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Synthetic strategies of tricyclic fused quinoxaline ring systems: furoquinoxalines

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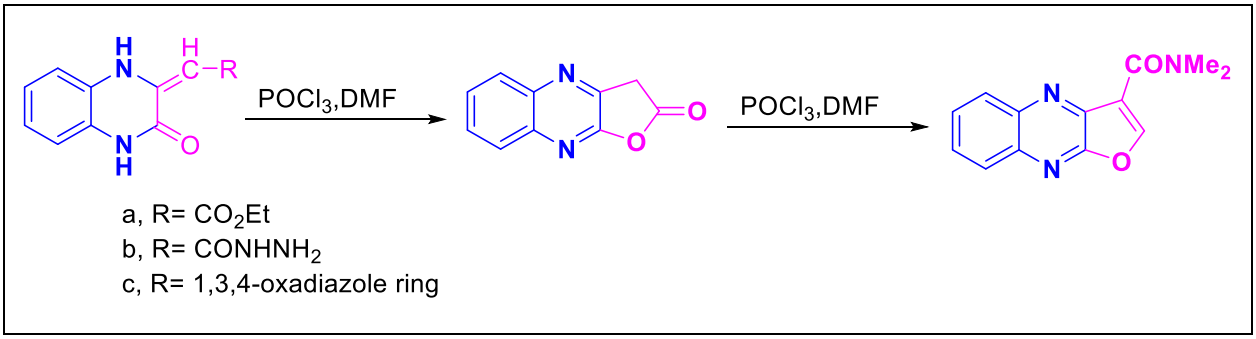
Abstract

The great therapeutic potential of furoquinoxalines has encouraged several researchers to develop distinct synthetic methods that lead to these heterocycles. The current review discusses and summarizes the numerous synthetic approaches of furoquinoxalines. Furo[2,3-*b*]quinoxaline and furo[3,4-*b*]quinoxaline are the two positional isomers of furoquinoxalines which gained much interest as biologically active compounds. This review offers a comprehensive survey of the different synthetic methods of both two compounds from various quinoxaline derivatives.



Keywords: Tricyclic fused quinoxalines, furo[2,3-*b*]quinoxalines, furo[3,4-*b*]quinoxalines and biological activities.

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1. Introduction

Heterocycles have long been recognized as one of the most active study areas in organic chemistry.[1] Quinoxaline is a member of the benzodiazine heterocyclic family, having nitrogen heteroatoms located at the 1- and 4-positions. Recent updates revealed that the chemistry of quinoxaline has sparked significant interest [2] due to its numerous chemical reactivities,[3-5] applicability in material science,[6, 7] and broad range of biological activities.[8, 9] The quinoxaline motif is known to constitute a class of medicinally relevant molecules that have antibacterial,[1, 2] antiviral,[10] antifungal,[8, 11] anticancer,[9, 12] antileishmanial[13] analgesic,[14] antimalarial,[15] antitumor, [16] antiamoebic,[17] antiepileptic,[18] anticonvulsant,[19] antitubercular,[20] antiproliferative,[21] anti-HCV,[22] and anti-inflammatory.[23] Compounds containing quinoxaline cores are employed as allosteric dual Akt1 and Akt2 inhibitors, human cytomegalovirus polymerase inhibitors,[24] Src-Family Kinase p56Lck inhibitors, [25] SRPK-1 inhibitors,[26] and monoamine oxidase A inhibitors.[27] Furthermore, the quinoxaline nucleus is found in many physiologically and pharmacologically active substances.[28]

Some nucleosides containing furan exhibit antiviral and antileukemic action in vitro (Figure 1).[29] The furo[2,3-*b*]pyrazine and furo[2,3-*b*]quinoxaline derivatives are effective inhibitors of PDE4B and sirtuins. The alkyl chain at the C-2 position of the furo[2,3-*b*]quinoxalines was important for the inhibition of the growth of cervical cancer (HeLa) cells **II** and **III** (Figure 1).[30, 31] Benthocyanin B prevents rat erythrocyte hemolysis and regulates the peroxidation of lipids generated by free radicals in rat liver microsomes **IV** (Figure 1).[32]

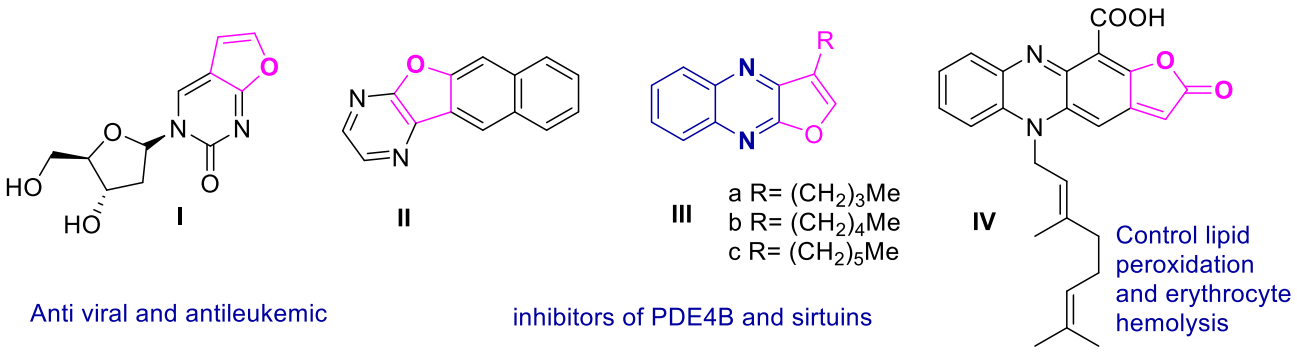

Figure 1. Some biologically active furo-fused *N*-heterocyclic derivatives

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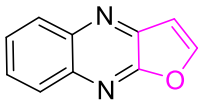
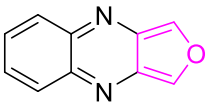
Furo[2,3-*b*]quinoxaline **1** and furo[3,4-*b*]quinoxaline **2** are the two positional isomers of furoquinoxalines that have the furan ring fused onto the quinoxaline ring at the side of pyrazine part. This review article aims to focus on these two isomers and their preparation. We reported herein the different synthetic methods of furoquinoxalines.



Furo[2,3-*b*]quinoxaline (**1**)



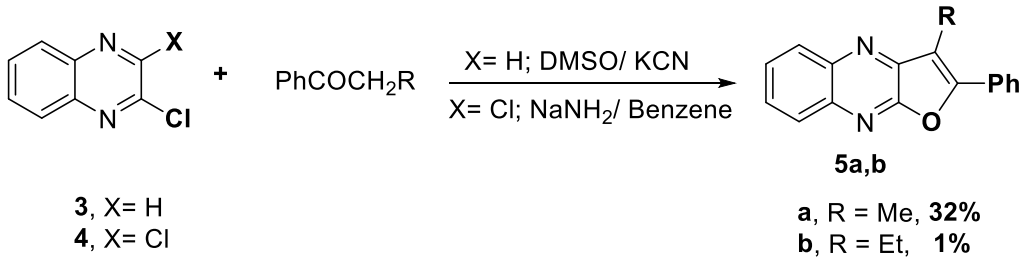
Furo[3,4-*b*]quinoxaline (**2**)

2. Synthesis of furo[2,3-*b*]quinoxalines

The documented synthesis of furo[2,3-*b*]quinoxaline ring systems was accomplished by building a furan ring onto a 2,3-disubstituted quinoxaline ring.

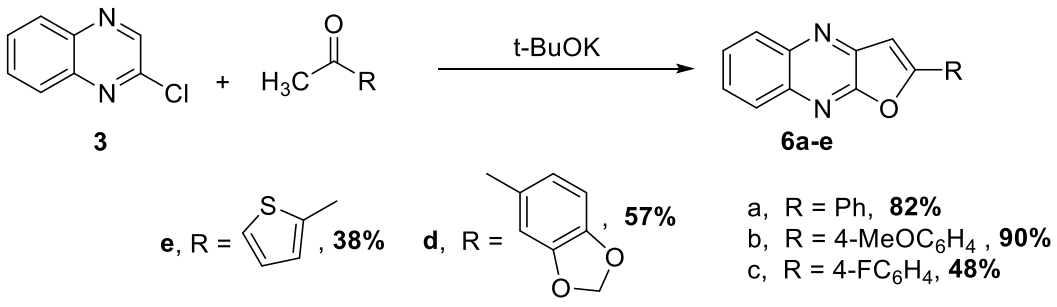
2. 1. From chloro/dichloroquinoxalines

It was reported that furo[2,3-*b*]quinoxaline derivatives **5a,b** were produced through the reaction of either chloroquinoxaline (**3**) with acetophenones in DMSO in the presence of KCN acting as a catalyst or the reaction of 2,3-dichloroquinoxaline **(4)** with acetophenones in benzene in the presence of sodamide ($NaNH_2$) as a catalyst (Scheme 1).[33]



Scheme 1. Synthesis of 2-phenylfuro[2,3-*b*]quinoxaline derivatives **5a,b**.

Ponomareva, *et al.*[34] modified this process with other ketones by conducting the reaction in THF with potassium t-butoxide as a catalyst (Scheme 2).



Scheme 2. Reaction of 2-chloroquinoxaline **3** with ketones.

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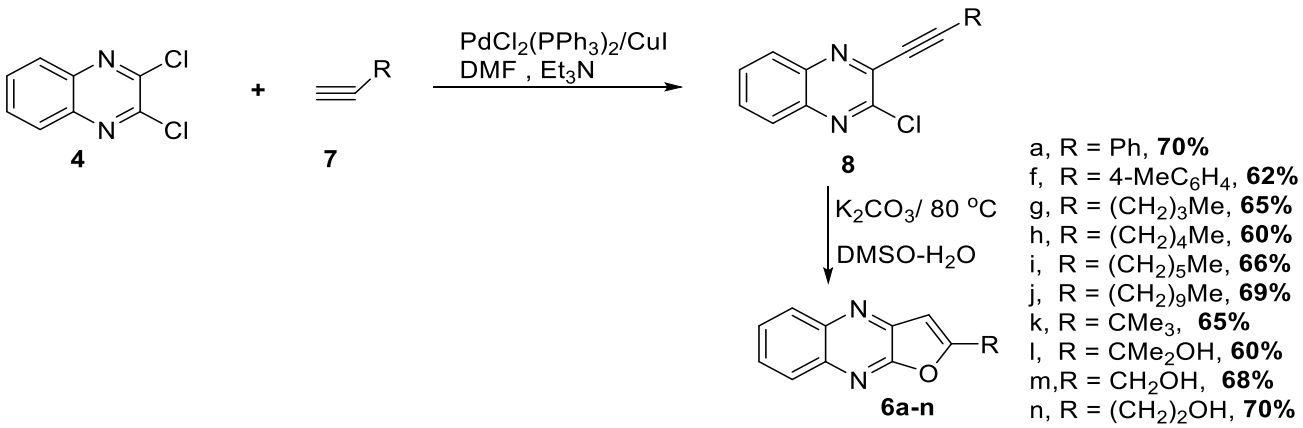
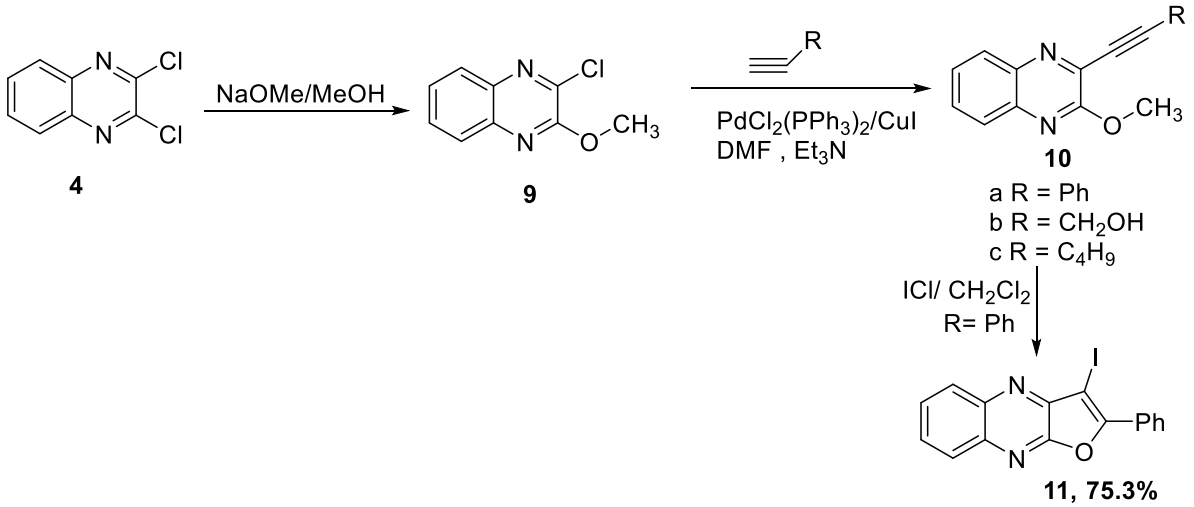
In 2013, Pal *et al.*[35] reported that the key starting material 2-chloro-3-(phenylethynyl) quinoxaline (**8**) which is required for the synthesis of furoquinoxaline derivatives was obtained via a selective mono alkylation of 2,3-dichloroquinoxaline (**4**) with terminal alkynes **7** under Pd–Cu catalysis. Hydrolysis of **8** followed by cyclization in the presence of K_2CO_3 afforded the corresponding furoquinoxaline derivatives **6a** and **6f-n** in fairly good yields (Scheme 3).



Scheme 3. Reaction of 2,3-dichloroquinoxaline **4** with terminal alkynes (**7**).

In 2016, Keivanloo et *al*[36] reported that a two-step process was used to illustrate the synthesis of 3-iodo-2-phenylfuro[2,3-*b*]quinoxaline (**11**). First, a Sonogashira coupling between phenyl acetylene and 2-chloro-3-methoxyquinoxaline (**9**), which was prepared by reacting 2,3-dichloroquinoxaline (**4**) with a mixture of NaOMe in MeOH at room temperature. Second, an iodine monochloride (ICl)-based electrophilic cyclization. Treatment of 2-chloro-3-methoxyquinoxaline (**9**) with a variety of terminal alkynes under the standard Sonogashira coupling conditions [$PdCl_2(PPh_3)_2$], CuI, Et_3N as the base, and DMF as the solvent] afforded high yields of the desired products (Scheme 4). Cyclization of **10** for the synthesis of 3-unsubstituted-2-phenylfuro[2,3-*b*]quinoxaline, as well as the one-pot Sonogashira coupling reaction/ heteroannulation of **9** with terminal alkynes, was failed.



Scheme 4. Two steps synthesis of 3-iodo-2-phenylfuro[2,3-*b*]quinoxaline (**11**).

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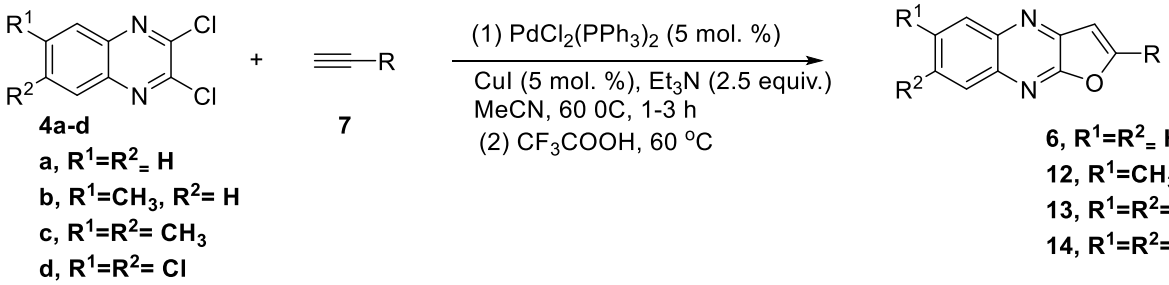
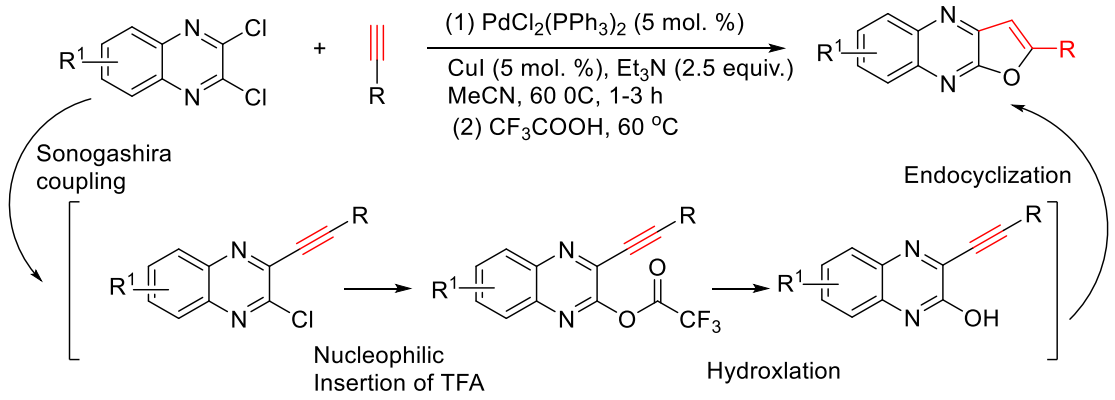


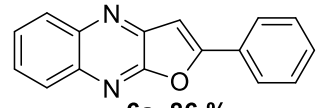
4a-d
a, R^1=R^2= H
b, R^1=CH_3, R^2= H
c, R^1=R^2= CH_3
d, R^1=R^2= Cl

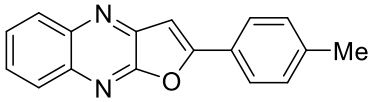
7

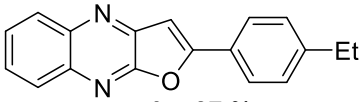
6, R^1=R^2= H
12, R^1=CH_3, R^2= H
13, R^1=R^2= CH_3
14, R^1=R^2= Cl

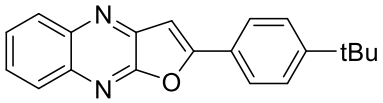
Designed approach for the synthesis of furoquinolines**.**

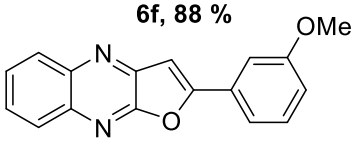


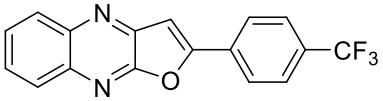

6a, 86 %

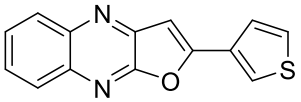

6f, 88 %

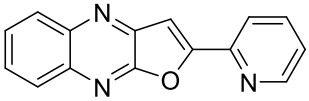

6o, 87 %

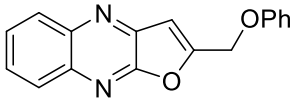

6p, 86 %

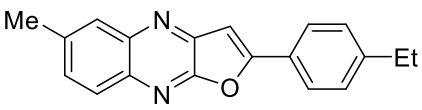

6q, 84 %

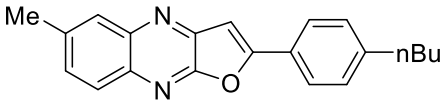

6R, 80 %

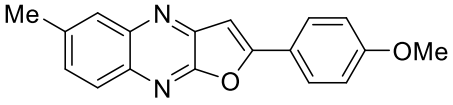

6S, 88 %

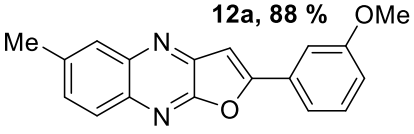

6t, 82 %

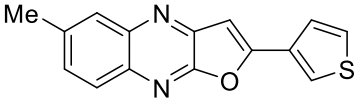

6u, 0%

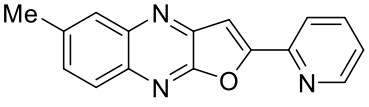

12a, 88 %

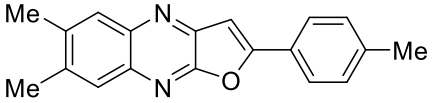

12b, 86 %

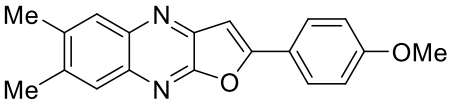

12c, 94 %

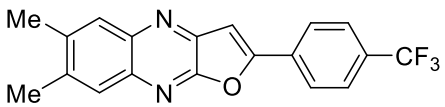

12d, 86 %

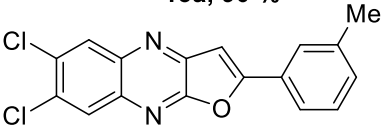

12e, 90 %

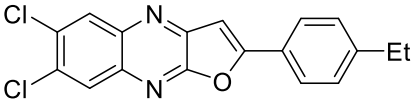

12f, 83 %

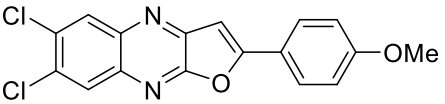

13a, 90 %


13b, 95 %


13c, 82 %


14a, 76 %


14b, 78 %


14c, 79 %

Scheme 5. Synthesis of highly functionalized furo[2,3-*b*] quinoxalines **6**, **12**-**14**.

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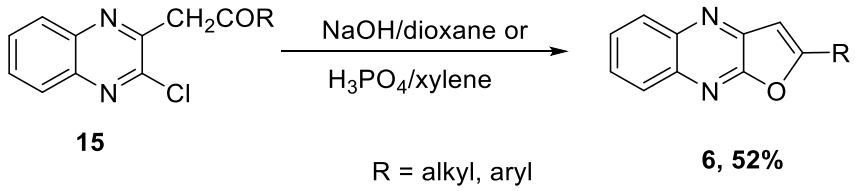
In 2017 Verma and co-workers[37] demonstrated an efficient metal-free approach for the synthesis of highly functionalized furo[2,3-*b*]quinoxalines. The reaction commences with a Pd/Cu-catalyzed alkylation of 2,3-dichloroquinoxaline (**4**), followed by ring closure in the presence of trifluoroacetic acid (TFA). This approach is appealing since no external oxidant is required. TFA serves as an oxygen source for oxyarylation and aids in the activation of the alkyne (Scheme 5). The alkylation of 2,3-dichloroquinoxaline derivatives (**4**) followed by ring closure in the presence of trifluoroacetic acid (TFA) can be explained in the Scheme 2.

A facile production of 2-substituted furo[2,3-*b*]quinoxalines **6** was accomplished by refluxing chloroquinoxaline derivative **15** with either sodium hydroxide in dioxane[38] or phosphoric acid in xylene[39] (Scheme 6).



Scheme 6. Synthesis of 2-substituted furo[2,3-*b*]quinoxalines **6** by using chloroquinoxaline derivatives **15**.

2.2. From 2-quinoxalinone derivatives

Recently, Jiang and co-workers[40] reported that furo[2,3-*b*]quinoxalines **6** were synthesized utilizing a copper catalyst and an oxidant in reactions of quinoxalin-2(1*H*)-ones **16a-g** and alkynes **7**. As a result, the extent of this C-H functionalization/annulation process was investigated with a range of *N*-unsubstituted quinoxalin-2(1*H*)-ones and alkynes (Scheme 7). Many phenyl ring substituents (*meta*-methyl, -fluorine, -chlorine, and -bromine) were efficient in producing the corresponding furo[2,3-*b*]quinoxalines **6a, 6v-z,** and **6i-iv** with yields ranging from 69 to 80%. The reactions involving alkyne derivatives with different substituents in the *para* position of the phenyl rings proceeded smoothly, and the corresponding furo[2,3-*b*]quinoxaline derivatives **6z** and **6i-iii** were generated in excellent yields. Additionally, the C-H functionalization/annulation was effective in producing the predicted compounds in yields of 60 (**17**), 74 (**18**), 77 (**19**), 85 (**20**), and 73% (**21**) from a variety of **16**. Finally, phenylacetylene and 6,7-dimethylquinoxalin-2(1H)-one were effectively coupled to generate the corresponding derivative **13d** in a 76% yield.

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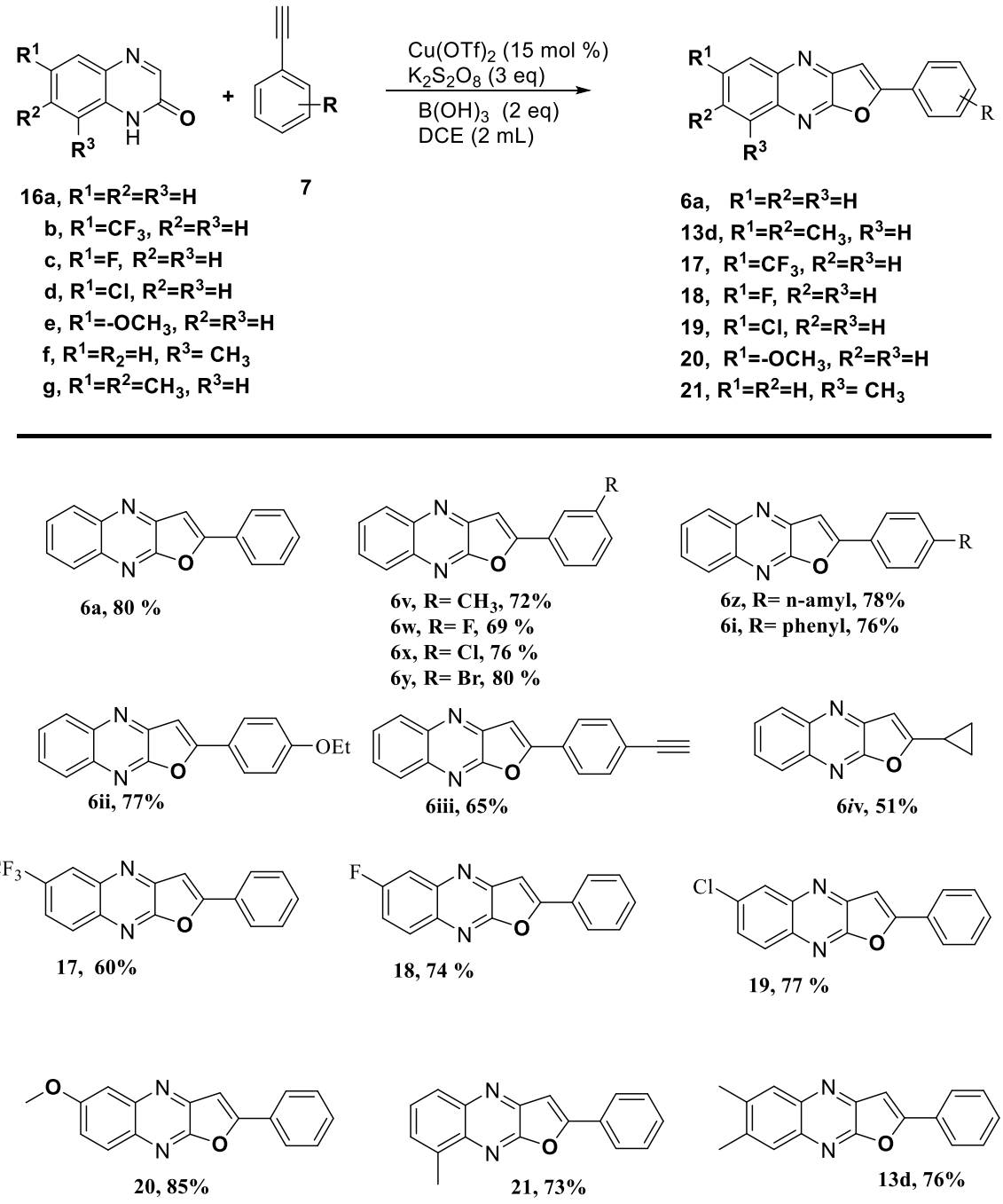

Scheme 7. Reaction of quinoxalin-2(1*H*)-ones **16** and alkynes **7** in the presence of copper catalyst and an oxidant.

In 2022, Mamedov and co-workers[41] reported that (*E*)-3-(styryl)quinoxalin-2(1H)-ones **22** might be employed as a structural basis for the synthesis of furo[2,3-*b*]-quinoxalines. Treatment of compounds **22a-g** with bromine in DMSO as a solvent afforded furo[2,3-*b*]-quinoxalines **23-29** with unexpected thiomethylation. at C-3 (Scheme 8).

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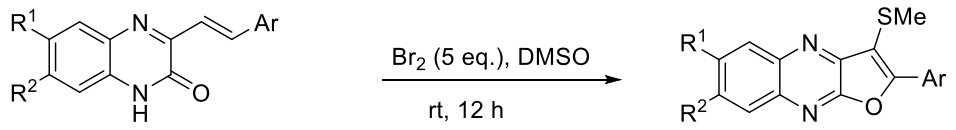
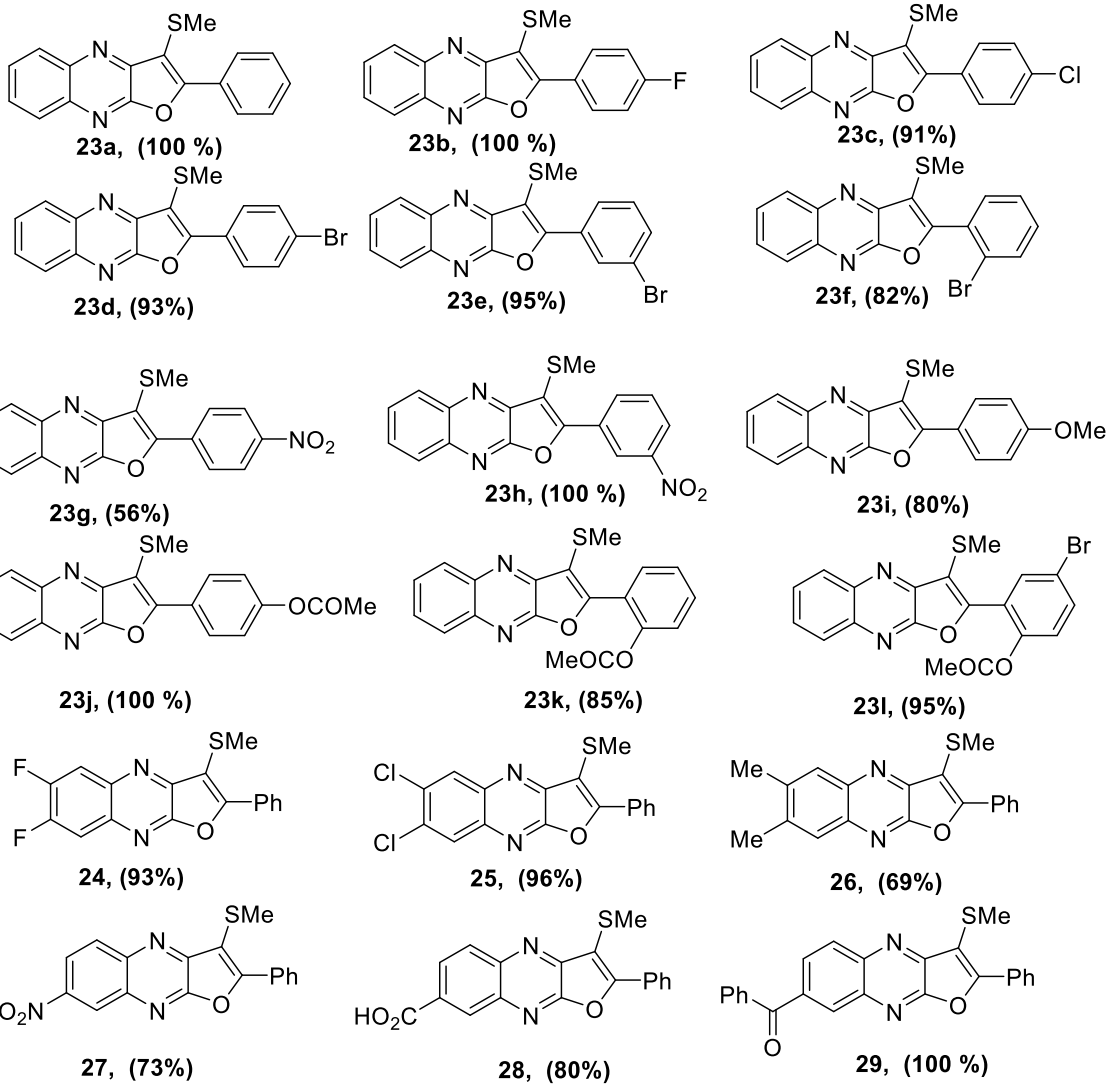


22 a, R^1=R^2=H
b, R^1=R^2=F
c, R^1=R^2=Cl
d, R^1=R^2=-CH_3
e, R^1=H, R^2=-NO2
f, R^1=H, R^2=-COOH
g, R^1=H, R^2= COPh

23a-l, R^1=R^2=H
24, R^1=R^2=F
25, R^1=R^2=Cl
26, R^1=R^2=-CH_3
27, R^1=H, R^2=-NO_2
28,R^1=H, R^2=-COOH
29, R^1=H, R^2=-COPh



Scheme 8. Synthesis of unexpected thiomethylated furo[2,3-*b*]-quinoxalines **23**-**29**.

The 2-keto quinoxalinone derivative **30** was cyclized by refluxing in Ac_2O with conc. H_2SO_4 to produce 2-substituted furo[2,3-*b*]quinoxalines **6** (Scheme 9).[42]

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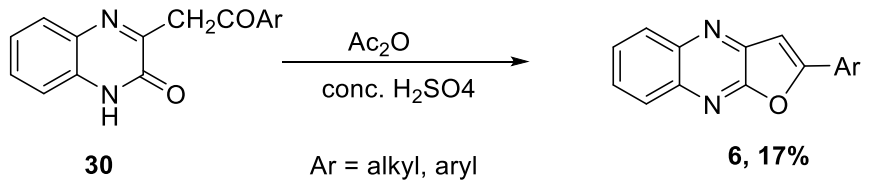
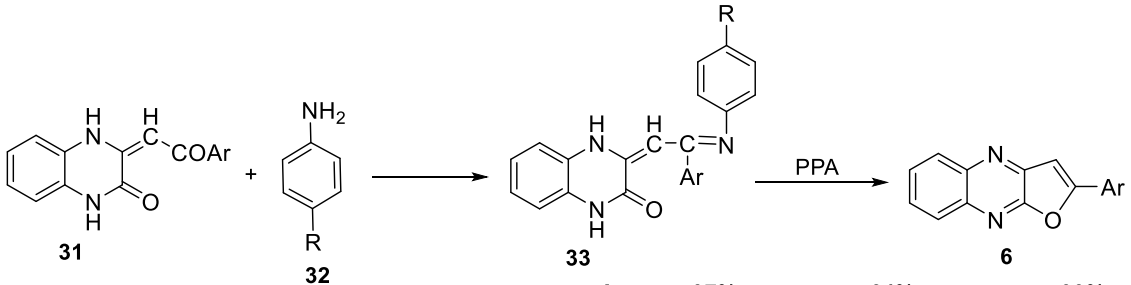


30 **6, 17%**

Scheme 9. Synthesis of substituted furo[2,3-*b*]quinoxalines **6** by cyclization of 2-keto quinoxalinone derivatives **30**.

Iminoquinoxalone derivative **33** was synthesized by reacting phenacylidene quinoxaline derivative **31** with *p*-substituted aniline **32** and then cyclized with polyphosphoric acid (*PPA*) to 2-substituted furo[2,3-*b*] quinoxalines **6** with removing of the imino moiety from the starting material (Scheme 10).[43]

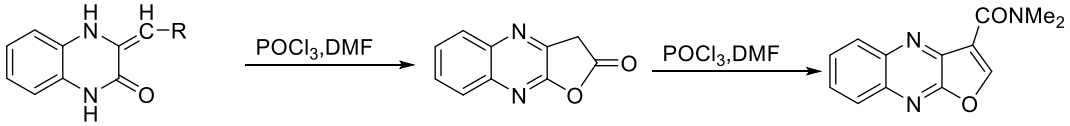


31 **32** **33** **6**

Ar = Ph, **97%,** 4-MeC_6H_4 , **64%**, 4-$MeOC_6H_4$,**99%,** 4-ClC_6H_4 , **90.5%**, 4-BrC_6H_4 , **50%**

Scheme 10. Synthesis of furo[2,3-*b*]quinoxalines starting with phenacylidene quinoxaline derivatives.

Treatment of 3-substituted methylene-2-quinoxalinone (**34a**, R=CO_2Et) with $POCl_3$ in DMF gave the 3-(*N,N*-dimethylaminocarbonyl)furo[2,3-*b*]quinoxaline **36.**[44] In the case of other substituents of compound (**34b**, R= $CONHNH_2$, and **34c**, R= oxadiazole ring) gave the same product **36**, which ascertains that the reaction should pass through the formation of intermediate **35**(Scheme 11).[45]



34a, R=-CO_2Et **35** **36, 62.2%**
b, R=- $CONHNH_2$
c, R= 1,3,4-oxadiazole ring

Scheme 11. Synthesis of the 3-(*N,N*-dimethylaminocarbonyl)furo[2,3-*b*]quinoxaline **36**.

It has been reported that the acetylenic quinoxalinone derivative **37** was cyclized to **6a** when treated with potassium hydroxide in dioxane (Scheme 12).[46]

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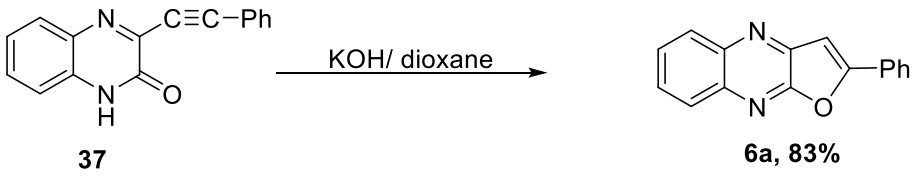
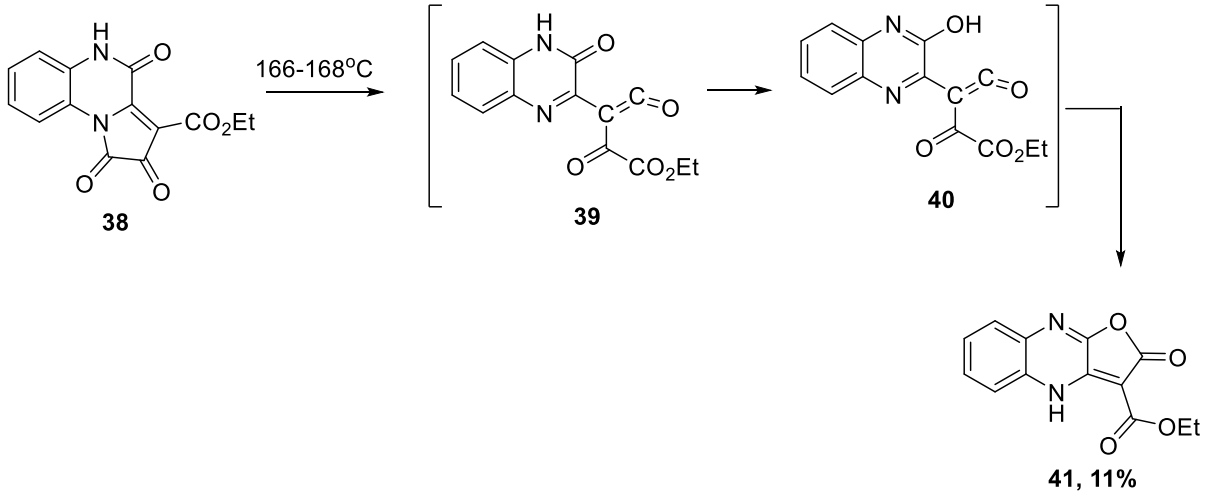


Scheme 12. Synthesis 2-substituted furo[2,3-*b*]quinoxaline **6a** by Cyclization of acetylenic quinoxalinone **37**.

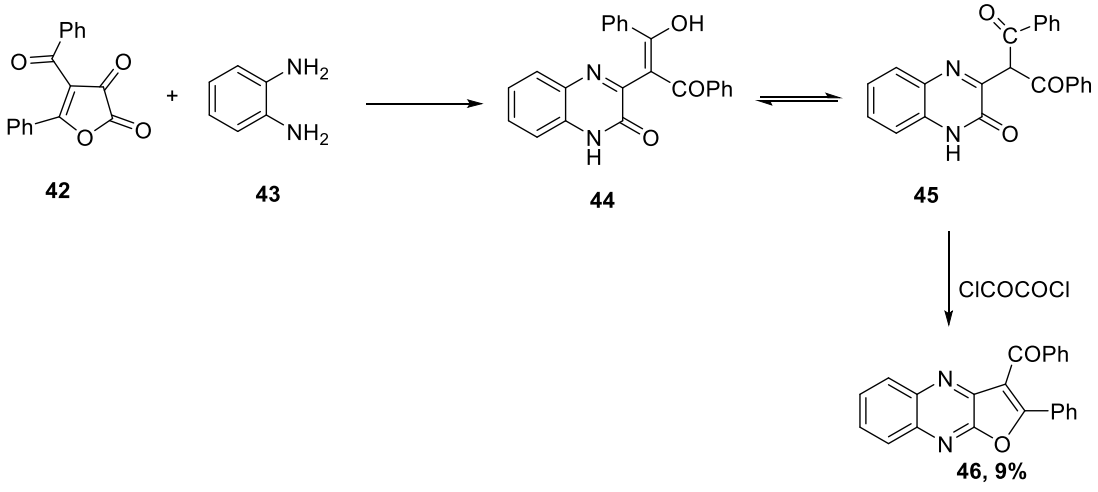
Moreover, It has been found that the pyrolysis of pyrroloquinoxalinone derivative **38** at 166-168 °C produced furoquinoxaline derivative **41** *via* intermediates **39** and **40** (Scheme 13).[47]



Scheme 13. Synthesis of furoquinoxalines **41** by pyrolysis of pyrroloquinoxalinone derivative **38**.

2.3. Synthesis from *o*-phenylenediamine

Furthermore, condensation of furandione derivative **42** with *o*-phenylenediamine **43** gave ketoquinoxalinone derivative **44**, which could toutmerized to keto structure **45** under reaction condition. Refluxing of compound **45** with oxalyl chloride,[48,49] gave the furoquinoxaline derivative **46** (scheme 14).



Scheme 14. Reaction of *o*-phenylenediamine **43** and furandione **42** derivative to give furoquinoxaline **46**.

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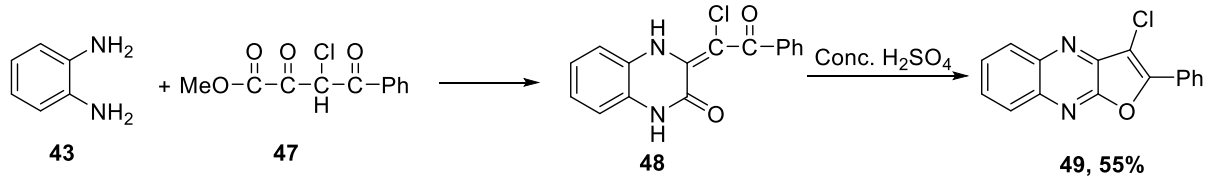
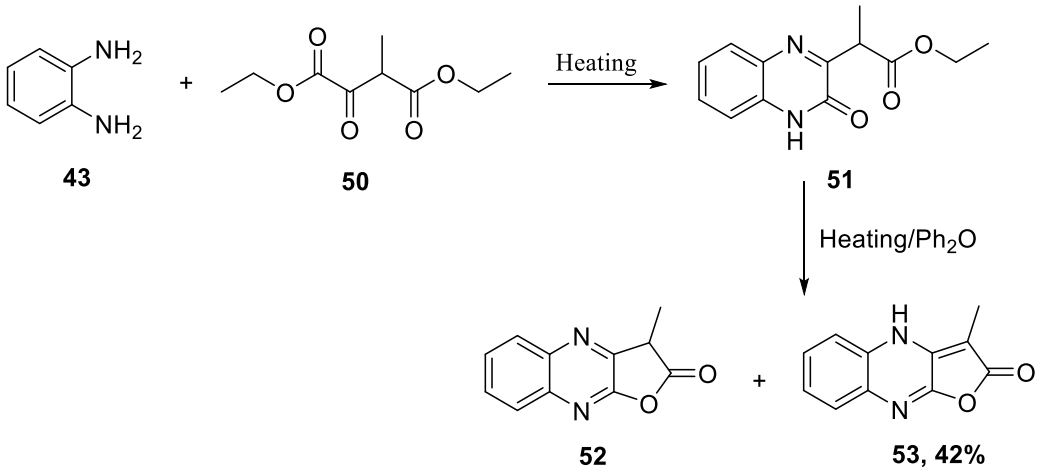
Reaction of chlorobenzoyl pyroracemic acid esters **47** with **43** afforded, ketoquinoxaline derivative **48** which cyclized in the presence of conc. H_2SO_4 giving 3-chloro-2-substituted furo[2,3-*b*]quinoxaline **49**.[50, 51]



Scheme 15. Synthesis of 3-chloro-2-substituted furo[2,3-*b*]quinoxaline **49**.

L'Italien and Banks[52] originally synthesized quinoxalinone ester **51** through the reaction between **43** and ethyl ethoxalylpropionate **50**. Heating of **51** in diphenyl ether afforded furoquinoxalines **52** and **53** (Scheme 16).[53]



Scheme 16. Synthesis of furoquinoxalines **52** and **53.**

Condensation between *o*-phenylenediamine **43** and *o*-hydroxyacetophenones **54** afforded benzofuroquinoxalines **55a-i**. The reaction was facilitated using an elemental sulphur mediator, DABCO (1,4-diazabicyclo[2.2.2]octane) as a base, and DMSO as a solvent (Scheme 17).[54]

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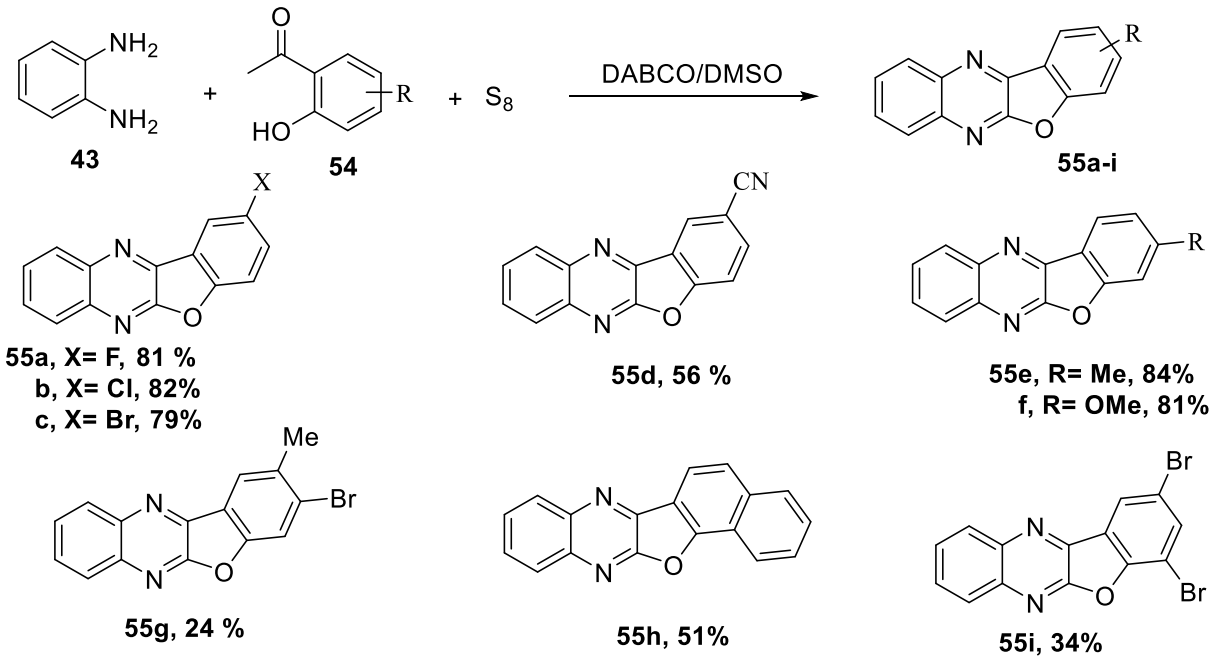
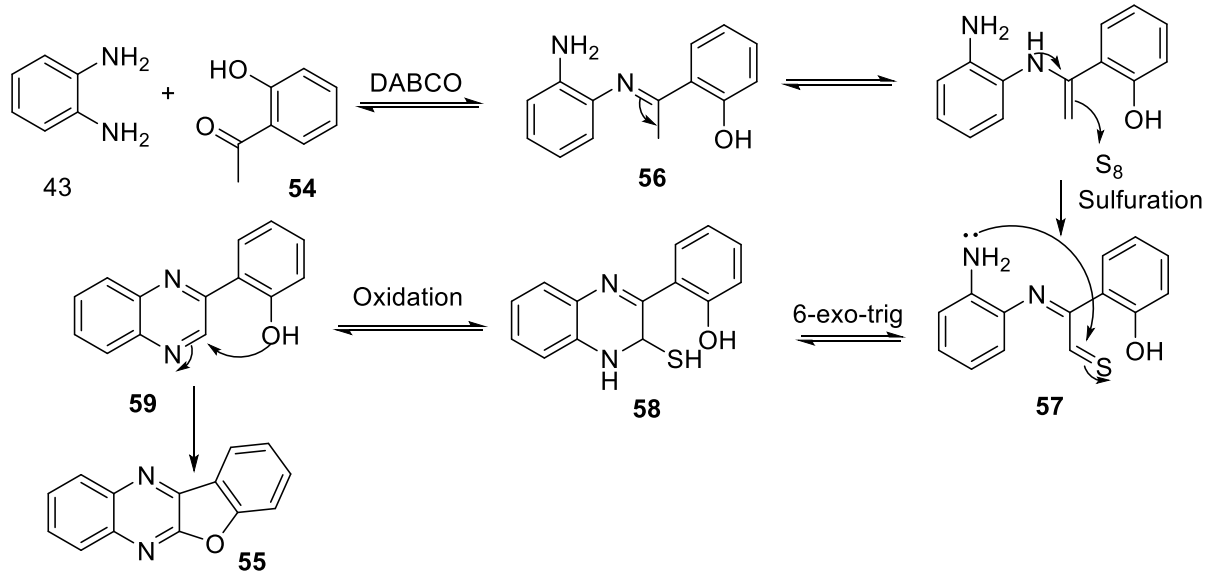


Scheme 17. Synthesis of benzofuroquinoxalines **55a-i** by reaction between *o*-phenylenediamine **32** and *o*-hydroxyacetophenones **54**.

The proposed mechanism for the condensation of **43** and the ketone functionality **54** would produce the corresponding imine **56**. Tautomerization of formed imine followed by sulfuration of α C–H bonds afforded Willgerodt–Kindler type iminothioaldehyde **57**. A hemi thioaminal **58** would result from a fast 6-exo-trig cyclization. The oxidation of **58** resulted in the corresponding furoquinoxaline **55** (Scheme 18).



Scheme 18. The proposed mechanism for the condensation of *o*-phenylenediamine **43** and the ketone **54**.

In 2014, Narender and co-workers [55] described an effective one-pot approach for the synthesis of furo[2,3-*b*]quinoxalines (**6a**, **12d**, **13d**, **14d**, **17**, **18**, **19**, and **20**) from commercially available *o*-

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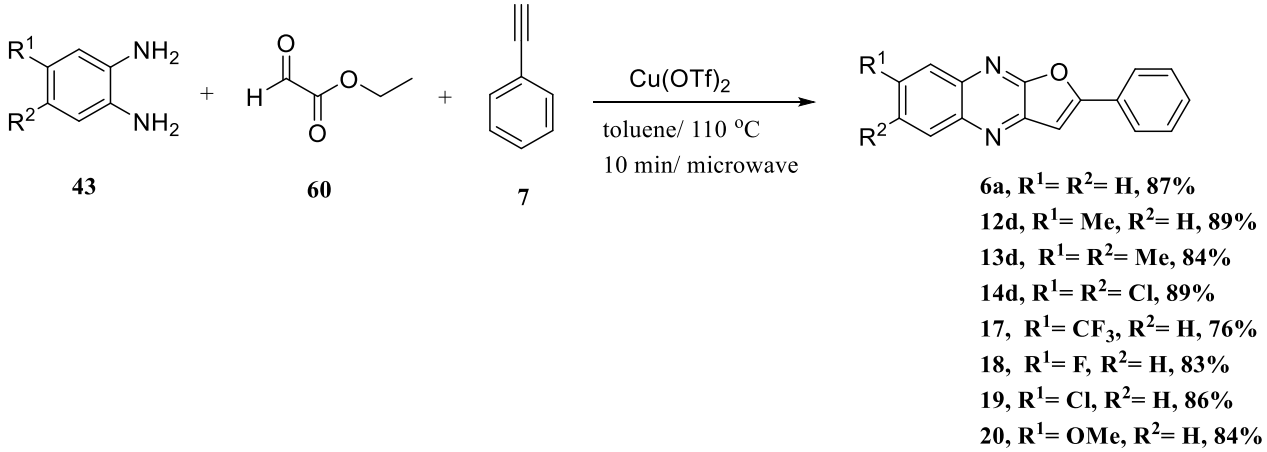
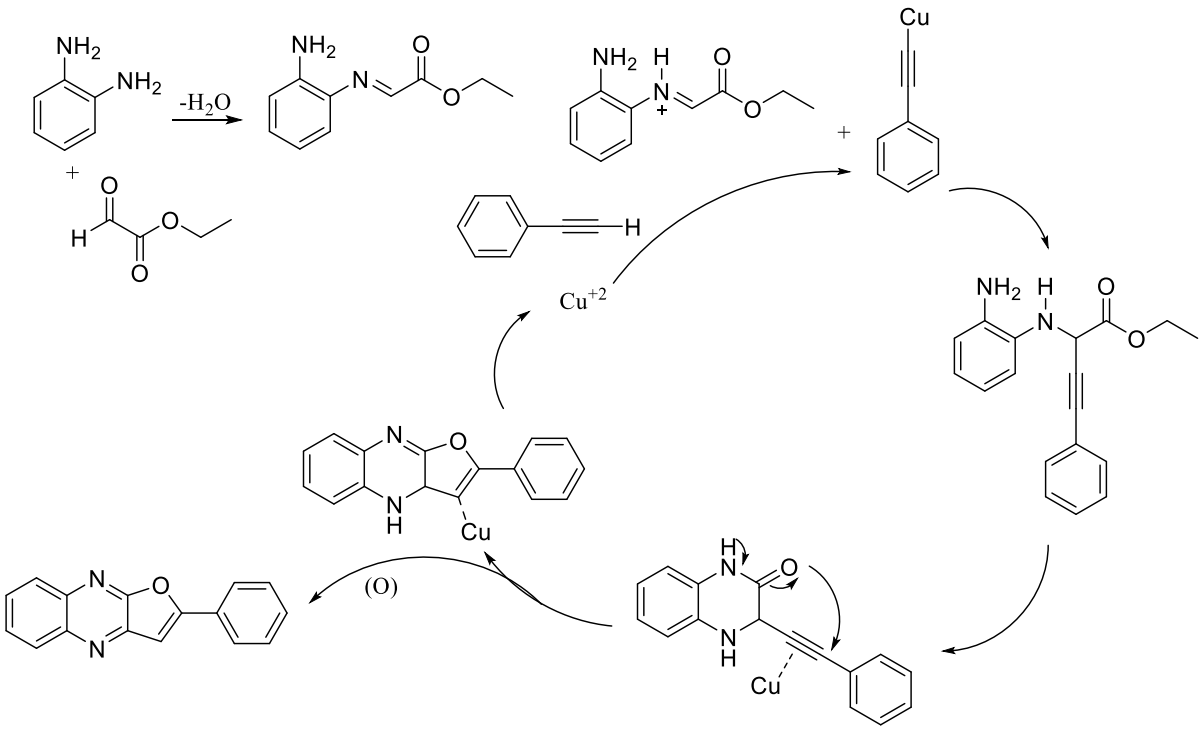
phenylenediamine **43**, an ethylglyoxalate **60** in 50% solution in toluene, and phenylacetylene **7** using copper (II) trifluoromethanesulfonate (10 mol%) as the catalyst in a microwave reactor. The requested furoquinoxaline (**6a, 12d, 13d, 14d, 17**, **18**, **19**, and **20**) was isolated in a 35% yield consequently, with a 50% conversion of the starting materials (Scheme 19).



Scheme 19. One pot three components reaction for the synthesis of furo[2,3-*b*]quinoxalines (**6**a, **12d**, **13d**, **14d**, **17**, **18**, **19**, and **20**).

A probable reaction mechanism for the production of furo[2,3-*b*]quinoxalines (**6**a, **12d**, **13d**, **14d**, **17**, **18**, **19**, and **20**) appears to involve tandem C−C bond formation followed by a 5-endo-dig cyclization reaction as outlined in scheme 20.



Scheme 20. A probable reaction mechanism for the production of furo[2,3-*b*]quinoxalines (**6a**, **12d**, **13d**, **14d**, **17**, **18**, **19**, and **20**).

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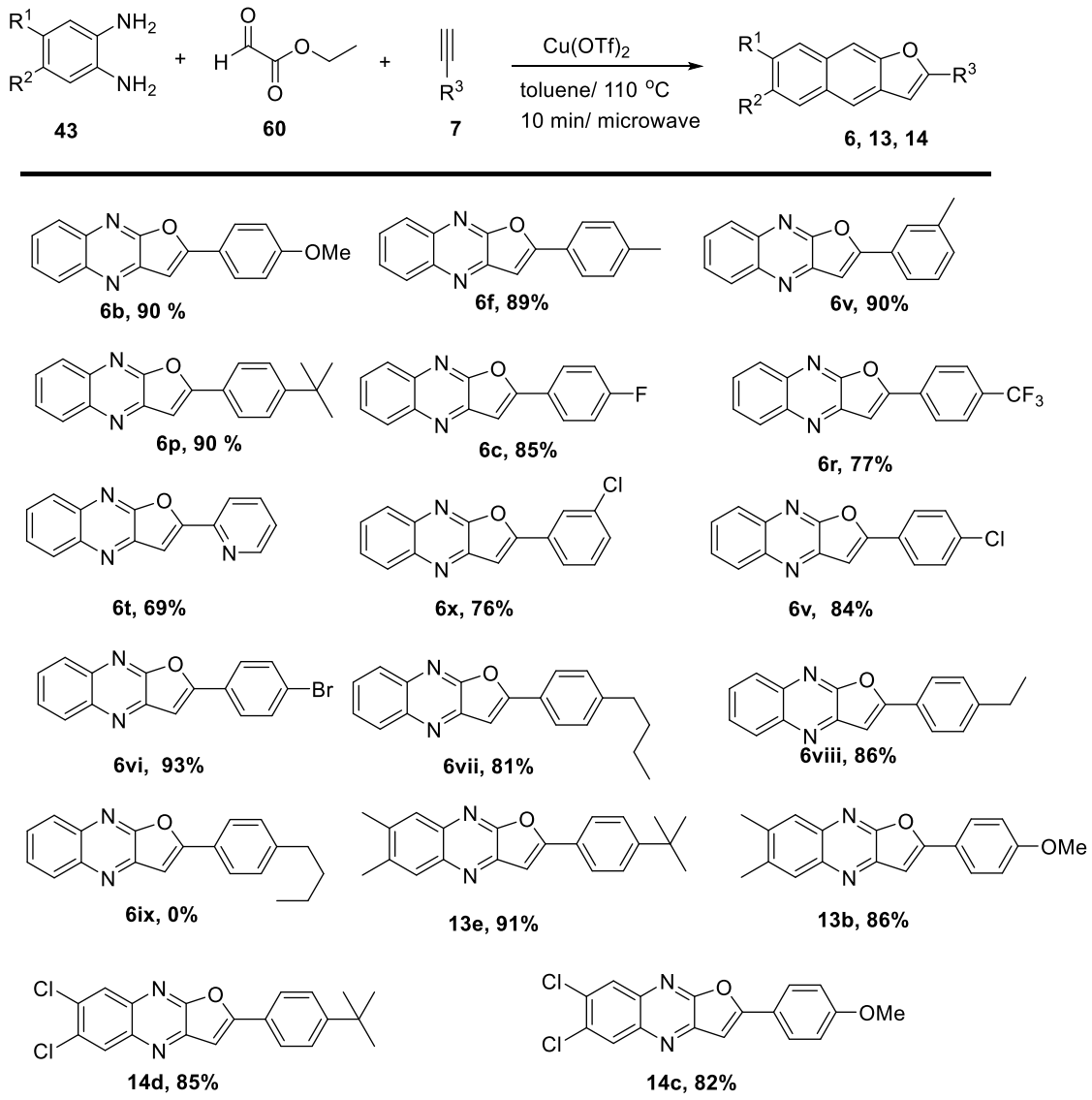
In addition, interesting derivatives of furo [2,3-*b*]quinoxalines **6, 13** and **14** were synthesized from widely accessible *o*-phenylenediamine derivatives **43**, ethylglyoxalate **60**, and terminal alkynes via tandem A_3-coupling followed by cyclization in a single step. In this revolutionary approach, four new bonds (2C−C, C−N, and C−O) are formed in a cascade pathway (Scheme 21).[55]



Scheme 21. Synthesis of furo[2,3-*b*]quinoxalines **6, 13** and **14** using *o*-phenylenediamine **43** ethylglyoxalate **60**, and terminal alkynes **7**.

In 2018, Reddy *et al.* reported a straightforward and useful procedure for the synthesis of a series of furo[2,3-*b*] quinoxalines **6a, 13d, 14e, 61-65** employing novel $Cu(OTf)_2$ loaded protonated trititanate nanotube [HTNT] catalysts by refluxing *o*-phenylenediamines **43**, ethylglyoxalate **60** 50% solution in toluene, and phenylacetylene in acetonitrile (Scheme 22).[56]

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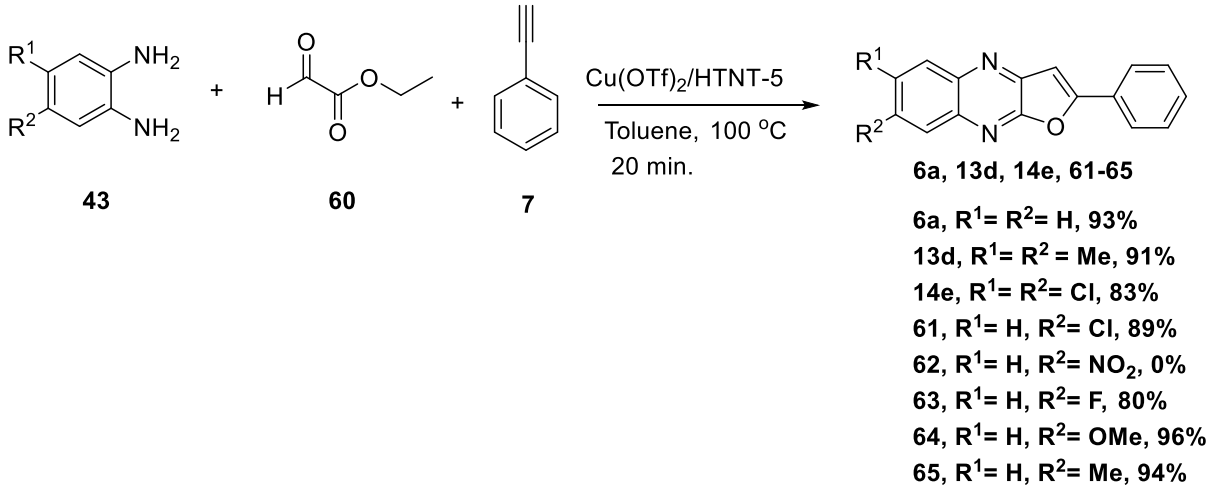
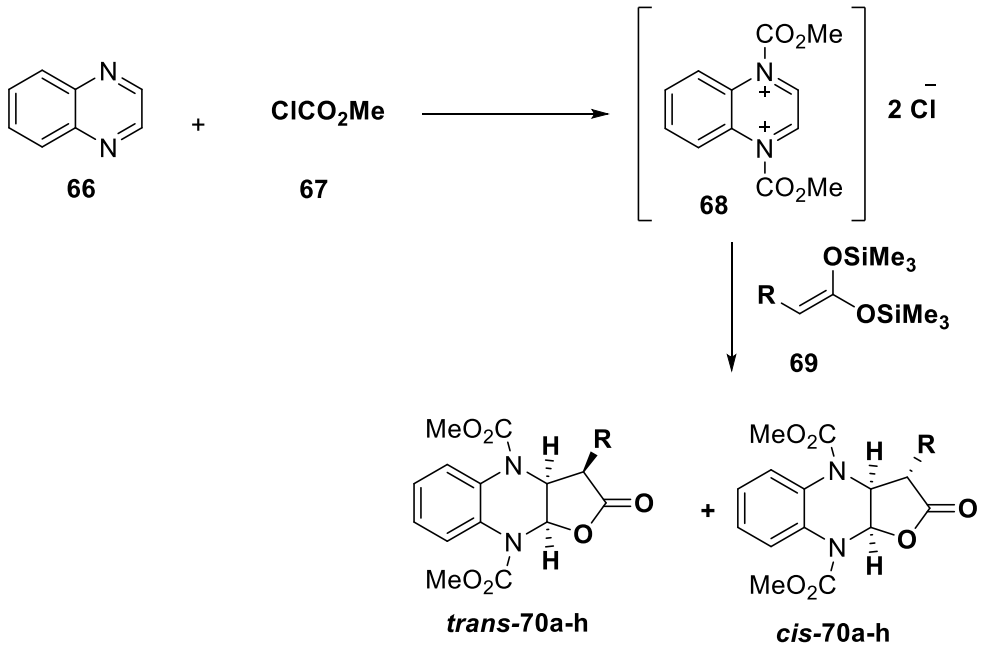


Scheme 22. Synthesis of furo[2,3-*b*] quinoxalines **6a, 13d, 14e, 61-65** using novel $Cu(OTf)_2$ loaded protonated tri titanate nanotube [HTNT] catalysts.

2.4. Synthesis from quinoxaline

Langera *et al.*[57] described that furo[2,3-*b*]quinoxalines were synthesized by reacting 1,1-bis(trimethylsiloxy)ketene acetal **69** with quinoxaline **66** in the presence of methyl chloroformate **67** to produce a separable mixture of diastereomers of *trans*- and *cis*-**70** *via* the formation of bis(iminium salt) **67** (Scheme 23, table 1)



Scheme 23. Synthesis of furo[2,3-*b*]quinoxalines as two diastereomers (*cis*- and *trans*-) **70a-h**.

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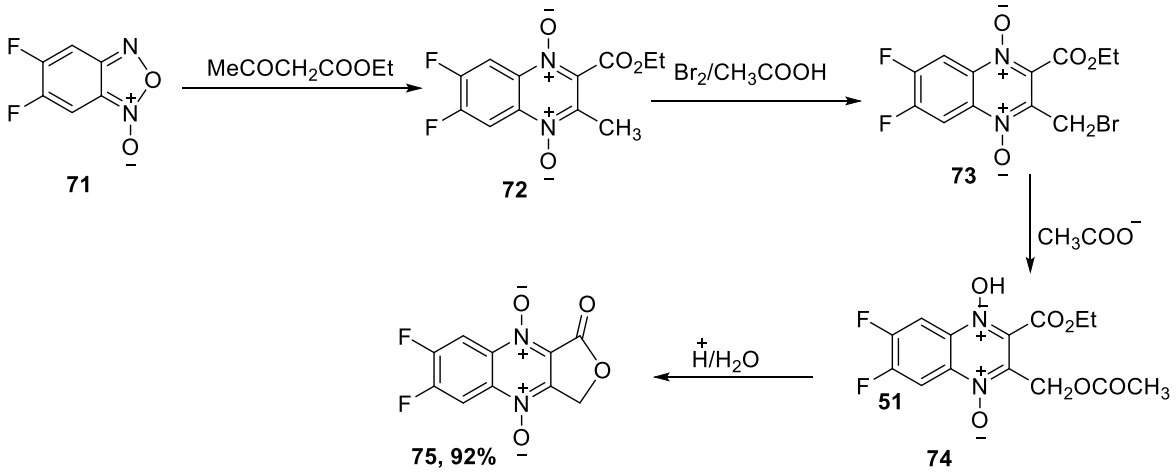
Table 1. Products and yields of **70**

70	R	% (trans-**70**)	% (cis-**70**)
a	Et	19	28
b	^{n}Pr	29	21
c	^{n}Bu	11	25
d	^{n}Dodec	30	15
e	^{i}Pr	27	33
f	^{c}Hex	28	27
g	$CH_2(^{c}Pent)$	32	24
h	$(CH_2)_2(^{c}Hex)$	25	12

3. Synthesis of furo[3,4-*b*]quinoxaline

The first synthesis of fluorinated derivatives of furo[3,4-*b*] quinoxaline 4,9-dioxides was reported.[58, 59] This uncommon ring system was created by starting with 5,6-difluorobenzofuroxane **71** which was converted to 2-ethoxycarbonyl-6,7-difluoro-3-methylquinoxaline-1,4-dioxide (**72**) by the Beirut reaction with ethyl acetoacetate in the presence of triethylamine. Bromination of **72** in DMF-$CHCl_3$ or in a mixture of acetic acid and conc. H_2SO_4 yielded the bromomethyl derivative **73.** Nucleophilic substitution of the bromo atom of **73** with acetate anion gave the corresponding acetoxy derivative **74** with retention of both fluorine atoms. Acidic hydrolysis of **74** with conc. HCl caused a spontaneous cyclization of the intermediate hydroxymethyl derivative into lactone 6,7-difluoro-1-oxo-2,3-dihydrofuro[3,4-*b*]quinoxaline 4,9-dioxide (**75**) (Scheme 24).



Scheme 24. Straightforward synthesis of furo[3,4-*b*]quinoxaline **75** starting with 5,6-difluorobenzofuroxane **71**.

Conclusions

Quinoxalines are interesting because certain naturally occurring substances, such as triostine and echinomycine, have strong biological activity and include the quinoxaline skeleton. Quinoxaline condensates are significant quinoxaline derivatives due to their structural, biological, physiological-pathological, and

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medicinal properties. This review summarizes the different synthetic methods and recent development approaches of two furoquinoxaline derivatives namely, furo[2,3-*b*]quinoxalines and furo[3,4-*b*]quinoxaline .

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