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Exploring The Synthesis of 1,2,4-Triazole Derivatives: A Comprehensive Review

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ABSTRACT

The pharmacological activities of triazole derivatives have been studied extensively by researchers. Different derivatives of triazole have shown promise in treating various diseases. Most triazole derivatives have demonstrated anti-inflammatory, anti-cancer, anti-bacterial, and anti-fungal activities. The ability of these compounds to modulate various biological processes has made them attractive for pharmaceutical development. Furthermore, the low cost and wide availability of triazoles have made them even more attractive for drug development. In addition to the pharmacological activities, triazole derivatives have also been reported to possess antioxidant properties. Studies have shown that 1,2,3-triazole can protect against oxidative damage and inhibit lipid peroxidation. Furthermore, 1,2,4-triazole has been found to act as an antioxidant and scavenge free radicals. The antioxidant properties of triazoles make them attractive for the development of new drugs. The synthesis of triazole derivatives has also been studied extensively. Various methods have been developed to synthesize triazole derivatives, including chemical and enzymatic methods. Chemical methods involve the formation of cyclic structures by the reaction of alkyl halides with azides. Enzymatic methods involve the use.

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Introduction

The history of heterocyclic compounds, when Luigi Brugnatelli in the nineteenth century found alloxan (2,4,5,6-pyrimidinetetrone) in 1818. The chemistry of heterocyclic has an accounting close to a third of new publications. However, two from the third part of organic chemistry are heterocyclic compounds. The compounds of cyclic are defined as all carbon atoms combined in a cyclic. If one or more Carbone atom in cyclic compounds is replaced by other heteroatoms the heterocyclic compounds were designed. Oxygen, nitrogen, and sulfur are common hetero atoms in heterocyclic compounds, but heterocyclic compounds also contain other atoms. There are significantly important in the biological activity Five-member ring of heterocyclic systems 1,3,4-Thiadiazoles and 1,2,4- Triazoles, constitute the structure of features cyclic compounds. The first scientist who gives the name Triazole is Bladin in 1885[1]. Triazole widely different activities for instance anti-inflammatory [2-4], anticancer [5, 6], antibacterial [7-9], antifungal [10, 11], antitubercular [12, 13], antiviral [14, 15], anti-convulsant [10, 16, 17], antihelmintic [18], anti-nociceptive [19-21], analgesic [22], anti-corrosive [23], antioxidant [24-27], hypoglycemic [28], urease & lipase inhibitors [29], anti-proliferative diuretic, sedative, anti-migraine, anti- HIV and muscle relaxant [30].

Triazole And Tautomer's

Triazole with a five-member ring is a heterocyclic compound. It contains three nitrogens and two carbon atoms

at nonadjacent positions. Triazole has two isomers 1,2,4-triazoles and 1,2,3-triazoles Fig. 1.

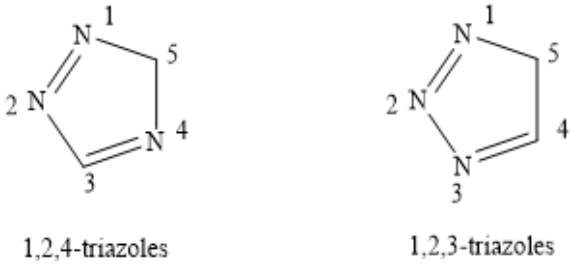


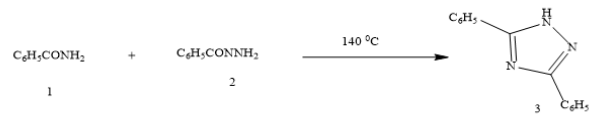
Fig. 1: Triazole

Also, 1,2,4-triazole has two tautomers from Fig.2. 1H and 4H-1,2,4-triazoles are important in pharmacological activity [31, 32].

Fig. 2: 1,2,4-triazole tautomer's

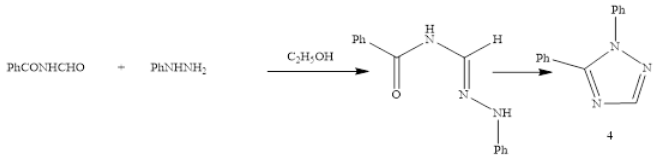
Triazole Synthesis

Triazoles are synthesized in two methods, first method is the Pellizzari reaction method the synthesis of Triazole from acyl hydrazide and amide, then a mixture with KOH was heated to yield 1,2,4-Triazoles. For instance, with benzoyl hydrazide 1 with benzamide 2, the yield is 3,5-diphenyl-1,2,4-triazole 3 (Scheme 1).



Scheme 1

The second one is the Einhorn Brunner methods are condensation reaction method between monosubstituted hydrazine like phenylhydrazine with diacylamines, for example, N-formyl benzamide in the present weak acid to yield 1,5-diphenyl-1,2,4-triazole 4 (Scheme 2) [31, 33, 34].

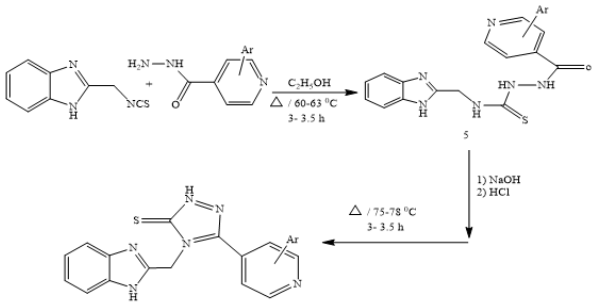


Scheme 2

Synthesis Triazole Derivatives

Synthesized 4-(4-(1H-benzo[d] imidazol-2-yl) methyl)-3-(pyri-din-4-yl)-1H-1, 2, 4-triazole-5(4H)-thione

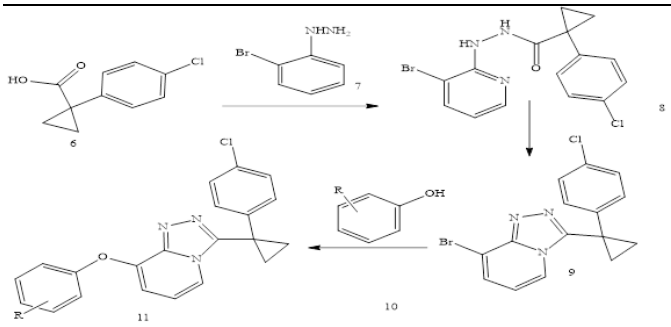
From N-(4-(1H-benzo[d] imidazol-2-yl) methyl)-2-isonicotinoylhydrazine carbothioamide 5 when refluxed in HCl and neutralization by NaOH (Scheme 3). [35]



Scheme 3

Synthesis of 3-[1-(4-Chlorophyenyl) cyclopropyl]-8-aryloxy-TZP Analogues

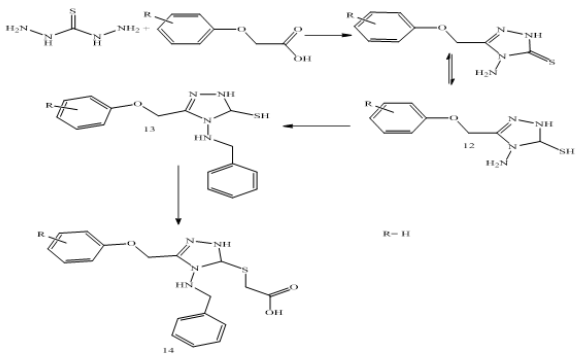
From 1-(4-chlorophenyl) cyclopropane-1-carboxylic acid 6 and hydrazine 7 to produced acyl hydrazide 8. Cyclodehydration compound 8 by PPh3Cl2 Bromo-triazolopyridine was formed 9 with a good yield. Compound 9 was joined with phenols 10, the compound 11 was produced under the modification conditions (Scheme 4). [36]



Scheme 4

Prepared 2-[4-(substituted benzylidene amino)-5-(substituted phenoxy methyl)-4H-1,2,4-triazole-3-yl thio] acetic acid derivatives

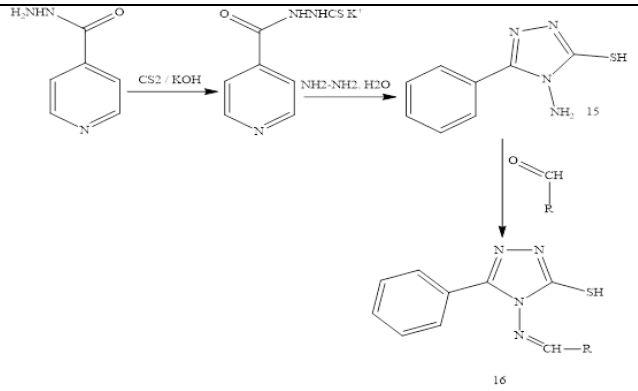
Starting the reaction of thiocarbohydrazide and substituted phenoxy acetic acid the product is 3- (substituted phenoxy methyl)-4-amino-5-mercapto-1,2,4-triazoles 12. Product 12 was substituted by numerous aromatic aldehydes in present CH3OH and concentrated HCl for 2h at 90 0C, the product is 13 converted to 14 by the reaction with $ClCH_2CO_2H$ in CH3OH medium with a drop of pyridine and 3h was refluxed (Scheme 5). [24]



Scheme 5

Synthesis 4-Ethylideneamino-5-pyridine-4-yl-4H-[1,2,4] triazole- 3-thiol

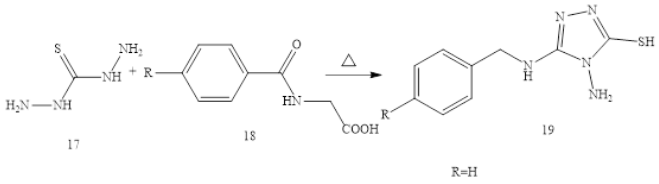
By a mix of equimolar 4-amino-5-pyridine-4-yl-1,2,4-triazole-3-thiol 15 with aldehydes in CH3OH (50, 70 mL) respectively, then added a few drops of Conc. HCL and refluxed for 4h. The mixtures were taken at room temperature overnight. The yield was obtaining then filtered. Purification with evaporation on silica gel Colum, compound 16 was produced (Scheme 6).[37]



Scheme 6

Prepared N-[(4-amino-5-sulfanyl-4H-1,2,4-triazole-3-yl)methyl]-4-substituted-benzamide

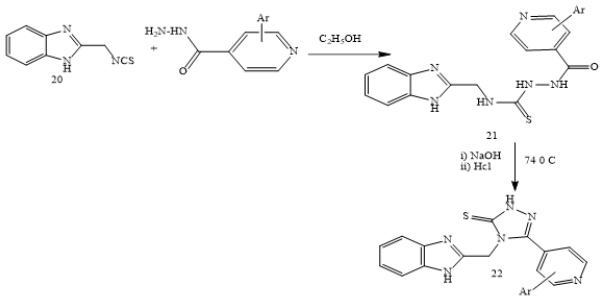
A mixture of thiocarbohydrazide 17 with N-benzoylglycine/N-(p-tolyl)glycine 18 (0.01674 mol) in the equimolar ratio was fused in the water bath for 1h, after cooled and dried with 5 %NaHCO3 solution. The product compound 19 was filtered, washed with water, and recrystallized with ethanol (Scheme 7).[38]



Scheme 7

Synthesis 4-((1H-benzo[d]imidazol-2-yl) methyl)-5-(pyridine-4-yl)-2H-1,2,4-triazole-3(4H)-thione

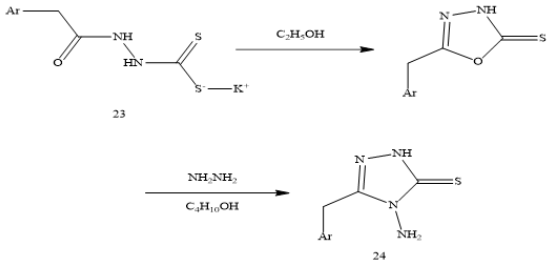
by dissolved (7.5 mmol) 2-(isothiocyanatomethyl)-1H-benzo[d]imidazole 20 in water, added (7.0 mmol) isoniazid and refluxed the mixture with 40 mL ethanol for 4h. The mixture was cooled at 0-5 0C and distilled to remove ethanol and used ethyl acetate to extract. The product crude was formed after the organic layer was dried by sodium sulfate. For further purification used column chromatography to obtain compound product 21 in yellow color. Compound 21 (12.5 mmol) was dissolved in (2 M, (30 mL)) sodium hydroxide (NaOH) solution and refluxed for 6h at 75 0C. When the reaction is completed, the mixture is cooled and acidified with HCl (20 mL), and the extracted product is with (C4H8O2). The organic layer was dry with Na2SO4 and distilled, and the crude yield product was formed. Column chromatography was used for father purification to get the white product 22(Scheme 8).[25]



Scheme 8

Synthesis 4-amino-5-(aryl methyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione

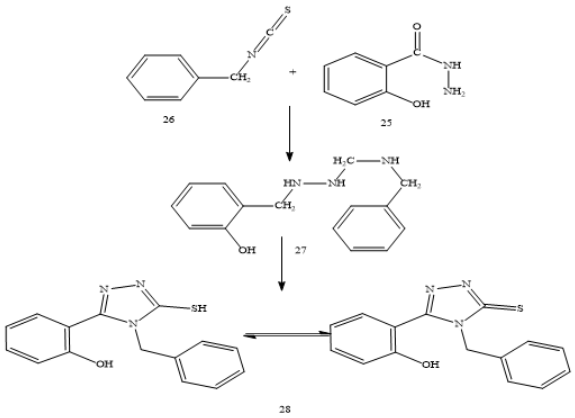
Dithiacarbazate 23 (1 g) in ethanol (20 mL) with hydrazine hydrate (0.02 mole) for 10h was refluxed. The reaction cooled at room Temp. then dissolved in H2O, after acidification with HCl, Filtered, washed, dried, and recrystallized by CH3OH to find product 24 (Scheme 9). [39]



Scheme 9

Synthesis of 4-benzyl-3-(2-hydroxyphenyl)-1H-1,2,4-triazole-5(4H)-thione

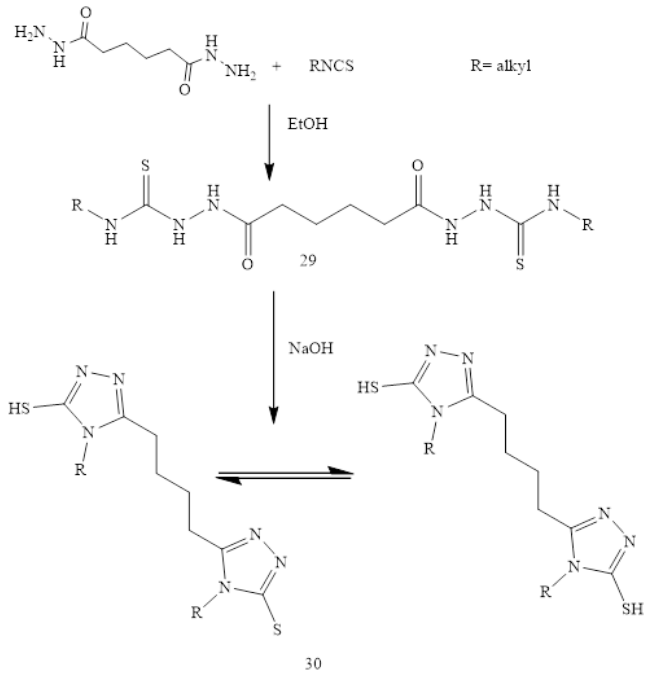
A mixture of (0.01 mol) compound 25 and equimolar benzyl isothiocyanates 26 in (100 mL) CH3OH then for 8h was refluxed. Product 27 was filtered, washed by Et2O, dried then crystallized from ethanol-dioxane. For 4 hours, compound 27 (0.01 mol) and NaOH (0.01 mol, in water) were a mix and refluxed. Next cooling the solution was used hydrochloric acid was to acidify and then collected by filtration. Recrystallized products from CH3OH- dioxane to get compound 28 (Scheme 10)[40].



Scheme 10

Synthesis 5,5'-Butane-1,4-diylbis(4-allyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione

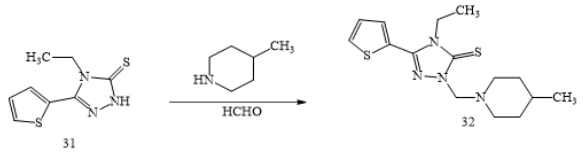
From a mixture (0.01 mol) of bis-thiosemicarbazides compound 29 with (10 mL) of 10 % NaOH, for 3h the reaction mixture was refluxed. After that cooled at RT and filtered. Product 30 was neutralized with glacial gel acidic acid. After that dried and recrystallized with CH3OH (Scheme 11). [41]



Scheme 11

Synthesis 4-Ethyl-2-[(4-methyl piperidine-1-yl)methyl]-5-(2-thienyl)- 2,4-dihydro-3H-1,2,4-triazole-3-thione

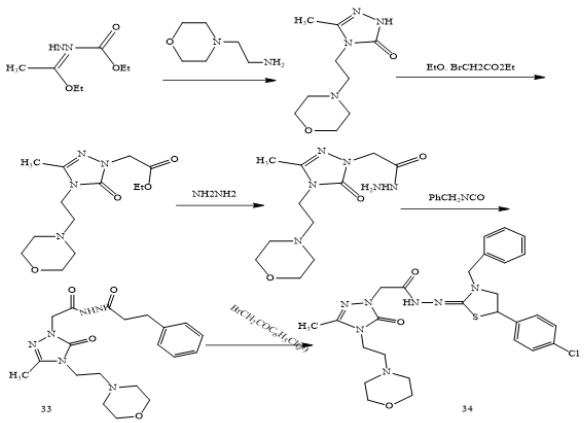
A mixture of 31 (0.01 mol), suitable amines (0.01) in (20 mL) ethanol, and formaldehyde (1.5 mL) at room temp was stirred for 1h. The product was filtrated, dried, and crystallized with CH3OH to give compound 32 (Scheme 12) [42].



Scheme 12

Synthesis N-[3-Benzyl-4-(4-chlorophenyl)-1,3-thiazol-2(3H)-ylidene]-2-[3-methyl-4-(2-morpholine-4-ylethyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl]acetohydrazide

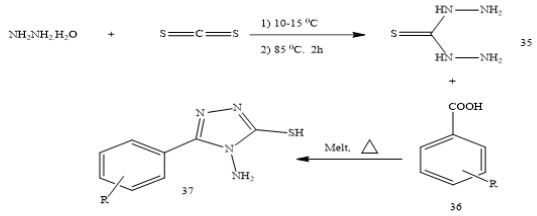
From 4-chlorophenyl bromide (10 mmol) added to the compound 33 in ethanol were refluxed for 8h in the presented of dried sodium acetate. The reaction was cooled at RT, then poured into ice water with stirring, and left overnight. The solid creation was filtered, washed with ice water, dried, and recrystallized from the ethylacetate-ethyl ether (1:2), and the target compound 34 was yielded (Scheme 13) [43].



Scheme 13

Prepared 4-Amino-5-(substituted-phenyl)-4H- [1,2,4]-triazole-3-thiol

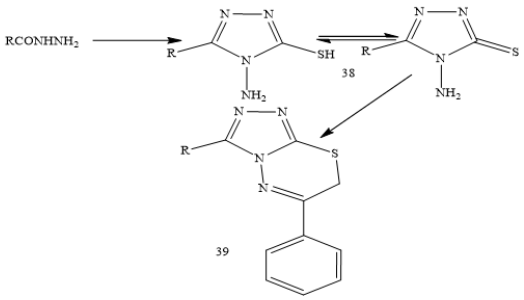
From benzoic acid 35 (0.01 mol) and thiocarbohydrazide 36 (0.015 moles) the round flask was heated until the mixture was melted. The cooled mixture was then acidified by sodium bicarbonate. After that washed with H2O and filtration the product. Recrystallized product 37 from CH3OH (Scheme 14).[44]



Scheme 14

Synthesis 3-long chain alkenyl/hydroxyalkenyl-6-phenyl-7H-1,2,4-triazol-o[3,4-b]-1,3,4-thiadiazines

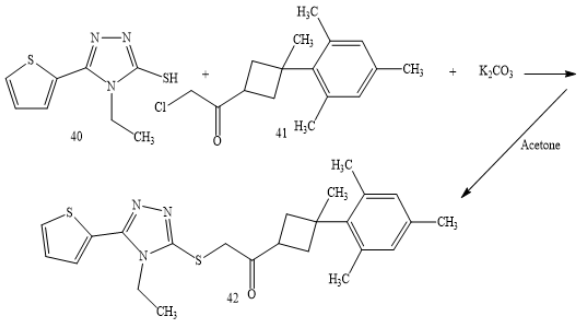
From 4-amino-5-long chain alkenyl/ hydroxyalkenyl-1,2,4-triazole-3-thiones 38 which was synthesis from (NaOH, 0.01 mol, 50 mL ethanol), alkenyl/hydroxyalkeny hydrazide (0.01 mol) and added carbon disulfide (0.013 mol). At 8h at r.t, the mixture was stirred. After diluting with 30 mL CH3OH then stirred for 1h. Potassium salt (0.02 mol, 20 mL H2O) was gradually stirred then added to the above mixture and for 4h refluxed. Cooled the reaction and used HCl to acidify. Filtered product 38, washed by H2O and purified with ether by using column-chromatography. The mixture of 38 (0.0025 mol, 15 mL CH3CH2OH), and added (0.0025 mol, $C_6H_5CCH_2Br$) was refluxed for 12h at 90 0C in an oil bath. To neutralize triazole, ammonium hydroxide was used. Water: Dichloromethane was used to extract produce. Dried the organic by sodium sulfate anhydrous. Evaporated solvent and for further purification, Compound 39 was obtained using column chromatography (ether: diethyl ether). (Scheme 15).[45]



Scheme 15

Synthesis of 1-(3-methyl-3-mesityl)-cyclobutyl-2-(5-thiophen-4-ethyl-2h-[1,2,4]triazol-3-ylsulfanyl)- ethanon

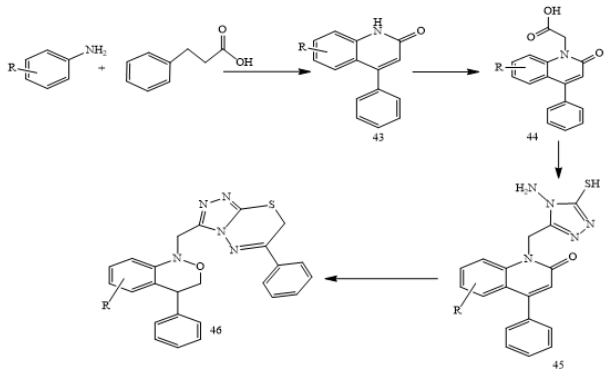
A mix of (2 mmol) of 2-chloro-1-(3-Methyl-3-mesityl-cyclobutyl)-ethanone compound 40 which was synthesized according to [46] with (30 mL) acetone contained (2 mmol) K2CO3. (2 mmol) of 4-ethyl-5-(2-thienyl)-2,4-dihydro-3H1,2,4-triazole-3-thione 41 in (20 mL) acetone, added dropwise into the above solution for 1 hour while stirring. The solid products 42 (Scheme 16) were filtrated, washed, dried, and recrystallized from ethyl alcohol.[47]



Scheme 16

Prepared 4-phenyl-1-({6-phenyl-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-3-yl)methyl)-(substituted)-1,2-dihydroquino line-2-one

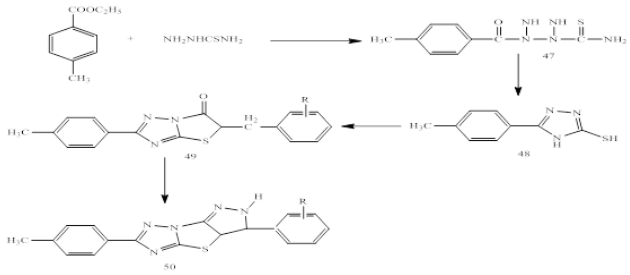
From the starting material phenylquinoline-2-one 43 this compound was obtained cyclo condensation aniline with 3-phenyl-2-propenoic acid in present H2SO4 (Conc.), ethanol and Nitrobenzene. 2-oxophenyl-(substituted)-quinolin-1-ylacetic acid derivatives 44 were provided after compound 43 treatment with chloro-acetic acid in the alkaline medium. The next 44 were heated with thiocarbohydrazide produced 4-amino-5-sulfanyl-4,5-dihydro-1,2,4-triazol-4-phenyl-(substituted)-quinolin-2-one 45. The desired product 46 was formed by cyclizing 45 with ($C_6H_5CCH_2Br$) in the presence of anhydrous C2H5OH (Scheme 17) [48].



Scheme 17

Synthesis 3-Phenyl-6-(p-tolyl)-3, 3a-dihydro-2H-pyrazolo[3',4':4,5] thiazole [3,2-b] [1,2,4] triazole

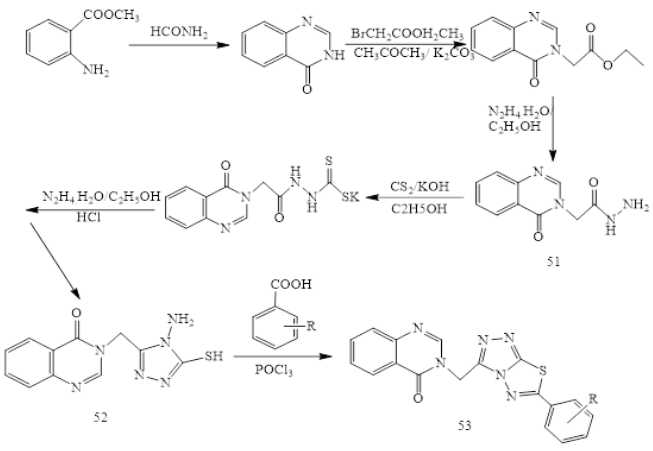
A mixture of equimolar (0.01 mol) ethyl-p-methyl-benozate and thiosemicarbazide in (25 mL, methanol) was refluxed for 10h. The viscous mass was formed after removing the solvent and poured with cooled water. The product was filtered and recrystallized from CH3OH, and H2O to obtain 4-methyl benzol thiosemicarbazide 47. (2 g) of compound 47 in (8 %, NaOH, 30 mL) was refluxed under heat for 5h. Cooled the reaction and acidified it with diluted CH3COOH. The product was filtered, washed, and recrystallized with CH3OH to get 5-mercapto-3-p-tolyl-s-triazole 48. Compound 48 (0.01 mol), aromatic aldehyde(0.01 mol), chloroacetic acid(0.01 mol), glacial acetic(30 mL) acid, and sodium acetate (0.02 mol) were refluxed under heat for 4h. The solid brown products were formed cooled, filtered, then washed, and recrystallized from glacial CH3COOH, the compound (Z)-5-(substituted-benzylidene)-2-(p-tolyl) thiazole [3,2-b] [1,2,4] triazole-6(5H)-one 49 was formed. Equimolar compound 49 was mixed with hydrazine hydrate (0.005 mol) and sodium acetate in (0.01 mol) CH3COOH was refluxed under heating for 5h. at RT cooled the mixture and poured it by H2O. filtrated the brown solid color washed and recrystallized with CH3CCOH the desired compound 50 was formed (Scheme 18) [49].



Scheme 18

Synthesis 3-((6-phenyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-3-yl)methyl)quinazolin-4(3H)-one

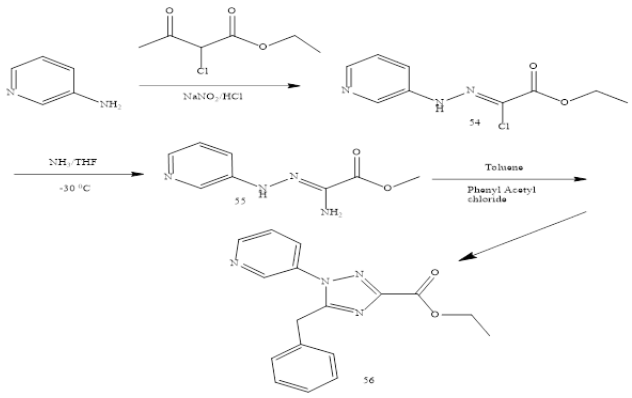
(16 mmol) of compound 51 was dissolved in (60 mL, CH2CH3OH) containing (20.0 mmol) KOH and (23.2 mmol) carbon disulfide, stirred in the mixture for 18 h at room temp. The precipitate was formed, filtered, washed with (CH2CH3OH), dried, reacted with 80% hydrazine hydrate (131.7 mmol), and refluxed for 5 hours. The yield was formed, dissolved in cold water, and acidified with (HCl). To obtain compound 52, the resulting product was filtered, washed, dried, and recrystallized with (CH2CH3OH). (1.0 mmol) of compound 52 was mixed with (1.2 mmol) corresponding aromatic carboxylic acid in (12 mL) phosphorus oxychloride, heated the mixture, and refluxed for 5h. After that cooled mixture at RT. POCl3 and potassium carbonate solution were used for a neutralized solution. To obtain compound 53, the precipitate was formed, filtered, dried, and recrystallized from DMF (Scheme 19) [50].



Scheme 19

Synthesis Ethyl 5-benzyl-1-(pyridin-3-yl)-1H-1,2,4-triazole-3-carboxylate.

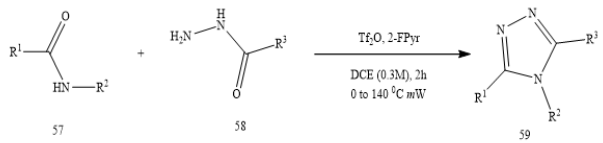
A (0.265 mol) 3-aminopyridine was dissolved in (250 mL) HCl 6N, added sodium nitrite (0.265 mol) dropwise. (0.265 mol) ethyl-2-chloroacetoacetate in (100 mL) ethanol was added dropwise for 1h to the first solution. (0.795 mol) sodium acetate in (200 mL) water, drop by drop added to the above mixture and stirred for 12h. filtered the solid precipitate, washed with water, and dried pale yellow crystal Ethyl 2-chloro-2-[2-(3-pyridyl)hydrazono]acetate 54 was formed. (0.044 mol) the solution of compound 54 at -30 0C for 30 min to bubble the ammonia gas, then stirred for 2h at RT. The solvent was extracted using a vacuum. The residue was dissolved in 50 mL of dry (CHCl3). NH4Cl was removed by filtering and evaporating the amount of solvent (25 ml) diethyl ether was used to triturate the product and formed a solid as compound 55. A solution compound 55 (0.024 mol) in (25 ml) toluene at 0 0C added dropwise phenyl acetyl chloride (0.0288 mol). Refluxed mixtures for 12h. The solvent was evaporated after the reaction was completed. The residue was dissolved in (120 ml) of methyl chloride and then in a solution (1N HCl & 10 %NaHCO3). Drie organic layer with Na2SO4 has then purified the product was by silica-gel to obtain Ethyl 5-benzyl-1-(pyridine-3-yl)-1H-1,2,4-triazole-3-carboxylate 56 (Scheme 20). [51]



Scheme 20

Synthesis of 3,4,5-Trisubstituted 1,2,4-Triazoles

A mixture of amide 57 (1.0 mmol), 2-fluoropyridine (1.1 mmol), and Dichloroethane (3.33 mL) was put in a 5 mL microwave vial containing rubber septum and cooled at 0 0C. Added (1.1 mmol) anhydride Trifluoromethanesulfonic (Tf2O) and stirred the mixture for 10min at 0 0C. Hydrazide 58 (1.1 mmol) was added to the mixture with stirring at R.T. for 10h. Removed rubber septum and vial was capped quickly by Teflon cap with aluminum then heated the reaction mixture to 140 0C for 2h. The reaction was cooled and added saturated with Sodium bicarbonate (3 mL). Transferred the mixture to a separation funnel and added an equilateral (10 mL) of DCM & Saturated bicarbonate. Dry organic layer by anhydrous Na2SO4. The product was filtered and purified by column chromatography. Compound 59 was formed (Scheme 21) [52].

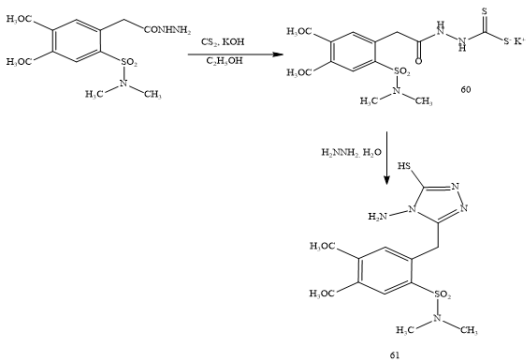


Scheme 21

Synthesis 5-[2-(N,N-dimethylsulfamoyl)-4,5-dimethoxy-benzyl]-4-amino-3-mercapto-1,2,4-triazole

A cold solution of 2-(N,N-dimethylsulfamoyl)-4,5-dimethoxy-phenyl acetyl hydrazide (0.01 mol) in (150 mL)

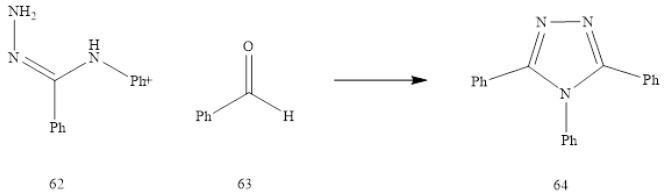
ethanol, KOH (0.015 mol) and added gradually CS2. Stirred mixture for 2 days at RT. The corresponding potassium-dithiocarbamate was precipitated then separated and added (150 mL) ether to complete the precipitated. The salt was product 60 filtered, washed with ether then dried. Compound 60 was suspended hydrazine hydrate (0.02), refluxed for 2h under heat, and stirred. The mixture was cooled and diluted with ice water then neutralized HCl. After precipitated was filtered, washed with (H2O), and recrystallized from methanol, compound 61 was obtained. (Scheme 22) [53].



Scheme 22

Synthesis 3,4,5-Triphenyl-4H-1,2,4-triazole, using polyethylene glycol

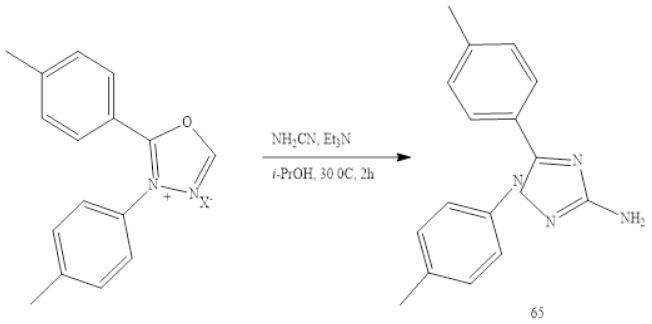
A mixture of (0.0047 mol) amidrazone 62, 5(mol %) Ceric ammonium nitrate, (0.0047) benzaldehyde 63, and (5 mL) polyethylene glycol was heated for 1h at 80 0C. TLC showed for completion reaction mixture, cooled the mixture, and used Et2O (20 mL) to extract. Washed organic layer with a mixture of water and sodium bicarbonate (30 mL & 30 mL), dried with (Na2SO4) anhydrous. purified crude product by column chromatography (EtOAc & Hexane) to yield a pure compound 64. (Scheme 23) [54].



Scheme 23

Synthesis of aminotriazole

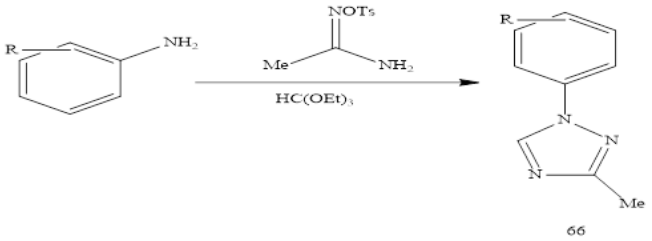
From Oxadiazolium salt. A mixture of aminotriazole salt (1.0 mmol), cyanamide (3.0 mmol, i-PrOH (2.0 mL), and Et3N (0.42 mL) were added to a (20 mL) vial and then heated for 2h at 80 0C. HPLC was used for the completion reaction. Diluted mixture (20 Ml, CH3Cl)) and washed three times with (10 mL, H2O). The organic layer was purified by column chromatography (MeOH & CH2Cl2) to obtain 1,5-Di-p-tolyl-1H-1,2,4-triazole-3-amine 65 (Scheme 24) [55].



Scheme 24

Prepared 1-Aryl 1,2,4-Triazoles

Aniline substrate (1.0 mmol), THF (10 mL of aniline), ethanesulfonic acid (0.1 mmol), and triethyl orthoformate (2.0 mmol) were mixed. a mixture was heated to 60 0C with stirring for 24h. HPLC was determined as the completion reaction. the reaction was cooled at RT, the removed solvent was in a vacuum, the residue was dissolved in (10 mL) CH3Cl2, and K2CO3 solution in water (2 mmol & 5 mL) was added. The organic layer was washed, brined, and dried with ($MgSO_4$) and filtered. Purified product by gel chromatography (EtOAc-Hexanes) to produce desired compounds 66 (Scheme 25) [56].

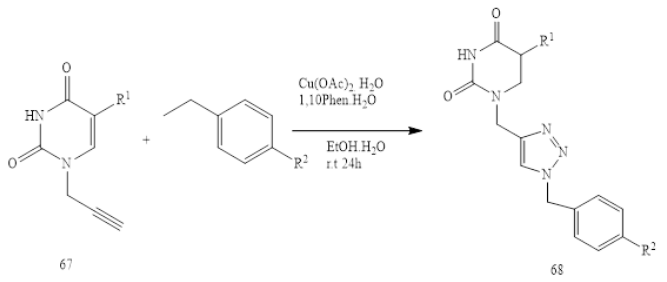


Scheme 25

Synthesis 1-((1-Benzyl-1H-1,2,3-triazole-4-yl)methyl) pyrimidine-2,4-(1H,3H)-dione

A mixture of the 1,10-phenanthroline monohydrate (0.02 mmol), Cu(OAc)2·H2O (0.02 mmol), and sodium L-ascorbate (0.3 mmol) in a solvent mixture ethanol/water (3 mL, 2:1 v/v). In a 50 mL round bottom flask for 5 min the mixture was stirred. Added subsequently compound 67 (0.4 mmol), sodium oxide (0.44 mmol), and benzyl chloride (0.44 mmol) to the above mixture, stirring for 24h at RT. After that added (10 mL) of water was to form a precipitated, filtered, washed by ice water then dried under a vacuum. Purified the product with column chromatography

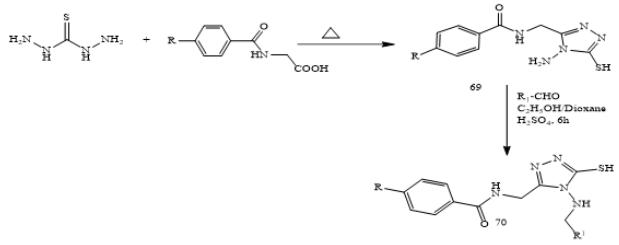
(methyl chloride/ methanol, 9/1) and recrystallized it from methyl chloride and hexane. To give compound 68 (Scheme 26) [57].



Scheme 26

Synthesis N-[(4-[(E)-substituted]amino}-5-sulfanyl-4H-1,2,4-triazole-3-yl) methyl]-4-substituted-benzamide

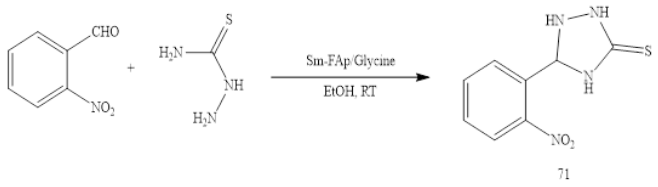
Compound 69 (0.0004 mol) and substituted benzaldehyde (0.0004 mol) then a mixture of 3 drops of Cone. H2SO4 in ethanol dioxane was added. Refluxed the total mixture for 6h, then cooled, filtered, washed with (CH2CH3OH), and recrystallized from ethanol. The desired compound 70 was formed (Scheme 27) [58].



Scheme 27

Synthesis 5-(2-nitrophenyl)-1,2,4-triazolidine-3-thione using Sm-FAp as Catalysts

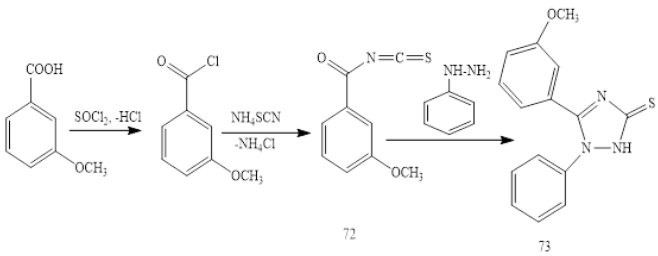
Rathinam et al. synthesized 5-aryl-1,2,4-triazolidine-3-thione using polyethylene glycol [59]. Jayavant et al reported the substituted aldehyde and thiosemicarbazide with [C16MPy]AlCl3Br for synthesis 1,2,4-triazolidine-3-thiones [60]. Mane et al. synthesized 5-aryl-1,2,4-triazolidine-3-thiones and used sulfamic acid as a catalyst [61]. Synthesis of the desired compound used Sm-FAp catalysts with 2-nitrobenzaldehyde and thiosemicarbazide. For preparing the Sm-FAp catalysts, in 25 mL D.W H2O, a mixture of Na3PO4 (1.5 mmol), H2SO4 (2.0 mmol), and NaF (0.5 mmol) was added and then stirred. After that added slowly (0.074 g) Sm(NO3)3.6H2O with stirred for 5h. then the mixture was centrifuged with washing by D.W, the mixture was dictated then collected the sample and dried. Then the catalyst was used for synthesis the motion compounds 71 (Scheme 28) [62].



Scheme 28

Synthesis 5-(3-methoxyphenyl)-1-phenyl-1H-1,2,4-triazole-3(2H)-thione compound

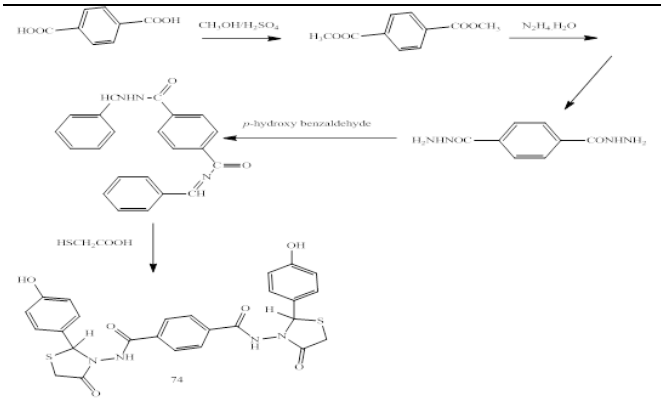
The equimolar compound 72 (0.01 mol) was added to phenylhydrazine, then refluxed for 5h. The solid product was filtered and washed with cold (H2O), added acetone to produce compound 73 (Scheme 29) [63].



Scheme29

Synthesis 1,4-Bis –[2-p-hydroxy phenyl - 4– oxo – 1,3–thiazolidine-3 –yl] terephthalic hydrazide according to this procedure

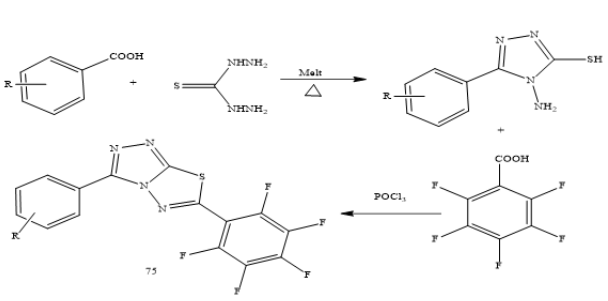
Thioglycolic acid (0.005 mol) dissolved in (5 mL) DMSO. The above mixture was added dropwise for 10 mint to compound 5(0.0025 mol) and then refluxed for 1 day. Removed solvent under pressure and (NaHCO3) was used to neutralize the product. The precipitate was collected, washed, and dried to form the desired compound 74 (Scheme 30).[64]



Scheme 30

Synthesis 3,6-diphenyl-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazole derivatives

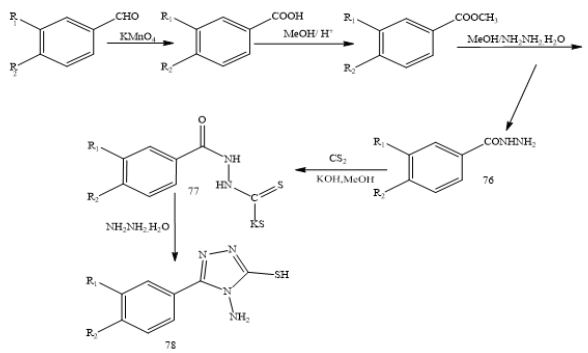
A mixture of 4-amino-5-substituted-3-mercapto-(4H)-1,2,4-triazoles (0.1 mol) and 2,3,4,5,6-pentafluorobenzoic acid (0.1 mol) in POCl3 (10 mL), refluxed for 5h. after that cooled at RT, then poured with ice crush and stirred. The solid precipitated was filtered and treated with NaOH and then washed with ice water. The final product 75 was obtained and recrystallized from ethanol (Scheme 31) [65].



Scheme 31

Synthesis 4-amino-5-(3,4-dialkoxyphenyl)-4H-[1,2,4]-triazole-3-thiol

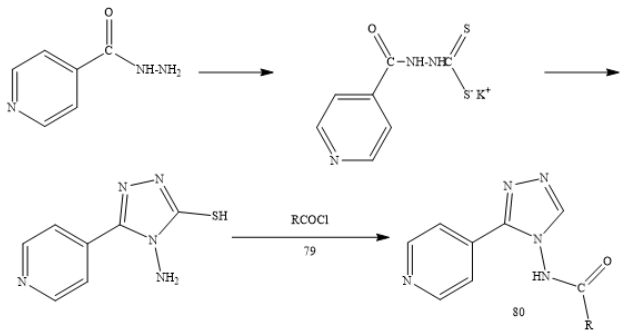
Compound 76 was treated with (7 g) KOH & MeOH (50 mL), stirred for 10h under 0 0C., added slowly CS2 (10 g) then stirred for 24h at RT. Compound 77 was obtained after being filtered, washed with ether, and dried. Compound 77 (0.1 mol) in H2O (5 mL) and hydrazine hydrate (0.3 mol) was refluxed for 7h and shaken. The reaction mixture was cooled, and diluted with (100 mL, of H2O). The product was acidifed with HCl, and the corresponding material was formed as precipitated and recrystallized from methanol to get compound 78 (Scheme 32) [66].



Scheme 32

Synthesis N-(3-Mercapto-5-(pyridine-4-yl)-4H-1,2,4-triazole-4-yl)acetamide

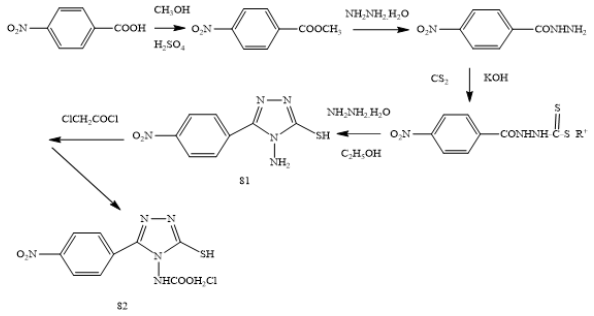
A mixture of compound 79 (0.01 mol) and (RCOCl) (0.01 mol) was heated with reflux for 5h in DMF and triethylamine (0.5 mL). The mixture was cooled, then poured over ice, and acidified by HCl. Filtered product, washed with H2O, and recrystallized from (CH2CH3OH) to produce compound 80 (Scheme 33) [67].



Scheme 33

Synthesis of 4-chloroacetylamino-3-mercapto-5-(4-nitro)phenyl 1,2,4-triazole

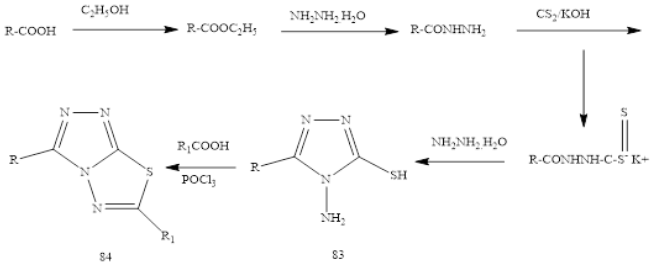
A compound 81 (0.1 mol) was refluxed in 50 mL dioxane and added dropwise chloroacetyl chloride (0.11 mol) in dioxane then continues refluxed for 1h, cooled the content, and poured with cooled water. The products were filtered and washed to obtain the desired compound 82 (Scheme 34) [68].



Scheme 34

Synthesis 3,6-Disubstituted-[1,2,4]-triazolo-[3,4-b][1,3,4]-thiadiazoles

A mixture of compound 83 (0.01 mol), RCOOH (0.01 mol), and POCl3 (10 mL) were refluxed for 12h. the mixture was cooled at RT and poured with ice crush. The solid product was filtered, neutralized by NH3OH, washed, and recrystallized from ethanol and DMF equal mol ratio. To obtain compound 84 (Scheme 35) [69].



Scheme 35

Conclusion

Thiazoles have become increasingly popular due to their unique structure and properties, which makes them attractive for medicinal chemistry. Researchers have developed a variety of methods to synthesize compounds containing thiazoles, which can provide valuable insights into drug synthesis. The 1,2,4-triazole ring system has been widely studied and has proven to be useful for a variety of medical applications. 1,2,4-thiazole compounds have been used for many years and their potential for future drug synthesis is continuously being evaluated. Their versatility and potential for new drug development are driving further research into new methods for synthesizing compounds containing thiazoles. This research is essential for advancing our understanding of how thiazoles can be used to create new drugs and treatments and to improve existing ones.

Acknowledgments

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