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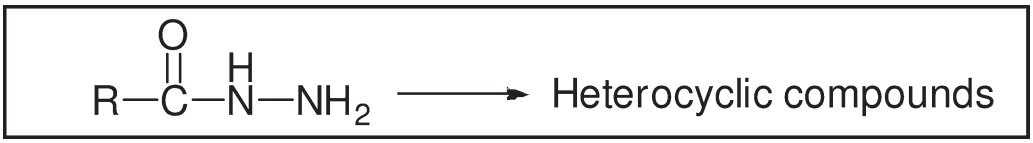
Received October 5, 2009
DOI 10.1002/jhet.405
Published online 9 June 2010 in Wiley InterScience (www.interscience.wiley.com).



The review summarizes recent literatures dealing with the synthesis of carbohydrazide derivatives, chemical reactions and their applications in the synthesis of important heterocyclic as well as fused heterocyclic compounds.

J. Heterocyclic Chem., **47**, 745 (2010).

Contents

1. INTRODUCTION

Hydrazide compounds, such as indole-2-carbohydrazide derivatives have been shown to inhibit monoamine oxidase A activity [1]. Furan carbohydrazide, thiophene carbohydrazide, and isonicotinic acid hydrazide react with a series of 4-alkoxy-4-alkyl(aryl)-1,1,1-trifluoro-3-alken-2-ones to give 3-alkyl(aryl)-5-trifluoro-methyl substituted pyrazoles [1]. One-pot reactions between carboxylic hydrazides and 2-isothiocyanato-benzonitrile afforded pharmacologically relevant 1,2,4-triazolo[1,5-*c*]quinazoline-5-thiones [2]. Hydrazide compounds were also converted to triazole-3-thiols [3], imidazopyrazolopyrimidine [3], 1,3,4-oxadiazole [4], 1,3,4-oxadiazine [4], pyrazolotriazolopyrimidine [5,6], and pyrazolotriazoloquinoline derivatives [7]. Bis (pyridinyl-2,3-dihydrooxadiazolyl)benzenes were obtained by heating the corresponding bis(hydrazides) with benzaldehyde [7]. Such compounds have attracted attention not only as model compounds for polymers but also because many biologically active natural and synthetic products have molecular symmetry [7].

The condensation of an acyl hydrazide and an amidine to afford acylamidrazone, followed by thermal cyclization, provides a convenient method for preparing 3,5-disubstituted-1,2,4-triazoles [8].

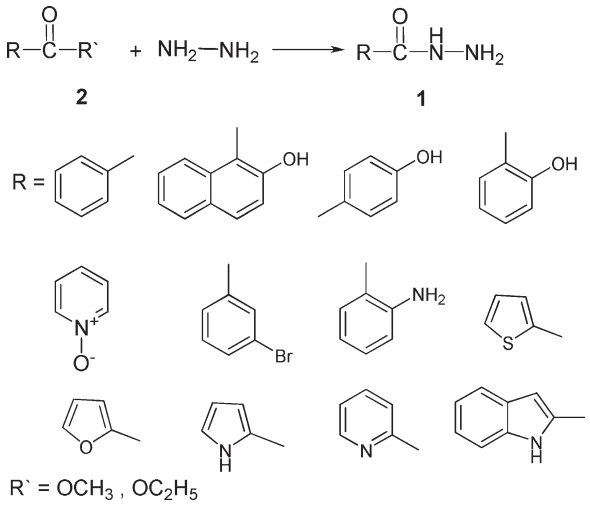
1,2,4-Triazines were formed *via* the condensation of 1,2-diketones with acylhydrazides in the presence of ammonium acetate under both traditional heating and dry media microwave assisted reaction conditions [9].

Carbohydrazides and their derivatives occupy a specific place among the other N,O-containing compounds used in the synthesis of heterocyclic systems because of their accessibility and ability to act as nucleophiles.

Accordingly, it is important to shed more light on the recent literatures dealing with that chemistry, especially in the field of heterocycles. Therefore, the present review was aimed at summarizing and systematizing available published data on the reactions of carbohydrazides with activated ethylenes, ethynes, benzo- and naphthoquinones, compounds containing C=N and C≡N moiety. Several types of reactions involving nucleophilic addition, condensation followed by heterocyclization were observed. Various heterocyclic and fused heterocyclic as well as spiro-heterocyclic compounds have been synthesized from carbohydrazides.

2. METHODS OF PREPARATION

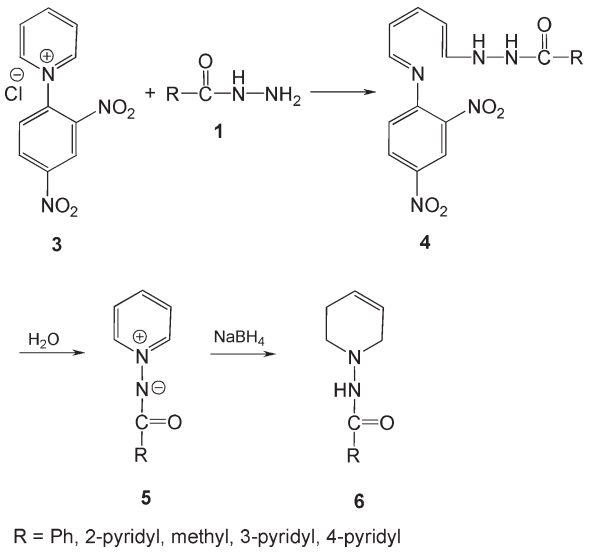
Carbohydrazides **1** can be prepared by refluxing aromatic carboxylic acid methyl or ethyl ester **2** with hydrazine hydrate in neat or in methanol. After cooling to room temperature, the resulting colorless solids were collected by filtration and dried *in vacuo* [10,11].



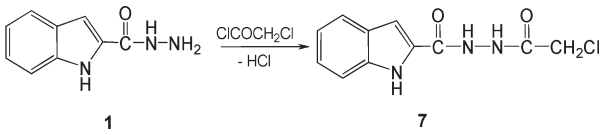
2-Thiophenecarbohydrazide 1 refluxed for 5 h [12], 2-pyridincarbohydrazide 1 refluxed for 4 h [13,14], 2-indolecarbohydrazide 1 refluxed for 15 h [4,15–18], and 2-furancarbohydrazide 1 refluxed for 2 h [19]. Some derivatives of carbohydrazide can be prepared like picolinic-*N*-oxidehydrazide [20] and 2-pyrrolecarbo-hydrazide [21]. Carbohydrazides have been prepared by hydrazinolysis of diethyl carbonate [22] and diphenyl carbonate [23] in satisfactory yields. The interaction of phosgene and hydrazine hydrate in refluxing benzene afforded carbohydrazides as dihydrochloride [24]. Also, hydrazinolysis of carbazic acid [25] and cyanuric acid [26] gave carbohydrazides.

3 REACTIONS OF CARBOHYDRAZIDES

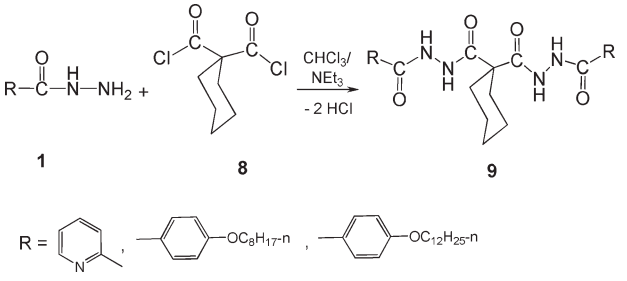
3.1. Synthesis of linear compounds. *N*-(2,4-Dinitrophenyl)pyridinium chloride **3** reacted with carbohydrazides **1** in methanol containing triethylamine at room temperature for 12 h to furnish 2,4-dinitroanilino derivatives **4**. Hydrolysis of **4** with water/*p*-1,4-dioxane mixture, at reflux temperature for 2 h, produced substituted carbonyliminopyridinium compounds **5**. Reduction of **5** with sodium borohydride in ethanol at 0°C for 4 h afforded alkyl substituted carbonylamino-1,2,3,6-tetrahydropyridines **6** [27–29].



A solution of chloroacetyl chloride was added dropwise to a solution of 2-indole carbohydrazide **1** in dry dioxane. After stirring at room temperature for 6 h, N^2-(2-chloroacetyl)indole-2-carbohydrazide **7** was formed [4].

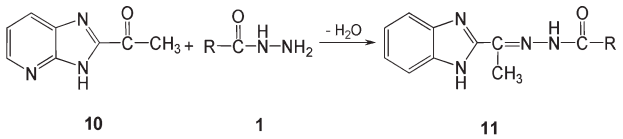


Substituted carbohydrazides **1** reacted with cyclohexane-1,1-dicarbonylchloride **8** in chloroform/triethylamine to yield cyclohexane-1,1-dicarboxylic acid-*N*,*N*′-di(2-octyloxybenzoyl)hydrazide **9** [30].

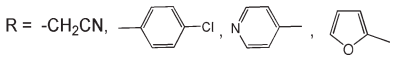


Condensation of carbohydrazides **1** with 2-acetyl-imidazo[4,5-*b*]pyridine **10** in absolute ethanol containing a

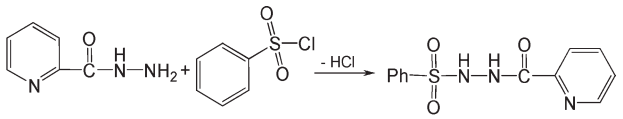
catalytic amount of piperidine afforded the corresponding hydrazones **11** [31].



10 **1** **11**

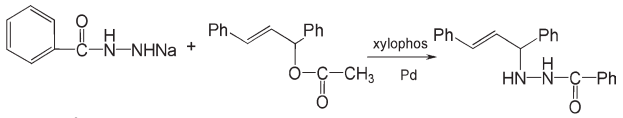


Benzenesulfonyl chloride **12** reacted with 2-pyridinecarbohydrazide **1** to give 1-isonicotinyl-2-benzene-sulfonyl hydrazine **13** [32].



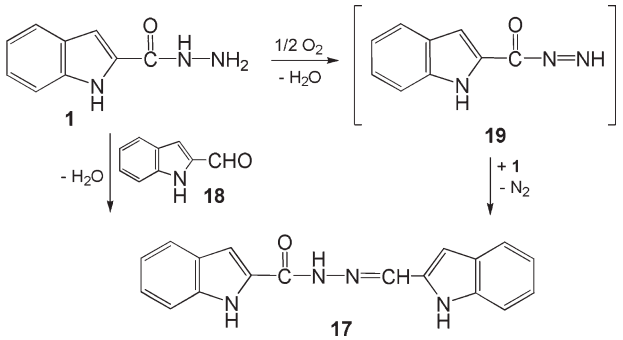
1 **12** **13**

Allylic substitution of carbohydrazide was prepared by reaction of sodium derivative **14** with 1,3-diphenyl-prop-2-enylacetate **15** to give *N*′-1,3-diphenylallylbenzohydrazide **16** [33].



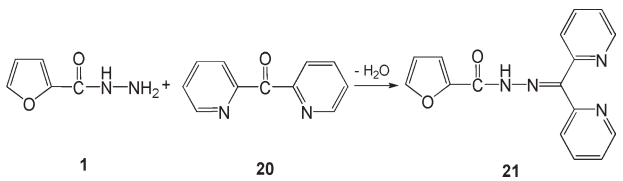
14 **15** **16**

Hydrazone **17** was formed when 2-indole carbohydrazide **1** was dissolved in ethanol for 3 h at room temperature. On other hand, compound **17** was also obtained by condensing **1** with the aldehyde **18** [34].



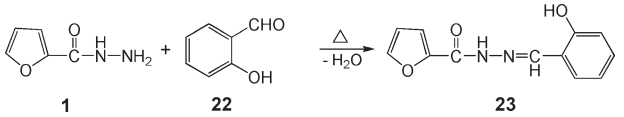
1 **19** **18** **17**

Refluxing equimolar amounts of di-2-pyridyl ketone **20** and carbohydrazid **1** in ethanol for 3 h afforded di-2-pyridyl ketone 2-furoylhydrazone **21** [35].



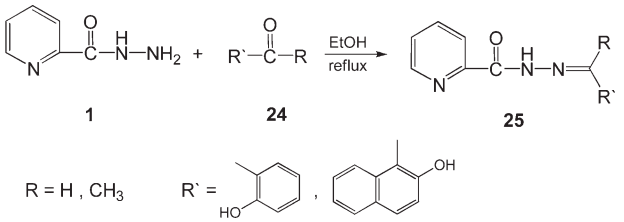
1 **20** **21**

Refluxing an ethanolic solution of salicylaldehyde **22** and 2-furancarbohydrazide **1** for 30 min gave salicylaldehyde-2-furoic acid hydrazone **23** [36].



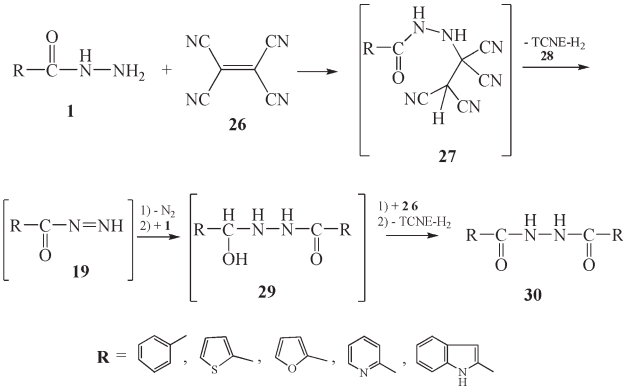
1 **22** **23**

Condensation of 2-pyridine carbohydrazide **1** with some aldehydes or ketones **24** in ethanol gave the corresponding hydrazones **25** [37].

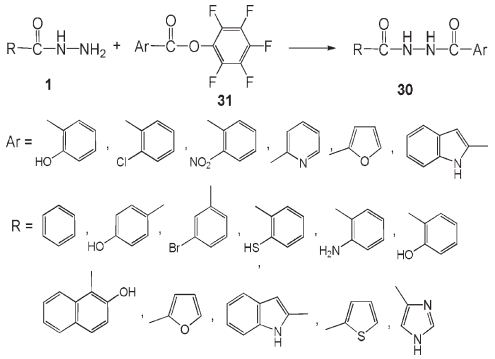


1 **24** **25**

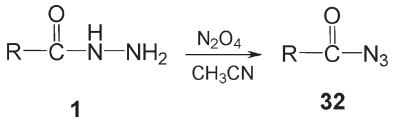
To a stirred solution of ethenetetracarbonitrile (TCNE) (**26**) in dimethylformamide (DMF), carbohydrazides **1** was added to give diaroylhydrazines **30** and 1,1,2,2-tetracyanoethane (TCNE-H_2) **28** [38]. Formation of these products may be rationalized *via* the following steps [38].

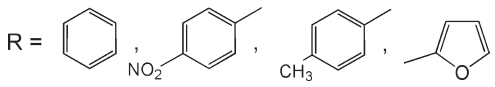


N,*N*′-Diaroylhydrazines **30** were formed by using pentafluorophenyl ester to activate arylcarboxylate **31** with carbohydrazides **1**, mild conditions which avoid intermediate were subjected; both symmetrical and unsymmetrical diaroylhydrazines **30** were formed in a high yields [39].

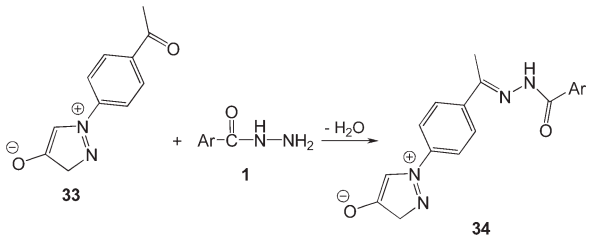


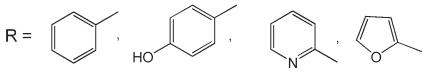
Carbohydrazides **1** reacted rapidly with dinitrogen tetraoxide (N_2O_4) [40] in acetonitrile at low temperature (−20 to −40°C) to give the corresponding azides **32** in mostly quantitative yields [41].



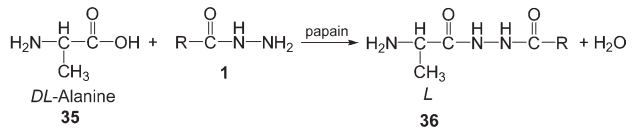


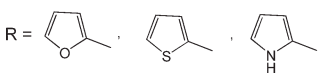
Mixtures of carbohydrazides **1** with 3-(4-acetylphenyl)-sydnone **33** were heated under reflux to produce hydrazone derivatives **34** [42].



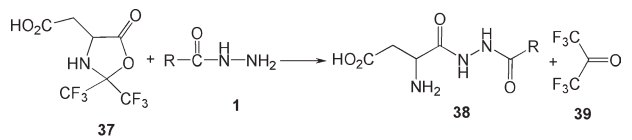


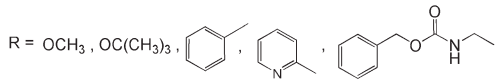
Reaction of carbohydrazides **1** with *DL*-alanine **35** under papain catalysis gave **36**; this represented an example of the power of papain to exert stereochemical preference during catalyzed reaction [43,44].



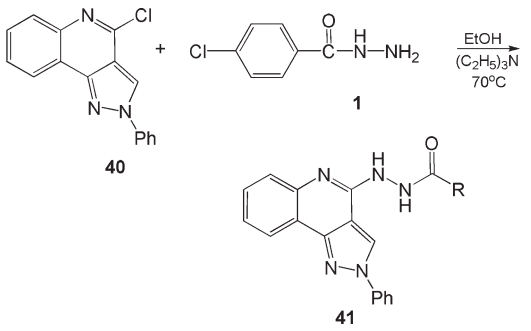


[(4-L)-2,2-Bis(trifluoromethyl)-5-oxo-1,3-oxazolidin-4-yl] acetic acid 37 reacted with carbohydrazides 1 in ethyl acetate at room temperature to give 38 [45].

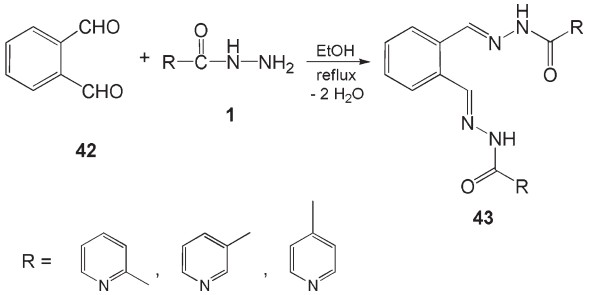




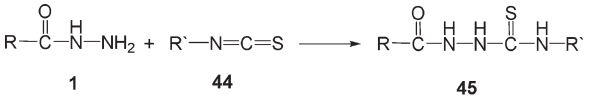
Reaction of carbohydrazides **1** with 4-chloro-2-phenyl-*2H*-pyrazolo[4,3-*c*]quinoline **40** in ethanol and in the presence of triethylamine afforded 4-chloro-*N*′-(2-phenyl-*2H*-pyrazolo[4,3-*c*]quinolin-4-yl)benzohydrazide **41** [46].

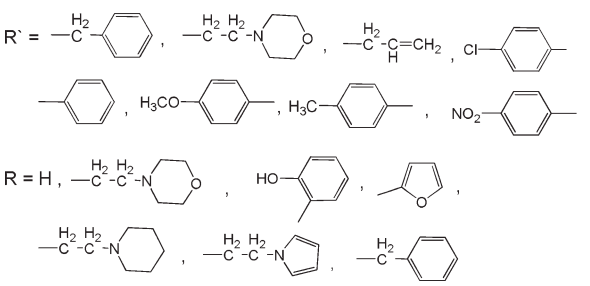


Reaction of phthalaldehyde **42** with carbohydrazides **1** in refluxing ethanol for 2–3 h afforded the corresponding bis(hydrazones) **43** [7].

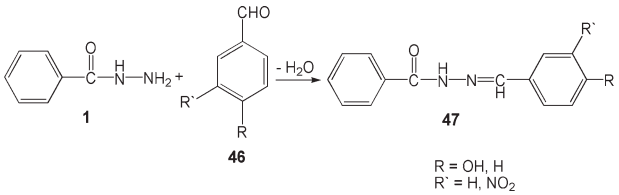


Reaction between an isothiocyanates **44** and carbohydrazides **1** in benzene gave acylthiosemicarbazides **45** in yields ranging from 88 to 95% [47–52].

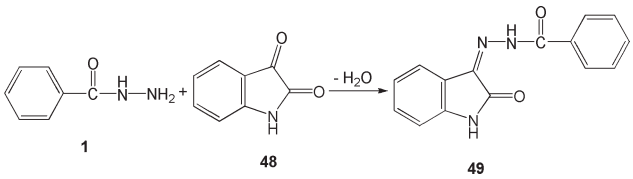




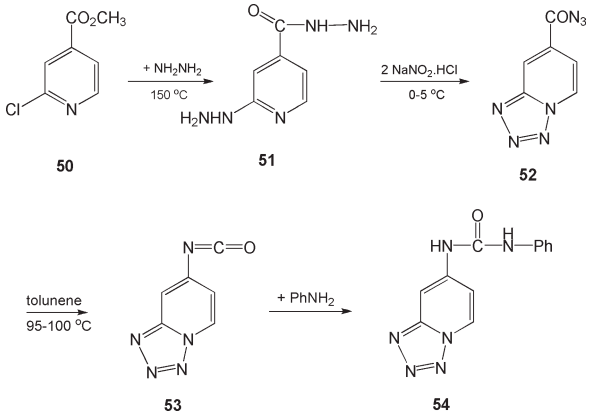
Substituted benzaldehyde **46** reacted with phenyl carbohydrazide **1** in ball-milled for 1 h to give *N*-substituted benzoylhydrazones **47** in spectroscopically pure form [53].



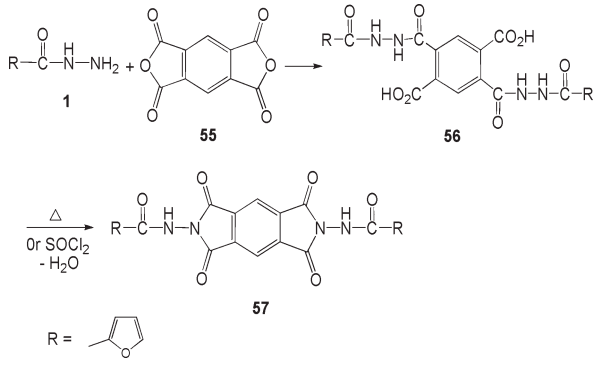
Condensation of isatin **48** with phenyl carbohydrazide **1** required 3 h ball-milling for complete reaction to give isatin-3-benzoylhydrazone **49** [53].



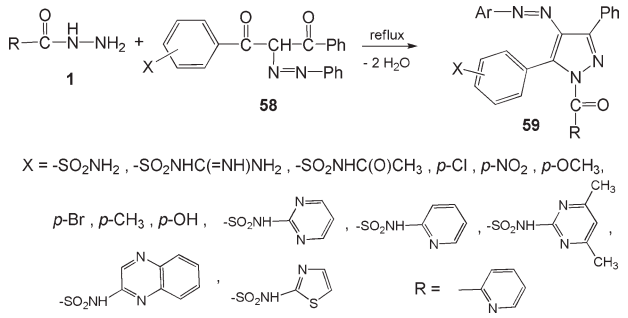
Heating methyl-2-chloroisonicotinate **50** with $N_2H_4.H_2O$ at 150°C in sealed tube gave the substituted carbohydrazide **51** [49]. Treatment of **51** with sodium nitrite in the presence of hydrochloric acid yielded carbonyl azide **52**, which was heated in toluene at 90–100°C for 1 h, sole product to form isocyanate **53** (*Curtius* rearrangement). The later was further reacted *in situ* with aniline at room temperature to give the expected urea derivative **54** [54].



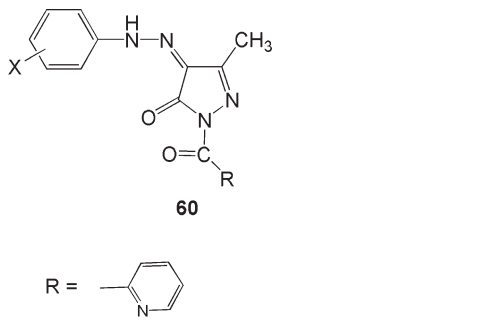
3.2. Synthesis of pyrrole derivatives. Reaction of carbohydrazide **1** with acid anhydride **55** to produce pyrrole derivative **57** was carried out *via* thermal cyclodehydration of the dicarboxylic acid **56** at 150°C or during heating with thionyl chloride [55].



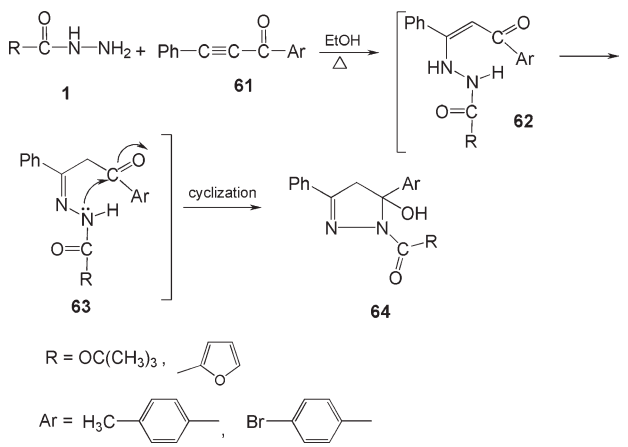
3.3. Synthesis of pyrazole derivatives. A mixture of substituted 2-phenylazo-1,3-diphenyl-propane-1,3-dione (**58**) and carbohydrazide **1** in glacial acetic acid was heated under reflux to form *N′*-picolinyl-3-phenyl-5-aryl-4-(substituted phenylazo)pyrazoles **59** [56].



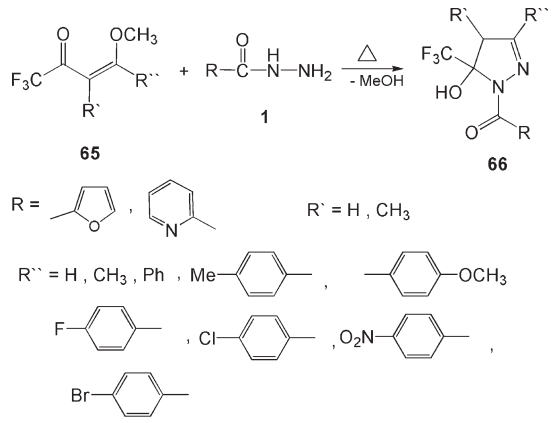
2-Pyridine carbohydrazides **1** reacted with sulpha-substituted phenylhydrazomethyl-2,3-dioxobutyrate in glacial acetic acid to form *N′*-(2-pyridinecarbonyl)-3-methyl-4-(substituted)hydrazono-2-pyrazoline-5-one **60** [57].



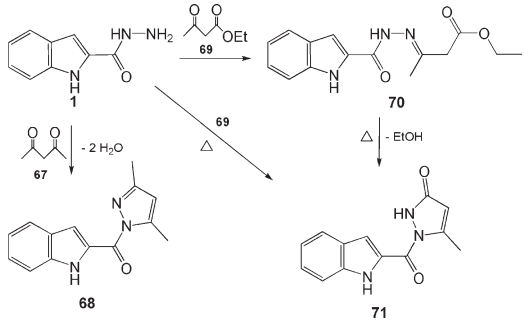
When aroylphenylacetylenes **61** was refluxed with carbohydrazides **1** in ethanol for 5 h, the reaction mixture afforded 5-aryl-4,5-dihydro-5-hydroxy-3-phenyl-1*H*-pyrazole derivatives **64** [58] rather than open chain compounds **63** [59–61].



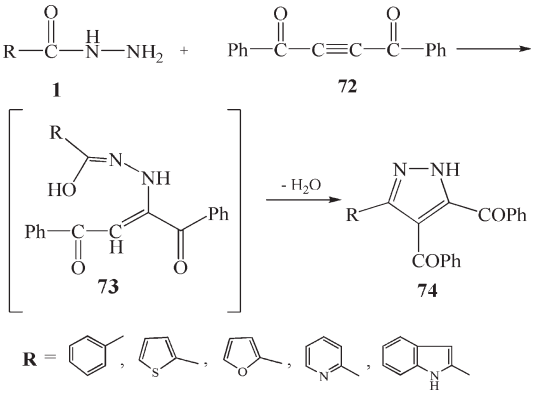
Cyclocondensation reaction of carbohydrazides **1** with a series of 4-methoxy-4-alkyl(aryl)-1,1,1-trifluoro-3-alken-2-one derivatives **65** in refluxing methanol afforded 3-alkyl(aryl)-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-1(2-aryl) pyrazoles **66** [62].



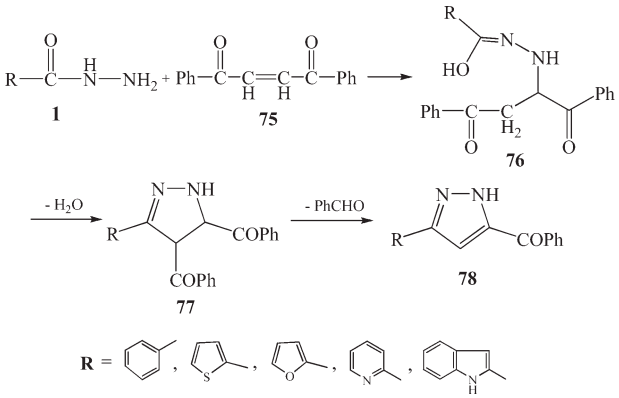
Condensation of 2-indole carbohydrazide **1** with acetyl acetone **67** in ethanol containing a catalytic amount of acetic acid resulted in the formation of the corresponding pyrazole derivative **68** [1]. Carbohydrazides **1** reacted with ethylacetoacetate **69** in the absence of solvent to give the ester derivative **70**, which could be cyclized to pyrazolone derivative **71** by heating above its melting point for 10 min followed by refluxing in methanol for further 2 h. Compound **71** was also obtained independently *via* direct refluxing of **1** with ethylacetoacetate **69** in ethanol/acetic acid mixture for 5 h [1].



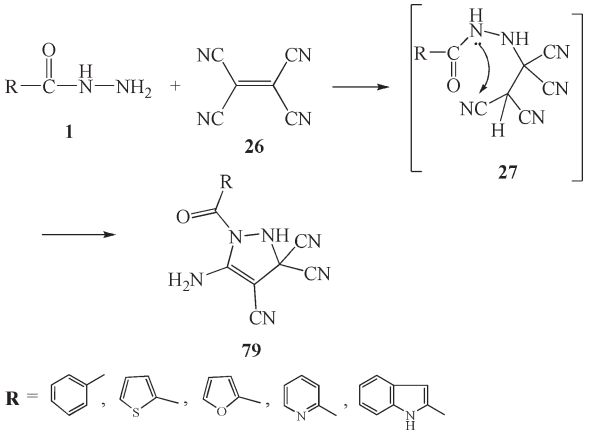
Addition of substituted carbohydrazides **1** to 1,4-dibenzoylacetylene **72** afforded the 4,5-dibenzoyl-3-substituted-1*H*-pyrazole **74** *via* the intermediate **73** [63].



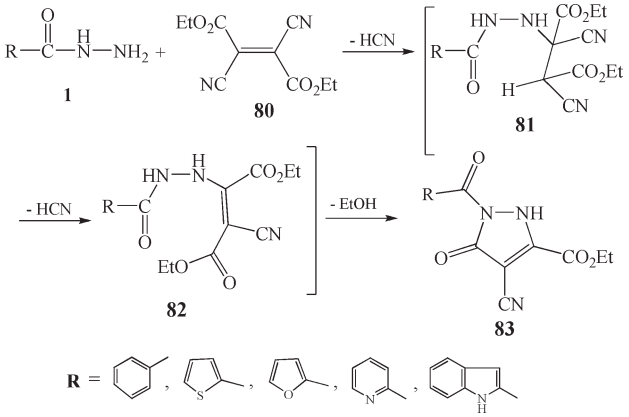
On the other hand, the reaction of substituted carbohydrazides **1** with 1,4-diphenylbut-2-ene-1,4-dione **75** in refluxing acetic acid gave 4-benzoyl-3-substituted pyrazoles **78** [63].



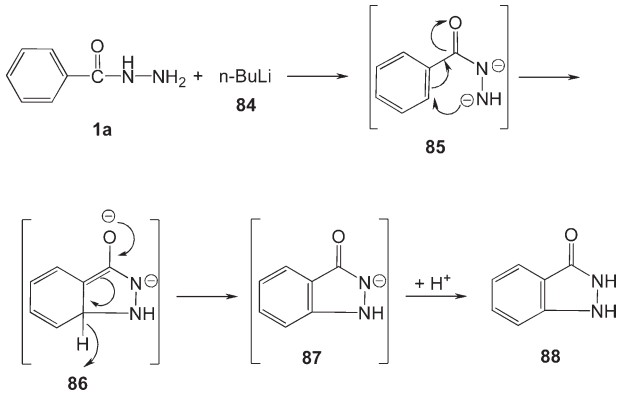
Reaction of substituted carbohydrazides **1** with **26** in DMF afforded 5-amino-1(substituted)-1*H*-pyrazole-3,3,4(2*H*)-tricarbonitriles **79** [38].



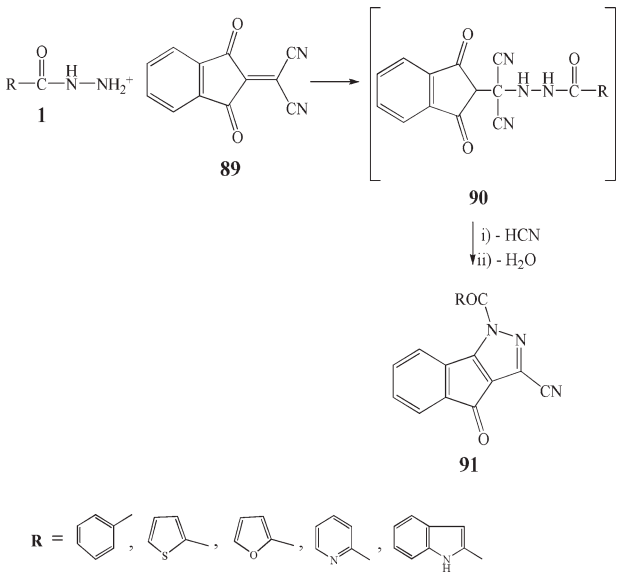
Mixing equimolar amount of carbohydrazides **1** with diethyl(*E*) 2,3-dicyanobutenedioate **80** in ethyl acetate under reflux led to the formation of pyrazole derivatives **83** [38].



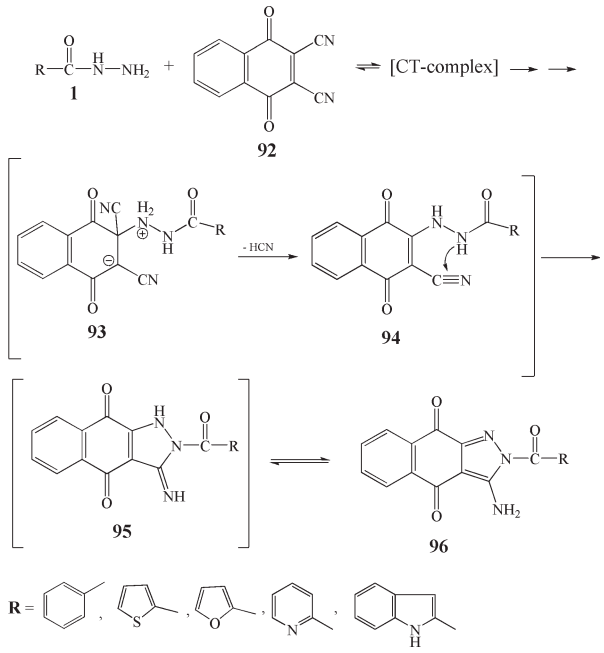
3.4. Synthesis of fused pyrazole derivatives. When phenyl carbohydrazide **1** in tetrahydrofuran (THF) was treated with n-butyl-lithium **84** in hexane under nitrogen atmosphere at −78°C for 1.5 h and allowed to reach the room temperature overnight, indazol-3(2*H*)-one **88** was isolated [64].



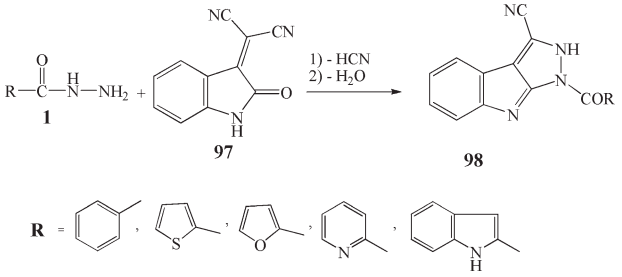
The reaction of (1,3-dioxo-2,3-dihydro-1*H*-inden-2-ylidene)propanedinitrile **89** and **1** in DMF with admission of air afforded 4-oxo-1-substituted-1,4-dihydroindeno[1,2-*c*]pyrazole-3-carbonitrile **91** [65].



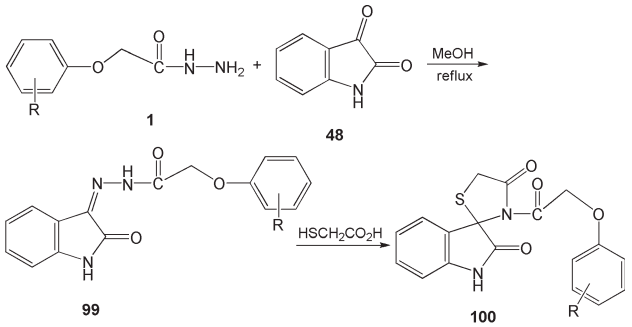
3.5. Synthesis of indazole derivatives. In a different manner, 1,4-naphthoquinone-2,3-dicarbonitrile **92** reacted with **1** to give substituted benzo[*f*]indazoledione **96** [66].



Carbohydrazides **1** reacted with 3-(dicyanomethylene)-2-indolone **97** in the presence of pipridine to give substituted carbonylpyrazolo[3,4-*b*]-indole-3-carbonitrile **98** [65].



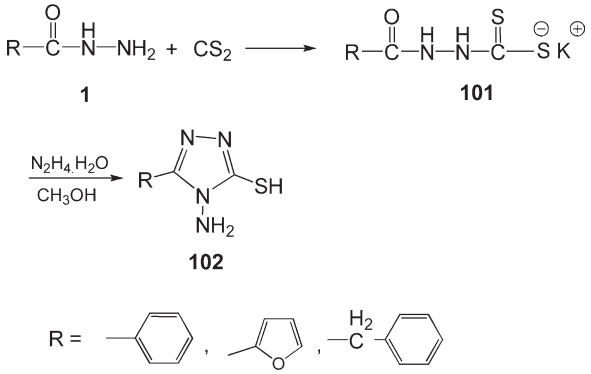
3.6. Synthesis of thiazolidine derivatives. Refluxing carbohydrazides **1** with **48** in methanol afforded isatin-β-arylhydrazones **99**, which reacted with 2-mercapto acetic acid in dioxane to furnish the interesting spiro[3*H*-indole-3,2ʾ-thiazolidine] derivatives **100** [67].



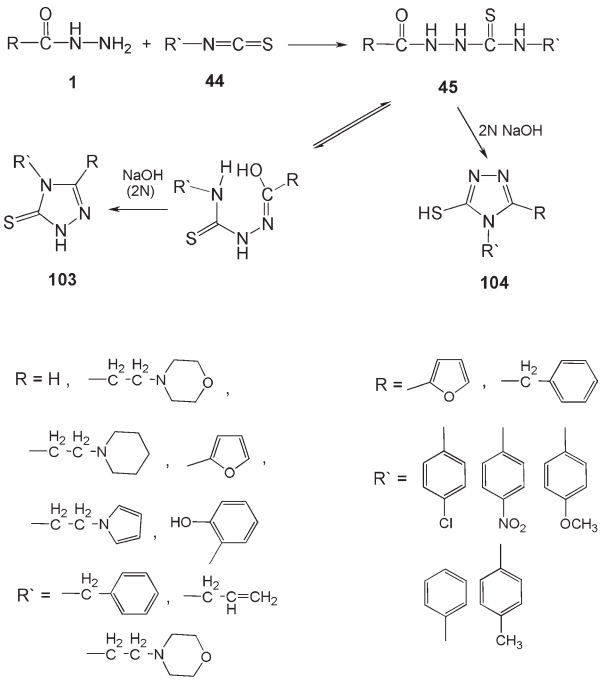
R = 2,4-$(CH_3)_2$, 4-Cl , 4-CH_3 , 2-CH_3 , 4-Cl-3-CH_3 , 2-Cl , 3,4-$(CH_3)_2$, 3,5-$(CH_3)_2$, 2,5-$(CH_3)_2$

3.7. Synthesis of 1,2,4-triazole derivatives. Reaction of carbohydrazides **1** with carbon disulfide in ethanolic

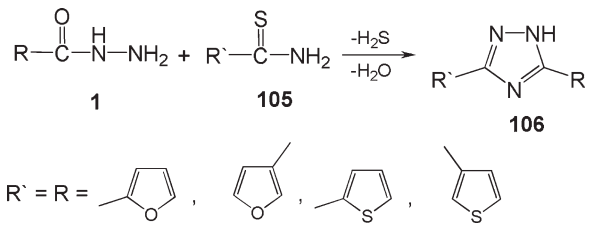
potassium hydroxide gave dithiocarbazate **101**, which reacted with hydrazine hydrate to form 4-amino-5-aryl-4*H*-1,2,4-triazole-3-thiol **102** [51].



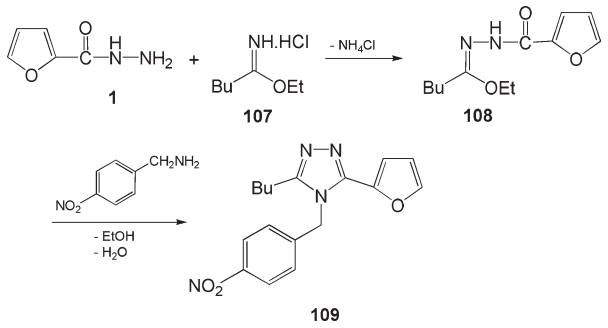
Ring closer acylthiosemicarbazides **45**, prepared by reacting **1** with **44**, in an alkaline medium, led to the formation of 1,2,4-triazole-3-thione derivatives **103** [51] and 1,2,4-triazolethiol derivatives **104** [47,48,68–70].



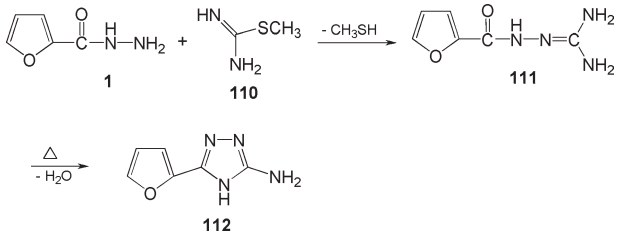
1,2,4-Triazole derivatives **106** were also obtained *via* the reaction of thiocarbamides **105** with carbohydrazides **1** [71].



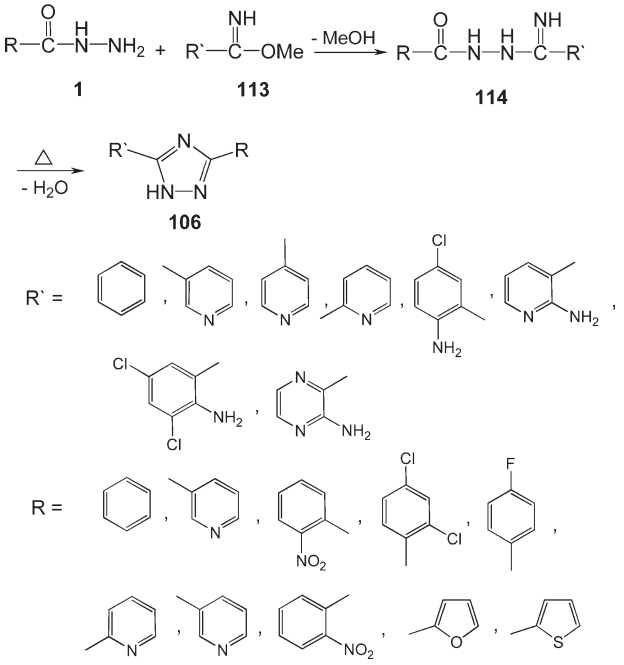
The reaction of carbohydrazide **1** with imidate hydrochloride **107** gave compound **108**, which was converted into 1,2,4-triazole derivative **109** upon heating with 4-nitrobenzylamine [72].



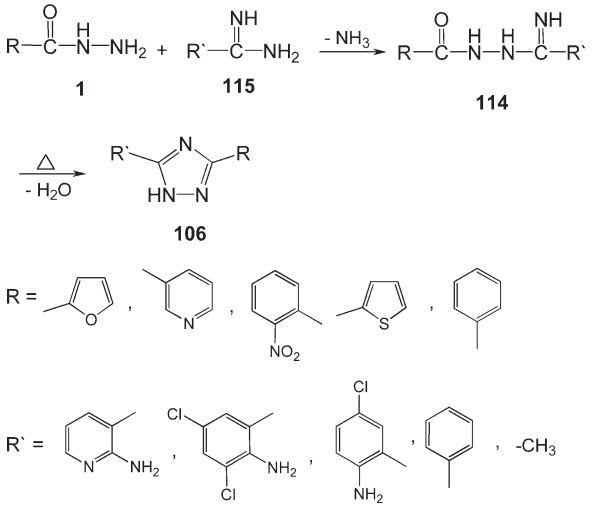
2-Furan carbohydrazide **1** reacted with *S*-methyl-isothiourea **110** to give the corresponding guanidine **111**. Upon heating **111**, 3-amino-1,2,4-triazole derivative **112** was formed [73,74].



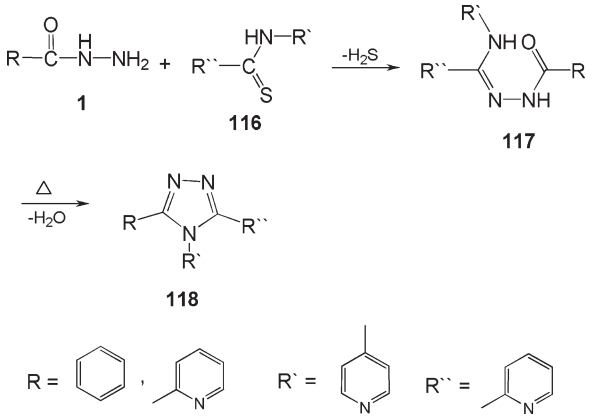
Most of 3,5-disubstituted-1,2,4-triazoles **106** were readily synthesized from imidates **113** and carbohydrazides **1**. For example, condensation of imidates **113** with carbohydrazides **1** gave acylamidrazones **114**, which underwent thermal cyclization to give 3,5-disubstituted-1,2,4-triazoles **106** [75–79].



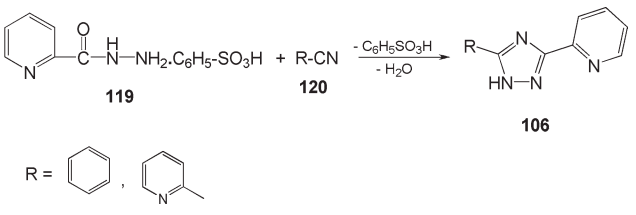
Also, reaction of carbohydrazides **1** with acetamidine or benzamidine **115** afforded 1,2,4-triazole derivatives **106** [80–82].



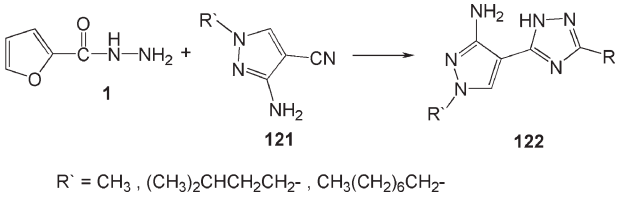
Substituted 1,2,4-triazoles **118** were synthesized by thermal cyclization of N^3-substiuted-N^1-acylamidrazone derivatives **117**, prepared by the reaction of carbohydrazides **1** with thioamides **116** in ethanol at room temperature [83–85].



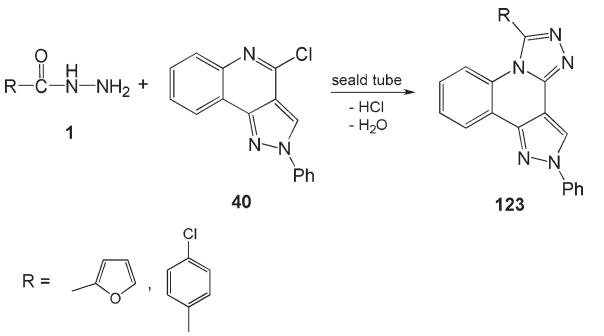
1,2,4-Triazole derivatives **106** were prepared *via* the reaction of 2-pyridine carbohydrazide benzenesulphonate **119** with substituted nitriles **120** [86] according to Pott's method [87–90].



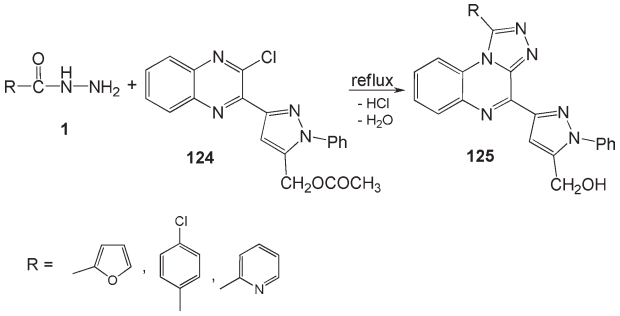
Reaction of pyrazole derivatives **121** with carbohydrazide **1** afforded 1,2,4-triazole derivatives **122** [91]. Also, the reaction of **121** with carbohydrazides **1** in refluxing diphenyl ether gave the 1,2,4-triazole derivatives **122** [3].



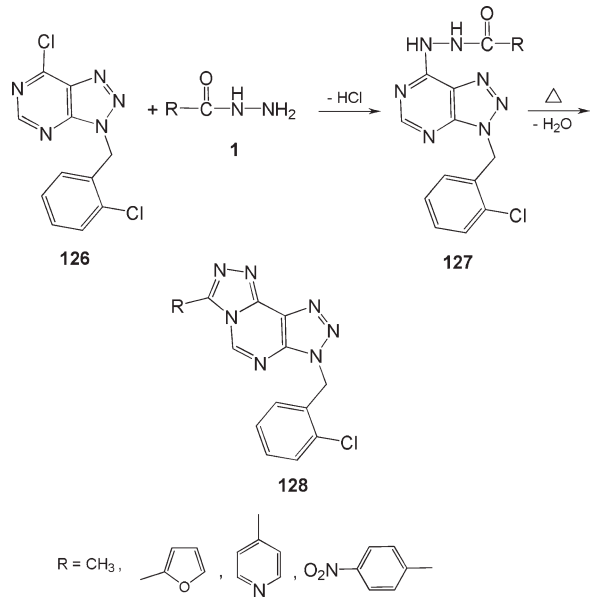
3.8. Synthesis of fused triazole compounds. 4-Chloro-2-phenyl-2*H*-pyrazolo[4,3-*c*]quinoline **40** reacted with carbohydrazides **1** in ethanol to form 2-phenyl-6-(furan-2-yl or 4-chlorophenyl)-2*H*-pyrazolo[4,3-*c*]-1,2,4-triazolo[4,3-*a*]quinolines **123** [46].



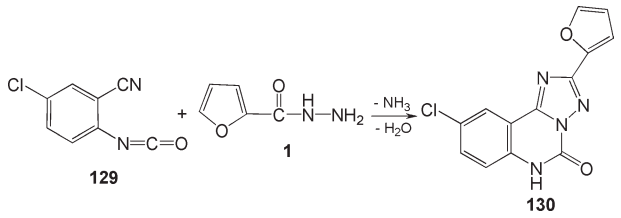
The reaction of carbohydrazides **1** with 2-chloro-3-[5-(acetoxymethyl)-1-phenylpyrazol-3-yl]quinoxaline **124** in boiling n-butanol resulted in the formation of the corresponding 1-aryl-4-[5-(hydroxymethyl-1-phenyl-pyrazol-3-yl]-1,2,4-triazolo[4,3-*a*]quinoxalines **125** [92].



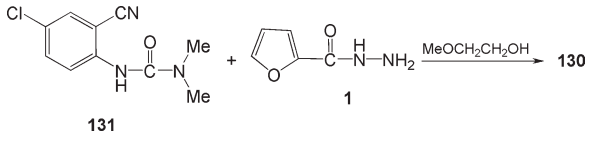
3-(2-Chlorobenzyl)-7-chloro-1,2,3-triazolo[4,5-*d*]-pyrimidine **126** reacted with carbohydrazides **1** in boiling ethanol to give hydrazo derivatives **127**, which underwent intramolecular thermal cyclization to form 3-(2-chlorobenzyl)-7-substituted-1,2,3-triazolo [4,5-*e*]-1,2,4-triazolo[4,3-*c*]-pyrimidine derivatives **128** [93].



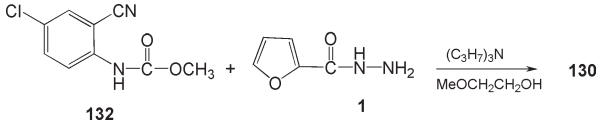
The reaction of carbohydrazide **1** with 5-chloro-2-isocyanatobenzonitrile **129** in presence of tripropylamine and 2-methoxyethanol afforded 9-chloro-2-(2-furyl)-1,2,4-triazolo[1,5-*c*]quinazolin-5-(6*H*)-one **130** [94,2].



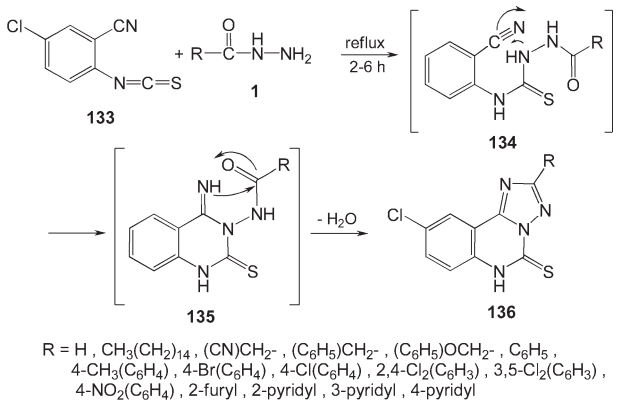
Also, the reaction of *N,N*-dimethyl-*N*\-(4-chloro-2-cyanophenyl)urea **131** with 2-furan carbohydrazide **1** in 2-methoxyethanol gave triazoloquinazolinone derivatives **130** [94].



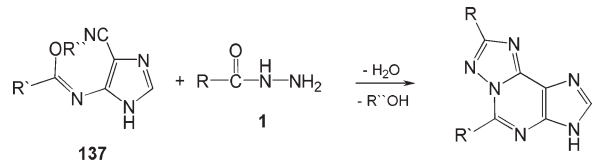
On the other hand, compound **130** was synthesized by the reaction of 5-chloro-2-[(methoxycarbonyl)-amino]-benzonitrile **132** with 2-furan carbohydrazide **1** in tripropylamine and 2-methoxyethanol [94].



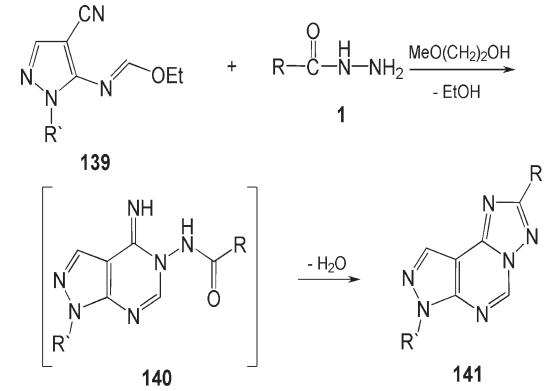
One-pot reaction between carbohydrazides **1** and 5-chloro-2-isothiocyanatobenzonitrile **133** afforded 1,2,4-triazolo[1,5-*c*]quinazoline-5(6*H*)-thiones **136**, in good yields [95].



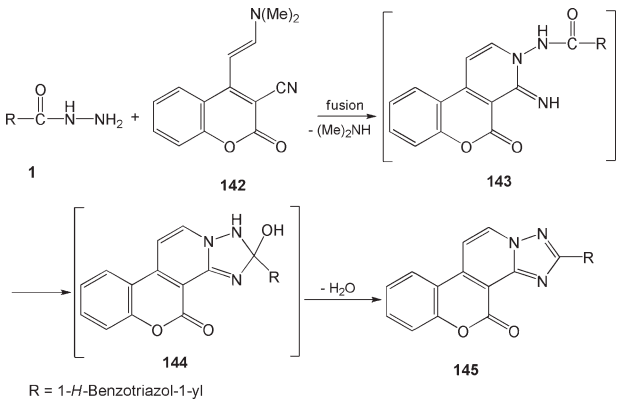
Refluxing alkyl-*N*-[4-cyano-1*H*-imidazol-5-yl]alkyl-imidate **137** with carbohydrazides **1** in DMF gave substituted 3*H*-1,2,4-triazolo[5,1-*i*]purines **138** [96].



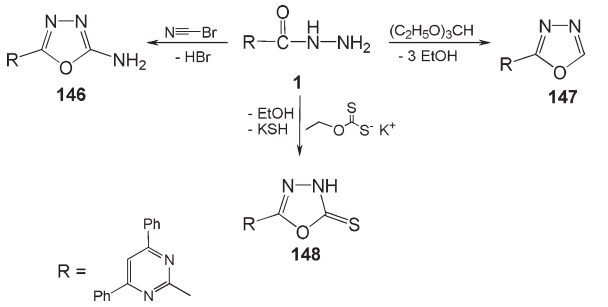
Reaction of 2-furan carbohydrazide **1** with imidate **139** in refluxing 2-methoxyethanol gave pyrazolo[4,3-*e*]-pyrimidine derivatives **140**, the non-isolable which converted *via* a thermally induced cyclization in diphenyl ether into pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidine derivatives **141** [5, 6, 97–99].



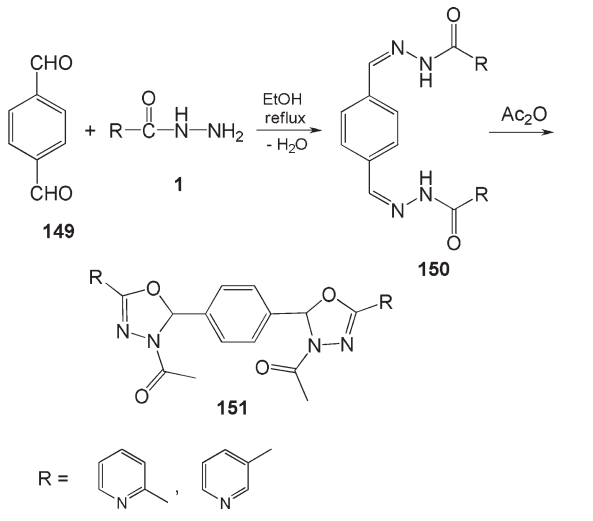
Fusion of *E*-dimethylaminoethylene derivatives **142** with carbohydrazide **1** afforded the corresponding 1,2,4- triazolo[1,5-*a*]pyrido[3\,4\-*c*]coumarin derivative **145** [100].



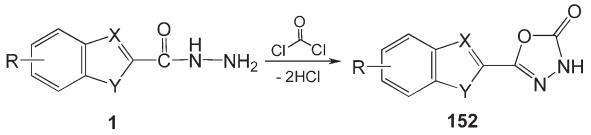
3.9. Synthesis of oxadiazole derivatives. Oxadiazole derivative **146** was obtained from the reaction of carbohydrazide **1** with cyanogen bromide [101]. Also, compound **1** reacted with triethoxymethane or potassium *o*-ethylxanthate to give, 1,3,4-oxadiazole and 1,3,4-oxadiazolethione **147** and **148** respectively [47].



Reaction of terephthalaldehyde **149** with carbohydrazides **1** in refluxing ethanol afforded the corresponding bis(carbohydrazone) **150**. Heating **150** in acetic acid/ethanol mixture at reflux temperature afforded bis(dihydroxadiazolyl)benzene derivatives **151** [102].

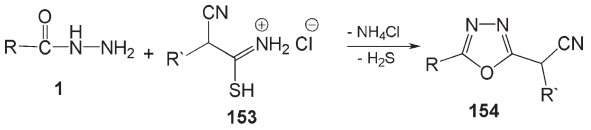


2-(2,3-Dihydro-2-oxo-1,3,4-oxadiazol-5-yl)benzo-heterocycles **152** were prepared by treatment of carbohydrazides **1** with excess of phosgene in methylene chloride at room temperature [103].



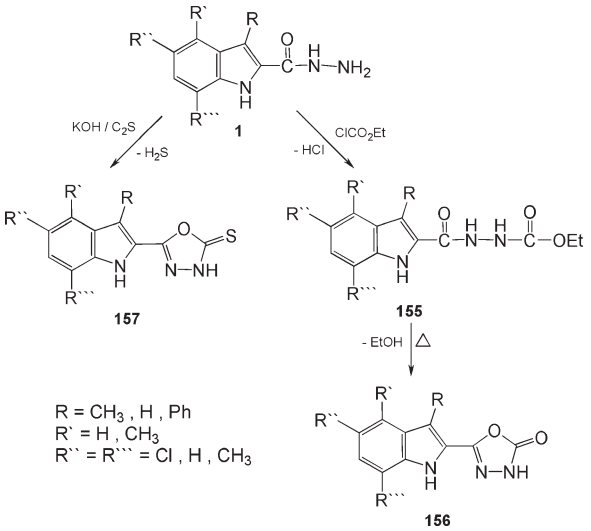
R = H , 5-Cl , 5-CO_2CH_3 , 7-OCH_3 , 6-CH_3
5-CO_2Et , 4-CH_3 , 5-CH_3 , 6-CH_3 , 6-Cl
X = N , C-Cl , C-CH_3 , CH
Y = N-CH_3 , S , CH_2 , NH , O

Carbohydrazides **1** reacted with **153** in refluxing ethanol to give 2-cyanomethyl-5-substituted-1,3,4-oxadiazole **154** [103].

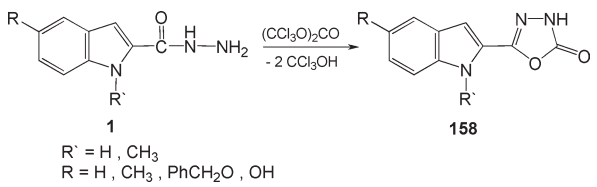


R` = H , n-Bu , $PhCH_2$
R = Ph , n-$C_{11}H_{23}$, 2-indolyl

Carbohydrazides **1** underwent condensation with ethyl chloroformate to give *N*-carbethoxy-5-substituted indole-2-carbohydrazides **155**, which were refluxed in diethyl ether to give 2-(5′-oxo-1′,3′,4′-oxadiazol-2′-yl)indole derivatives **156** [104].

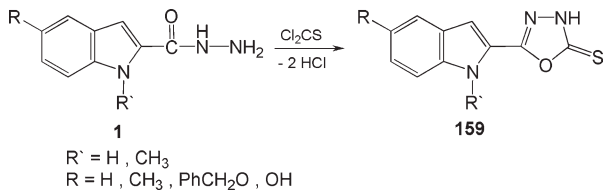


Treatment of carbohydrazides **1** with triphosgene afforded oxadiazolone derivatives **158** in one step [16].

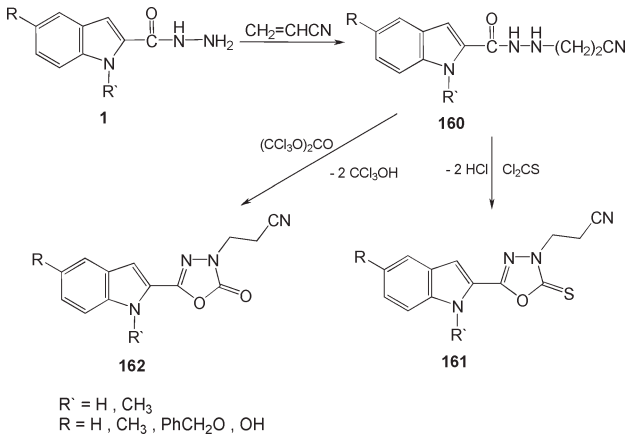


Also, **1** was refluxed with appropriate quantities of KOH and CS_2 in ethanol to give oxadiazolethione derivatives **157** [104].

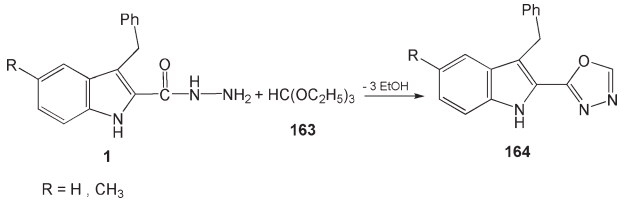
1,3,4-Oxadiazolethiones **159** were generated directly by treatment of the corresponding carbohydrazides **1** with thiophosgene [4].



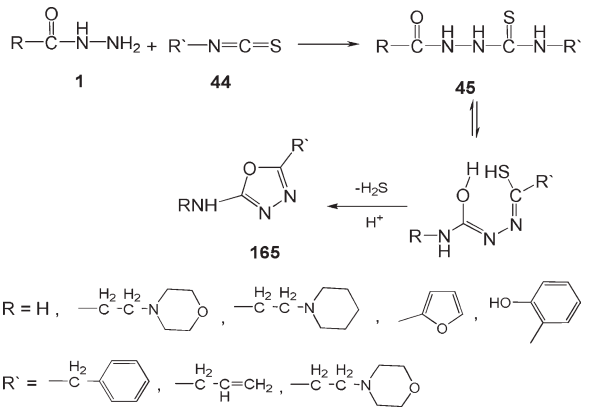
Monosubstituted indole-2-cyanoethylhydrazides **160**, prepared by Michael addition of acrylonitrile on the corresponding carbohydrazides **1**, were used as good precursors for the synthesis of indolyl-1,3,4-oxadiazole-3-(2-cyanoethyl)-2-one derivatives **161** and **162**, during the reaction with thiophosgene and triphosgene, respectively [4].



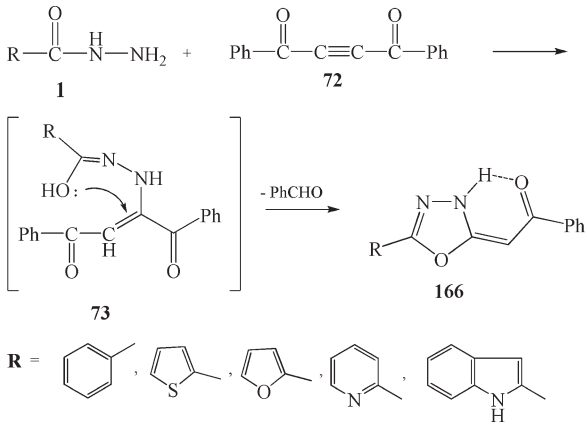
Refluxing carbohydrazides **1** with triethylorthoformate (TEO) **163** afforded 1,3,4-oxadiazole derivatives **164** [105].



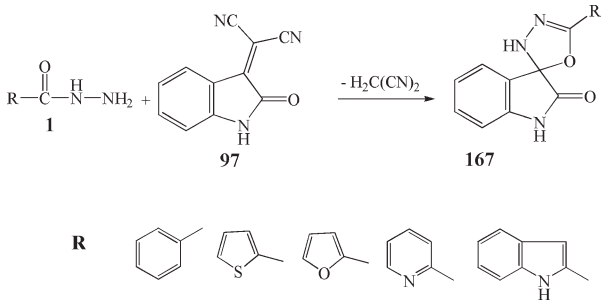
Isothiocyanates **44** reacted with carbohydrazides **1** to form acylthiosemicarbazides **45**. Ring closure of **45** in acidic medium gave 1,3,4-oxadiazole **165** derivatives [47,106].



Reaction of **1** with **72** in acetic acid gave the intermediate **73** which loss a molecule of PhCHO to form 1-phenyl-2-(5-substituted-1,3,4-oxadiazol-2-(3*H*)-ylidene) ethanone **166** [63].

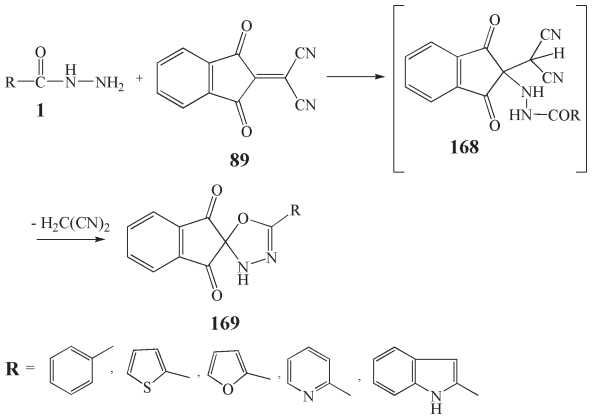


Carbohydrazides **1** reacted with 3-(dicyanomethylene)-2-indolone **97** in the presence of pipridine to give substituted spiro(indoline-3,2\-1,3,4-oxadiazol)-2-one **167**. Nucleophilic attack of **1** on C=C of **97** followed by loss of one molecule of malononitrile afforded **167** [65].

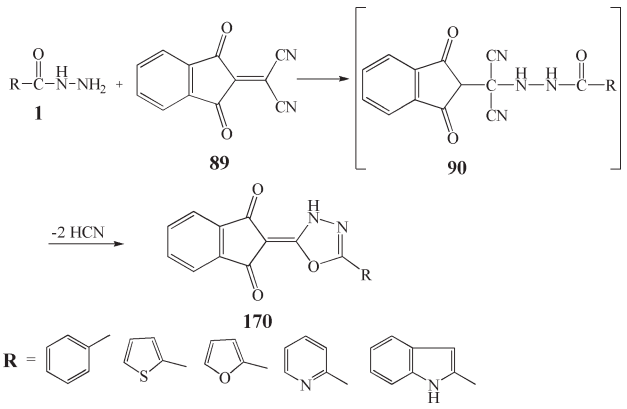


Carbohydrazides **1** reacted with (1,3-dioxo-2,3-dihydro-1*H*-inden-2-ylidene)propanedinitrile **89** in DMF with

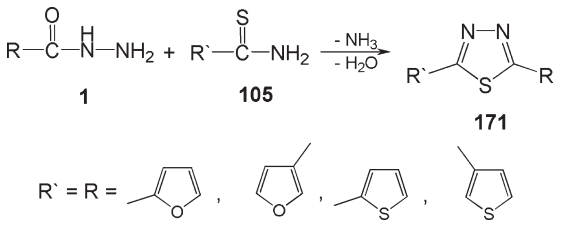
admission of air, to afford 5′-substituted-3′*H*-spiro(indene-2,2′-1,3,4-oxadiazole)-1,3-dione **169** [65].



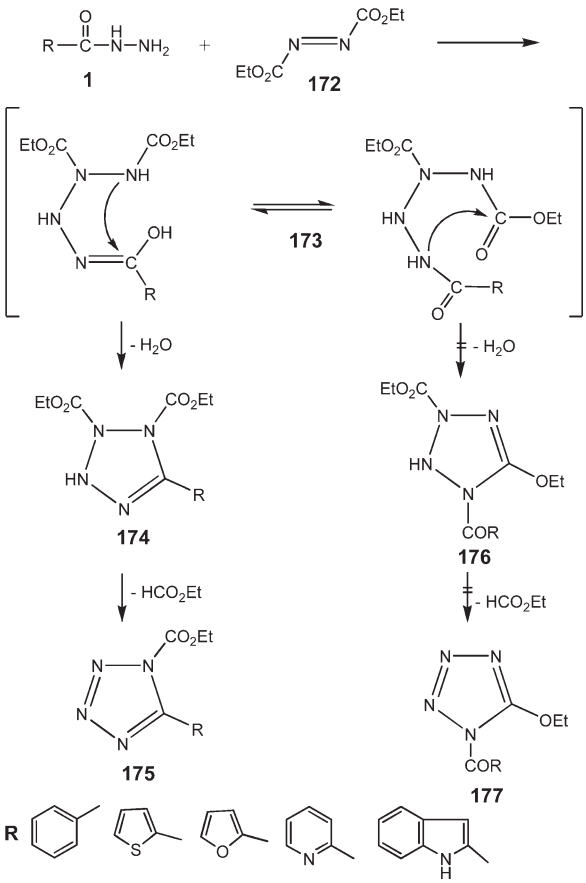
On the other hand, reaction of carbohydrazides **1** with **89** gave 2-(5-substituted-1,3,4-oxadiazol-2-(3*H*)-ylidene)-1*H*-indene-1,3-(2*H*)-diones **170** *via* the formation of the intermediate **90** and elimination of two molecules of HCN [65].



3.10. Synthesis of thiadiazole derivatives. Thiadiazole derivatives **17**1 were obtained from the reaction of carbohydrazides **1** and thiocarboxamides **105** [71].



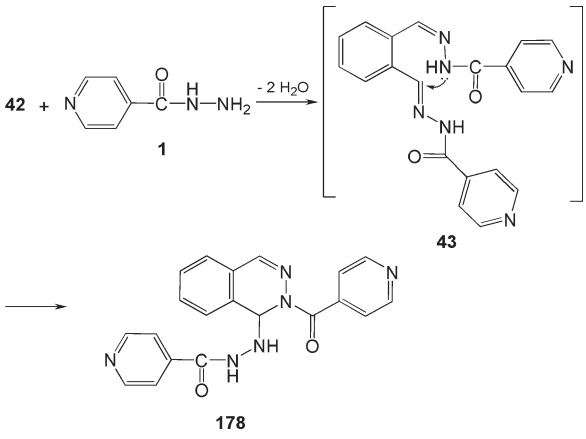
3.11. Synthesis of tetrazole derivatives. A mixture of **1** and diethyl diazene-1,2-dicarboxylate **172** in glacial acetic acid was heated at reflux temperature for 6-8 h, during which time tetrazole derivatives **175** were formed [63].



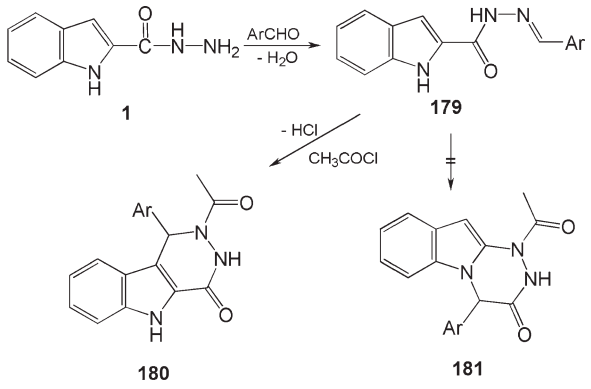
Nucleophilic attack of **1** to **172** with loss one molecule of H_2O followed by elimination of another molecule of ethyl formate afforded tetrazole derivatives **175** rather than the alternative structure **177** [63].

3.12. Synthesis of diazine derivatives.

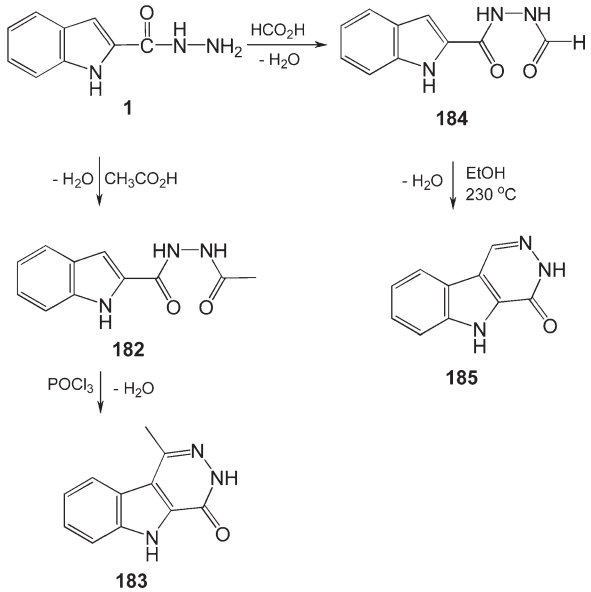
3.12.1. Synthesis of phthalazine derivatives. Reaction of *o*-phthalaldehyde **42** with 4-pyridine carbohydrazide **1** in refluxing ethanol gave a pure sample of hydrazone **43**, which underwent intramolecular cyclization afford the phthalazine derivatives **178** [102].



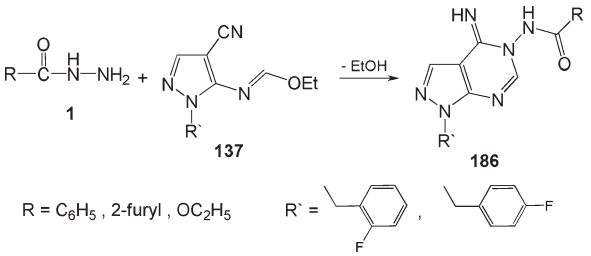
3.12.2. Synthesis of pyridazine derivatives. Condensation of indole carbohydrazide **1** with aromatic aldehydes gave the corresponding hydrazone derivatives **179** were obtained in varying yields, which heated to reflux in acetyl chloride to give the interesting tricyclic indolo[2,3-*d*]pyridazine derivatives **180** rather than indenotriazines **181** [64].



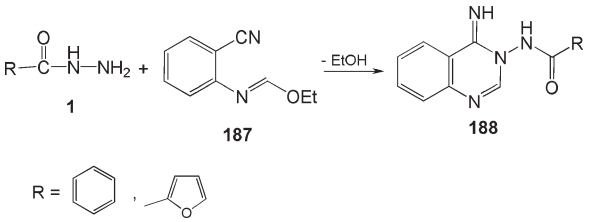
Acetylation of **1** by refluxing in acetic acid afforded 2-acetyl-hydrazinocarbonylindole **182**, in high yield. Compound **182** was cyclized directly by refluxing in dioxane containing $POCl_3$ to the indolo[3,2-*b*]pyradizines **183** [64]. On the other hand, refluxing **1** in formic acid for 5 h afforded the *N*-formyl derivative **184**, which was heated for 10 min in ethanol to afford 2,3-dihydro-indolo[3,2-*b*]pyridazin-1-one **185** [64].



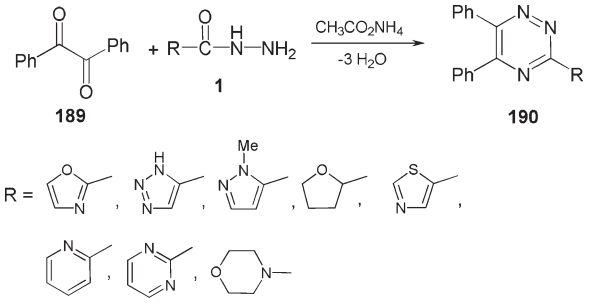
3.12.3. Synthesis of pyrimidine derivatives. Carbohydrazides **1** reacted with 4-cyano-5-[(ethoxymethylene)amino]pyrazoles **137** to give 5-acyl-amino-4-imino-4,5-dihydropyrazolo[3,4-*d*]pyrimidines **286** [91].



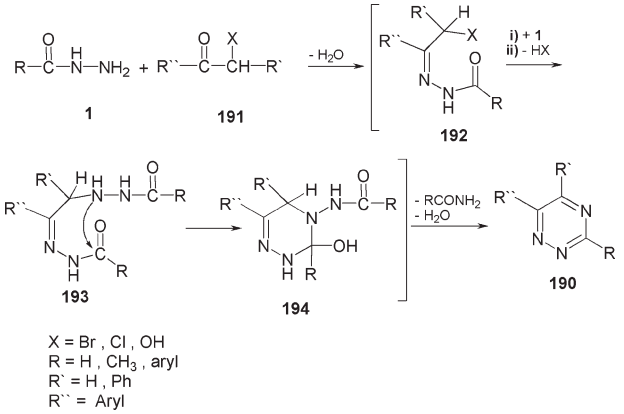
3.12.4. Synthesis of quinazoline derivatives. Refluxing of carbohydrazides **1** with *N*-ethoxy-methylene-2-amino-benzonitrile **187** in ethanol gave 3-acylamino-4-imino-3,4-dihydroquinazolines **188** [107].



3.13. Synthesis of 1,2,4-triazine derivatives. Benzil **189** reacted with carbohydrazides **1** in the presence ammonium acetate under microwave irradiation to give 1,2,4-triazine derivatives **190** [9,108–110].

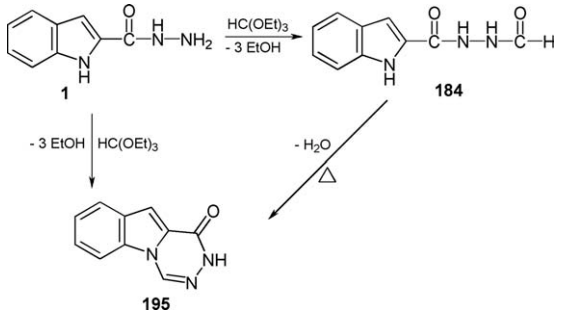


1,2,4-Triazine derivatives **190** were obtained by the reaction of carbohydrazides **1** with halomethyl ketone **191** [111,112].

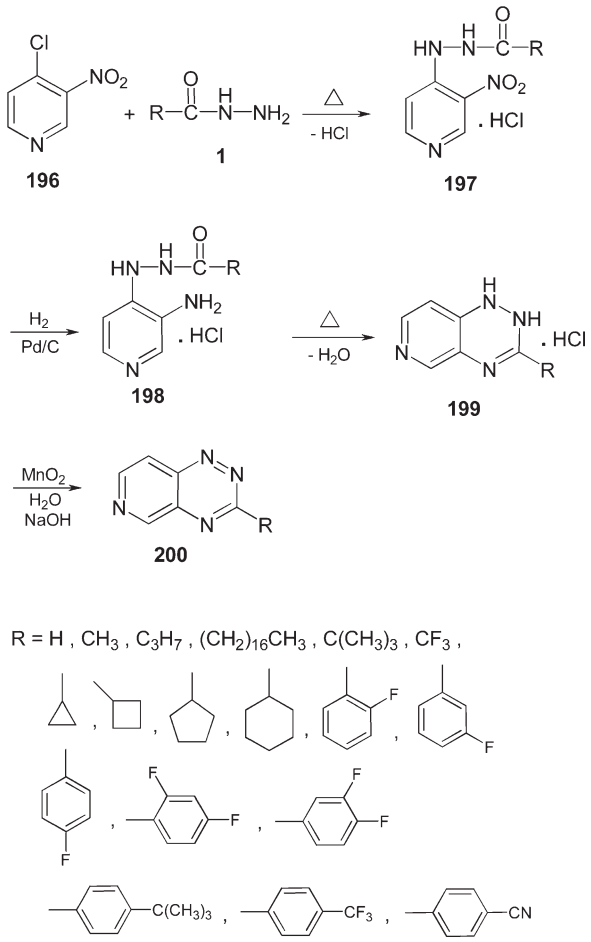


Boiling of 2-indole carbohydrazide **1** with triethyl-orthoformate in DMF, or thermal cyclodehydration of

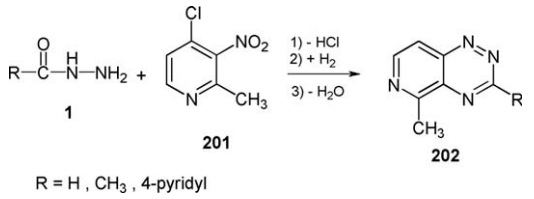
184 gave 1,2-dihydro-1-oxo-1,2,4-triazino[4,5-*a*]indole **195** [113].



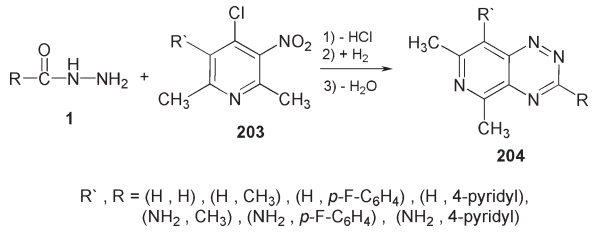
Carbohydrazides **1** reacted with 4-chloro-3-nitropyridine **196** in ethanol to form the acyl derivatives of 4-hydrazino-3-nitropyridine hydrochloride **197**. The nitro group in **197** was rapidly reduced over palladium catalyst to give **198**, ring closure of the latter compound under acidic conditions gave pyrido[3,4-*e*]-1,2,4-triazine derivatives **199**, which was oxidized by MnO_2 in presence of alkaline solution to form 3-substiuted pyrido[3,4-*c*]-1,2,4-triazine derivatives **200** [114,115].



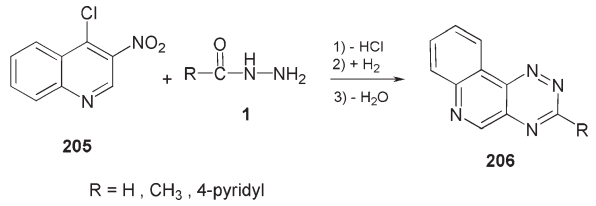
Similarly, carbohydrazides **1** reacted with 4-chloro-2-methyl-3-nitropyridine **201** to give 3,5-disubstituted pyrido[3,4-*c*]-1,2,4-triazine derivatives **202** [114,115].



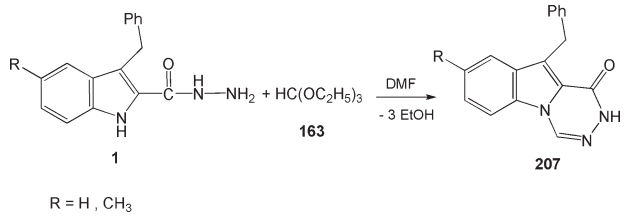
The reaction of carbohydrazides **1** with 5-substituted-4-chloro-2,6-dimethyl-3-nitropyridine **203** afforded pyridotriazine derivatives **204** [114,115].



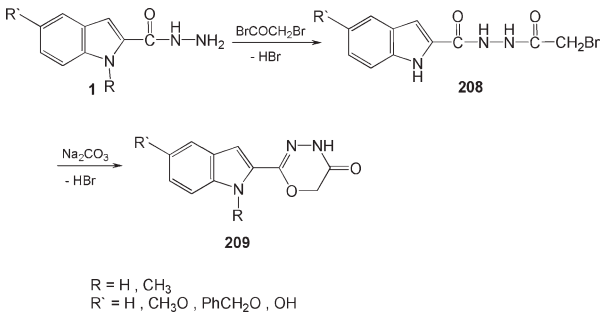
Reaction of 4-chloro-3-nitroquinoline **205** with carbohydrazides **1** gave 1,2,4-triazino[5,6-*c*]quinolines **206** [114,115].



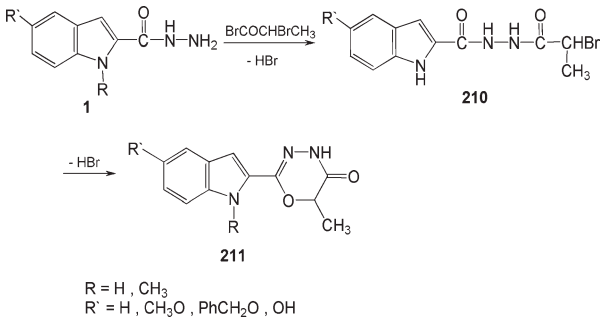
Reaction of carbohydrazides **1** with triethylorthoformate **163** in DMF gave 10-benzyl-1,2-dihydro-1-oxo-1,2,4-triazino[4,5-*a*]indole derivatives **207** [105].



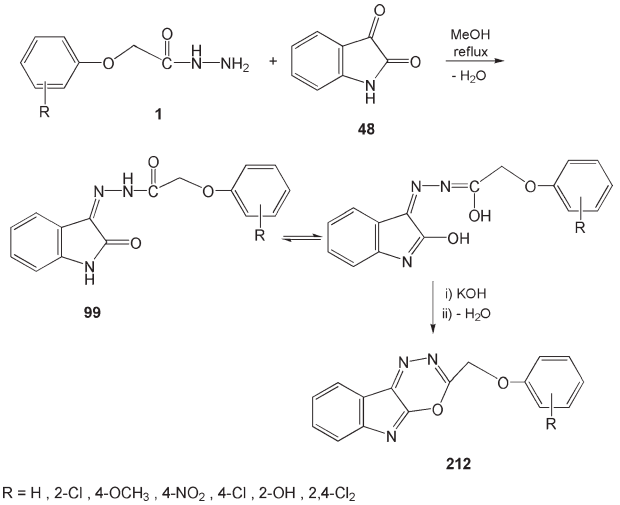
3.14. Synthesis of 1,3,4-oxadiazine derivatives. 2-Indolyl-4*H*-1,3,4-oxadiazine-5(6*H*)-one derivatives **209** have been synthesized by reaction of Na_2CO_3 with N^2-(2-bromoacetyl)indole-2-carbohydrazides **208**, prepared by reaction of carbohydrazides **1** with α-bromoacylbromide [4].



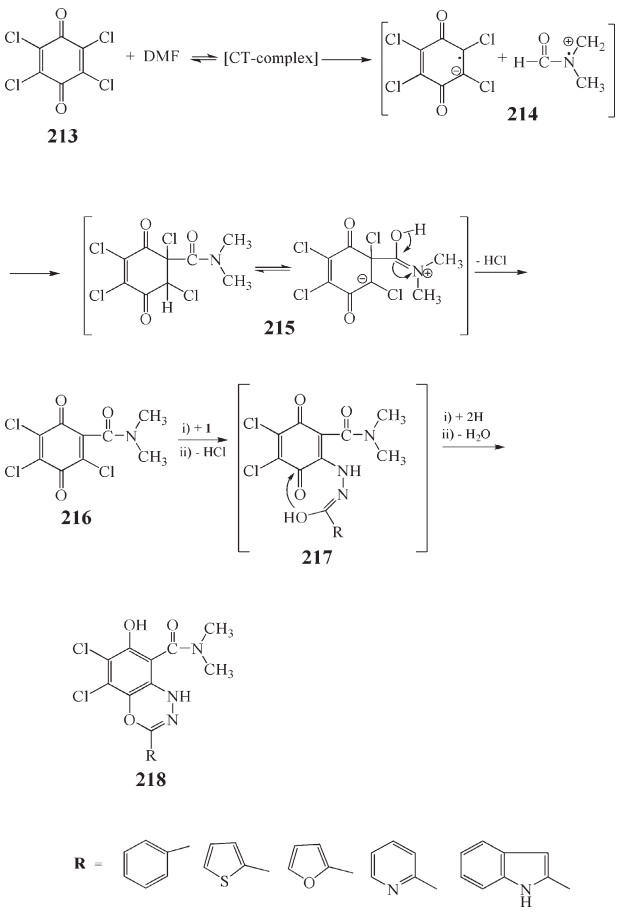
Reaction of carbohydrazides **1** with 2-bromopropanoylbromide gave N^2-(2-bromopropanoyl)-indole-2-carbohydrazide **210**, which cyclized to produce 2-indolyl-4*H*-1,3,4-oxadiazine-6-methyl-5-one derivatives **211** [4].



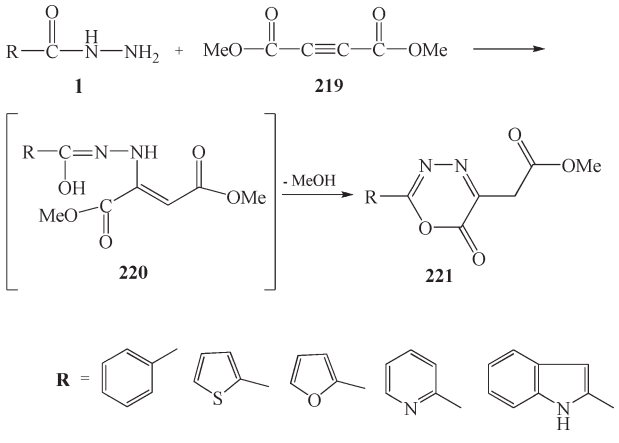
Isatin **48** was refluxed with carbohydrazides **1** in methanol to furnish isatin-β-aroylhydrazones **99**, which heated to reflux in aq. KOH to afford 2-aryl-1,3,4- oxadiazino[5,6-*b*]indole derivatives **212** [67].



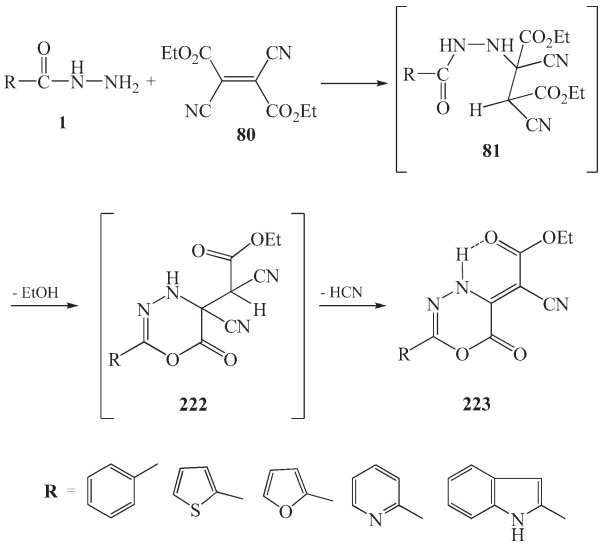
A mixture of 2,3,5,6-tetrachloro-1,4-benzoquinone **213** and **1** in DMF with admission of air afforded substituted benzo[1,3,4]oxadiazinecarboxamide **218** [66].



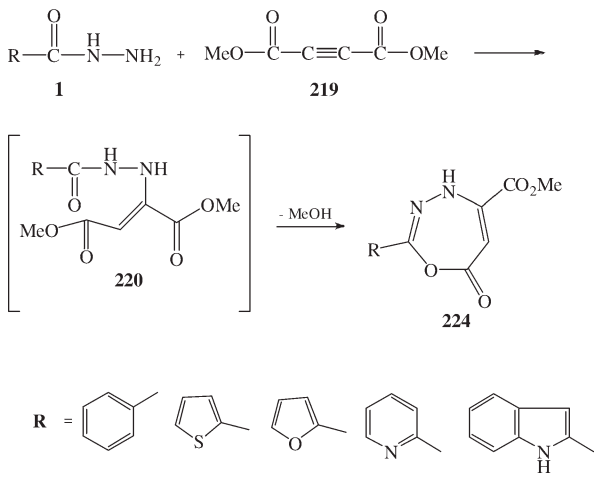
A mixture of dimethyl but-2-ynedicarboxylate **219** and substituted carbohydrazides **1** was refluxed in methanol to afford 1,3,4-oxadiazine derivatives **221** [63].



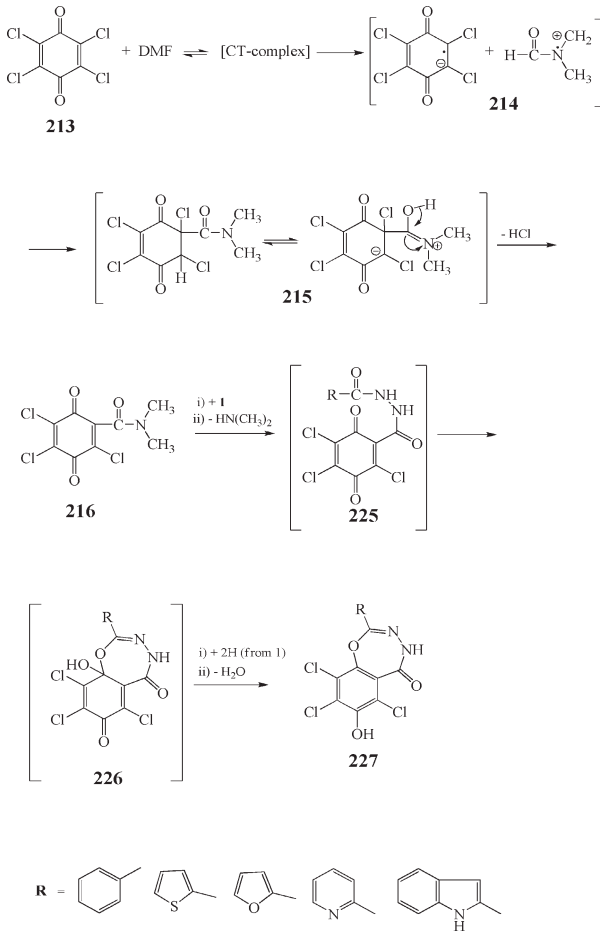
Solutions of diethyl (*E*) 2,3-dicyanobutenedioate **80** and **1** were refluxed for 4–18 h in ethyl acetate to give 1,3,4-oxadiazinone **223**, *via* elimination of one molecule of ethanol follwed by HCN [38].



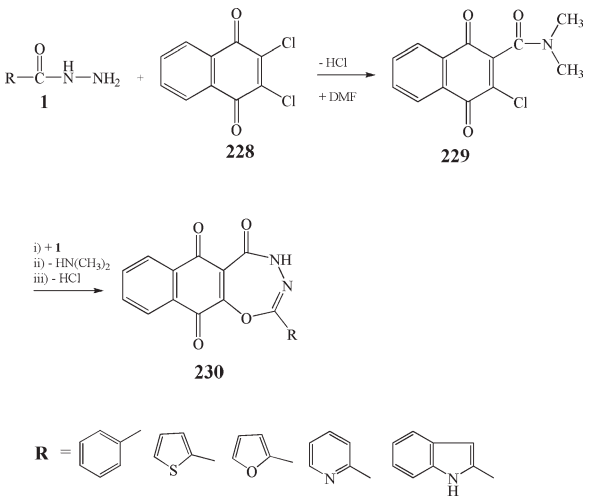
3.15. Synthesis of oxadiazepine derivatives. A mixture of dimethyl but-2-ynedicarboxylate **219** and substituted carbohydrazides **1** was heated to reflux in methanol to afford 1,3,4-oxadiazepine derivatives **224**. Nucleophilic attack of the NH_2 group of **1** to the triple bond of **219** afforded the adduct **220**, followed by elimination of one molecule of methanol and intramolecular cyclization to give **224** [63].



The reaction of 2,3,5,6-tetrachloro-1,4-benzoquinone **213** and **1** in DMF, with admission of air, afforded substituted benzo[1,3,4]oxadiazepine **227** [66].



On the other hand, the reaction of 2,3-dichloro-1,4-naphthoquinone **228** with **1** in DMF afforded substituted naphtho[2,3-*f*]-1,3,4-oxadiazepine-5,6,11-(4*H*)-trione **230** [66].



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