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SYNTHESES OF TRIAZOLOQUINOXALINES

Mohammed A. Baashen,[1] Bakr F. Abdel-Wahab,[1,2]* and Gamal A. El-Hiti[3]*

[1]Department of Chemistry, College of Science and Humanities, Shaqra University, Duwadimi, Saudi Arabia; [2]Applied Organic Chemistry Department, National Research Centre, Dokki, Giza, Egypt; [3]Cornea Research Chair, Department of Optometry, College of Applied Medical Sciences, King Saud University, P.O. Box 10219, Riyadh 11433, Saudi Arabia; bakrfatehy@yahoo.com and gelhiti@ksu.edu.sa

Abstract – This review summarizes the synthetic procedures for the production of various types of triazoloquinoxaline derivatives. Synthesis of triazolo[1,5-*a*]-, triazolo[4,3-*a*]-, triazolo[4,5-*g*]- and *bis*-triazoloquinoxalines are given. The main synthetic methods involve diazotization of 2-nitroanilines, then reaction with acid chloride derivatives followed by reduction of nitro groups and ring closure; ring closure of *N*-(2-alkynyl)-2-azido-anilines; reaction of 2,3-dichloroquinoxalines with acid hydrazides, or hydrazine hydrates and carbonyl compounds and reaction of 1,2-diaminobenzenes with hydrazonoyl halides. Triazoloquinoxalines are important intermediates for the design of novel biologically active molecules.

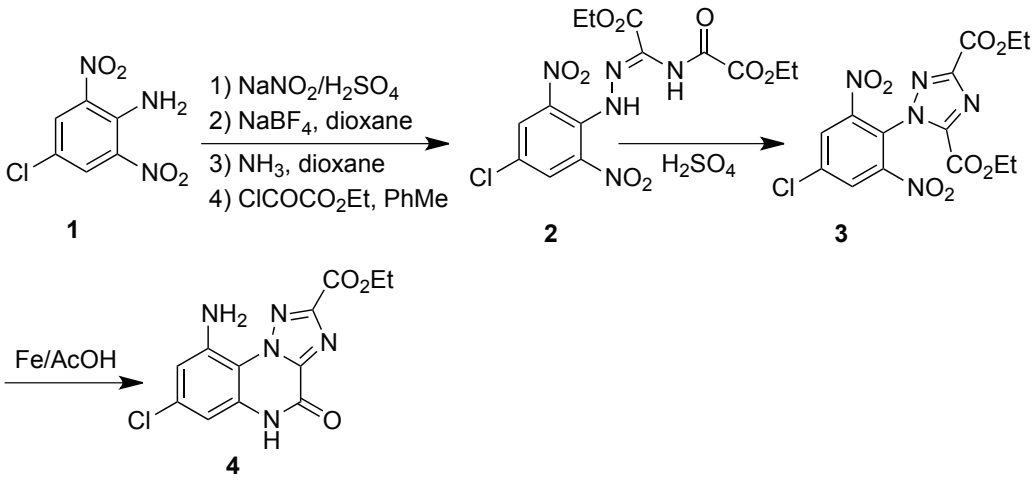
1. INTRODUCTION

Triazoloquinoxaline derivatives are an important class of heterocycles that have considerable interest due to their diverse range of biological activities. For example, triazoloquinoxalines can be used as inhibitors for phosphodiesterase 2 (PDE2) and phosphodiesterase 10 (PDE10), but to less extent.[1] Also, they act as histamine receptor inhibitors,[2] glycogen synthase kinase 3 (GSK-3) inhibitors,[3] anti-inflammatory drugs allergy inhibitors,[4] antimicrobial,[5,6] antitumor,[7] anticonvulsant,[8] and antidepressant.[9] The chemistry of *s*-triazolo[4,3-*a*]- and tetrazolo[1,5-*a*]quinoxalines has been reviewed in 1984.[10] As part of our interest in heterocyclic chemistry, we have published several review articles that cover the chemistry of a number of heterocycles.[11–17] We now report the literature survey on the synthetic routes for various triazoloquinoxaline derivatives.

2. SYNTHESIS OF TRIAZOLOQUINOXALINES

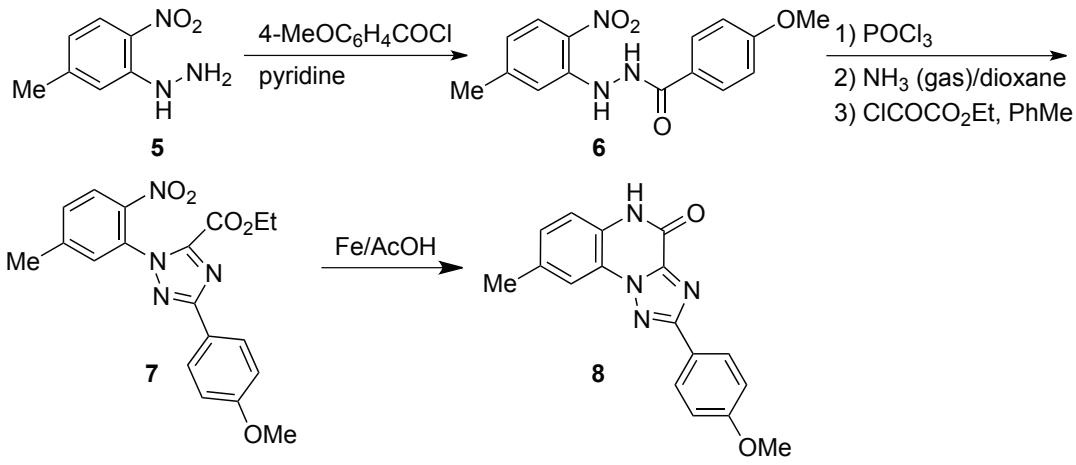
2.1. SYNTHESIS OF TRIAZOLO[1,5-*a*]QUINOXALINES

Diazotization of 4-chloro-2,6-dinitroaniline **1**, using sodium nitrite ($NaNO_2$) in concentrated sulfuric acid (H_2SO_4), followed by reaction with sodium tetrafluoroborate and ammonia gave the corresponding diazonium salt.[18] Reaction of diazonium salt with ethyl 2-chloro-3-oxobutanoate in toluene afforded ethoxalyl derivative **2** (80%), which dehydrated to give diethyl 1-(4-chloro-2,6-dinitrophenyl)-1,2,4-triazole-3,5-dicarboxylate (**3**; 74%) on treatment with concentrated H_2SO_4.[18] Reduction of **3** followed by contemporary cyclization gave ethyl 9-amino-4,5-dihydro-4-oxo-1,2,4-triazolo[1,5-*a*]quinoxaline-2-carboxylate (**4**; Scheme 1) in 53% yield. Alkaline hydrolysis of **4** followed by acid treatment gave the corresponding carboxylic acid derivative in 93% yield. The procedure has been applied to produce various 9-substituted triazoloquinoxalines.[18]



Scheme 1

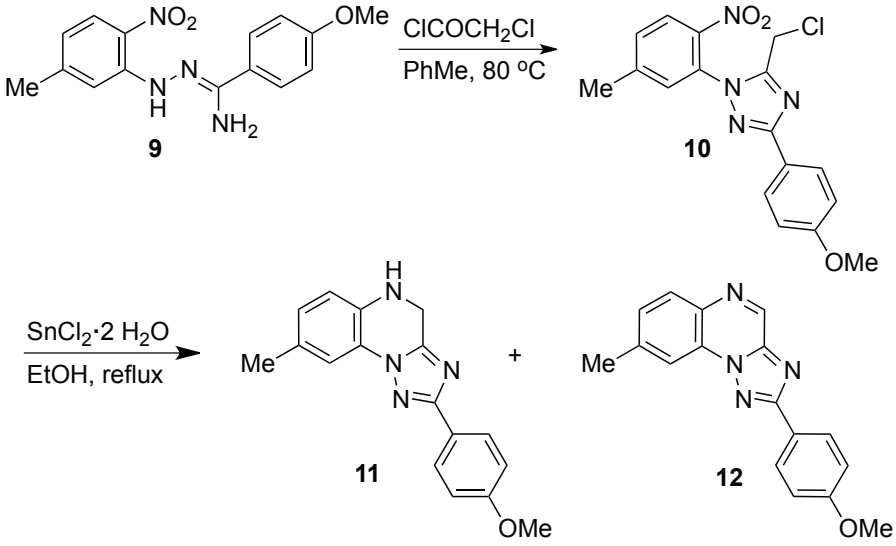
Reaction of 5-methyl-2-nitrophenylhydrazine **5** with 4-anisoyl chloride in pyridine gave the corresponding 4-methoxy-*N*'-(5-methyl-2-nitrophenyl)benzohydrazide **6** (89%). Treatment of **6** with



Scheme 2

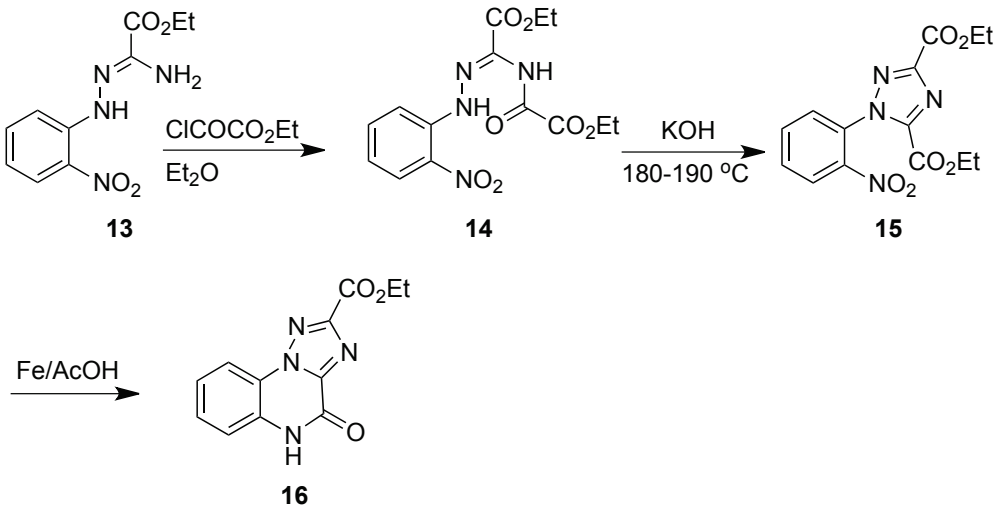
phosphoryl chloride ($POCl_3$) followed by reaction with ethyl oxalyl chloride in anhydrous toluene gave ethyl 1-(5-methyl-2-nitrophenyl)-3-(4-methoxyphenyl)-1,2,4-triazole-5-carboxylate **7** in 48% yield.[19] Reduction of **7** (Scheme 2) using iron in acetic acid followed by contemporary cyclization produced the corresponding 1,2,4-triazolo[1,5-*a*]quinoxaline (**8**; 70%), a human A3 (hA3) adenosine receptor (AR) antagonists.[19]

Reaction of 4-methoxy-*N*′-(5-methyl-2-nitrophenyl)benzohydrazonamide (**9**) with chloroacetyl chloride in toluene at 80 °C gave 5-(chloromethyl)-3-(4-methoxyphenyl)-1-(5-methyl-2-nitrophenyl)-1*H*-1,2,4-triazole (**10**; 72%). Reduction of **10** using dihydrated tin(II) chloride ($SnCl_2 \cdot 2\ H_2O$) in refluxing ethanol for 40 h under inert atmosphere gave a mixture of 2-(4-methoxyphenyl)-8-methyl-4,5-dihydro[1,2,4]triazolo[1,5-*a*]quinoxaline (**11**) and 2-(4-methoxyphenyl)-8-methyl-[1,2,4]triazolo[1,5-*a*]-quinoxaline (**12**; Scheme 3) in 35 and 30% yields, respectively.[20]



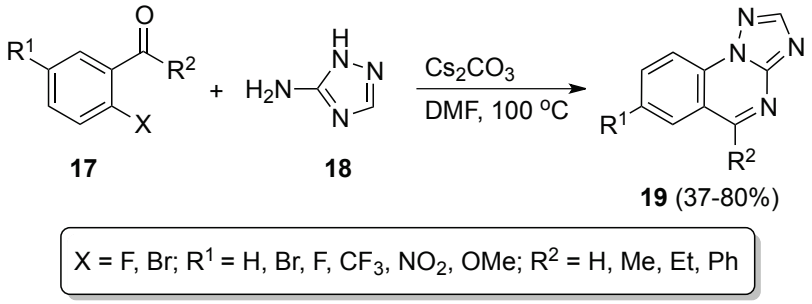
Scheme 3

A stirred mixture containing ethyl 2-amino-2-(2-(2-nitrophenyl)hydrazono)acetate (**13**) and ethyl 2-chloro-2-oxoacetate in diethyl ether gave the corresponding ethoxalyl derivative **14** (79%), which on heating (180–190 °C for 30 min) followed by treatment with potassium hydroxide (0.5 M) furnished diethyl 1-(2-nitrophenyl)-1*H*-1,2,4-triazole-3,5-dicarboxylate **15** (66%; Scheme 4).[21] Reduction of nitro group in intermediate **15**, using iron in acetic acid at 90 °C for 1 h, followed by cyclization gave ethyl 4-oxo-4,5-dihydro[1,2,4]triazolo[1,5-*a*]quinoxaline-2-carboxylate **16** (Scheme 4) in 70% yield.[21]



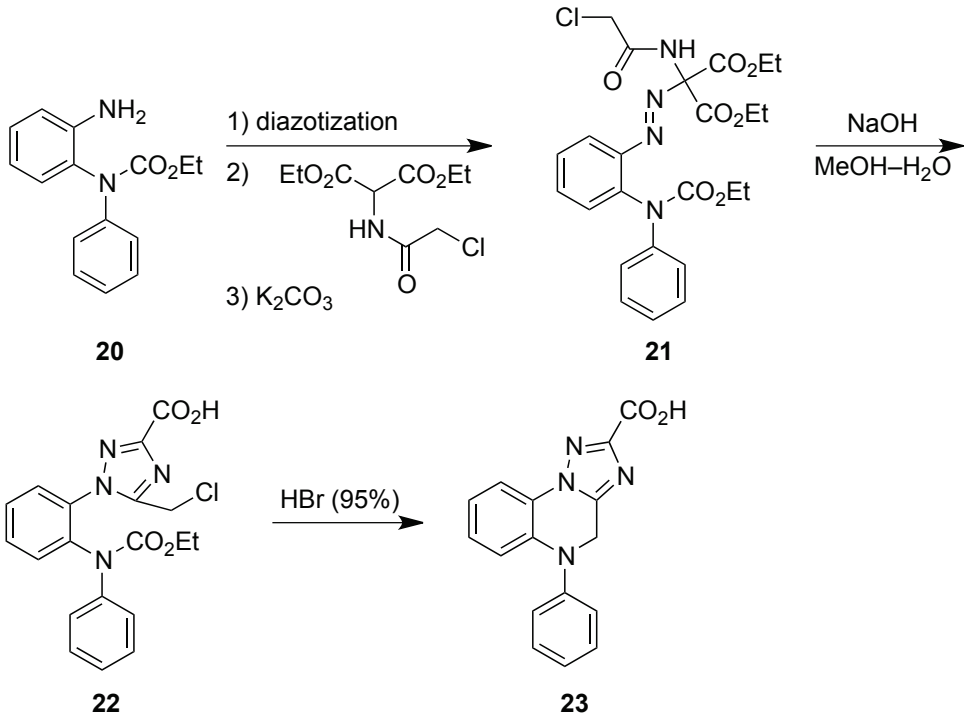
Scheme 4

Reaction of 2-halobenzaldehydes or 2-haloacetophenones **17** with 5-amino-1*H*-1,2,4-triazole **18** at 100 °C in dimethylformamide (DMF) containing cesium carbonate afforded the corresponding [1,2,4]triazolo[1,5-*a*]quinazolines **19** (Scheme 5) in 37–80% yields.[22] The reaction involves a one-pot condensation and nucleophilic substitution process that can be applied for the production of various substituted triazoloquinoxalines. The yields were generally low when R^1 was electron withdrawing groups (*e.g*. NO_2 and CF_3) and maximum when electron donating groups were employed (*e.g*. OMe).



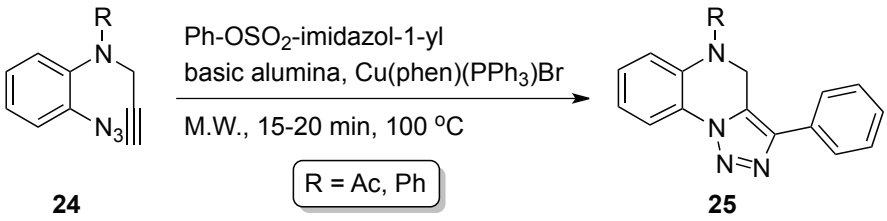
Scheme 5

Diazotization (HCl and $NaNO_2$) of **20** followed by reaction with diethyl 2-(2-chloroacetamido)malonate in methanol at 15 °C in the presence of potassium carbonate gave triethyl ester **21** (91%) which on treatment with excess sodium hydroxide (three mole equivalents) in aqueous methanol at room temperature gave triazole carboxylic acid **22** in 98% yield.[23] Ring closure of **22** using HBr at 100 °C for 22 h led to 5-phenyl-4,5-dihydro[1,2,4]triazolo[1,5-*a*]quinoxaline-2-carboxylic acid (**23**; Scheme 6) in 95% yield.[23]



Scheme 6

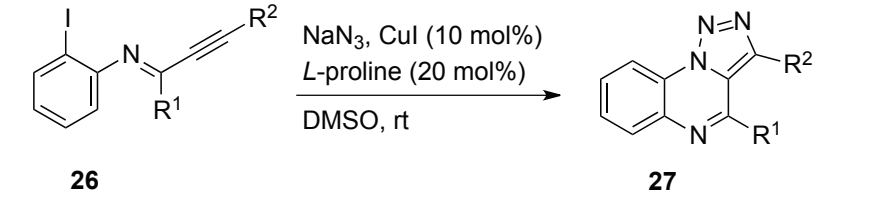
A microwave (M.W.)-assisted synthesis of triazole fused quinoxalines **25** (Scheme 7) in the yield of 67 (X = Ac) and 66% (R = Ph) was reported through ring closure of 2-azido-*N*-(prop-2-ynyl)anilines **24** in the presence of phenylimidazol-1-yl sulfonate using basic alumina as a solid support and Cu(phen)(PPh_3)Br as a catalyst.[24] The reaction involves single step using inexpensive catalyst without solvent.



Scheme 7

Treatment of *N*-(2-iodoaryl)alkynylimines **26** with sodium azide in the presence of copper iodide and *L*-proline in dimethyl sulfoxide (DMSO) at room temperature gave a series of [1,2,3]triazolo[1,5-*a*]-quinoxalines **27** (Scheme 8) in 56–94% yields.[25] The reaction involves formation of a C=N bond through a tandem copper-catalyzed process. It was successful for a range of aryl halides and electron-rich alkynes. However, the yields were low for reactions involve electron-deficient alkynes and such reactions have to

be carried out a 100 °C.[25] The reaction was also successful for *N*-(2-haloaryl)alkynylimines (Br and Cl) and for the iodo derivatives of **26** containing various substituents on the aryl ring.

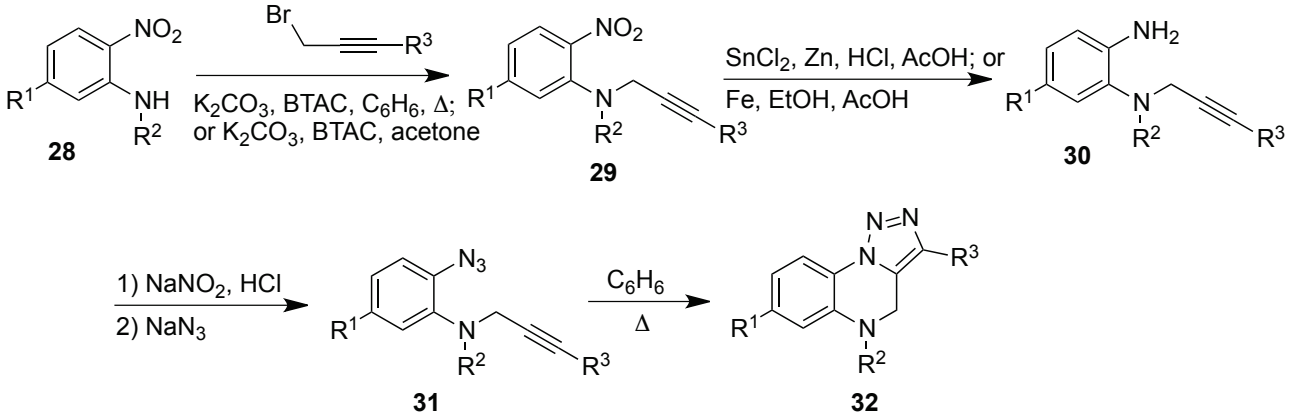


26 **27**

R^1 = CF_3, CF_2Cl
R^2 = Ph, 4-MeC_6H_4, 4-ClC_6H_4, 2-thienyl, *n*-Bu, *t*-Bu, CH_2OCOMe, CO_2Me

Scheme 8

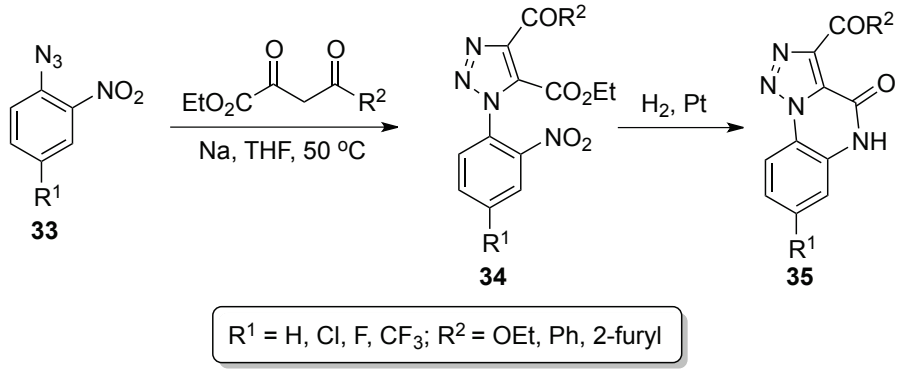
Intramolecular cycloaddition of aryl azides **31** afforded [1,2,3]triazolo[1,5-*a*]quinoxalines **32** (Scheme 9) in 60–96% yields.[26] *N*-Substituted *N*-(2-alkynyl)-*o*-nitroanilines **29** were synthesized from reaction of 2-nitroanilines **28** with alkynyl bromides. Reduction of **29** at the NO_2 group gave **30** which underwent diazotization followed by reaction with sodium azide to produce **31** (Scheme 9).[26]



R_1 = H, Cl; R_2 = Ph, 4-$MeC_6H_4SO_2$, COMe; R_3 = H, Me, Ph

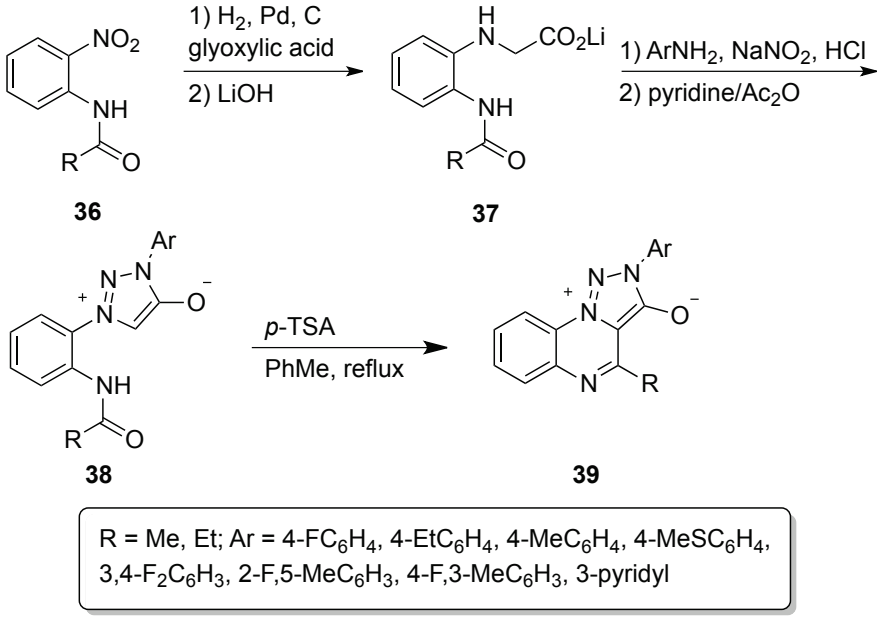
Scheme 9

Reaction of 2-nitrophenylazides **33** with ethyl oxalacetate in dry tetrahydrofuran (THF) containing sodium at 50 °C gave triazole diesters **34** (Scheme 10) in 17–28 % yields.[27] Catalytic reduction of the nitro group in **34** under mild condition (normal pressure and room temperature) gave the corresponding triazoloquinoxalinones **35** in 53–74% yields.[27]



Scheme 10

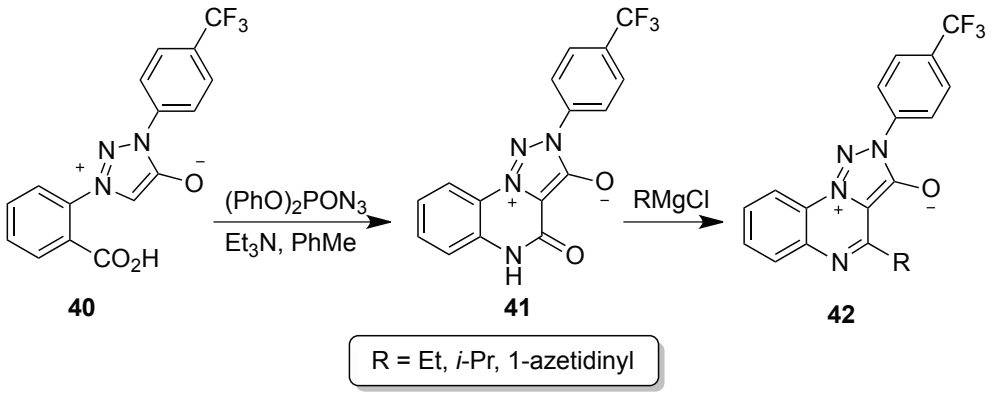
Hydrogenation of 2-nitroanilines **36** in the presence of glyoxylic acid followed by treatment with lithium hydroxide gave **37** (Scheme 11).[28] Treatment of **37** with aryldiazonium salt followed by acetic anhydride and pyridine gave triazolium hydoxide **38** in 20–55% yields (Scheme 11). Triazoloquinoxaliniums **39** was produced in 16–59% yields from treatment of **38** with *p*-toluenesulfonic acid (*p*-TSA).[28] The procedure was general but provided low to moderate yields of triazoloquinoxalines **39**.



Scheme 11

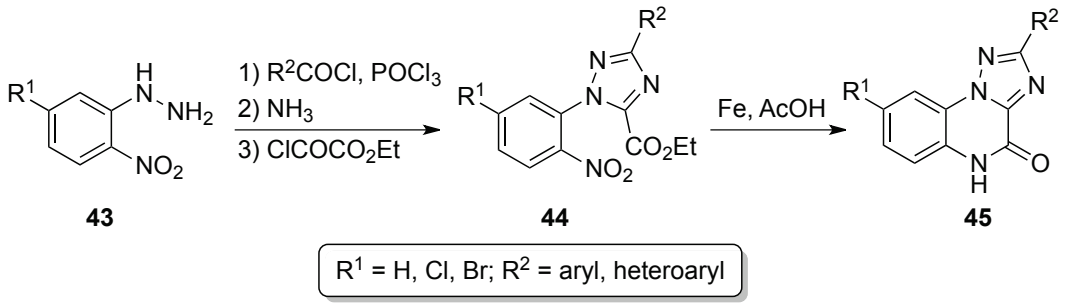
Reaction of 3-(2-carboxyphenyl)-1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazol-3-ium-5-olate **40** and diphenyl phosphorazidate in the presence of triethylamine (Et_3N) in a non-nucleophilic solvent gave 2-aryl-4-oxo-4,5-dihydro-2*H*-[1,2,3]triazolo[1,5-*a*]quinoxalin-10-ium-3-olate (**41**; Scheme 12) *via* Curtius rearrangement.[28] Reaction of **41** with Grignard reagent in the presence of phosphoryl chloride or amine to give 2*H*-[1,2,3]triazolo[1,5-*a*]quinoxalin-10-ium-3-olates **42** (Scheme 12) in 12–18% yields.[28] This process is not efficient and provided low yields of **42** compared to the process described in Scheme

11. Moreover, the generality of the approach never been tested.



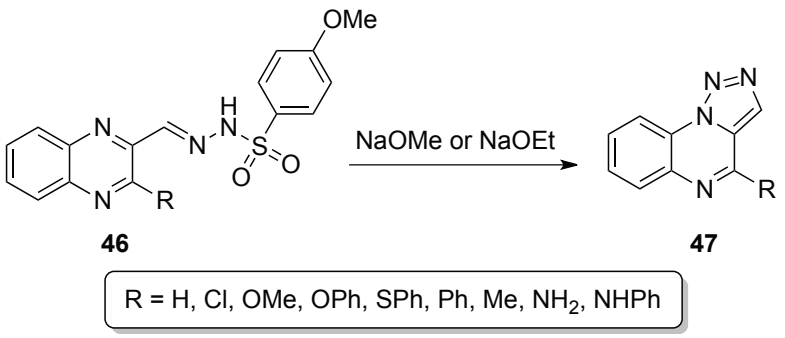
Scheme 12

Reaction of arylhydrazines **43** with aroyl chlorides followed by treatment with ammonia and then with ethyl oxalyl chloride yielded ethyl 1,3-diaryl-1,2,4-triazole-5-carboxylates **44** (Scheme 13) in 33–70% yields. Reduction of **44** using iron in acidic medium afforded the tricyclic derivatives **45** in 40–66% yields.[29]



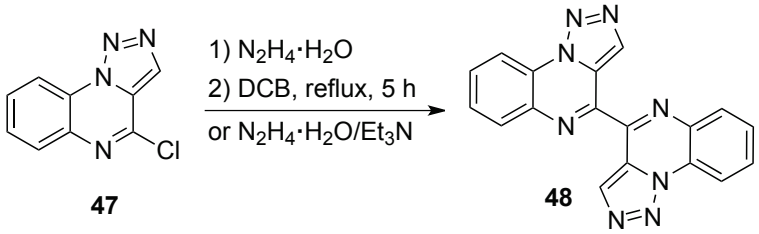
Scheme 13

Treatment of sulfonohydrazides **46** with sodium methoxide or ethoxide under reflux condition, Bamford-Stevens reaction, led to the corresponding 1,2,3-triazolo[1,5-*a*]quinoxalines **47** in 76–92% yields (Scheme 14).[30] The reaction involves 1,5-cyclization of the intermediate being formed *in-situ*.



Scheme 14

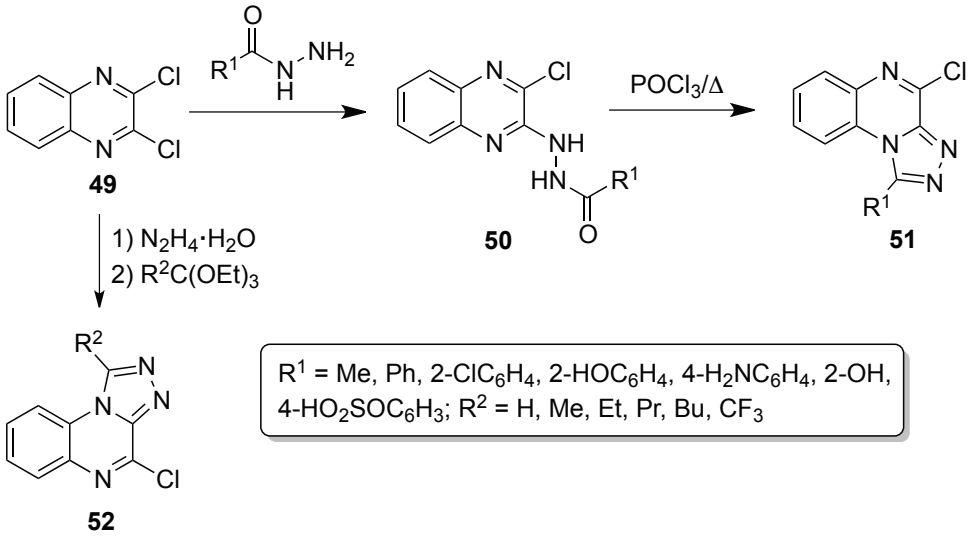
Reaction of **47** (R = Cl) with hydrazine hydrate in 1,2-dichlorobenzene (DCB) under reflux for 5 h gave *bis*(triazoloquinoxalinyl)hydrazine (**48**; Scheme 15) in 80% yield. Also, the reaction was successful when hydrazine hydrate was used in the presence of Et_3N to provide a moderate yield (57%) of **48**.[31]



Scheme 15

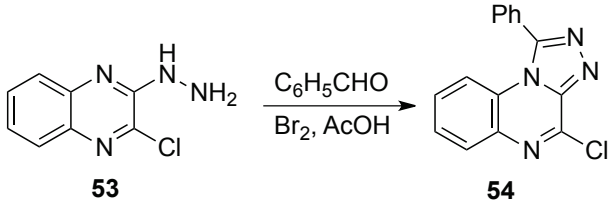
2.2. SYNTHESIS OF TRIAZOLO[4,3-*a*]QUINOXALINES

Condensation of 2,3-dichloroquinoxaline **49** with acid hydrazides yielded *N*-substituted-*N*′-(2-chloroquinoxalin-3-yl)hydrazines **50** which on thermal cyclization, in the presence of phosphoryl chloride, gave triazolo[4,3-*a*]quinoxalines **51** (Scheme 16) in good yields.[32] In a similar way, condensation of **49** with hydrazine hydrate in ethanol followed by treatment with triethyl orthoalkanoate gave the corresponding triazoloquinoxalines **52** (Scheme 16) in high yields, as selective adenosine receptors.[33–37] The reaction was successful for the production of many derivatives that have different substituents within quinoxaline ring.



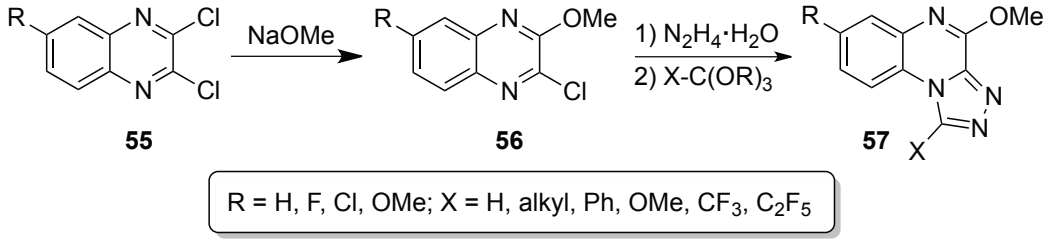
Scheme 16

Condensation of 2-chloro-3-hydrazinoquinoxaline **53** with benzaldehydes in the presence of bromine in acetic acid gave 4-chloro-1-phenyl-1,2,4-triazolo[4,3-*a*]quinoxaline **54** (Scheme 17).[38]



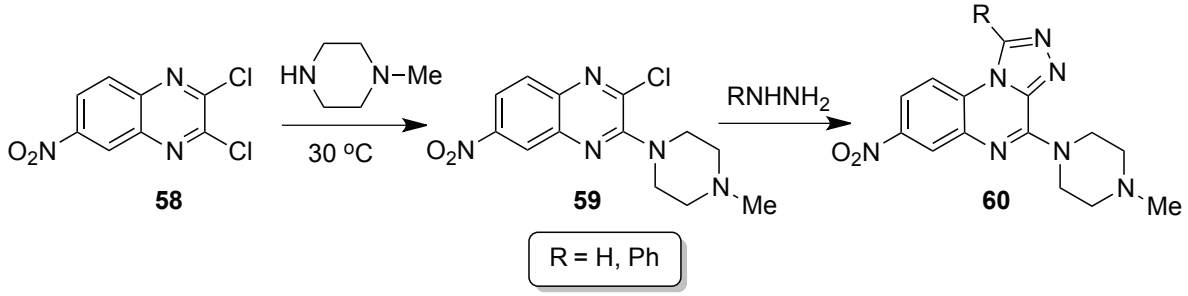
Scheme 17

2,3-Dichloroquinoxalines **55** were treated with sodium methoxide to form **56** (Scheme 18) in 86–95% yields. Reaction of **56** with hydrazine gave the corresponding hydrazones which subsequently treated with orthoesters to give **57** in 64–96% yields.[34]



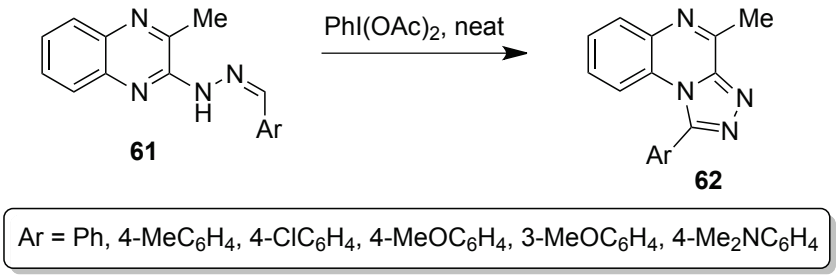
Scheme 18

2,3-Dichloro-6-nitroquinoxaline **58** underwent displacement reaction with 1-methylpiperazine selectively at the 2-position, at 30 °C, to afford **59** (Scheme 19) in 74% yield. Reaction of **59** with hydrazines gave the corresponding triazoloquinoxalines **60** (Scheme 19) in 33–40% yields.[39]



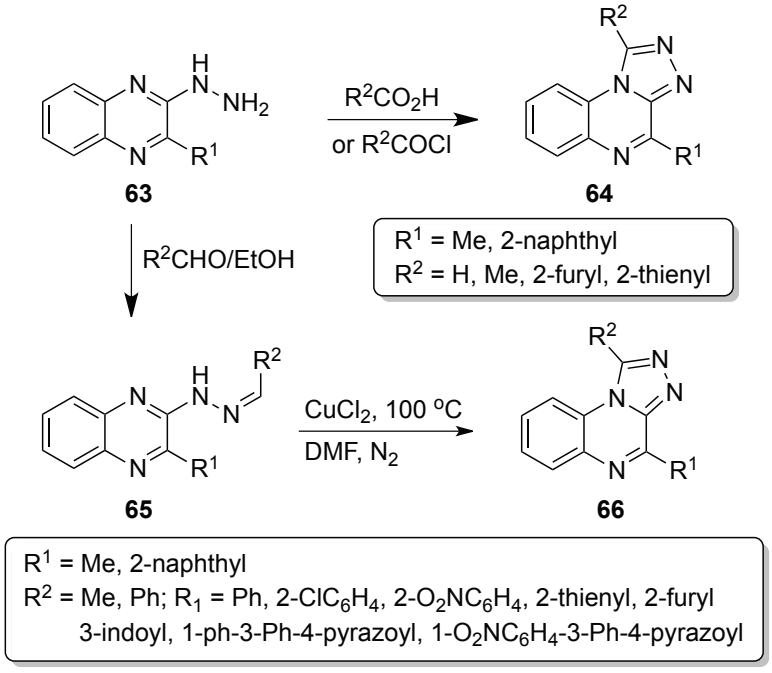
Scheme 19

1-Aryl-4-methyl-1,2,4-triazolo[4,3-*a*]quinoxalines **62** were obtained in 65–76% yields from oxidative cyclization of 3-methyl-2-quinoxalinylhydrazones **61** (Scheme 20) in a solvent free system.[40] The reaction involves use of iodobenzene diacetate which is a green oxidant catalyst that does not contain metals.



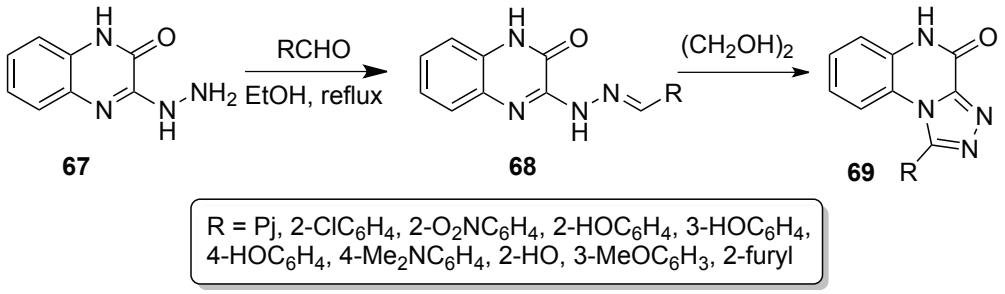
Scheme 20

Reaction of 2-hydrazinoquinoxalines **63** with carboxylic acids or acid chlorides gave [1,2,4]triazolo[4,3-*a*]quinoxalines **64** (Scheme 21) in 23–70% yields.[41,42] Condensation of **63** with a number of aromatic and heteroaromatic aldehydes in ethanol under reflux condition gave 2-(arylidenehydrazino)quinoxalines **65** (Scheme 21) in 73–92% yields. Compounds **65** underwent oxidative intramolecular cyclization in the presence of excess copper(II) chloride (two molar equivalents), in dry DMF under inert atmosphere, to afford 1-aryl-1,2,4-triazolo[4,3-*a*]quinoxalines **66** (Scheme 21) in 74–91% yields.[43,44]



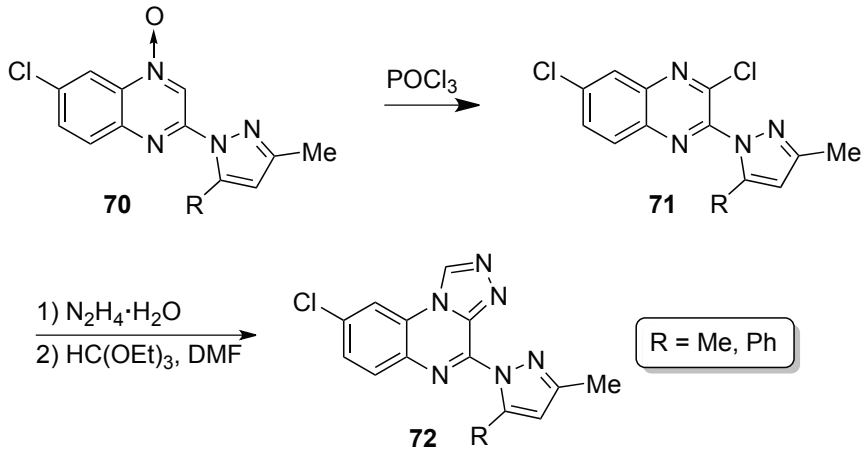
Scheme 21

Condensation of 3-hydrazino-2-quinoxalinone **67** with a range of aldehydes in boiling ethanol for 3–4 h gave the corresponding hydrazones **68** (77–97%) which were subsequently thermally annelated, at 200 °C in ethylene glycol for 5–7 h, to give triazoloquinoxalinones **69** (Scheme 22) in 72–97% yields.[45]



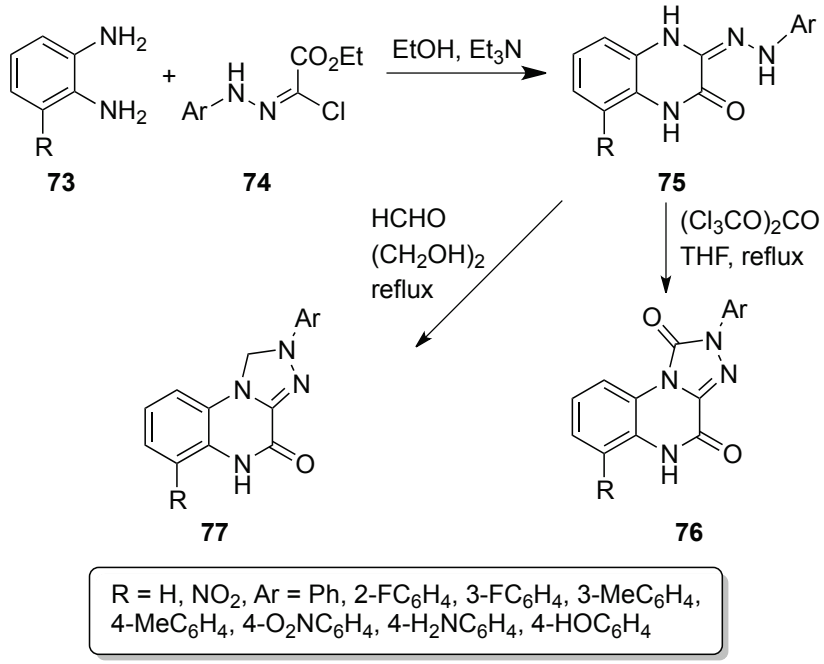
Scheme 22

Reaction of **70** with phosphoryl chloride under reflux for 1 h gave 3,6-dichloro-2-(3,5-dimethylpyrazol-1-yl)quinoxalines **71** (Scheme 23) in high yields (R = Me, 88%; R = Ph, 80%). Reaction of **71** with hydrazine hydrate in boiling ethanol for 2 h followed by treatment with triethyl orthoformate in DMF under reflux for 2 h afforded triazolo[4,3-*a*]quinoxalines **72** (Scheme 23) in high yields (R = Me, 81%; R = Ph, 71%).[46]



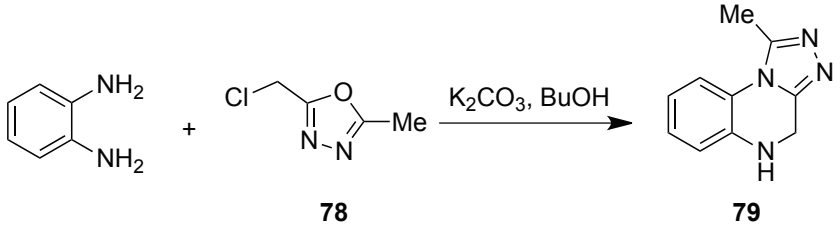
Scheme 23

Reaction of 1,2-phenylenediamines **73** with ethyl *N*′-arylhydrazono-N_2-chloroacetates **74** gave 3-arylhydrazonoquinoxalin-2-ones **75** (Scheme 24) in 60–80% yields.[47–49] Cyclization of **75** with triphosgene afforded compounds **76** in 31–94% yields. Similarly, reaction of **75** with formaldehyde in ethylene glycol yielded tricyclic derivative **77** (Scheme 24; R = H, Ar = Ph) in 80% yield.[49]



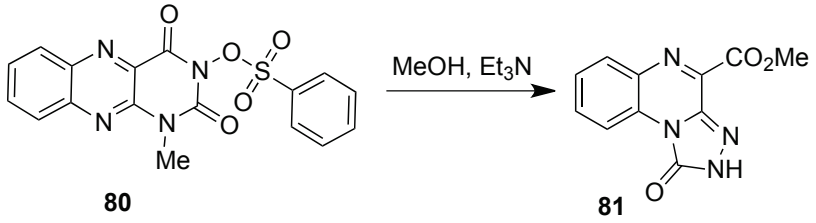
Scheme 24

Reaction of 1,2-phenylenediamine with 2-(chloromethyl)-5-methyl-1,3,4-oxadiazole **78** in the presence of K_2CO_3 in butanol gave 1-methyl-4,5-dihydro[1,2,4]triazolo[4,3-*a*]quinoxaline **79** (Scheme 25). Such compound can be used as a useful intermediate for agrochemicals and pharmaceuticals.[50]



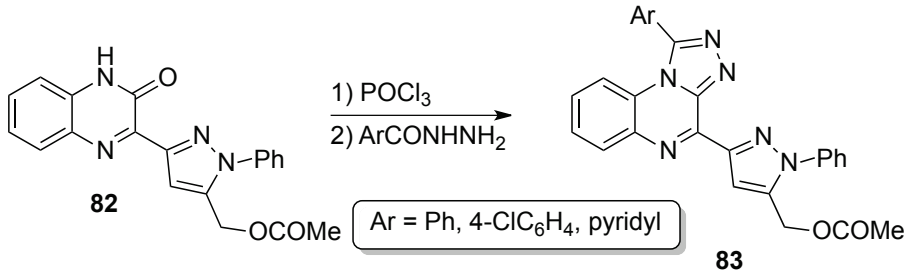
Scheme 25

Treatment of benzenesulfonyl oxyalloxazine **80** with a base (*e.g.* Et_3N) in methanol gave the corresponding triazoloquinoxaline (**81**; Scheme 26) in 98% yield.[51]



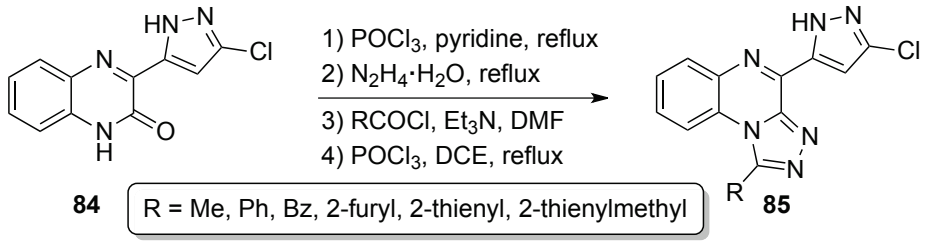
Scheme 26

4-(Pyrazol-3-yl)[1,2,4]triazolo[4,3-*a*]quinoxalines **83** (Scheme 27) were obtained in 56–82% yields from treatment of quinoxaline **82** with $POCl_3$ followed by reaction with excess aroylhydrazines in boiling butanol under reflux for 8 h.[52]



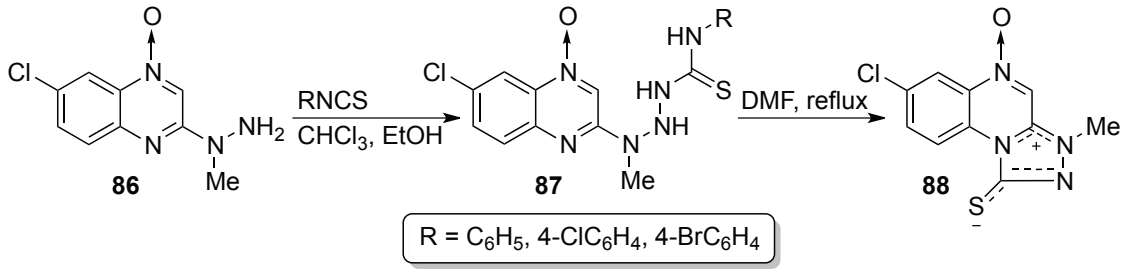
Scheme 27

Treatment of 3-(3-chloro-1*H*-pyrazol-5-yl)quinoxalin-2(1*H*)-one **84** with phosphoryl chloride in pyridine followed by reaction with hydrazine, acid chloride and phosphoryl chloride afforded triazoloquioxalines **85** (Scheme 28) in 62–71% yields.[53]



Scheme 28

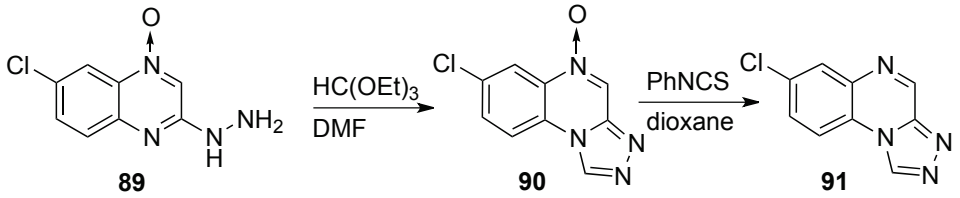
Reaction of 6-chloro-2-(1-methyl-2-thiocarbamoylhydrazino)quinoxaline 4-oxide **86** with aryl isocyanate, in a mixture of chloroform and ethanol under reflux for 1 h, gave thiosemicarbazides **87** (Scheme 29) in 74–93% yields. Refluxing **87** in DMF for 5 h afforded mesoionic triazolo[4,3-*a*]quinoxaline **88** (Scheme 29) in a yield ranging from 32 to 63% depending on the type of substituents in **87**.[54]



Scheme 29

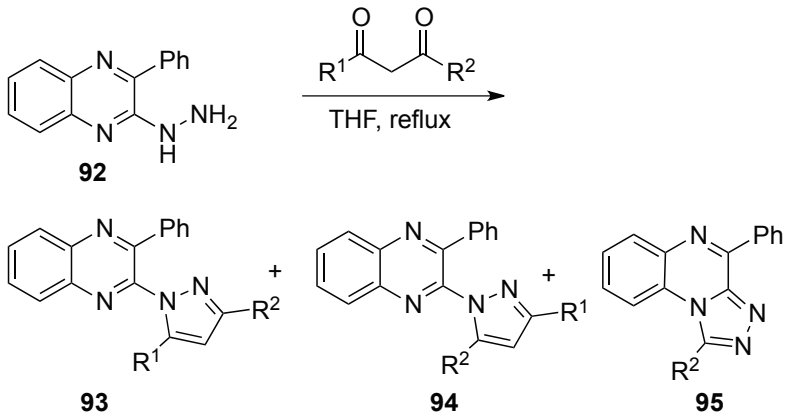
Cyclocondensation of 6-chloro-2-hydrazinoquinoxaline 4-oxide **89** with triethyl orthoformate in DMF under reflux for 3 h gave 7-chloro-1,2,4-triazolo[4,3-*a*]quinoxaline 5-oxide (**90**; Scheme 30) in 83% yield.

Deoxygenation of **90** with phenyl isocyanate in dioxane under reflux for 1 h afforded 7-chloro-1,2,4-triazolo[4,3-*a*]quinoxaline (**91**: Scheme 30) in 67% yield.[55]



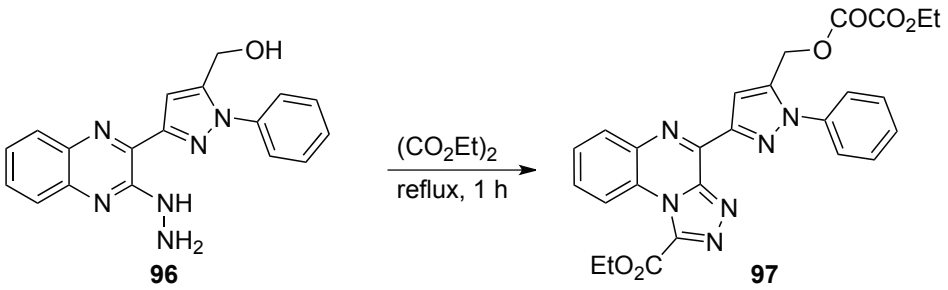
Scheme 30

Reaction of 2-hydrazino-3-phenylquinoxaline **92** with several 1,3-diketones (Scheme 31) in boiling THF for 6 h revealed a mixture of regioisomeric 3,5-disubstituted pyrazoles **93** (9–60%) and **94** (26–51%) and 1,2,4-triazolo[4,3-*a*]quinoxalines **95** (X = Me, 30%; X = Ph, 75%).[56]



Scheme 31

Triazoloquinoxaline **97** was synthesized in 75% yield from treatment of 3-hydrazinoquioxaline **96** with diethyl oxalate under reflux for 1 h in a solvent free system (Scheme 32). Reaction of **96** with diethyl oxalate in dioxane under reflux for 8 h gave the corresponding hydrazinyl-2-oxoacetate (80%) which on

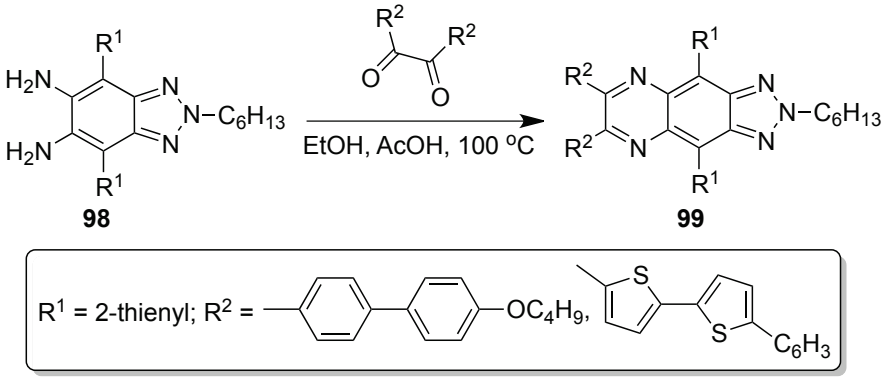


Scheme 32

treatment with acetic anhydride under reflux for 1 h provided the corresponding 4-(5-acetoxymethyl)triazolo[4,3-*a*]quinoxaline in 82% yield.[57]

2.3. SYNTHESIS OF TRIAZOLO[4,5-*g*]QUINOXALINES

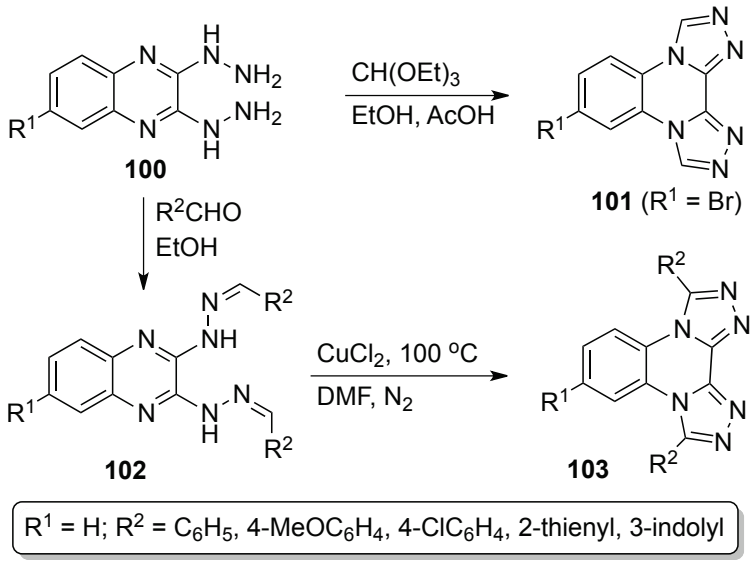
Condensation of 2-hexyl-4,7-di(2-thienyl)-2*H*-benzo[*d*][1,2,3]triazole-5,6-diamine **98** with 1,2-diketones in ethanol under acidic condition at 100 °C for 1 day afforded 2-hexyl-2*H*-[1,2,3]triazolo[4,5-*g*]-quinoxalines **99** (Scheme 33) in 76–81% yields.[58]



Scheme 33

2.4. SYNTHESIS OF *BIS*-TRIAZOLOQUINOXALINES

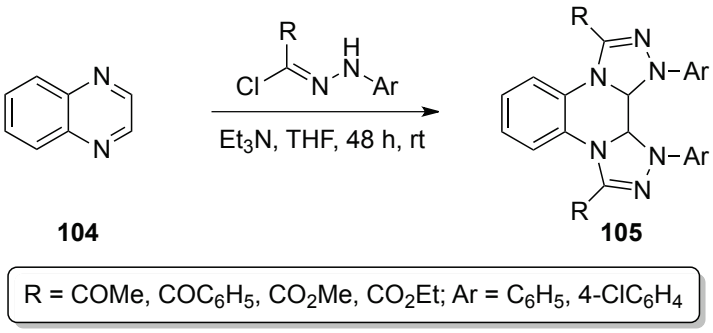
Formation of di-triazoloquinoxalines **101** (R^1 = Br) was achieved in 81% yield from reaction of 2,3-dihydrazinylquinoxalines **100** (Scheme 34) with triethyl orthoformate in ethanol at 90 °C for 10 h in the presence of a catalytic amount of acetic acid.[59] While, condensation of **100** (R^1 = H) with a number of



Scheme 34

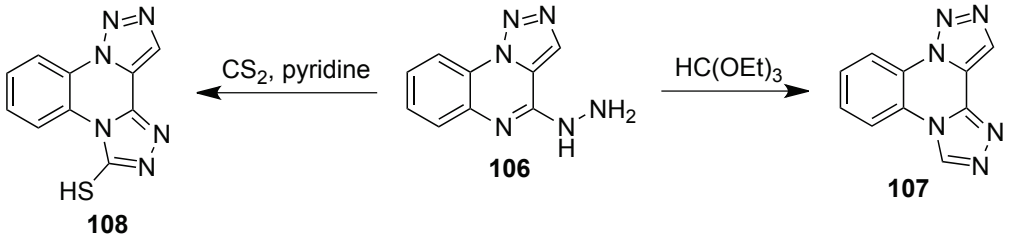
aromatic aldehydes in boiling ethanol afforded the corresponding 2,3-*bis*-(arylidenehydrazino)quinoxalines **102** which subsequently underwent oxidative cyclization in the presence of excess of copper dichloride (four equivalents) in dry DMF under nitrogen to yield the corresponding di-triazoloquinoxalines **103** (Scheme 34) in 65–88% yields.[60]

1,3-Dipolar cycloaddition of quinoxaline **104** and chloroarylhydrazones (two mole equivalents) in the presence of excess triethylanime in anhydrous THF at room temperature for 48 h gave the corresponding *bis*-cyclo adduct **105** (Scheme 35) in 15–48% yields.[61]



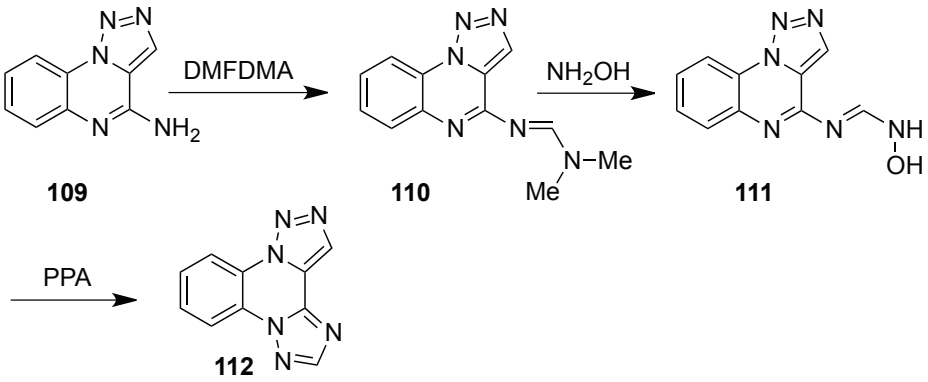
Scheme 35

Treatment of 4-hydrazinyl-[1,2,3]triazolo[1,5-*a*]quinoxaline **106** with triethyl orthoformate or carbon disulfide in pyridine afforded *bis*[1,2,4]triazolo[4,3-*a*:5',1'-*c*]quinoxaline **107** or *bis*[1,2,4]triazolo[4,3-*a*:5',1'-*c*]quinoxaline-6-thiol (**108**; Scheme 36) in 83 or 74% yield, respectively.[62]



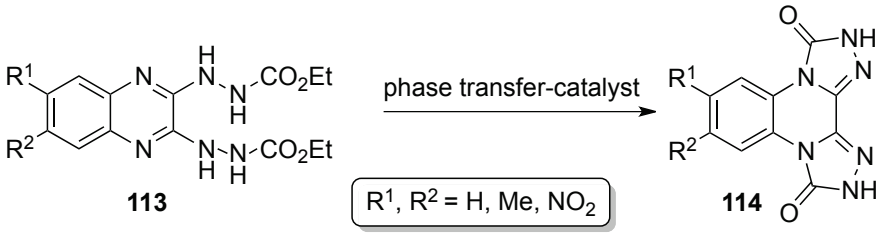
Scheme 36

Treatment of 4-amino-[1,2,3]triazolo[1,5-*a*]quinoxaline **109** with dimethylformamide dimethyl acetal (DMFDMA) afforded *N*'-([1,2,3]triazolo[1,5-*a*]quinoxalin-4-yl)-*N,N*-dimethylformimidamide **110** in 91% yield which on reaction with hydroxylamine gave *N*'-([1,2,3]triazolo[1,5-*a*]quinoxalin-4-yl)-*N*-hydroxyformimidamide (**111**; Scheme 37) in 74% yield.[62] Ring closure of **111** in the presence of polyphosphoric acid (PPA) furnished *bis*[1,2,4]triazolo[1,5-*a*:5',1'-*c*]quinoxaline **112** (Scheme 37) in 39% yield.[62]



Scheme 37

Phase transfer-catalyzed cyclization of 2,3-*bis*(carbethoxyhydrazino)quinoxalines **113** gave triazoloquinoxalines **114** (Scheme 38) in 90–94% yields.[63]



Scheme 38

3. CONCLUSION

The synthetic access to four different types of triazoloquinoxalines including triazolo[1,5-*a*]-, triazolo[4,3*a*]-, triazolo[4,5-*g*]- and *bis*-triazoloquinoxalines was reviewed. The work provides a useful up-to-date data to researchers working in the area of organic chemistry and in particular heterocycles.

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Mohammed A. Baashen is an Assistant Professor of Organic Chemistry at Shaqra University, College of Sciences and Humanities, Duwadmi, Saudi Arabia. He was educated as a Chemist at King Faisal University, Saudi Arabia (1995), and got his PhD from the University of Sussex with Professor Mark C Bagley (2013). His research involves the development of novel organic synthetic methods, especially using a relatively short reaction time to synthesised heterocyclic targets in high yield efficiently under microwave-assisted organic synthesis (MAOS) conditions and using Suzuki Coupling reactions for the development of a procedure for "palladium-catalyzed cross coupling," as an organic chemistry process, which enables the synthesis of large carbon-based molecules.

Bakr F. Abdel-Wahab was born in 1978 in Mansoura, Egypt. He is associated professor of organic chemistry at National Research Centre, Giza, Egypt. He has got his B.Sc. in 1999 from Chemistry Department, Faculty of Science, Mansoura University, Egypt. He received his M.Sc. in 2003 from the same university. He has awarded his Ph.D. degree in 2007 from Ain-Shams University, Cairo, Egypt. He worked as an assistant professor at Department of Chemistry, Faculty of Science, King Abdul-Aziz University, Saudi Arabia during the period 2009–2011. Currently, he is working as assistant professor of organic chemistry at Shaqra University, College of Sciences and Humanities, Duwadmi, Saudi Arabia from Sept. 2012 till now. In 2012 he received the State-Award in Chemistry, Egypt, and in 2013 he received the award of Arab chemists Union for youth. His current research interests cover the development and mechanistic aspects of organic reactions and their applications in medicinal and industrial chemistry.

Gamal A. El-Hiti received his BSc and MSc degrees from Tanta University, Egypt in 1986 and 1990, respectively. He received his PhD degree from Tanta University in 1996 including two years at Swansea University, UK (K. Smith). Lecturer (1996), Associate Professor (2001) and Professor (2006–2013) at Tanta University. Academic Visitor (1998–1999), Lecturer and Research Officer at Swansea University (2002–2007, K. Smith). Research Fellow and Research Associate, Cardiff University (2007–2012, K. Smith and P. Kille). Appointed as a Teacher in Organic Chemistry, Cardiff, in 2012–2013. Technical Director of CatCelt Limited since 2006. He is currently a Professor at King Saud University, College of Applied Medical Science, Department of Optometry, Saudi Arabia since 2013. His research interests are primarily in the development of novel organic synthetic methods, especially ones that are "greener" than traditionally, and synthesis of compounds with interesting properties. Particular current research projects involve the use of zeolites and solid-supported reagents and catalysts to gain selectivity in organic reactions; lithiation reactions, which they have been used to devise novel heterocyclic ring syntheses and to introduce selectivity into aromatic and heterocyclic substitution reactions; heterocyclic chemistry and design and synthesis of novel compounds with interesting chemiluminescent or other photoactive properties.