anhydrous EtOH

(20 mL) was heated under reflux for 3 hours. The solid formed on cooling was filtered, washed with EtOH, and dried. Pure compound 8 was obtained in 74–82% yields.

3-(1-(4-Bromophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)-6-phenyl-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**8a**): Yield: 82%; Mp: 257–259 °C. ¹H NMR: δ 2.56 (s, 3H, CH₃), 4.55 (s, 2H, CH₂), 7.51 (d, J = 9.2 Hz, 2H, Ar), 7.59 (d, J = 9.2 Hz, 2H, Ar), 7.65–7.82 (m, 5H, Ph). ¹³C NMR: δ 9.8, 35.0, 123.5, 125.4, 128.1, 128.6, 131.1, 131.6, 131.9, 133.0, 134.9, 143.9, 147.2, 154.0, 162.8. Anal. Calcd. for C₁₉H₁₄BrN₇S (451.02): C, 50.45; H, 3.12; N, 21.68%. Found: C, 50.59; H, 3.32; N, 21.73%.

6-(4-Bromophenyl)-3-(1-(4-bromophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**8b**): Yield: 78%; Mp: 282–283 °C. ¹H NMR: δ 2.53 (s, 3H, CH₃), 4.69 (s, 2H, CH₂), 7.61 (d, J = 9.2 Hz, 2H, Ar), 7.66 (d, J = 9.4 Hz, 2H, Ar), 7.72 (d, J = 9.2 Hz, 2H, Ar), 7.78 (d, J = 9.4 Hz, 2H, Ar). Anal. Calcd. for C₁₉H₁₃Br₂N₇S (528.93): C, 42.96; H, 2.47; N, 18.46%. Found: C, 43.07; H, 2.88; N, 18.66%.

6-(Benzofuran-2-yl)-3-(1-(4-bromophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**8c**): Yield: 74%; Mp: 267–268 °C. ¹H NMR: δ 2.53 (s, 3H, CH₃), 4.56 (s, 2H, CH₂), 6.90 (s, 1H, furyl), 7.58 (d, J = 9.4 Hz, 2H, Ar), 7.64 (d, J = 9.4 Hz, 2H, Ar), 7.69–7.84 (m, 4H, Ar). ¹³C NMR: δ 10.0, 32.9, 112.4, 114.8, 123.3, 123.7, 124.6, 127.7, 127.8, 128.5, 132.8, 133.3, 135.3, 136.2, 143.1, 146.3, 147.2, 149.1, 156.0. Anal. Calcd. for C₂₁H₁₄BrN₇OS (491.02): C, 51.23; H, 2.87; N, 19.91%. Found: C, 51.46; H, 2.97; N, 20.21%.

Synthesis of 5-methyl-N⁰-(5-methyl-1-aryl-1H-1,2,3-triazole-4-carbonyl)-1-aryl-1H-1,2,3-triazole-4-carbohydrazides **10**: A mixture of **1c,d** (3.0 mmol) and **9** (0.65 g, 3.0 mmol) in anhydrous EtOH (20 mL) was refluxed for 3 h. The solid obtained on cooling was filtered, washed with EtOH, and dried. Pure compounds **10a** and **10b** were obtained in 55 and 56% yields, respectively. The analytical and spectral data for the products were in agreement with those reported previously.^[29]

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CONFLICT OF INTEREST

The authors have no competing interest to declare.

ORCID

Gamal A. El-Hiti  <https://orcid.org/0000-0001-6675-3126>

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