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A Regioselective and Convenient One-Pot Multi-Component Synthesis of 9-Amino-3,5-Diaryl-4,9-Dihydro-5*H*-[1,2,4]Triazolo[5,1-*C*] [1,2,4]Triazepine-8-Thiol

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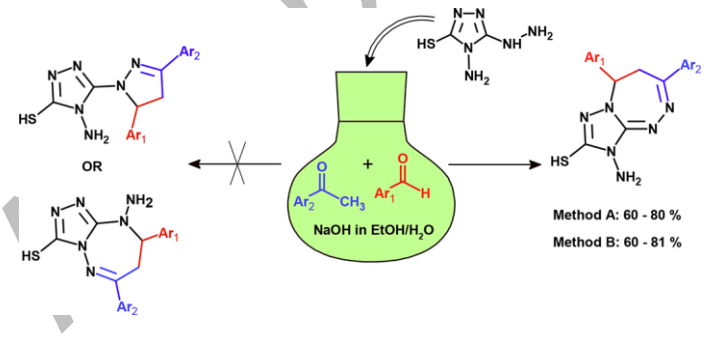
Abstract

An efficient and environment-friendly procedure for the synthesis of a new series of nitrogen bridge-head [1,2,4]triazolo[5,1-*C*][1,2,4]triazepine derivatives via one-pot three component reaction of polyfunctional triazole with aromatic aldehydes and acetophenone derivatives using alcoholic sodium hydroxide solution. The same new products were prepared in classical route via reaction of triazole with the corresponding chalcones under the same conditions.

GRAPHICAL ABSTRACT:



KEYWORDS: Triazole, Triazolotriazepine, Chalcone, Multi-component reaction, Regioselectivity.

INTRODUCTION

Triazolethiones possess various biological activities including anticancer,[1,2] antiviral,[3,4] anti-inflammatory,[5,6] antiproliferative,[7] antifungal,[8-10] antidepressant,[11] antioxidant,[12,13] antiulicer,[12,14] and hypoglycaemic activities.[15] On the other hand, compounds with triazepine skeletons have exhibited significant biological activities.[16,17] The area of biological interest of this family of compounds have been extended to various diseases such as cancer,[18] viral infections (HIV)[19] and cardiovascular disorders.[20,21] 1,2,4-Triazepines condensed with heterocycles were found to have salidiuretic and renal vasodilator, antioxidant, and analgesic and immune modulating activities.[22–24] Moreover, fused triazepine derivatives with a bridgehead nitrogen atom exhibit interesting biological properties.[25] Therefore, the development of new methods for the synthesis of these functionalized [1,2,4]triazolo[5,1-*C*][1,2,4]triazepine derivatives is an important direction of synthetic chemistry. The use of multicomponent reactions as an efficient method in the development and modification of various types of heterocyclic systems, is a convenient approach to the preparation of a wide number of products with certain substituents.[26,27] Hence, the discovery of novel protocols using multicomponent strategy has become an increasingly active area of research for generating biologically active polysubstituted nitrogen scaffolds for drug discovery program.

In view of the aforementioned facts, we have designed and developed a strategy to bring together the [1,2,4]triazole and [1,2,4]triazepine moieties in a single fused structure by

one-pot multi-component reaction of polyfunctional triazole **1** with aromatic aldehydes and acetophenone derivatives using sodium hydroxide as basic catalyst.

RESULTS AND DISCUSSION

In our previous work,[28] we have described the reaction of polyfunctional triazole **1**[29] with some enaminones in *ortho*-phosphoric acid to give pyrazolyltriazole derivatives **I**, (Figure 1). In the present work, a facile method has been described for the synthesis of title products **II** via an efficient one-pot synthesis of three-component reaction of triazole **1**, aromatic aldehydes **2** and acetophenone derivatives **3** using an alcoholic solution of sodium hydroxide as non-toxic and inexpensive catalyst, (Scheme 1). This protocol offers flexibility in tuning the molecular complexity and diversity. The reactions proceeded to completion in almost 8 hours and the products were obtained in good yield. From previous work[28] and these results it's clear that, the regioselective of the reaction of triazole **1** with dienophiles is depends on the pH of the reaction medium.

As an introductory test, we run a model reaction in one pot by stirring at 0-5 ^{o}C of an equimolecular amounts of benzaldehyde **2a** and acetophenone **3a** in aqueous ethanolic sodium hydroxide for 1 hr. and then 4-amino-5-hydrazino-4*H*-[1,2,4]triazol-3-thiol **1** was added. After addition, the reaction mixture was refluxed for 8 hours to produce the desired product of 9-amino-3,5-diphenyl-4,9-dihydro-5*H*-[1,2,4]triazolo[5,1-*c*][1,2,4]triazepine-8-thiol (**4a**) in 70 % yield. The scope of the method was investigated with a series of aromatic aldehyde and acetophenone derivatives to afford the corresponding product **4b-l**. The same products **4a-l** was also produced in the classical

method via reaction of **1** and chalcones **5a-l**, respectively, under the same conditions, (Scheme 1).

The plausible mechanism for the formation of product **4** was assumed to proceed via production of chalcone **5** by reaction between aromatic aldehydes **2** and acetophenones **3**, then the condensation of 3-amino-[1,2,4]triazole (**1**) with chalcone **5** can proceed in two possible ways, as shown in Scheme 1. In route 1, the NH group attacks the double bond via a Michael addition reaction to give intermediate **III**, which cyclized by dehydration through path **A** to give product **6** or through path **B** to give compound **7**. On the other hand, in route 2, the nucleophilic NH_2 group of hydrazino group attacks the C=O group, followed by elimination of H_2O molecule to afford intermediate **IV** in tautomer with **IV'**. Then, the endo-cyclic NH group of triazole ring in **IV** or the exo-cyclic NH of hydrazino group in **IV'** attacks the double bond via a Michael addition reaction giving product **4** or **6**, respectively. The formation of product **4** and its regioselectivity has been substantiated through *NOESY* spectral data.

The *NOESY* spectrum of compound **4j** shows a correlation peak between the proton of H-5 and two hydrogens of the exocyclic methylene group, also there is a correlation peak between aryl protons and two hydrogens of the methylene group, in addition to a correlation peak between the proton of the SH group and the protons of the NH_2 group in triazole ring. Also, there is no overlapping between the aromatic protons or H-5 with the protons of the NH_2 group, this results support the structure **4** and show that the structures **6** and **7** are incorrect.

The structures of the newly synthesized compounds **4a-l** were confirmed by their spectral (IR, ^{1}H, ^{13}C NMR, *NOE*) and elemental analyses. For example, the IR spectrum of compound **4j** shows seven absorption peaks at 1603 cm^{-1} for C=N, 2834, 2910, 2956 cm^{-1} for C-H aliphatic, 3062 cm^{-1} for C-H aromatic and 3160, 3268 cm^{-1} for NH_2 group. Its ^{1}HNMR spectrum shows the disappear of signals corresponding to hydrazino group, and exhibits three singlet signals at δ 3.74, 5.73 and 13.15 characteristic of OCH_3, NH_2 and SH groups, respectively, also it appears four doublet signals at δ 6.90, 7.34, 7.52 and 7.84 for aromatic protons, triplet signal at 5.50 with coupling constant (*j*) 10.6 Hz due to $CH_{triazepine}$, and two doublet of doublets signals at δ 3.24 and 3.85 for CH_2 group. The ^{13}C NMR spectrum of **4j** shows two peaks at δ 42.3 and 64.9 which are assigned to CH_2 and $CH_{triazepine}$, respectively, one peak at δ 55.6 due to methoxy carbon, also there are three peaks at δ 153.2, 159.4, 164.7 could be attributed for –C=N, while the other aromatic carbon are characterized by peaks at δ 114.5, 128.6, 128.8, 129.2, 130.6, 132.2, 135.0 and 149.2.

We have then looked into possible replacing aromatic aldehydes by heterocyclic aldehyde such as furfural; and acetophenones by 3-acetyl-, 4-acetylpyridine hoping to obtain 9-amino-5-(furan-2-yl)-3-aryl-4,9-dihydro-5*H*-[1,2,4]triazolo[5,1-*c*][1,2,4]triazepine-8-thiol **8a-d**, 9-amino-5-aryl-3-(pyridin-3-yl)-4,9-dihydro-5*H*-[1,2,4]triazolo[5,1-*c*][1,2,4]triazepine-8-thiol **9a-c** and/or 9-amino-5-aryl-3-(pyridin-4-yl)-4,9-dihydro-5*H*-[1,2,4]triazolo[5,1-*c*][1,2,4]triazepine-8-thiol **10a,b**, respectively, (Scheme 2). In each case the reaction underwent smoothly resulting in similar good

yields. The same products **8-10** were also produced in the classical route via reaction of **1** with corresponding chalcone. The chemical structure of the new products **8-10** could be assigned to the reaction product based on IR, NMR and elemental analyses.

Reaction of triazole **1** with acetone and 4-chlorobenzaldehyde cannot proceed via one pot multicomponent reaction, as a result of dimerization of acetone with two mole of aldehydes in basic medium, but the reaction was optimized via two component reaction of an equimolecular amounts of triazole **1** and 4-(4-chlorophenyl)but-3-en-2-one in an aqueous ethanolic sodium hydroxide solution to afford the desired product **11**, (Scheme 2). The structure of compound **11** was confirmed by IR, ^{1}H, ^{13}C NMR, *NOE* and elemental analyses. Its IR spectrum shows seven absorption peaks at 3230, 3328 cm^{-1} due to NH_2 group, 3060 cm^{-1} for C-H aromatic, 2874, 2948, 2987 cm^{-1} for C-H aliphatic and 1636 cm^{-1} for C=N. Its ^{1}HNMR spectrum shows the disappear of signals corresponding to hydrazino group, and exhibits four singlet signals at δ 2.03, 5.59, 7.39 and 12.17 ppm characteristic of CH_3, NH_2, 4CH aromatic and SH groups, respectively; triplet signal at δ 5.31 ppm with coupling constant (*j*) 10.6 Hz due to $CH_{triazepine}$, and two doublet of doublets signals at δ 2.81 and 3.40 ppm for CH_2 group with coupling constants (*j*) 11.0, 17.4. The ^{13}C NMR spectrum of **11** shows seven peaks at δ 128.9, 129.1, 132.6, 139.8, 149.8, 156.5, 164.6 ppm, which are assigned to aromatic carbons, while there are three peaks at δ 15.8, 46.3 and 64.0 ppm due to CH_3, CH_2, $CH_{triazepine}$, respectively. The *NOESY* spectrum of product **11** shows across peak between CH_3 (δ 2.03) and two protons of CH_2 (δ 2.82, 3.93), also there are correlation peaks between the protons of the CH aromatic at δ 7.39 with $CH_{triazepine}$ (δ 5.31) and one proton of CH_2 (δ 2.82), while there is

no overlapping between the protons of NH_2 group in triazole ring (δ 5.59) and the protons of CH aromatic (δ 7.39).

CONCLUSIONS

In summary, we have developed a novel method for the synthesis of 9-amino-3,5-diaryl-4,9-dihydro-5*H*-[1,2,4]triazolo[5,1-*c*] [1,2,4]triazepine-8-thiol via one-pot three component reaction of triazole with aromatic aldehydes and acetophenone derivatives using alcoholic sodium hydroxide solution. Also, the same products were prepared in classical route via reaction of triazole with the corresponding chalcones under the same conditions. Due to the availability of the starting materials, the simplicity of the procedures, and the comparatively reasonable yields of the products, this synthetic approach might be valuable for the synthesis of such ring systems.

EXPERIMENTAL

General Information

Melting points were detected with a Kofler melting points apparatus and uncorrected. Infrared spectra were recorded with a FT-IR-ALPHBROKER-Platinum-ATR spectrometer. ^{1}H NMR and ^{13}C NMR spectra for all compounds were recorded in DMSO-d_6 on a Bruker Bio Spin AG spectrometer at 400 MHz and 100 MHz, respectively. Elemental analyses were obtained on a Perkin-Elmer CHN-analyzer model.

General Procedure For Synthesis of Compounds 4a-L, 8a-D, 9a-C And 10a,B:

Method A: General Procedure (Three-Component Reaction)

A mixture of aromatic aldehydes (0.01 mol) and acetophenone derivatives namely: acetophenone, 4-chloro-, 4-methyl-, 4-methoxyacetophenone, 3-acetylpridine and/or 4-acetylpyridine (0.01 mol) was stirred in an ice bath for 1 hr in 60 ml alcoholic sodium hydroxide 0.5M (1.2 g NaOH in 40 ml ethanol and 20 ml water), then 4-amino-5-hydrazino-4*H*-[1,2,4]triazol-3-thiol **1** (0.01 mol) was added to the reaction mixture. The resulting mixture was heated for about 8 hrs. After completion of reaction (monitored with TLC), the reaction mixture was cooled to RT, poured into ice-cold distilled water and neutralized to pH ~ 6.5 with dilute hydrochloric acid. The crude precipitate which formed was collected by filtration, washed several times with distilled water and dried. For elemental analyses the products were recrystallized from ethanol.

Method B: General Procedure (Two-Component Reaction)

An equimolar amounts (0.01 mol) of chalcone and 4-amino-5-hydrazino-4*H*-[1,2,4]triazol-3-thiol **1** was heated in 60 ml alcoholic sodium hydroxide 0.5M (1.2 g NaOH in 40 ml ethanol and 20 ml water) for about 8 hrs. After completion of reaction (monitored with TLC), the reaction mixture was cooled to RT, poured into ice-cold distilled water and neutralized to pH ~ 6.5 with dilute hydrochloric acid. The crude precipitate which formed was collected by filtration, washed several times with distilled water and dried. For elemental analyses the products were recrystallized from ethanol.

9-Amino-3-(4-Chlorophenyl)- 5-(4-Methoxyphenyl)-4,9-Dihydro-5*H*-[1,2,4]-Triazolo[5,1-*C*][1,2,4]-Triazepine-8-Thiol (4j)

Yield (Method A 75%, Method B 81 %); greenish yellow solid; m.p.: 218-219 °C. IR (ATR) ν_{max} 3268, 3160, 3062, 2956, 2910, 2834, 1603 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.15 (s, 1H, SH), 7.84 (d, j = 8.4 Hz, 2H, $CH_{arom.}$), 7.52 (d, j = 8.4 Hz, 2H, $CH_{arom.}$), 7.34 (d, j = 8.6 Hz, 2H, $CH_{arom.}$), 6.90 (d, j = 8.6 Hz, 2H, $CH_{arom.}$), 5.73 (s, 2H, NH_2), 5.50 (t, j = 10.6 Hz, 1H, $CH_{triazepine}$), 3.85 (dd, j = 17.3, 11.0 Hz, 1H, CH_2), 3.74 (s, 3H, OCH_3), 3.24 (dd, j = 17.3, 10.2 Hz, 1H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.7, 159.4, 153.2, 149.2, 135.0, 132.2, 130.6, 129.2, 128.8, 128.6, 114.5, 64.9, 55.6, 42.3. Anal. Calcd. for $C_{18}H_{17}ClN_6OS$ (400): C, 53.93; H,4.27; N, 20.96. Found: C, 54.01; H, 4.19; N,20.89.

9-Amino-5-(2-Furyl)-3-Phenyl-4,9-Dihydro-5*H*-[1,2,4]Triazolo[5,1-*C*][1,2,4]-Triazepine-8-Thiol (8a)

Yield (Method A 64%, Method B 66 %); white solid; m.p.: 227-228 °C. IR (ATR) □$_{max}$ 3295, 3200, 3082, 2963, 2933, 1618 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) □ 13.16 (s, 1H, SH), 7.83 (s, 2H, CH_{phenyl}), 7.59 (s, 1H, CH_{furyl}), 7.48 (s, 3H, CH_{phenyl}), 6.48 (s, 1H, CH_{furyl}), 6.40 (s, 1H, CH_{furyl}), 5.73(t, j = 9.1 Hz, 1H, $CH_{triazepine}$), 5.66 (s, 2H, NH_2), 3.80 (dd, j = 16.6, 11.6 Hz, 1H, CH_2), 3.51 (dd, j = 16.9, 8.6 Hz, 1H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6) □ 165.2, 154.4, 151.7, 149.6, 143.6, 131.5, 130.5, 129.1, 127.1, 110.9, 109.2, 58.5, 38.5. Anal. Calcd. for $C_{15}H_{14}N_6OS$ (326): C, 55.20; H, 4.32; N, 25.75. Found: C, 55.28; H, 4.22; N,25.71.

9-Amino-5-Phenyl-3-Pyridin-3-Yl-4,9-Dihydro-5*H*-[1,2,4]Triazolo[5,1-*C*]-[1,2,4]-Triazepine-8-Thiol (9a)

Yield (Method A 69%, Method B 70 %); pale yellow solid; m.p.: 188-190 °C. IR (ATR) ν_{max} 3321, 3220, 3055, 2943, 2909, 1602 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.05 (s, 1H, SH), 9.01 (s, 1H, $CH_{pyridyl}$), 8.64 (d, j = 3.9 Hz, 1H, $CH_{pyridyl}$), 8.21 (d, j = 8.0 Hz, 1H, $CH_{pyridyl}$), 7.50 (dd, j = 7.9, 4.8 Hz, 1H, $CH_{pyridyl}$), 7.43 (d, j = 7.2 Hz, 2H, CH_{phenyl}), 7.36 (t, j = 7.2 Hz, 2H, CH_{phenyl}), 7.3 (m, 1H, CH_{phenyl}), 5.77 (s, 2H, NH_2), 5.57 (t, j = 10.8 Hz, 1H, $CH_{triazepine}$), 3.96 (dd, j = 17.4, 11.2 Hz, 1H, CH_2), 3.30 (dd, j = 17.0, 10.7 Hz, 1H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.8, 152.2, 151.0, 149.2, 148.2, 140.4, 134.2, 129.1, 128.3, 127.6, 127.3, 124.1, 65.3, 42.3. Anal. Calcd. for $C_{16}H_{15}N_7S$ (337): C, 56.96; H, 4.48; N, 29.06. Found: C, 56.99; H, 4.32; N,29.09.

Synthesis of 9-Amino-5-(4-Chlorophenyl)-3-Methyl-4,9-Dihydro-5*H*-[1,2,4]-Triazolo[5,1-C][1,2,4]Triazepine-8-Thiol (11)

An equimolar amounts (0.01 mol) of 4-(4-chlorophenyl)but-3-en-2-one and 4-amino-5-hydrazino-4*H*-[1,2,4]triazol-3-thiol was heated in 60 ml alcoholic sodium hydroxide 0.5M (1.2 g NaOH in 40 ml ethanol and 20 ml water) for 8 hrs (monitored with TLC). After completion of reaction, the reaction mixture was cooled to RT, poured into ice-cold distilled water and neutralized to pH ~ 6.5 with dilute hydrochloric acid. The crude precipitate which formed was collected by filtration, washed several times with distilled water and dried. For elemental analyses the crude was recrystallized from ethanol to give **11**. Yield 81 %; white solid; m.p.: 252-253 °C. IR (ATR) ν_{max} 3328, 3230, 3060, 2987, 2948, 2874, 1636 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.17 (s, 1H, SH), 7.39 (s, 4H, $CH_{arom.}$), 5.59 (s, 2H, NH_2), 5.31 (t, j = 10.6 Hz, 1H, $CH_{triazepine}$), 3.40 (dd, j = 17.4, 11.0 Hz, 1H, CH_2), 2.81 (dd, j = 17.4, 10.4 Hz, 1H, CH_2), 2.03 (s, 3H, CH_3). ^{13}C NMR

(100 MHz, DMSO-d_6) δ 164.6, 156.5, 149.8, 139.8, 132.6, 129.1, 128.9, 64.0, 46.3, 15.8. Anal. Calcd. for $C_{12}H_{13}ClN_6S$ (308): C, 46.68; H, 4.24; N, 27.22. Found: C, 46.71; H, 4.21; N,27.32.

SUPPORTING INFORMATION

Complete experimental procedures and characterization data of compounds **4 & 8-11** associated with this manuscript are found in the Supporting Information file.

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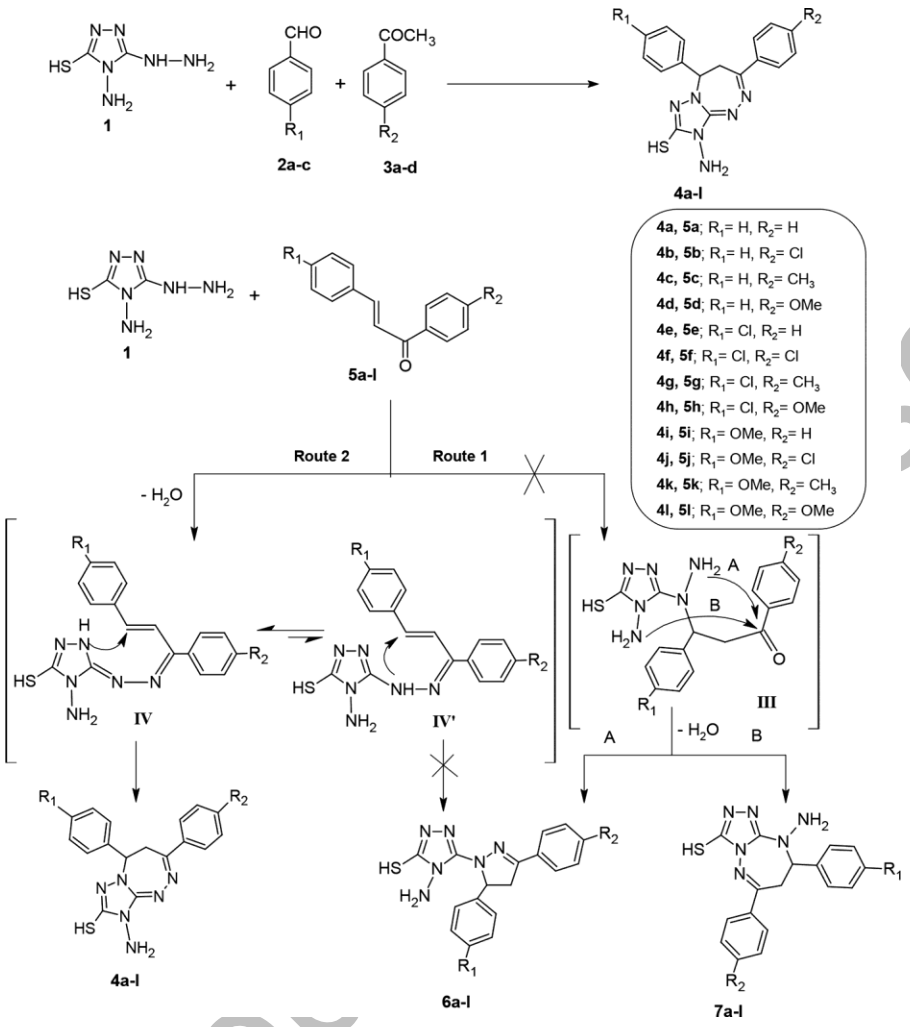
Scheme 1. Reaction mechanism and stereoselective synthesis of [1,2,4]triazolo[5,1-*c*][1,2,4]triazepines **4a-l**.



Scheme 2. Synthesis of [1,2,4]triazolo[5,1-*c*][1,2,4]triazepines **8-11**.

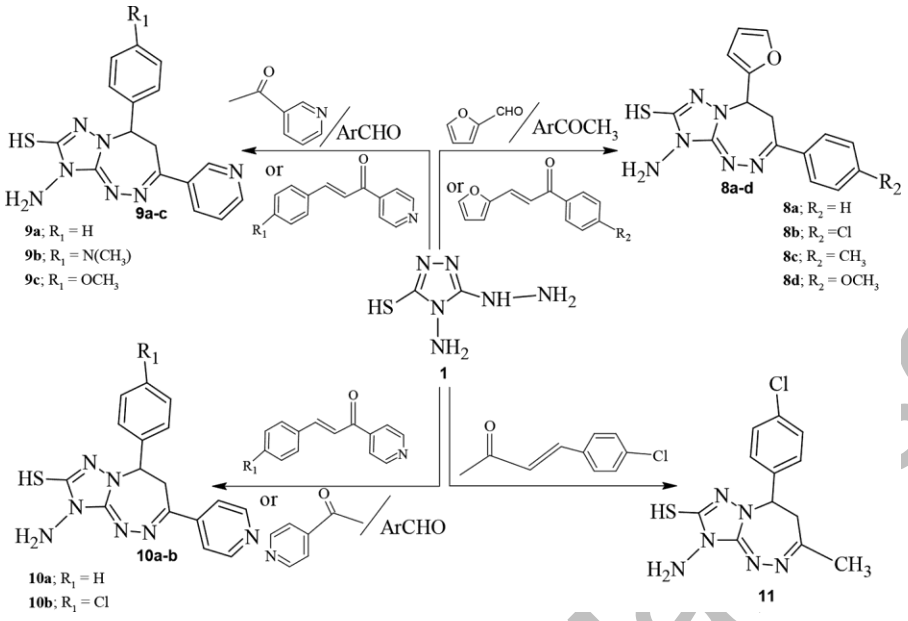


Figure 1.