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Recent advances in the transition-metal-free synthesis of quinoxalines

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Quinoxalines, also known as benzo[a]pyrazines, constitute an important class of nitrogen-containing heterocyclic compounds as a result of their widespread prevalence in natural products, biologically active synthetic drug candidates, and optoelectronic materials. Owing to their importance and chemists' ever-increasing imagination of new transformations of these products, tremendous efforts have been dedicated to finding more efficient approaches toward the synthesis of quinoxaline rings. The last decades have witnessed a marvellous outburst in modifying organic synthetic methods to create them sustainable for the betterment of our environment. The exploitation of transition-metal-free catalysis in organic synthesis leads to a new frontier to access biologically active heterocycles and provides an alternative method from the perspective of green and sustainable chemistry. Despite notable developments achieved in transition-metal catalyzed synthesis, the high cost involved in the preparation of the catalyst, toxicity, and difficulty in removing it from the final products constitute disadvantageous effects on the atom economy and eco-friendly nature of the transformation. In this review article, we have summarized the recent progress achieved in the synthesis of quinoxalines under transition-metal-free conditions and cover the reports from 2015 to date. This aspect is presented alongside the mechanistic rationalization and limitations of the reaction methodologies. The scopes of future developments are also highlighted.

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1. Introduction

Nitrogen-containing heterocycles, of natural and synthetic origin, represent a huge family of indispensable structural motifs and have attracted enormous attention in synthetic and medicinal chemistry as well as in material sciences owing to

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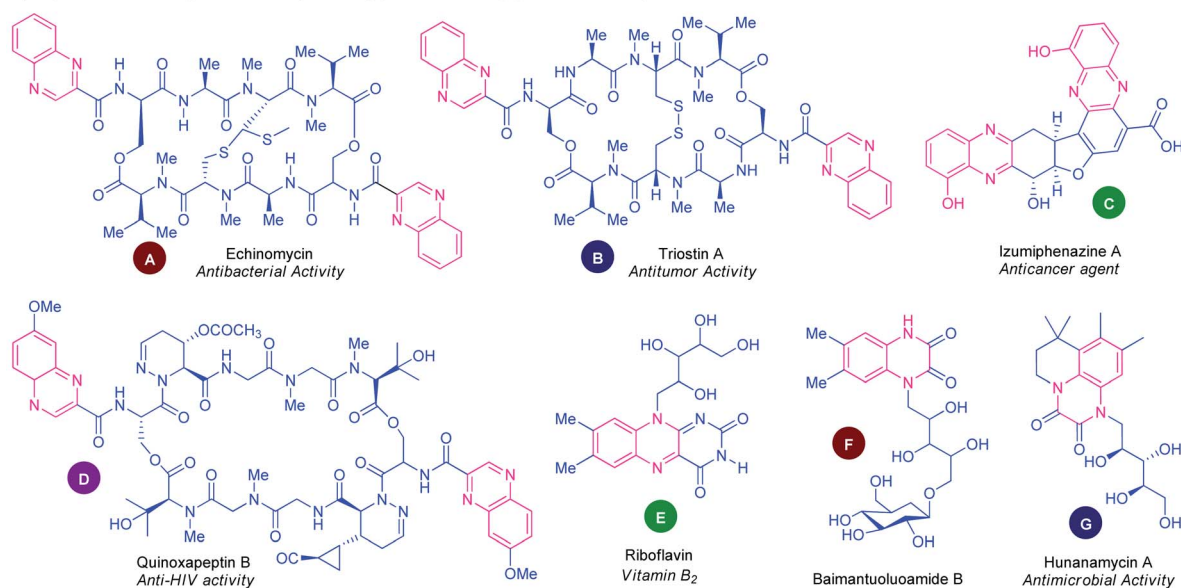


their wide-ranging chemical landscape and prolific bioactivity profiles.¹ Among various nitrogen heterocycles, quinoxalines and their derivatives have been considered as versatile and privileged structural scaffolds in synthetic and medicinal chemistry.² These well-established nitrogen-containing bicyclic heterocycles mainly consist of a benzene ring fused with a pyrazine ring in their structure. Quinoxalines structural motifs are widely distributed in the architecture of numerous natural products,³ pharmaceutical agents,⁴ agrochemicals,⁵ pharmacologically active synthetic compounds.⁶ They have been found to possess a diverse range of biological activities including anti-diabetic,⁷ antimicrobial,⁸ anticancer,⁹ antituberculosis,¹⁰ anti-bacterial,¹¹ anti-inflammatories,¹² anti-HIV,¹³ antiviral,¹⁴ PI3K γ inhibitors,¹⁵ cyclooxygenase 2 (COX-2) inhibitors,¹⁶ antimalarial,¹⁷ anti-dengue,¹⁸ antioxidant,¹⁹ anticonvulsant,²⁰ antidepressant,²¹ antitumors,²² antiplasmodial,²³ antileishmanial activity,²⁴ and antiprotozoal activity.²⁵

Several natural products that featured quinoxaline rings as an integral part are depicted in Fig. 1A. The natural product echinomycin (**A**) isolated from *Streptomyces echinatus* sp. was established for the first time in 1957.²⁶ They have been found to possess anti-bacterial activity against Gram-negative organisms and have good anti-tumour activity. Another natural product triostin A (**B**) was isolated from *Streptomyces aureus* S-2-210 and has antitumor and antibacterial activity.²⁷ Lumiphenazines (**C**) possesses anticancer activity was isolated from *Streptomyces* sp. IFM 11204.²⁸ The natural product quinoxapeptin B (**D**) isolated from *Betula papyrifera* has been known for its anti-HIV activity.²⁹ Quinoxalines are the building blocks of vitamin B₂. Two marine alkaloids baimantuoluamide B (**F**) and hunanamycin A (**G**) were isolated from alkaloidal fraction *Datura metel* L and *Bacillus hunanensis*.³⁰

Besides these natural products, non-natural quinoxalines displayed prominent biological activities. In this pursuit, several quinoxaline-containing drugs and synthetic compounds

A) Representative examples of naturally occurring products bearing quinoxaline moiety



B) Representative examples of commercially available drugs and bioactive synthetic compounds bearing quinoxaline moiety

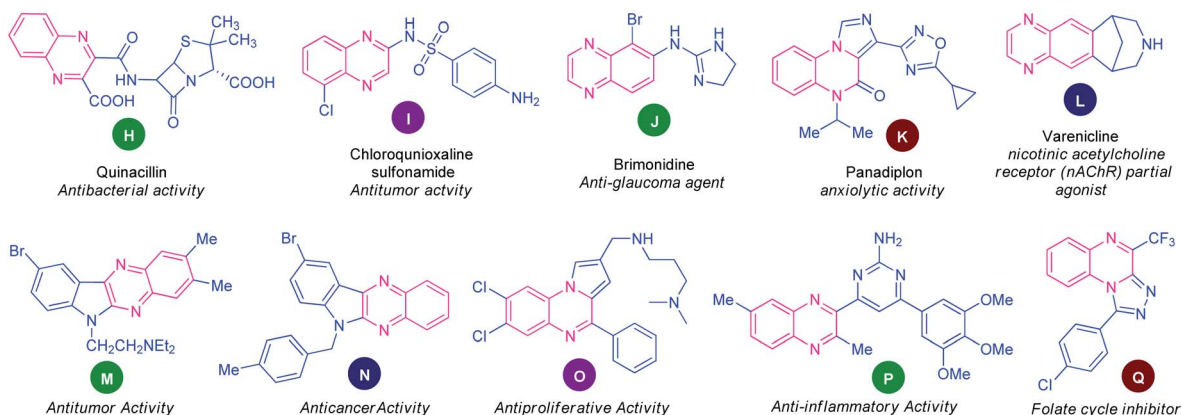


Fig. 1 Representative examples of natural products, drugs, and bioactive synthetic compounds containing quinoxaline ring.



of pharmacological profiles have been discovered (Fig. 1B). Quinacillin (**H**) is a quinoxaline-based semisynthetic penicillinase-resistant penicillin and has antibacterial activity.³¹ Chloroquinoxaline sulfonamide (**I**) is a topoisomerase II α/β -poison and is active against murine and human solid tumours.³² Brimonidine (**J**) is a commercially available α_2 adrenergic agonist used to treat open-angle glaucoma, ocular hypertension, and rosacea.³³ Panadiplon (**K**) acts as a high-affinity GABAA receptor partial agonist with anxiolytic activity.³⁴ Varenicline (**L**) is a quinoxaline-based $\alpha_4\beta_2$ nicotinic receptor partial agonist drug available in the market and is used for smoking cessation.³⁵ Still, there are lots of quinoxaline derivatives possessing different biological activities which are under the stage of preclinical or clinical development. Several synthetic quinoxaline-based compounds **M**, **N**, **O**, **P**, and **Q** exhibited potent pharmacological activities such as anti-tumor,³⁶ anticancer,³⁷ antiproliferative,³⁸ anti-inflammatory,³⁹ and folate cycle inhibitors⁴⁰ respectively.

Despite these wide-ranging biological activities, a diverse molecular structure that featured the quinoxaline framework has been established as potential fragments in diverse areas of materials science. The applications included organic photovoltaic devices,⁴¹ organic semiconductors,⁴² electroluminescent materials,⁴³ fluorescent probes,⁴⁴ organic light-emitting diodes (OLEDs),⁴⁵ organic solar cells,⁴⁶ sensitizers for dye-sensitized solar cells,⁴⁷ polymer light-emitting diodes (PLEDs),⁴⁸ and fuel cells.⁴⁹

Considering the wide-ranging application and tremendous chemical landscape, a great deal of attention has been subjected toward the synthesis of quinoxalines in the last decades. However, most of the synthetic strategy utilizes hazardous reagents, toxic volatile solvents, harsh reaction condition, and high energy inputs that adversely affects the overall chemical process as well as the environment from being making eco-friendly and sustainable nature.

Despite, transition metal catalyst has been proven as a powerful catalyst and successfully employed in many organic synthesis for the diverse construction of valuable structural frameworks,⁵⁰ they possess many limitations and drawbacks in terms of synthetic efficiency and green chemistry point of view. The high cost involved in the preparation of transition metal catalyst alongside the requirement of non-commercial supporting ligands marks major limitations of transition metal catalysis. In addition, they are very sensitive to air and moisture. The removal of transition metal catalysts from a reaction mixture which is particularly crucial to the pharmaceutical industry often becomes a formidable challenge and is very expensive. The requirements of co-catalysts and additives in some cases for enhancing the efficacy and reactivity of the transition metal-catalyzed transformation once again point towards the failure of green and more sustainable synthesis. Consequently, the occurrence of transition metal catalyst even at the lowest loading corresponds to disadvantageous effects on the eco-friendly and environmentally friendly nature of the chemical process.⁵¹ Intriguingly, the development of a chemical process that employed alternative materials for the synthetic purpose which are not only environmentally friendly but also

readily accessible at bulk quantities in anywhere at a very low price, for the construction of structural complexity with high atom- and step-economy by avoiding the requirements of transition metal catalysts, co-catalyst, any additives are highly desired.

Recently, transition-metal-free reactions have been demonstrated as an efficient and environmentally benign strategy toward the synthesis of heterocyclic compounds and have been emerged as a key fascinating area in synthetic organic chemistry.⁵² They have several advantages in comparison to organic transformations involving transition metal catalysts. Consequently, tremendous growth has been witnessed in the last decade on the transition-metal-free synthesis of quinoxaline and its derivatives. However, to date, no review articles have summarized the development achieved in the synthesis of quinoxalines under transition-metal-free conditions.

Several review articles covered the synthetic strategy of quinoxalines starting from the classical one to non-conventional green ones and compiled them in the last few years.⁵³ Recently, Maikhuri *et al.*, described the recent metal-catalyzed synthesis of quinoxalines.⁵⁴ Also, Yashwantrao and Saha reviewed the synthesis and reactivity of quinoxaline derivatives.⁵⁵ The present review article focuses on the recent progress achieved in the synthesis of quinoxalines and their fused structure under transition-metal-free conditions and covers the literature from 2015 to date. Besides, highlighting the so far advances realized in this fascinating area, we also point out the limitations and drawbacks of the strategy, and their possible scope of future developments has also been discussed. On behalf of a clear and understanding overview, the article is organized based on the different types of substrates used rather than compiled in chronological order.

2. Classical methods of quinoxaline synthesis

Several synthetic strategies for the preparation of quinoxaline and its derivatives have existed since the late 1800's. The quinoxaline moiety is generally synthesized by employing classical methods including Körner⁵⁶ and Hinsberg⁵⁷ synthesis. Both of these reactions were independently reported in 1884, which mainly involves the condensation of *o*-phenylenediamine with synthons possessing reactive 1,2-dicarbonyl core (*e.g.*, 1,2-diketones, 1,2-ketoesters, or oxalic acid derivatives).⁵⁸ A constructive modification of these synthetic methods introduces 1,2-dicarbonyl compound surrogates (*e.g.*, α -haloketones, α -hydroxyketones, epoxides, or alkynes)⁵⁸ (Fig. 2).

Though many of these methods are very attractive in terms of product yield as well as broad functionality, they often utilize various acids, metals, co-catalyst, or reagents that are not environmentally friendly, and produces a large amount of waste as well as hazardous by-products which is difficult to dispose of properly and remove from the reaction mixture and leads to the contamination of the products and the reaction required unusually longer reaction times to complete. Consequently, tremendous growths have been witnessed in the last few years

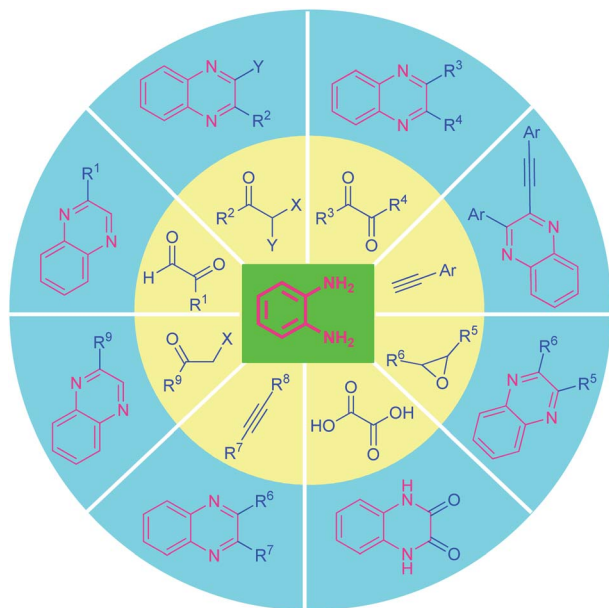


Fig. 2 Various classical routes for the synthesis of quinoxalines derivatives.

for the metal-free synthesis of quinoxalines, and are compiled in this review.

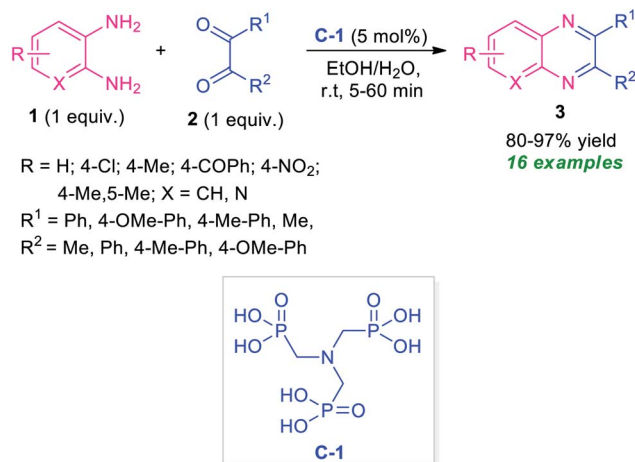
3. Synthesis of simple quinoxalines based on metal-free two-component reactions

Synthesis of quinoxalines based on a metal-free approach can be accomplished *via* different reaction types and pathways. Most of them proceed through the modification of classical strategy and newly developed strategy.

3.1 From 1,2-dicarbonyl compounds

After the renaissance of organocatalyst, the field of organic synthesis reached an excellent level from the perspective of green and sustainable chemistry. Inspired by the development achieved in the organocatalysis, Fathi and Sardarian demonstrated an efficient organocatalytic approach for the synthesis of various quinoxalines **3** from the reaction of 1,2-diamines **1** and 1,2-carbonyl compounds **2** (Scheme 1).⁵⁹ With the help of 5 mol% of nitrilotris(methylenephosphonic acid) **C-1** as the organocatalyst, the corresponding quinoxaline products have been synthesized in 80–97% yields within a very short reaction time. The reaction condition tolerates a wide variety of substituents on the 1,2-diamine ring as well as on the 1,2-dicarbonyl ring. The efficacy of the protocol was established by demonstrating the recyclability and reusability of the organocatalyst up to several consecutive cycles with a slight change in the product yield.

At the same time, Basu and co-workers disclosed a metal-free one-pot synthesis of quinoxalines **7** from 2-nitroaniline by using graphene oxide (GO) or reduced graphene oxide (rGO) as the



Scheme 1 Efficient organocatalytic approach towards the rapid access of quinoxaline derivatives **3**.

carbon catalyst (Scheme 2).⁶⁰ The reaction proceeded through the initial graphene oxide catalyzed reduction of 2-nitroaniline **4** with hydrazine hydrate and subsequent one-pot tandem reaction with 1,2-dicarbonyl compounds or α -hydroxy ketones **6**. Twenty-seven derivatives were synthesized in moderate to excellent yield. The catalyst was easily recovered and reused up to four runs without affecting the product yield.

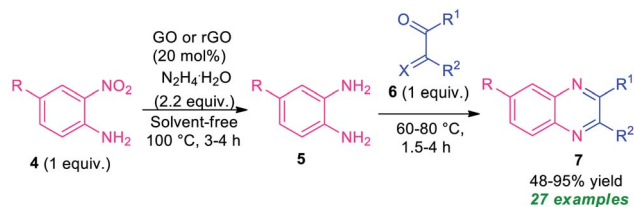
A mechanism was proposed by the author to explain this transformation which was depicted in Scheme 2. The first step of the reaction involves the reduction of 2-nitroaniline **4** *via* a four-electron pathway which utilized two-electron reducing agent hydrazine to afford the 1,2-diamine **5** where GO acts as an adsorbent as well as a collector of hydrazines in its surface. In the second step, the catalyst GO or rGO effectively facilitates the condensation of 1,2-dicarbonyls as well as oxidation of α -hydroxyketones to corresponding 1,2-dicarbonyls for subsequent condensation to final products **7**.

Treatment of various *o*-phenylenediamine **8** and 1,2-dicarbonyl compounds **2** was found to proceed under the influence of ammonium bifluoride (NH_4HF_2) as the catalyst and aqueous ethanol as the solvent system to efficiently provide the corresponding quinoxaline derivatives **9** in 90–98% yields (Scheme 3).⁶¹ A variety of alkyl, aryl- and heteroaryl-substituted 1,2-dicarbonyl compounds as well as substituted *o*-phenylenediamine participate in the reaction smoothly under this mild reaction condition. With unsymmetrical dicarbonyl compounds and *o*-phenylenediamine, the products were formed regioselectively in excellent yield. The mild reaction condition, simple work-up procedure, low catalyst loading, utilization of easily available starting material, recyclability for further reaction cycles with negligible loss in catalytic property, are some of the key features of this approach.

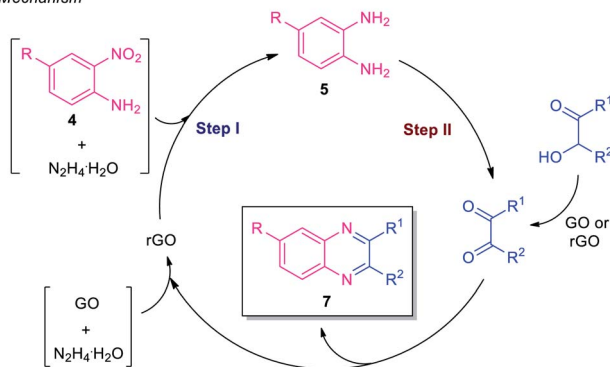
Recently, the utilization of ionic liquid as a catalyst as well as a solvent system in organic synthesis has attracted much more attention as they provide green alternatives to metal catalysts and hazardous organic solvents.⁶² In this regard, Moghaddam and Valizadeh designed and prepared ionic liquid 1-methyl-3-



Review

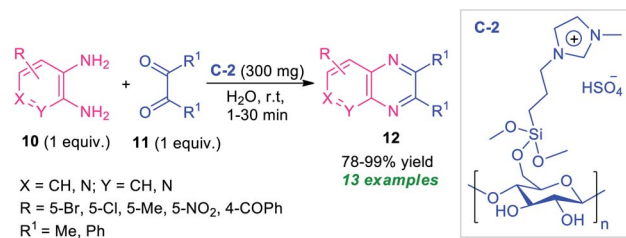


Mechanism

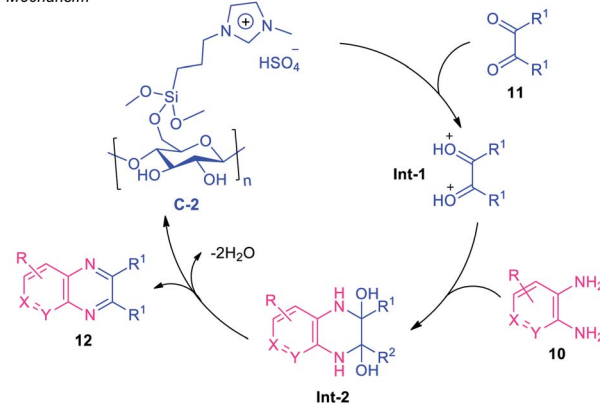


Scheme 2 One-pot reduction and subsequent tandem condensation to access diverse quinoxaline derivatives 7.

(3-trimethoxysilylpropyl) imidazolium hydrogen sulfate functionalized cellulose C-2 as a heterogeneous catalyst, and the catalytic activity was examined in the reaction of diverse *o*-phenylenediamine **10** with 1,2-dicarbonyl compound **11** (Scheme 4).⁶³ The prepared catalyst C-2 was found to be very effective in catalyzing this condensation reaction to afford the desired quinoxaline products **12** in 78–99% yields. This reaction required only 300 mg of the catalyst and by using water as the green solvent, a total of 13 compounds were synthesized.



Mechanism

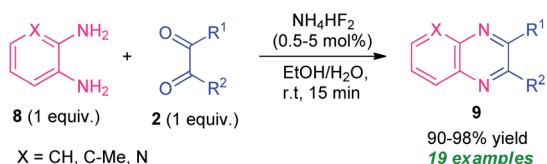


Scheme 4 Ionic liquid functionalized cellulose as an efficient catalyst for the rapid access to quinoxalines **12**.

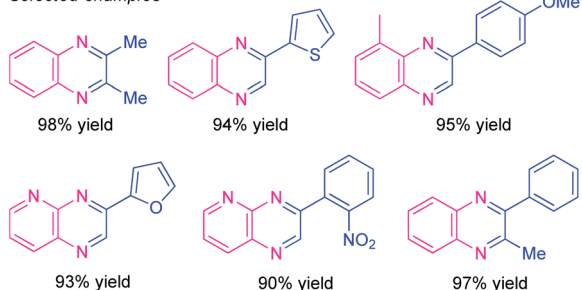
The reaction can proceed through the catalytic cycle as depicted in Scheme 4. Initially, the Brønsted acid catalyst C-2 enhances the nucleophilic character of 1,2-carbonyl compounds thereby facilitating the protonation of the carbonyl groups. The resulting intermediate **Int-1** experiences a nucleophilic attack from the nitrogen of diamines to deliver the intermediate **Int-2**, which is followed by dehydration to yield the final product **12**.

Considering the importance of quinoxaline rings along with the advantages associated with the transition-metal-free catalysis, several eco-friendly and environmentally benign strategies for the synthesis of quinoxaline derivatives **3** from *o*-phenylenediamine **1** and 1,2-dicarbonyl compounds **2** has been developed. All the reactions were performed in the presence of different catalytic systems including ionic liquid, bio-based organocatalyst, green catalyst as well as under catalyst-free conditions. The utilization of ethanol, aqueous ethanol, or solvent-free conditions makes the developed methodology green and sustainable. The products were obtained in moderate to excellent yield within a very short reaction time in almost all of the cases. All the reactions required a low amount of catalyst which marks the salient features of the developed methodologies. Broad functional group tolerance, mild reaction condition, recoverability, and reusability of the catalyst without affecting the outcome of the reaction, are some of the advantages of all of the developed strategies (Table 1).^{64–70}

Although their emergence in organic chemistry in only about the last decades, ultrasound irradiation has been considered as a powerful alternative energy source for the construction of value-added compounds to make them sustainable from the perspective of green chemistry.⁷¹




Selected examples



Scheme 3 Ammonium bifluoride catalyzed synthesis of various quinoxalines **9**.

Table 1 Reaction of various *o*-phenylenediamine **1** with 1,2-dicarbonyl compounds **2** under different reaction conditions for the synthesis of diverse quinoxaline derivatives **3**



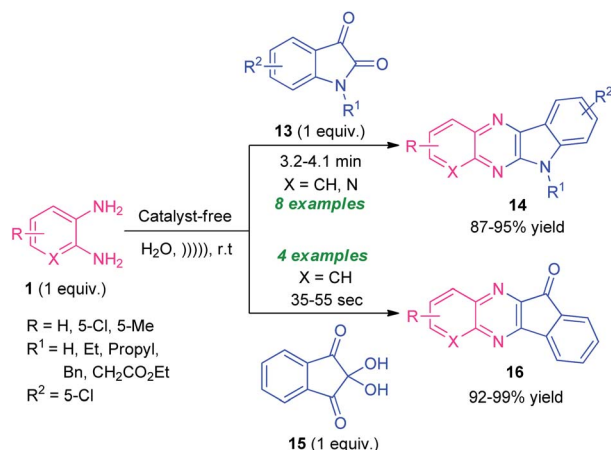
Entry	Catalyst	Loading	Solvent	Condition	Time (min)	Examples	Yield (%)	Ref.
1	DABCO : AcOH : H ₂ O ^a	5 mol%	Solvent-free	80 °C	20–45	12	86–98	64
2	PSA ^b	5 mol%	EtOH	r.t	10–30	15	88–95	65
3	RHA-SO ₃ H ^c	15 mg	Solvent-free	r.t	5–30	11	90–98	66
4	Vitamin C	11 mol%	EtOH	r.t	2–100	17	60–98	67
5	Sulfated polyborate	10 wt%	Solvent-free	100 °C	3–10	18	95–99	68
6	Catalyst-free	—	EtOH	Grinding, r.t	10–30	30	80–98	69
7	GA ^d	0.05 g	EtOH : H ₂ O (4 : 1)	r.t	0.6–18 ^e	11	55–98	70

^a 1 : 1 : 3 ratio is used. ^b Phospho sulfonic acid. ^c sulfonated rice husk ash. ^d Gum arabic. ^e Time expressed in hours.

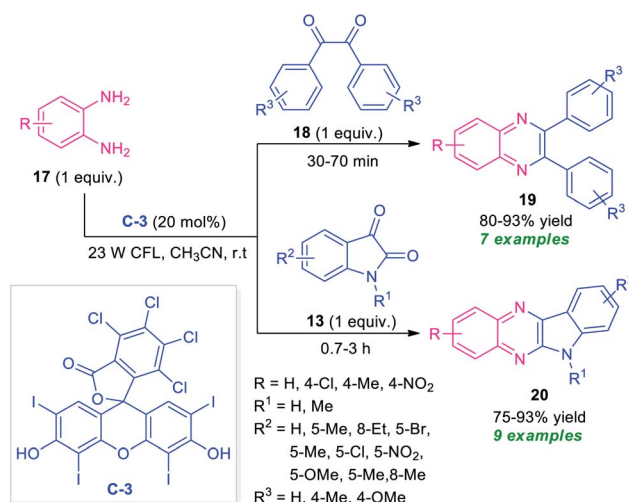
Given the importance of ultrasound irradiation in organic synthesis, Srivastava and co-workers in 2019, demonstrated an ultrasound irradiated catalyst-free protocol for the synthesis of diverse fused quinoxaline derivatives from several substituted *o*-phenylenediamines by utilizing water as the reaction medium (Scheme 5).⁷² Treatment of *o*-phenylenediamine **1** with isatin **13** under this optimized condition found to proceed smoothly to afford indolo[2,3-*b*]quinoxalines **14** in 87–95% yields; whereas the reaction of diamine **1** with ninhydrin **15** delivered the indeno[1,2-*b*]quinoxaline derivatives **16** in 92–99% yields within very short reaction time. The scope of the reaction was established by varying different substitutions on the diamine ring and isatin ring. It is interesting to note that, unsubstituted isatin ($R^1 = H$) as well as substituted isatin ($R^1 = Et, Bn, Pr$) were well tolerated by this approach.

At the same time, Singh and their groups disclosed a visible light promoted organo-photoredox catalyzed chemoselective strategy toward the synthesis of a variety of quinoxalines

(Scheme 6).⁷³ With the help of 20 mol% of Rose Bengal C-3 as the organo-photoredox catalyst, the treatment of 1,2-diamines and 1,2-dicarbonyl compounds including substituted benzil **18** or substituted isatin **13** were found to take place at room temperature to afford the desired quinoxaline products **19** and **20** in moderate to excellent yield respectively. The mechanism to explain this reaction has been covered in Scheme 7. Initially, the photoredox catalyst C-3 is excited to its singlet state under visible light irradiation, which can be further excited to the triplet state through intersystem crossing (ISC). Pleasingly, under influence of this triplet state, 1,2-diamine converts into radical-cation **Int-3** which reacts with isatin to form intermediate **Int-4**. Subsequent single electron transfer (SET) from C-3^{•−} followed by removal of proton results in the formation of intermediate **Int-5** from **Int-4**, which on dehydration afforded the intermediate **Int-6**. The cyclization of **Int-6** leads to the desired products **20**.

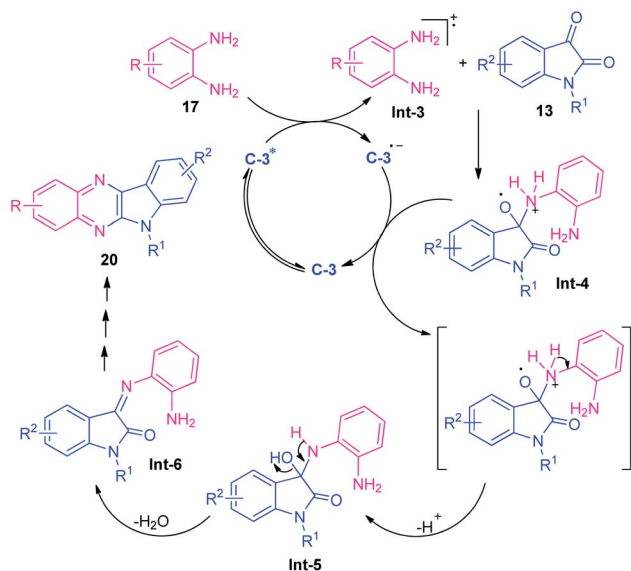


Scheme 5 Ultrasound irradiated catalyst-free synthesis of diverse quinoxaline derivatives **14** and **16**.



Scheme 6 Visible light-mediated Rose Bengal catalyzed synthesis of different quinoxaline derivatives **19** and **20**.





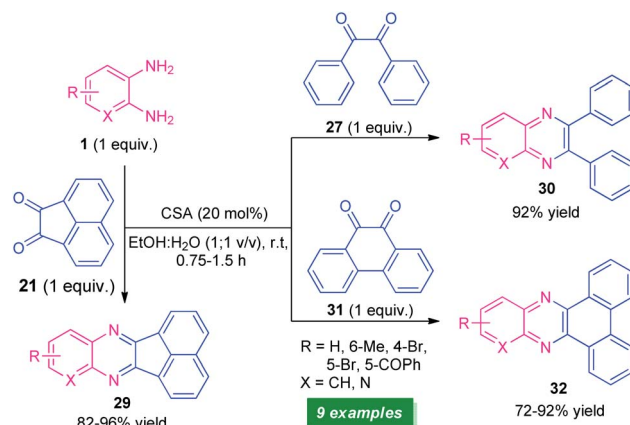
Scheme 7 The suggested mechanism to explain the formation of quinoxalines 20.

Bhargava *et al.*, synthesized a series of diverse quinoxaline derivatives 22, 24, 26, and 28 from the equimolar amount of *o*-phenylenediamine 17 and different types of carbonyl substrates such as acenaphthoquinone 21, substituted bromoacetophenone 23, isatin 25, and benzil 27 by using ionic liquid C-4 as the catalyst as well as reaction medium (Scheme 8).⁷⁴ Interestingly, the products were obtained in good to excellent yield within a very short reaction time at room temperature in all the cases. The effectiveness of the protocol was established by demonstrating the reactivity of recovered ionic liquids for up to six reaction cycles without loss in its catalytic activity. Also, wide substrates scope, high yields, simple work-up procedure, and short reaction time make this approach very efficient and environmentally benign.

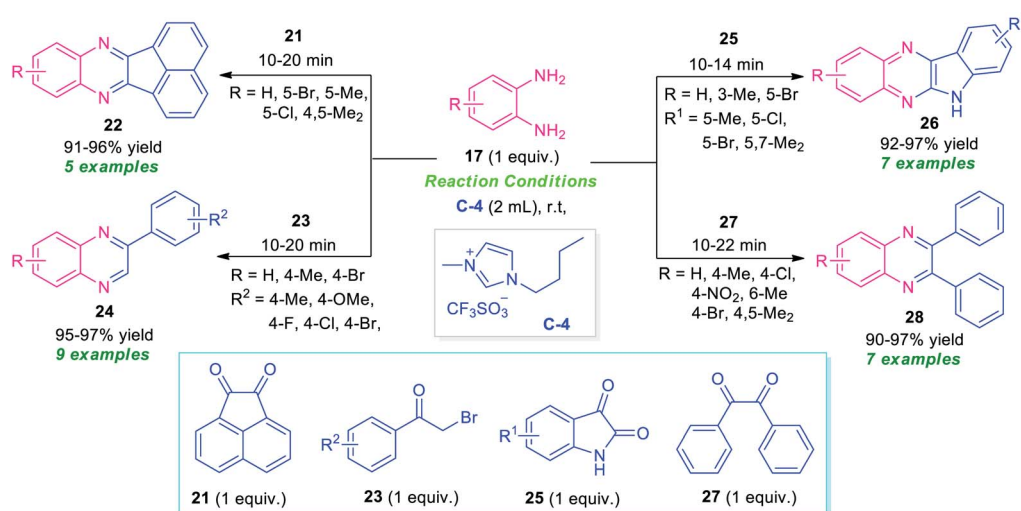
Recently, a straightforward organocatalytic strategy for the synthesis of different types of quinoxaline derivatives was developed by Banerjee's group (Scheme 9).⁷⁵ By using 20 mol% of camphor sulfonic acid as the organocatalyst, various quinoxaline derivatives 29, 30, and 32 derived from easily available starting material *o*-phenylenediamine 1 and carbonyl substrates acenaphthylene-1,2-dione 21, benzil 27, and phenanthrene-9,10-dione 31, have been obtained in moderate to excellent yield within a very short reaction time. Utilization of commercially available, camphor sulfonic acid as an organocatalyst, aqueous ethanol as the solvent, mild reaction conditions make this protocol environmentally and eco-friendly benign. However, low substrate scopes mark a major limitation of this approach and demand further developments otherwise outstanding work.

3.2 From α -halo-ketones

Owing to the dual functionality as they contain two electrophilic sites, α -halo-ketones are recently gained as important building

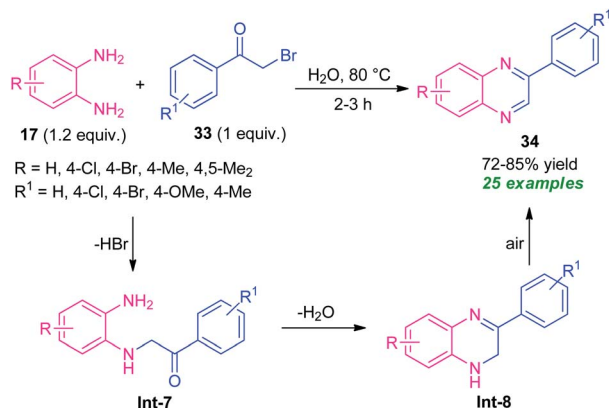


Scheme 9 Camphor sulfonic acid-catalyzed synthesis of quinoxalines 29, 30, and 32.

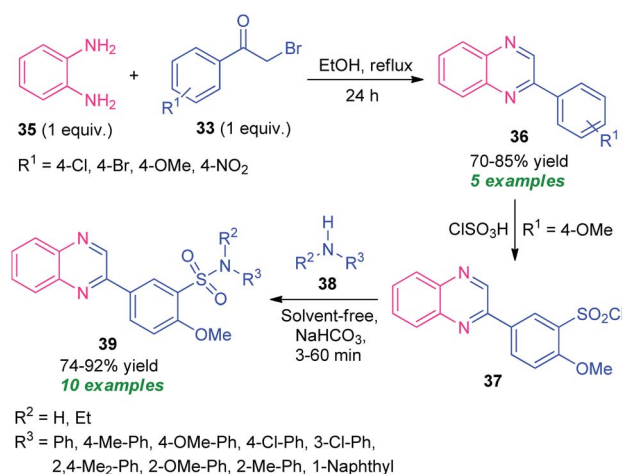


Scheme 8 Preparation of library of quinoxaline derivatives in ionic liquid.





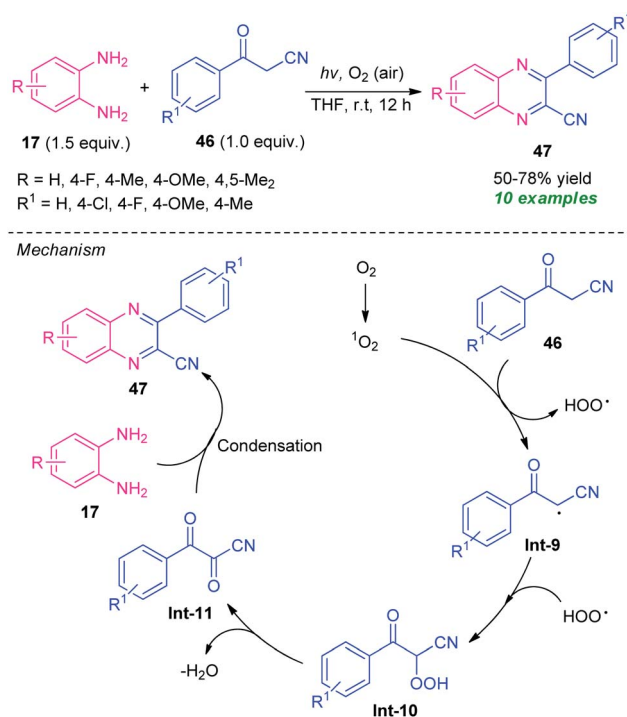
Scheme 10 Catalyst-free oxidative cyclization of diamines and phenacyl bromide to access quinoxalines.



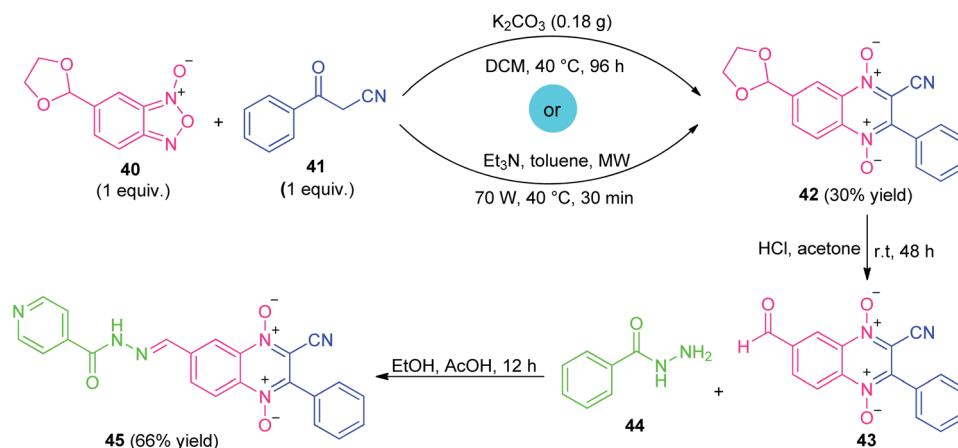
Scheme 11 Three-step synthesis of quinoxaline-sulfonamides based on a green catalyst-free strategy.

blocks for the synthesis of numerous active heterocycles as well as undergo various types of reaction.⁷⁶ α -Halo-ketones mainly phenacyl bromides were utilized in the synthesis of quinoxaline derivatives.

In 2015, a highly efficient and practicable one-pot strategy toward the synthesis of quinoxalines *via* oxidative cyclization of α -halo ketones and *o*-phenylenediamine was developed by Nair and their groups (Scheme 10).⁷⁷ Treatment of several diamines 17 with substituted phenacyl bromide 33 in water at 80 °C afforded the desired quinoxalines 34 in moderate to high yield. This reaction does not require any catalyst as well as co-catalyst, and additives. Phenacyl bromide-bearing electron-donating, as well as electron-withdrawing substituents and symmetrical diamines, smoothly underwent the reaction under this condition. However, when unsymmetrical diamines were employed, the products were formed regioselectively. The overall process



Scheme 13 Visible light-induced electron-transfer and oxidative cyclization to access quinoxaline derivatives.



Scheme 12 Metal-free conventional as well as the microwave-assisted synthesis of quinoxaline hybrid 45.



can initiate through the nucleophilic attack of diamines **17** with phenacyl bromide **33** to produce the intermediate **Int-7** that can then be cyclized into intermediate **Int-8**. Subsequently, the aromatization of intermediate **Int-8** was occurred in air oxidation to afford the final products **34**.

Massah *et al.*, in 2017, disclosed a catalyst-free protocol for the synthesis of quinoxaline derivatives **38** from the reaction of *o*-phenylenediamine **35** and phenacyl bromide **33** under reflux condition using ethanol as the green solvent (Scheme 11).⁷⁸ The products were obtained in 70–85% yields. The synthesized quinoxaline derivatives were extended to quinoxaline sulfonamides **39** *via* a two-step reaction. The first step involves the reaction of quinoxaline **36** ($R^1 = \text{OMe}$) with ClSO_3H to afford the quinoxaline sulfonyl chloride **37**. Treatment of **37** with different aryl amines **38** under solvent-free conditions lead to the final quinoxaline sulfonamides **39** *via* the second steps. The respective products were achieved in moderate to high yield. Most of the synthesized compounds have been established as good antibacterial agents against *Staphylococcus* spp. and *Escherichia coli* bacteria.

3.3 From β -ketonitriles

Similar to α -halo-ketones, β -ketonitriles represent an important class of highly reactive precursors for the preparation of diverse biologically active pharmaceuticals and heterocyclic compounds due to the wide functionality of ketone and nitrile groups present on it.⁷⁹

Considering their versatility, along with the prevalence of quinoxaline-1,4-di-*N*-oxide (QdNO) and *N*-acylhydrazone in medicinal chemistry, Santos *et al.*, realized a metal-free step-

wise approach for the synthesis of quinoxaline hybrid **45** through the Beirut reaction sequence (Scheme 12).⁸⁰ Initially, the reaction of dioxolan-benzofuroxan **40** with benzoylacetone **41** was successfully carried out *via* conventional as well as microwave-irradiation to afford the adduct **42** under the influence of either K_2CO_3 or Et_3N as metal-free bases. Although, both the method provides the same amount of yield of adduct **42** (30%), however, microwave technique was found to be very advantageous over conventional one in terms of reaction time. The subsequent deprotection of **42** by acid hydrolysis and *in situ* condensation of resulting adduct **43** with isoniazid **44** lead to the final quinoxaline-1,4-di-*N*-oxide-*N*-acylhydrazone **45** in 66% yields.

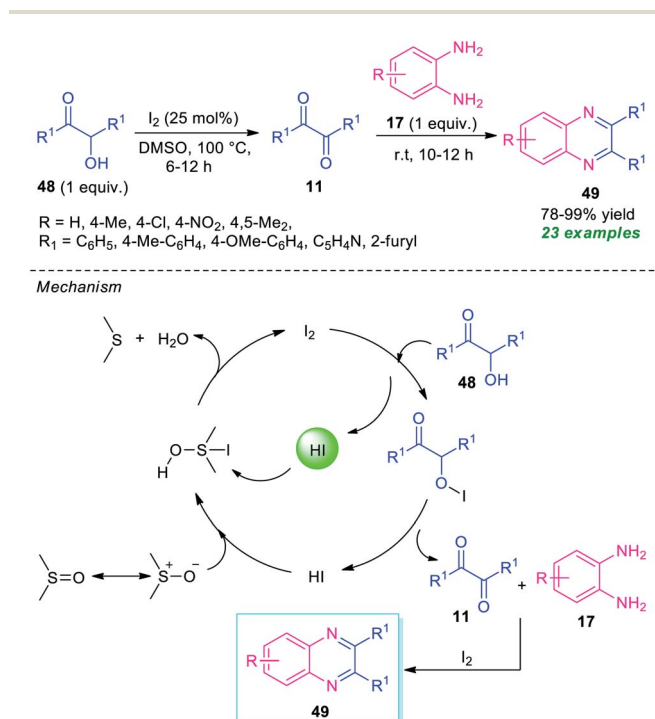
A highly efficient visible-light mediated metal-free synthesis of quinoxalines from easily available *o*-phenylenediamine **17** and benzoylacetone **46** *via* single electron-transfer and oxidative coupling strategy has been developed by Guo *et al.*, in 2019 (Scheme 13).⁸¹ Pleasingly, a total of 10 compounds were synthesized in 50–78% yields by this mild reaction condition at room temperature. A variety of substitutions on the diamine ring as well as on the benzoylacetone were found to effectively work by this approach. The mechanistic pathway behind this transformation involves the reaction of benzoylacetone **46** with singlet oxygen generated from the oxygen under the influence of visible light, to produce a radical intermediate **Int-9**. The intermediate **Int-9** then reacted with HOO radical and deliver the intermediate **Int-10** which underwent dehydration to afford the intermediate **Int-11**.

Consequently, condensation of **Int-10** with diamine **17** leads to the final product **47**.

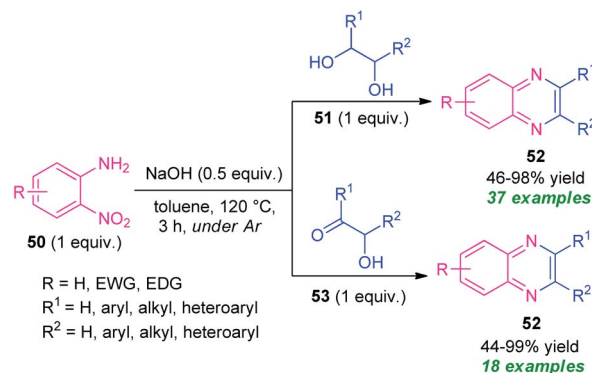
3.4 From α -hydroxy ketones/diols

Given the importance of α -hydroxy ketones in the compounds of the pharmaceutical interest and optically active value-added compounds, the synthesis and their derivatization into potential lead compounds has received tremendous attention in organic synthesis.⁸²

In 2015, Ma and his group demonstrated a straightforward one-pot two-step procedure for the synthesis of quinoxaline derivatives **49** from α -hydroxy ketones **48** (Scheme 14).⁸³ With

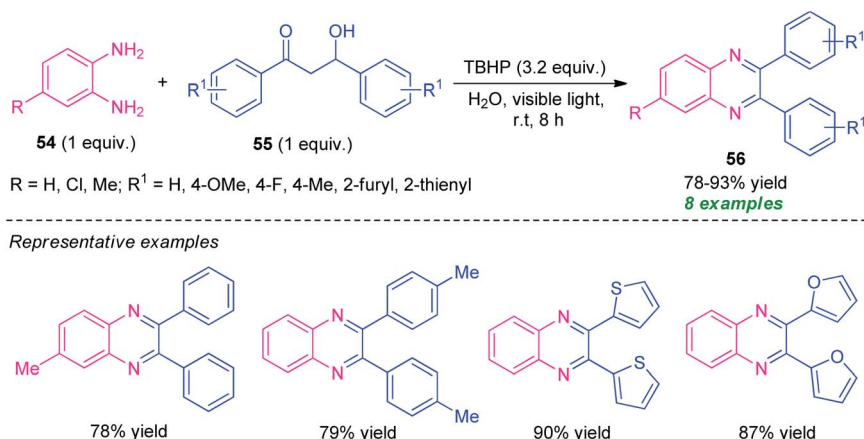


Scheme 14 Iodine catalyzed one-pot oxidation/cyclization to access quinoxalines **49**.



Scheme 15 Transition-metal-free redox condensation reaction to access quinoxaline derivatives **52**.





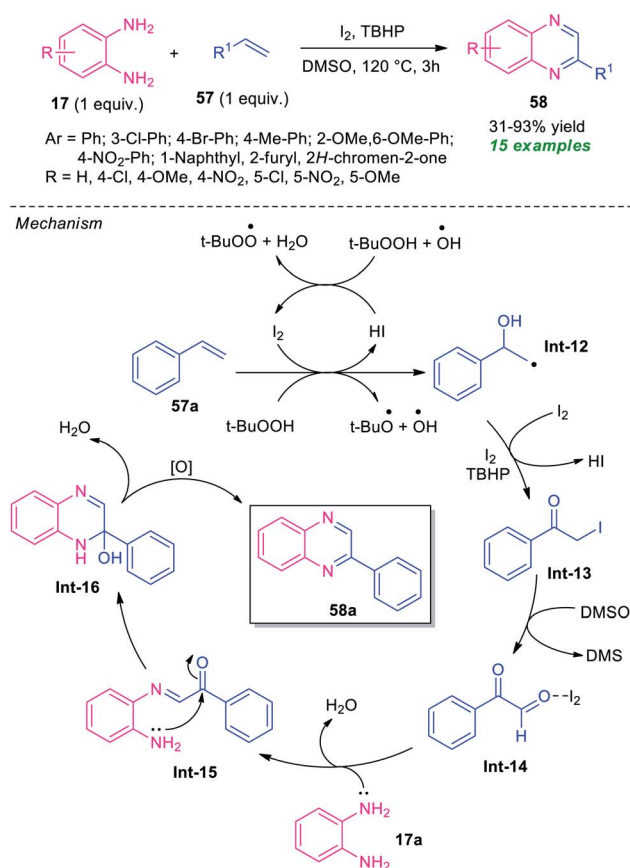
Scheme 16 Metal-free visible light-mediated domino synthesis of quinoxalines **56**.

the help of 20 mol% of I₂ as the catalyst and DMSO as the solvent as well as oxidant, the corresponding quinoxaline products **49** have been synthesized in 78–99% yields. Different substituted *o*-phenylenediamine **17** was found to proceed smoothly under this condition. A total of 23 compounds were synthesized by this method. Broad functional group tolerances, excellent level of yield, metal-free reaction conditions are some of the salient features of this approach. This process starts with the initial oxidation of hydroxy ketones **48** to the desired dicarbonyl compound **11** under the influences of I₂ as the oxidant. Then the subsequent condensation of **11** with diamine **17** takes place smoothly, to form the final product **49** under the influence of I₂ that acts as Lewis acid in this step. For recycling the catalytic system, HI was oxidized into iodine with DMSO as the oxidant, and then iodine was regenerated for further operation.

In 2020, a transition-metal-free highly convenient strategy for the construction of quinoxaline derivatives *via* redox condensation of 2-nitroamines with α -hydroxy ketone or diols was disclosed by Zhu, Song, and their groups (Scheme 15).⁸⁴ For optimizing the reaction condition, the reaction was initially carried out under the influence of different bases including NaOH, NaO^tBu, KO^tBu, KOH as well as in different solvent systems like toluene, *o*-xylene, dioxane, and also in solvent-free conditions. Among them, the exploitation of NaOH as the base catalyst in toluene was selected as the standard condition. Under this condition, the treatment of 2-nitroamine **50** with diols **51** afforded various quinoxaline derivatives **52** in moderate to excellent yields (46–98%), whereas the reaction of 2-nitroamine **50** and α -hydroxy ketone **53** delivered the corresponding product **52** in 44–99% yields. By employing both the substrates a total of 55 compounds were has been synthesized.

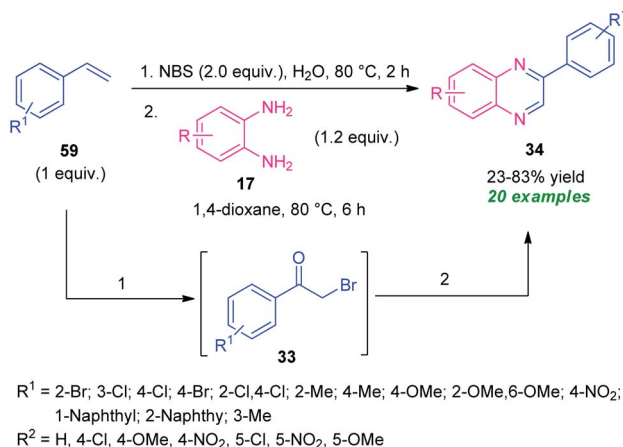
Later, Sarma and co-workers disclosed a visible light-assisted catalyst-free green protocol toward the synthesis of a series of quinoxaline derivatives **56** by employing easily accessible *o*-phenylenediamine **54** and α -hydroxy ketone **55** as the starting material (Scheme 16).⁸⁵ With the help of *tert*-Butyl hydroperoxide (TBHP) as the oxidizing agent, the corresponding quinoxaline products **56** were obtained in 78–93% yields. The

decomposition of TBHP into its radical was predominately promoted by metal or photocatalysts, or other reagents, however in this reaction, the decomposition of TBHP for the radical formation and its acceleration for the completion of the reaction was achieved simply by visible light irradiation and no extra metal- or photocatalyst is required. The successful utilization of photoinduced catalyst-free protocol in an aqueous



Scheme 17 I₂-catalyzed domino one-pot atom-economic approach to quinoxaline derivatives **58**.





Scheme 18 NBS-promoted one-pot two-step green synthesis of quinoxalines **34**.

medium makes this approach very efficient toward green and sustainable practices.

3.5 From alkenes

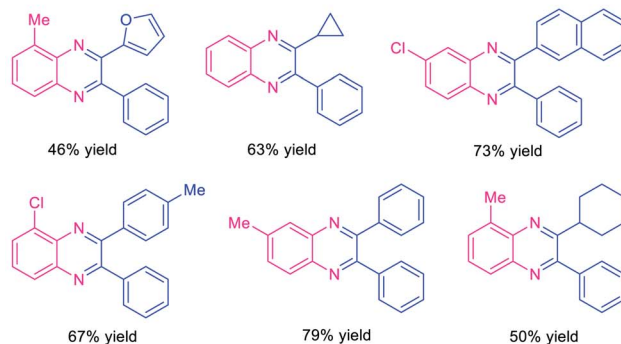
The utilization of alkenes in the metal-free domino synthesis of quinoxaline derivatives has been achieved by Chaskar *et al.*, in 2015 (Scheme 17).⁸⁶ Using I_2 as the catalyst and TBHP as the oxidant in DMSO, the corresponding quinoxaline products **57** derived from various *o*-phenylenediamine **17** and alkenes **57**, were obtained in 31–93% yields. Not only aromatic alkenes but also heteroaromatic alkenes were well tolerated by this atom economic and operationally simple method. A total of 15 compounds were synthesized under this mild reaction condition. Based on a series of experimental results the author proposed a mechanistic pathway for this transformation which involved the oxidation of styrene **57a** to the corresponding radical (**Int-12**) under the influence of I_2 /TBHP through a radical mechanism as depicted in Scheme 17. Iodination of **Int-12** by I_2 /TBHP afforded the key intermediate **Int-13** which undergo Kornblum oxidation to produce phenylglyoxal **Int-14**. Subsequent treatment with diamine **17**, the intermediate **Int-14** furnished intermediate **Int-15**, which on cyclization followed by oxidation provides quinoxaline **58a**.

A practical one-pot two-step NBS-promoted efficient synthesis of quinoxalines from the reaction of substituted alkenes **59** and *o*-phenylenediamines **17** was established (Scheme 18).⁸⁷ The synthesis involves the initial reaction of alkenes **59** with NBS in aqueous media to deliver the phenacyl bromide **33**. Subsequent condensation of **33** with diamine **17**.

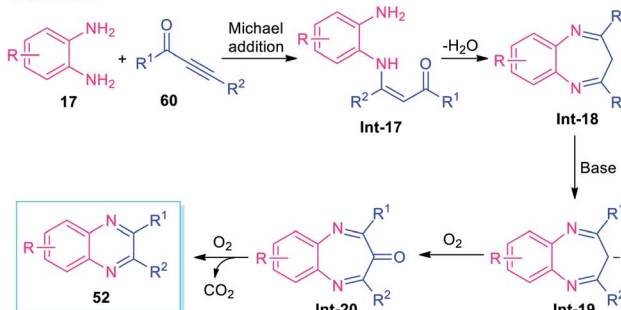
In presence of 1,4-dioxane formed the quinoxaline derivatives **34** in 23–83% yields. A wide variety of substituents present on the alkenes ring smoothly anticipated the reaction under this metal-free approach. Broad functional group tolerance, utilization of inexpensive NBS as bromine source as well as oxidant, water as green solvent, a high level of yield make this approach synthetically as well as environmentally viable.



Representative examples



Mechanism



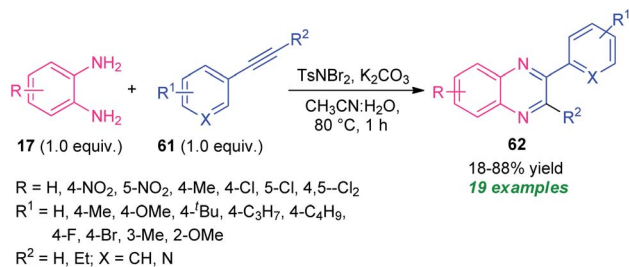
Scheme 19 Metal-free one-pot synthesis of quinoxalines via C- α -CH₂-extrusion process.

3.6 From alkynes

In 2016, Cui and his group disclosed a highly convenient one-pot approach for the regiospecific synthesis of quinoxalines **52** from readily available ynones **60** and *o*-phenylenediamines **17** under metal-free conditions (Scheme 19).⁸⁸ The reaction proceeded through an intermolecular Michael addition, followed by dehydration and subsequent base-promoted C- α -CH₂-extrusion process. A total of 33 quinoxaline derivatives were synthesized by this strategy in 36–95% yields. Various aryl, heteroaryl, and alkyl-substituted ynones were found to be suitable substrates for this reaction. However, when asymmetrical *o*-phenylenediamine and ynones were employed in the reaction, the products were formed in moderate to good yield with excellent regioselectivity (>20 : 1). The exploitation of O_2 as the environmentally benign oxidant, formation of H_2O and CO_2 as only the by-products directed this approach toward more environmentally friendly and sustainable.

The proposed mechanism for this C- α -CH₂-extrusion process involves the initial Michael addition of *o*-phenylenediamines **17** and ynones **60** to form intermediate **Int-17** regioselectively that can then undergo dehydration as well as condensation to give **Int-18**. Subsequent deprotonation of **Int-18** by KOtBu results in the formation of anion intermediate **Int-**



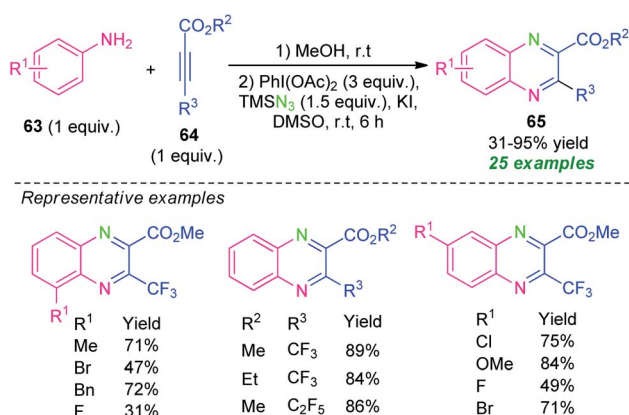


Scheme 20 Metal-free domino protocol for the synthesis of quinoxalines via oxidative cyclization.

19 which gets easily oxidized to **Int-20** by O₂. The final decarbonylation of **Int-20** under O₂ afforded the products **52**.

A metal-free cascade process toward the synthesis of diverse quinoxaline derivatives **61** from alkynes **60** has been developed by Hazarika and Phukan in 2017 (Scheme 20).⁸⁹ Treatment of alkynes **61** with TsNBr₂ (*N,N*-dibromo-*p*-toluene sulfonamide) in an aqueous medium first generated the α,α -dibromoketone intermediate which on reaction with **17** under influence of base deliver the desired products **62** in 18–88% yields within one hour. The scope of the reaction was found to be viable to a wide variety of substituents on the phenyl ring of the alkynes as well as diamines. However, the low yield of the products for the reaction with nitro- and chloro-substituted diamines represents a limitation of this approach.

In 2018, Zhang, Shen, Cao, and their group demonstrated a Michael addition initiated tandem azidation and cycloamination reaction for the construction of diverse fluoroalkylated quinoxalines (Scheme 21).⁹⁰ Under metal-free conditions, the corresponding quinoxalines derivatives **65** derived from anilines **63** and fluoroalkylated alkynes **64** and TMSN₃ as the nitrogen source, were obtained in 31–95% yields. The reactions with *ortho*-substituted anilines were found to lead to a decrease in the yield of the products as compared to *para*-substituted anilines. Alternatively, when *meta*-substituted anilines were employed as the substrates, two regioisomers has been formed in moderate to excellent yield. In this reaction, the utilization of



Scheme 21 Tandem Michael addition/azidation/cycloamination sequence toward the synthesis of quinoxalines.

KI as an additive provides the formation of iodine(i) species by reacting with PhI(OAc)₂ and thereby promoting the azidation and cycloamination sequence toward the synthesis of the final products.

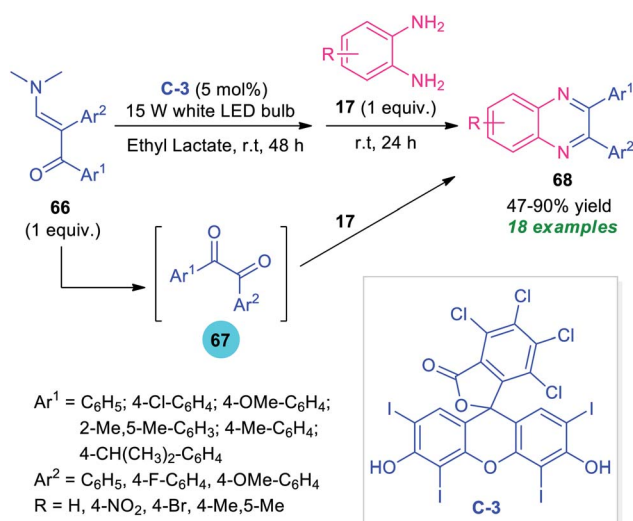
3.7 From enaminones

Enaminones are an important class of widely investigated organic compounds in organic chemistry. Due to the highly reactive nature and easy availability, a great variety of organic compounds have been synthesized by making the utilization of enaminones as key building blocks.⁹¹

By considering this key importance and taking advantage of the high photocatalytic activity of Rose Bengal **C-3**, Wan, Wen, and co-workers disclosed a one-pot procedure for the synthesis of quinoxalines from enaminones **66** (Scheme 22).⁹² With the help of 5 mol% of **C-3** as the photocatalyst, the visible light-mediated reaction of enaminones **66** afforded the corresponding products **68** in 47–90% yields. The overall process starts with the cleavage of C=C of enaminones **66** to furnish the adduct **67** which reacts *in situ* with *o*-phenylenediamines **17** under the ambient condition to form the resultant products **68**. Broad functional group tolerances, easy accessibility of the starting material, operational simplicity are some of the key advantages of this approach. The low yield of products for the reaction with *o*-phenylenediamines bearing electron-withdrawing group constitutes a major drawback of this method.

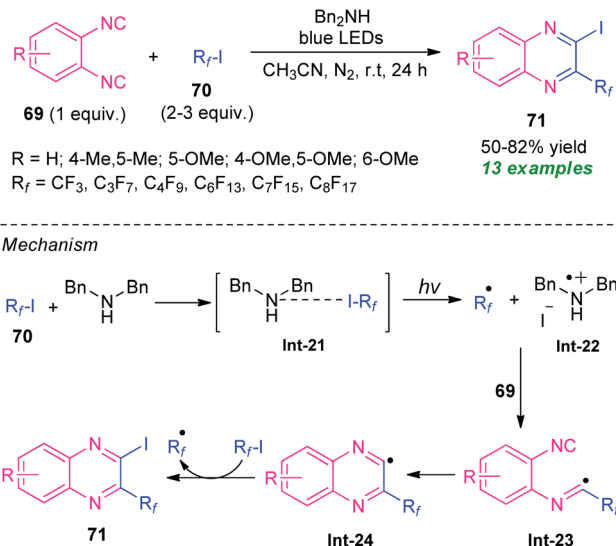
3.8 From isonitriles

In 2016, the research group of Ma and Yu developed a visible light-assisted halogen-bond-promoted strategy for the synthesis of quinoxaline derivatives through the double radical isocyanide insertion of *o*-diisocyanoarenes **69** with perfluoroalkyl iodides **70** (Scheme 23).⁹³ By using this strategy, a series of diverse 2-fluoroalkylated 3-iodoquinoxalines **71** were synthesized in moderate to high yield at room temperature. The



Scheme 22 Visible-light induced photocatalytic cleavage of C=C of enaminones to access quinoxalines.

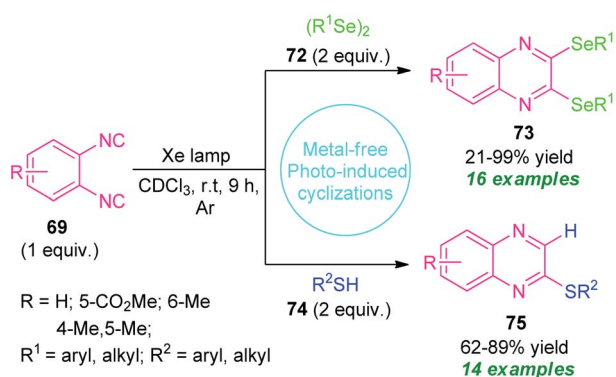




Scheme 23 Halogen-bond-promoted construction of various quinoxaline derivatives under visible light irradiation.

overall process can initiate through the formation of halogen-bond adduct **Int-21** which under the influence of visible light deliver the fluoroalkyl radical R_f^\bullet , Bn_2NH^+ , and iodide anion *via* a single electron transfer (SET) process. In this reaction, per-fluoroalkyl iodides serve as halogen-bond donors and Bn_2NH as halogen-bond acceptors. The addition of fluoroalkyl radical R_f^\bullet to *o*-diisocyanoarenes **69**, followed by radical cyclization produces the radical intermediate **Int-24** which then abstracts an iodine atom from **70** to yield the final products **71**.

Recently, a metal- and additive-free cyclization sequence under visible-light irradiation has been established for the synthesis of a vast array of quinoxaline derivatives from *o*-diisocyanoarenes **69** and organic diselenides or thiols (Scheme 24).⁹⁴ Initial optimization of the reaction condition revealed that utilization of Xe lamp as a light source in presence of CDCl_3 as the solvent provides high activity and reactivity of the reaction as compared to high-pressure Hg lamp. By using this condition, a series of 2,3-bis-(selanyl)quinoxalines **73** derived from **69** and **72**, were obtained in 21–99% yields. Not only the aryl-



Scheme 24 Visible light irradiated construction of different quinoxaline derivatives under metal-free conditions.

substituted selenides but also alkyl-substituted selenides were reacted efficiently under this condition.

Encourage by this result, they further attempted the reaction with **69** and **74** under the same reaction condition. Delightfully, a total of fourteen 2-thiolated quinoxaline compounds **75** were synthesized in moderate to high yield. Unlike diselenides, the reaction condition also tolerates several alkyl and aryl-substituted thiols. But unfortunately, thiols bearing unprotected alcohol groups, amines, and $(^i\text{Pr})_3\text{SiSH}$ failed to yield any products which represents a major limitation of this approach (Scheme 24).

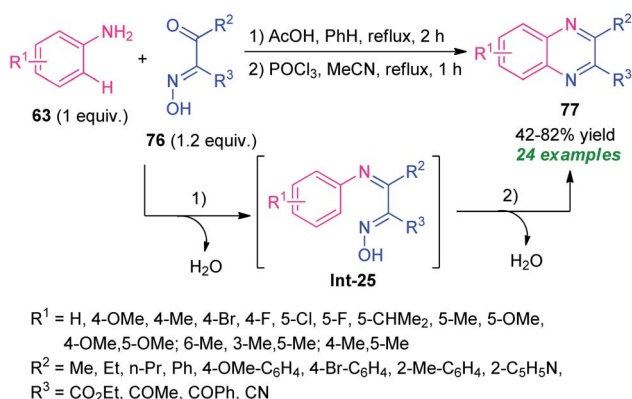
3.9 From oximes

A tandem one-pot protocol for the construction of functionalized quinoxalines from easily accessible arylamines **63** and β -keto oximes **76** has been developed by Pan, Mo, Su, and co-workers in 2017 (Scheme 25).⁹⁵ The reaction sequence involves the initial condensation of amines **63** with oximes **76** as the nitrogen source and subsequent metal-free *N*-arylation of key intermediate **Int-25** under Lewis acid catalysis was found to lead to the desired products **77** in 42–82% yields. The effectiveness of the developed protocol was established by its applicability in the gram-scale synthesis and other useful transformations. A wide range of substrate scopes, exploitation of the synthesized compounds in useful synthetic modifications, mild reaction conditions, water as only the by-products, systematic design of the metal-free sequence makes this protocol synthetically valuable and environmentally benign.

4. Synthesis of fused quinoxalines based on metal-free two-component reactions

4.1 Synthesis of pyrrolo/indolo[1,2-*a*]quinoxalines

Among various fused quinoxaline derivatives, pyrrolo/indolo[1,2-*a*]quinoxalines as the most important and well-established nitrogen-containing heterocycles play a vital role in medicinal and pharmaceutical chemistry due to their remarkable pharmacological profile.⁹⁶ In particular, the presence of this moiety



Scheme 25 One-pot tandem cyclization/metal-free *N*-arylation toward the synthesis of functionalized quinoxalines.



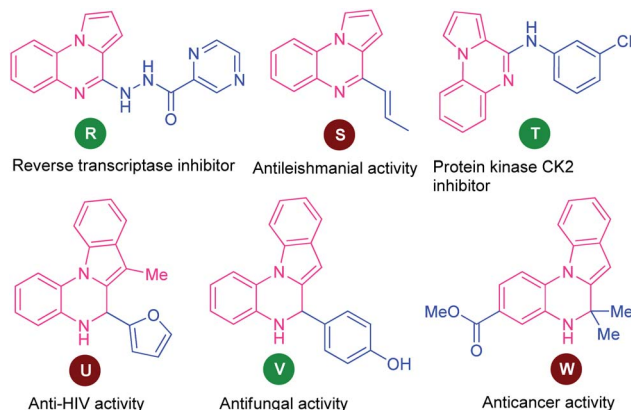
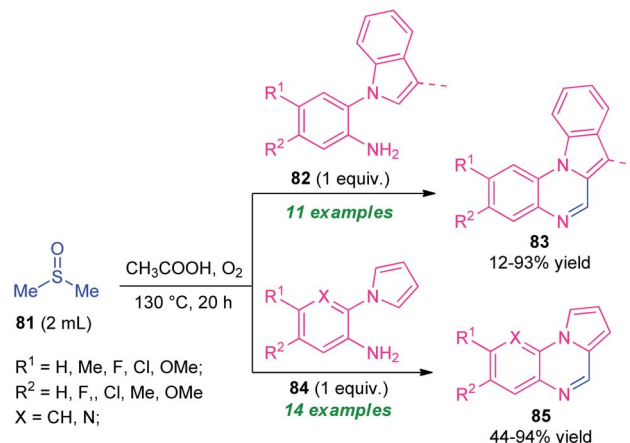


Fig. 3 Biologically active various pyrrolo/indolo[1,2-a]quinoxalines derivatives.

in many products found to exhibit reverse transcriptase inhibitor (R), antileishmanial activity (S), protein kinase CK2 inhibitor (T), anti-HIV activity (U), antifungal activity (V), and anticancer activity (W) (Fig. 3).⁹⁷ Owing to these tremendous properties, significant efforts have been demonstrated toward their synthesis in the last decades.

4.1.1 From carbonyl compounds. In the past decades, a vast array of procedures toward the rapid access of pyrrolo[1,2-a]quinoxaline motifs has been reported; among them, the Bischler–Napieralski reaction or modified Pictet–Spengler reaction and also one-pot reaction has widely been studied.⁹⁸ However, most of this reaction suffers serious drawbacks due to the exploitation of transition-metal-catalysts, volatile, and toxic reagents alongside the low yield of the products. Therefore, there is a need for developing a high atom economic, environmentally friendly, and eco-compatible approach to pyrrolo[1,2-a]quinoxaline structure.

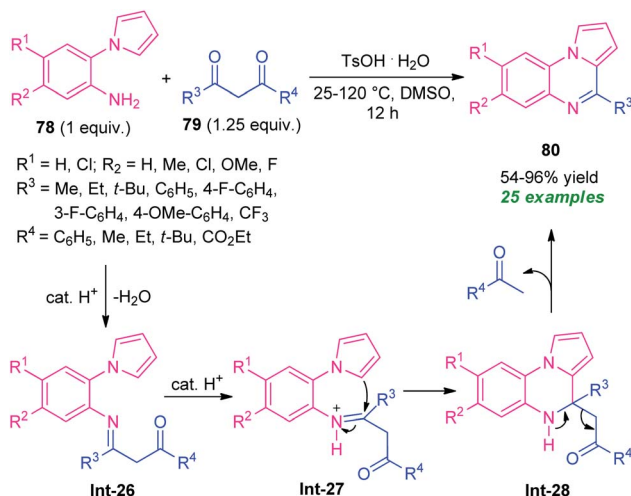
In this perspective, Ma and co-workers in 2016, developed a highly efficient one-pot domino strategy by employing 2-(1*H*-



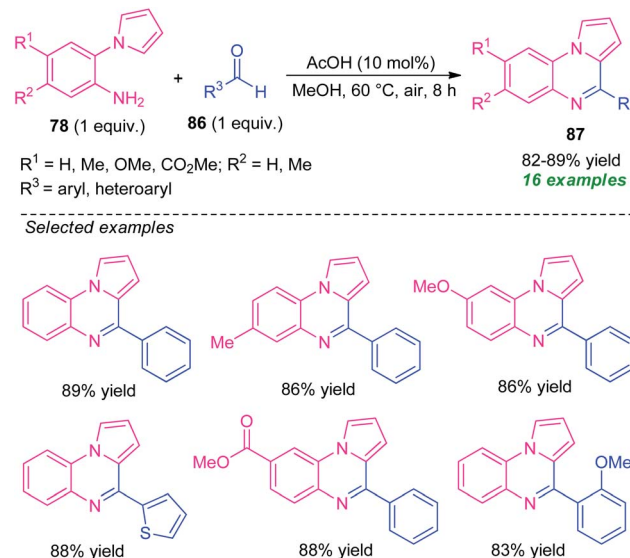
Scheme 27 Versatile activity of DMSO in the synthesis of quinoxaline.

pyrrol-1-yl)aniline **78** and 1,3-dicarbonyl compounds **79** as the easily available starting material (Scheme 26).⁹⁹ With transition metal-free condition, a variety of pyrrolo[1,2-a]quinoxalines **80** in 54–96% yields has been synthesized utilizing $\text{TsOH} \cdot \text{H}_2\text{O}$ as the organocatalyst. The reaction condition was found to be appropriate for both β -diketones **79** ($\text{R}^3 = \text{aryl, alkyl}$; $\text{R}^4 = \text{aryl, alkyl}$) and β -keto esters **79** ($\text{R}^3 = \text{aryl, alkyl}$; $\text{R}^4 = \text{OEt}$). However, the reaction with diketones **79** ($\text{R}^3 = \text{R}^4 = t\text{-Bu}$) failed to yield any product which represents the limitation of this approach.

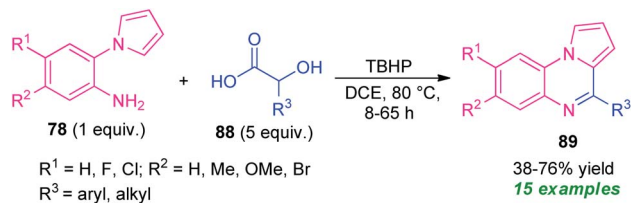
The requirement of a longer reaction time also points toward the drawback of this method. This transformation can proceed *via* the initial formation of the imine intermediate **Int-26**, which then abstracts a proton from the catalyst to form **Int-27**. Subsequently, an intramolecular cyclization of intermediate **Int-27** followed by cleavage of C–C bond in intermediate **Int-28** form the final product **80**.



Scheme 26 Brønsted acid-catalyzed one-pot domino synthesis of pyrrolo[1,2-a]quinoxalines.



Scheme 28 Acetic acid-catalyzed efficient synthesis of pyrrolo[1,2-a]quinoxalines through Pictet–Spengler reaction.



Scheme 29 TBHP catalyzed metal-free synthesis of quinoxalines based on *in situ* generated aldehydes.

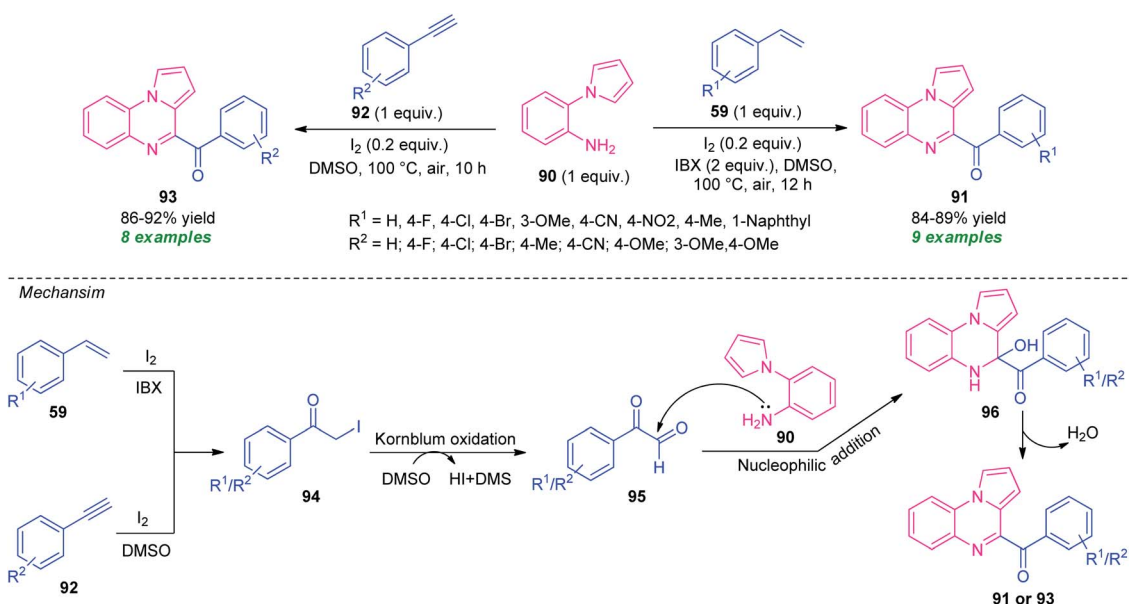
One year later, the same research group disclosed a novel one-pot green strategy for the synthesis of pyrrolo[indolo[1,2-*a*]quinoxalines by employing DMSO as reactant as well as the solvent system in metal-free condition (Scheme 27).¹⁰⁰ With the help of AcOH acid as the catalyst, treatment of dimethyl sulfoxide **81** with 2-(1*H*-indol-1-yl)aniline **82** was found to take place at 120 °C to deliver indolo[1,2-*a*]quinoxalines **83** in 12–93% yields while using 2-(1*H*-pyrrol-1-yl)aniline **83** instead of **82** under the same reaction condition provided pyrrolo[1,2-*a*]quinoxalines **85** in 44–94% yields. A wide variety of electron-rich, as well as electron-poor substituents present on **82** and **84**, were well tolerated by this condition. However, the low yield of the products **83** (12% yield) for the reaction with 2-(1*H*-indol-1-yl)aniline **82** ($\text{R}^1 = \text{H}$, $\text{R}^2 = \text{H}$; 3-Me is absent in indole ring) and no reaction for 3-methyl-2-(1*H*-pyrrol-1-yl)aniline **84** ($\text{R}^1 = \text{R}^2 = \text{H}$; X = C-Me), constitutes a major limitation of this approach. In addition, the strategy offers several advantages including mild reaction conditions, metal-free, utilization of oxygen as cheap and green oxidant, *etc.*

In 2019, Patel *et al.* reported an efficient acetic acid-catalyzed synthesis of pyrrolo[1,2-*a*]quinoxalines **87** via a Pictet–Spengler type reaction of 2-(1*H*-pyrrol-1-yl)aniline **78** to aldehyde **86** (Scheme 28).¹⁰¹ With only 10 mol% of AcOH acid as the catalyst,

a total of 16 compounds were synthesized in 82–89% yields. Pleasingly, various substituted and unsubstituted 2-(1*H*-pyrrol-1-yl)aniline **78** underwent the reaction smoothly to provide the desired product efficiently. While, the reaction with CF_3 and CO_2Me substituted **78** ($\text{R}^1 = \text{H}$, $\text{R}^2 = \text{CF}_3$, CO_2Me) failed to yield any product which draws a shortcoming of this approach. Similarly, aryl, as well as heteroaryl substituted aldehydes, were efficiently worked under this condition, except for electron-withdrawing substituents present on the *meta*-position of the aryl ring of aldehyde ($\text{R}^3 = 3\text{-NO}_2\text{-C}_6\text{H}_4$, $3\text{-Cl-C}_6\text{H}_4$, $3\text{-Br-C}_6\text{H}_4$) which affected the outcome of the reaction. Despite these limitations, the broad functional group tolerance, easily accessible starting material, are some advantages of this protocol. In addition, this reaction doesn't require any extra oxidant or additives, and the air was used as a green oxidant.

In 2020, Jung and their groups demonstrated α -hydroxy acid as an aldehyde surrogate for the construction of pyrrolo[1,2-*a*]quinoxalines based on a metal-free approach (Scheme 29).¹⁰² The synthesis involves the reaction of 2-(1*H*-pyrrol-1-yl)aniline **78** with α -hydroxy acid **88** in presence of TBHP (*tert*-butyl hydrogen peroxide) as the oxidant, leading to the desired products **89** in 38–76% yields. The key step behind this reaction is the *in situ* formation of aldehydes from α -hydroxy acid **88** and then condensation with **78**, followed by intramolecular cyclization and subsequent oxidation step. Although diverse substitutions on the 2-(1*H*-pyrrol-1-yl)aniline ring and α -hydroxy acid could be tolerable, the low yield of the products, as well as the longer reaction time, constitutes a major drawback of this approach other than outstanding work.

4.1.2 From alkenes and alkynes. In 2018, Reddy *et al.* demonstrated a highly efficient metal-free one-pot domino oxidative cyclization approach for the construction of several pyrrolo[1,2-*a*]quinoxaline derivatives from alkenes and alkynes (Scheme 30).¹⁰³ With the help of I_2 as the catalyst and 2-



Scheme 30 Metal-free diversity-oriented one-pot synthesis of fused quinoxaline derivatives from alkenes and alkynes.



iodoxybenzoic acid (IBX) as the oxidant, the treatment of alkenes **59** with 2-(1*H*-pyrrol-1-yl)aniline **90** was found to take place in DMSO to deliver the desired products **91** in good yield. A variety of electron-donating and electron-withdrawing substituents present on the aryl ring of alkenes smoothly participated in this reaction. On the other hand, treatment of **90** with alkynes **92** in presence of a catalytic amount of I₂ and DMSO as the solvent cum oxidant provides corresponding fused quinoxalines **93** in good to high yield. This reaction doesn't require IBX as an external oxidant. The methodology offers several advantages including mild reaction conditions, eco-compatible, *etc.* However, the requirement of a longer reaction time constitutes a limitation of this approach.

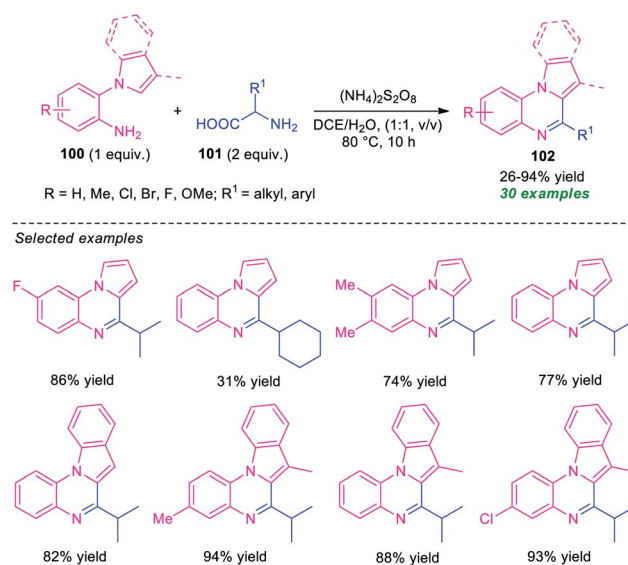
Initially, intermediate **94** was formed *in situ* either from **59** or from **92**, which undergo Kornblum oxidation with DMSO to form an intermediate **95**. A subsequent reaction of **95** with **90**, followed by dehydration afforded the final products **91** or **93**.

4.1.3 From amines. In order to formulate an eco-compatible, atom-economic as well as environmentally friendly approach for the synthesis of pyrrolo/indolo[1,2-*a*]quinoxalines, several metal-free methods have been devised from readily available aryl/heteroaryl/alkyl amines and 1-(2-aminoaryl)pyrrole in the past decades.¹⁰⁴

In 2015, Zhai *et al.*, and Jayaprakash *et al.*, independently reported two highly efficient metal-free one-pot strategies toward the synthesis of pyrrolo/indolo[1,2-*a*]quinoxalines **99** from 1-(2-aminoaryl)pyrrole/indole **97** and amines **98** (R¹ = aryl) by employing molecular iodine as the catalyst as well as the promoter respectively. In 2019, direct one-pot access to several pyrrolo/indolo[1,2-*a*]quinoxalines **99** under metal-free green reaction conditions from 1-(2-amino/nitroaryl)pyrrole/indole **97** and amine **98** (R¹ = aryl/alkyl/heteroaryl) were reported separately by Pardeshi, Chaskar, Patil and their groups and Wang *et al.* In all the cases, the corresponding products were formed in good to excellent yield (Table 2).^{105–109} Broad functional group tolerances, eco-friendly as well as environmentally friendly

nature, operational simplicity, metal-free, additive-free, redox reagent-free, toxic-free, gram-scale synthesis, are some of the advantages of all of the reported methods. Although all the reported methodology has several significant advantages, they also suffer some limitations including longer reaction time, low yield of the products, higher energy source; products were isolated by conventional purification techniques that utilize volatile solvents and are also involved in the waste of solvents. Therefore, attention has also needed to be paid to these reported methodologies, to solve the concerns raised.

Another successful example for the synthesis of fused quinoxalines from amines under transition-metal-free conditions has been realized by Ma and co-workers (Scheme 31).¹¹⁰ With the help of (NH₄)₂S₂O₈ as the oxidant, the pyrrolo/indolo[1,2-*a*]



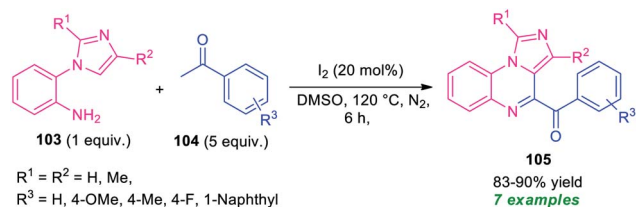
Scheme 31 Transition-metal-free synthesis of fused quinoxalines from α -amino acid.

Table 2 One-pot reaction of 1-(2-aminoaryl)pyrrole/indole **97** with aryl amine **98** to access pyrrolo/indolo[1,2-*a*]quinoxalines **99** under metal-free conditions

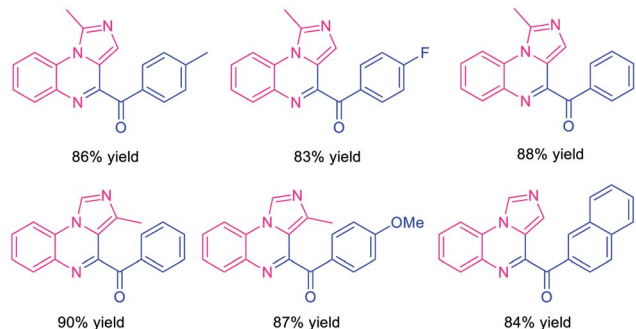
Entry	Catalyst/promoter	Loading	Oxidant	Solvent	Temperature	Time (h)	Examples	Yield (%)	Ref.
1	I ₂	5 mol%	O ₂	<i>o</i> -Xylene	140 °C	12	27	79–95	105
2	I ₂	2 equiv.	—	MeCN	80 °C	5–8	22	82–95	106
3	—	—	K ₂ S ₂ O ₈	PEG-400	r.t	8	25	65–92	107
4	—	—	1,2-DNB ^a	Diglyme	130 °C	9	25	62–89	108
9	Ac ^b	15 mol%	—	H ₂ O	140 °C	20	11	41–99	109

^a 1,2-Dinitrobenzene. ^b Activated carbon.





Selected examples

Scheme 32 Metal-free iodine catalyzed one-pot synthesis of imidazo[1,5-a]quinoxalines **105**.

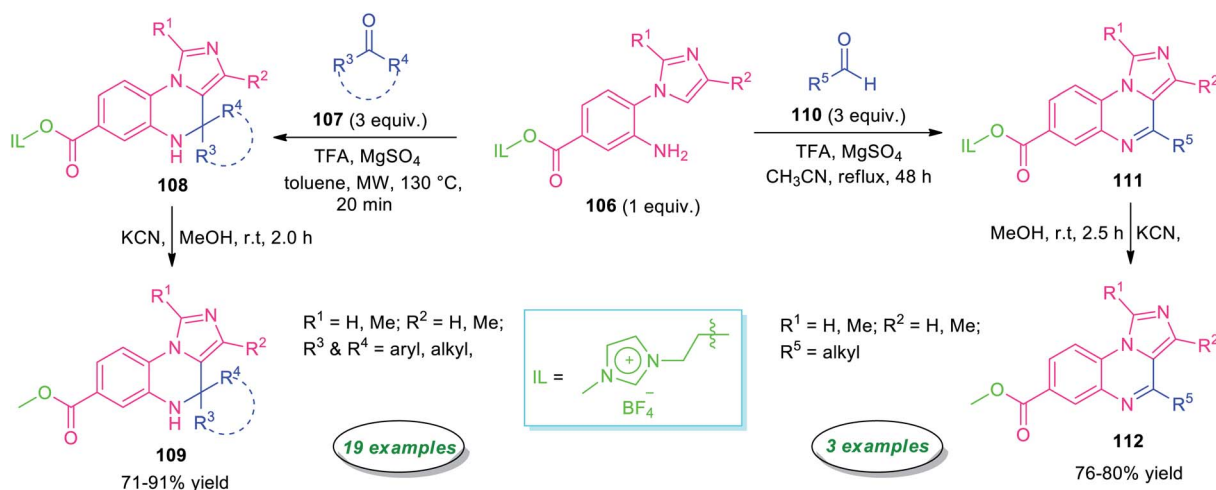
quinoxaline products **102**, derived from 1-(2-aminoaryl)pyrrole/indole **100** and α -amino acid **101**, were obtained in poor to high yield. The optimized reaction conditions were found to be very compatible for a wide range of substituted 1-(2-aminoaryl)pyrrole/indole **100** possessing electron-deficient and electron-rich groups as well as for a variety of short- and long-chain amino acids. However, the reaction with methyl, *tert*-butyl, and cyclohexyl substituted amino acids (R¹ = Me, *t*-Bu, cyclohexyl) gave only 26%, trace, and 31% yield of the products respectively. This is presumably due to involved steric hindrance that affects the outcome of this approach. Therefore, the development of a novel protocol that provides a clean pathway for expanding the hindered substrates scopes is highly desired.

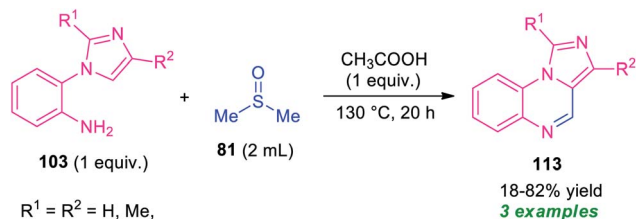
4.2 Synthesis of imidazo[1,5-a]- and imidazo[1,2-a]quinoxalines

Unlike pyrrolo/indolo[1,2-a]quinoxalines, the derivatives of imidazoquinoxalines including imidazo[1,5-a]quinoxalines and imidazo[1,2-a]quinoxalines have extensively been studied and attracted considerable attention in medicinal and organic chemistry due to their tremendous biological activity such as anticancer activity, antimicrobial activity, antiallergenic activity, anticonvulsant activity, and kinase inhibitory activity.¹¹¹ Because of this importance, significant efforts have been made for their synthesis.¹¹²

In 2015, Ma and co-workers developed a metal-free one-pot cascade coupling process for the construction of imidazo[1,5-a]quinoxalines **105** (Scheme 32).¹¹³ By using 20 mol% of molecular iodine as the catalyst and DMSO as the oxidant as well as solvent, the reaction of 2-(1*H*-imidazol-1-yl)aniline **103** and ketones **104** were found to proceed smoothly under nitrogen atmosphere to afford the desired products **105** in good to high yield. Aryl-substituted ketones as well as substituted 2-(1*H*-imidazol-1-yl)aniline efficiently participated in the reaction under this condition. The advantages of this approach included mild reaction conditions, eco-compatible, readily accessible starting material, *etc.* However, the low substrate scopes alongside high catalyst loading, long reaction time constitutes a major limitation of this approach and needs ample attention to extended the substrate scopes of this approach.

Highly regioselective synthesis of imidazo[1,5-a]quinoxalines *via* an unconventional Pictet–Spengler reaction was reported by Chung, Sun, and their group in 2016 (Scheme 33).¹¹⁴ Treatment of ionic liquid supported 2-(1*H*-imidazol-1-yl)aniline **106** with ketones **107** in presence of TFA under microwave condition at 130 °C, afforded ionic liquid immobilized imidazo[1,5-a]quinoxalines **108** within 20 minutes. Subsequently, cleavage of ionic liquid from **108** was accomplished by KCN in MeOH at room temperature to furnish the final products **109** in moderate to high yield. The reaction condition was found to be compatible with a broad range of aryl, heteroaryl, and alkyl-

Scheme 33 Regioselective metal-free synthesis of imidazo[1,5-a]quinoxalines from ionic liquid supported 2-(1*H*-imidazol-1-yl)aniline.



Scheme 34 Synthesis of imidazo[1,5-*a*]quinoxalines **113** by using DMSO as solvent cum reagent in metal-free condition.

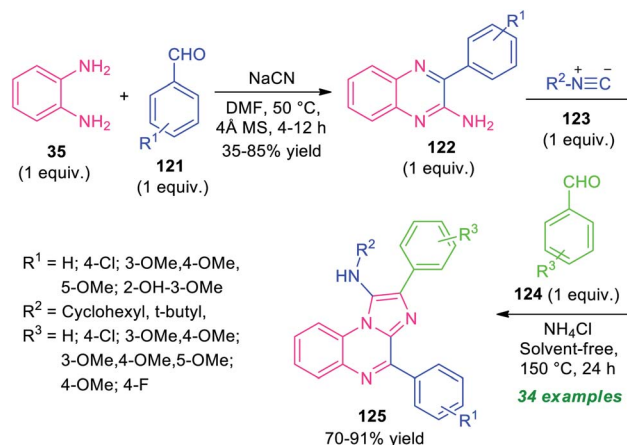
substituted ketones. However, when the same reaction was carried out with aryl aldehydes instead of ketones, aryl derivatives of imidazo[1,5-*a*]quinoxalines bearing ionic liquids were formed, but on treating with KCN for removal of ionic liquids, only cleavage of C(3*a*)-C(4) bond was observed rather than getting the final products. Pleasingly, modify the reaction condition from microwave to reflux in CH_3CN rather than toluene, aliphatic aldehydes found to underwent the reaction smoothly providing the final imidazo[1,5-*a*]quinoxalines **112** in 76–80% yields. However, narrow substrate scopes represent a limitation of this approach.

As a continuation of their outstanding work on the synthesis of pyrrolo/indolo[1,2-*a*]quinoxalines described in Scheme 27, Xie and co-workers also disclosed the synthesis of imidazo[1,5-*a*]quinoxalines **113** by employing metal-free reaction condition (Scheme 34).¹⁰⁰ With the help of DMSO as the solvent cum reagent, the corresponding imidazo[1,5-*a*]quinoxalines **113** derived from 1-(2-aminophenyl)imidazole **103**, has been achieved in 18–82% yields. However, narrow substrates scopes and low yield of the products call for further development of this approach.

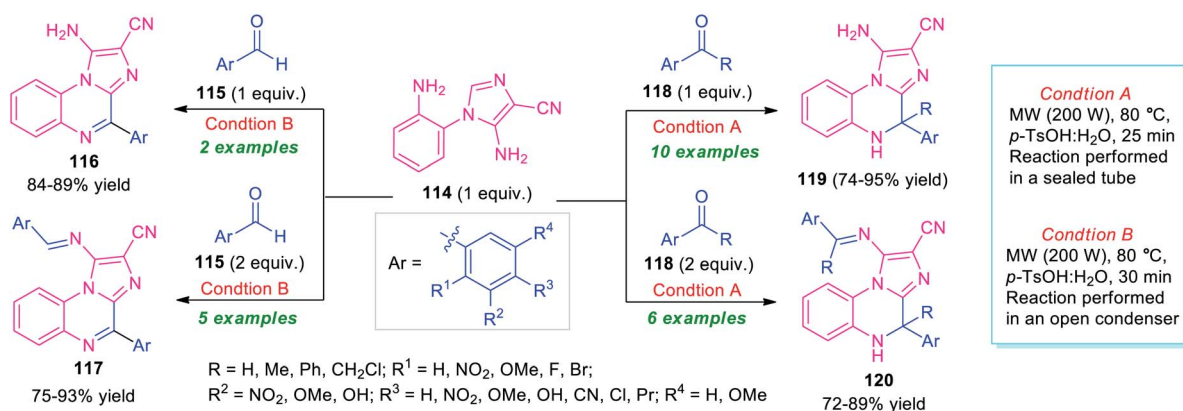
In 2018, Kumar *et al.* introduced the microwave technique as a powerful green energy source for the synthesis of diverse imidazo[1,2-*a*]quinoxalines *via* a 6-*endo-trig* cyclization of 5-amino-1-(2-aminophenyl)-imidazole-4-carbonitriles **114** with carbonyl compounds (Scheme 35).¹¹⁵ By using *p*-TsOH as a metal-free catalyst, treatment of the equimolar amount of aldehyde **115** with **114** performed in an open condenser under microwave heating at 80 °C, provides imidazo[1,2-*a*]

quinoxalines **116** in 84–89% yields. While the same reaction, when carried out with 2 equivalents of **115** and 1 equivalent of **114**, the products **117** were formed in 75–93% yields. Conversely, the reaction of an equimolar amount of ketone **118** and **114** performed in a sealed tube under microwave irradiation, afforded dihydroimidazo[1,2-*a*]quinoxalines **119** in 74–95% yields, whereas, employing 2 equivalents of **118** under the same reaction condition deliver products **120** in moderate to good yield. The utilization of microwave techniques not only reduces the reaction time in both cases but also provides a clean pathway for these reactions and improves the yield of the products as compared to the conventional method.

A step-wise synthetic route for imidazo[1,2-*a*]quinoxalines **125** has been realized recently by Amini and his groups (Scheme 36).¹¹⁶ In the initial step, the reaction of *o*-phenylenediamine **35** with aldehydes **121** was carried out by using NaCN as a catalyst in DMF at 50 °C. This step requires 4 Å molecular sieves as the additives. The resulting amino-substituted quinoxalines **122** were formed in 35–85% yields within 4–12 hours. The second step involves a multicomponent reaction of an equimolar amount of **122** with isocyanides **123** and aldehydes **124** using ammonium chloride as the catalyst in solvent-free condition at



Scheme 36 Two-step synthesis of imidazo[1,2-*a*]quinoxalines in metal-free condition.



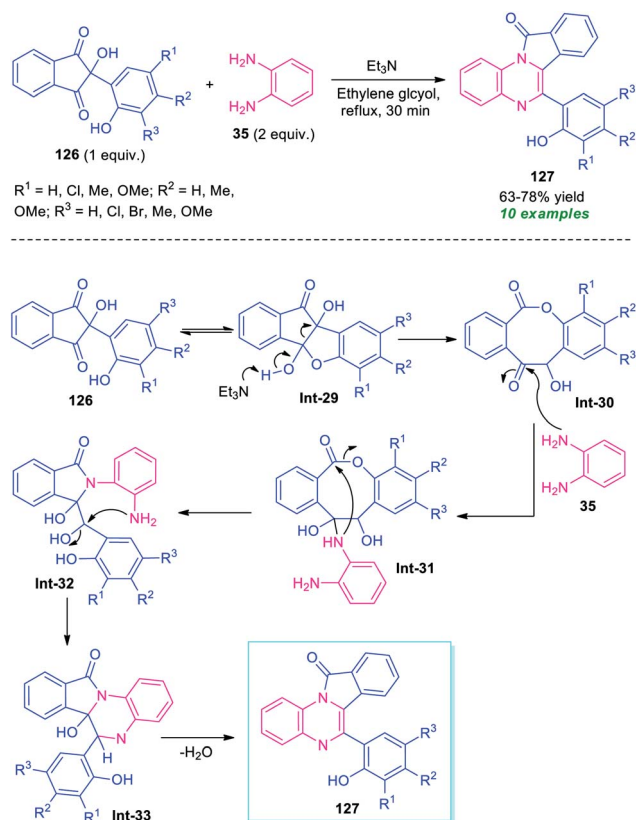
Scheme 35 Metal-free microwave-assisted one-pot preparation of library of imidazo[1,2-*a*]quinoxalines.



150 °C for 24 hours. The corresponding imidazo[1,2-*a*]quinoxaline derivatives **125** were formed in moderate to good yield. A variety of aryl aldehydes possessing different electron-withdrawing as well as electron-donating substituents well worked by this stepwise protocol. Broad functional group tolerances, solvent-free conditions, metal-free nature, a high level of yield are some of the salient features of this approach.

4.3 Synthesis of other fused quinoxalines

A metal-free tandem cyclization approach to access other fused quinoxalines, namely isoindolo[2,1-*a*]quinoxalines **127** has been demonstrated by Das *et al.*, in 2019 (Scheme 37).¹¹⁷ To find out the optimum condition, the reaction of ninhydrin **126** bearing phenolic adducts, with *o*-phenylenediamine **35** was initially performed in the presence of different bases including Et₃N, piperazine, pyridine, Et₂NH, and solvent system like ethylene glycol, water, MeOH, EtOH, glycerol. From these experiments, it was concluded that the utilization of Et₃N in ethylene glycol provides easy access to the products within a very short reaction time. The optimum reaction condition was found to be compatible for a wide range of substituted phenolic ninhydrin adducts **126** that smoothly underwent the reaction to deliver the isoindolo[2,1-*a*]quinoxaline products **127** in 63–78% yields. Most of the synthesized compounds were found to have a fluorescent activity which remarks outstanding achievements of this work.



Scheme 37 Metal-free base promoted tandem cyclization approach toward the rapid access of fused quinoxalines.

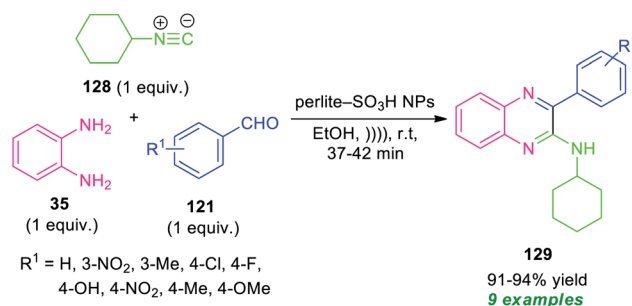
A mechanistic investigation suggests the initial formation of 8-membered lactone intermediate **Int-30** from Et₃N catalyzed cleavage of C–C bond of **Int-29**. The lactone **Int-30** then experiences nucleophilic attack from –NH of **35** to form an intermediate **Int-31**, which provides intermediate **Int-32** via an intramolecular nucleophilic attack of –NH to C=O moiety and subsequent breaking of C–O bond. Consequently, the intramolecular cyclization of (**Int-30**), followed by elimination of water leads to the final products **127** (Scheme 37).¹¹⁷

5. Synthesis of simple quinoxalines based on metal-free multicomponent reactions

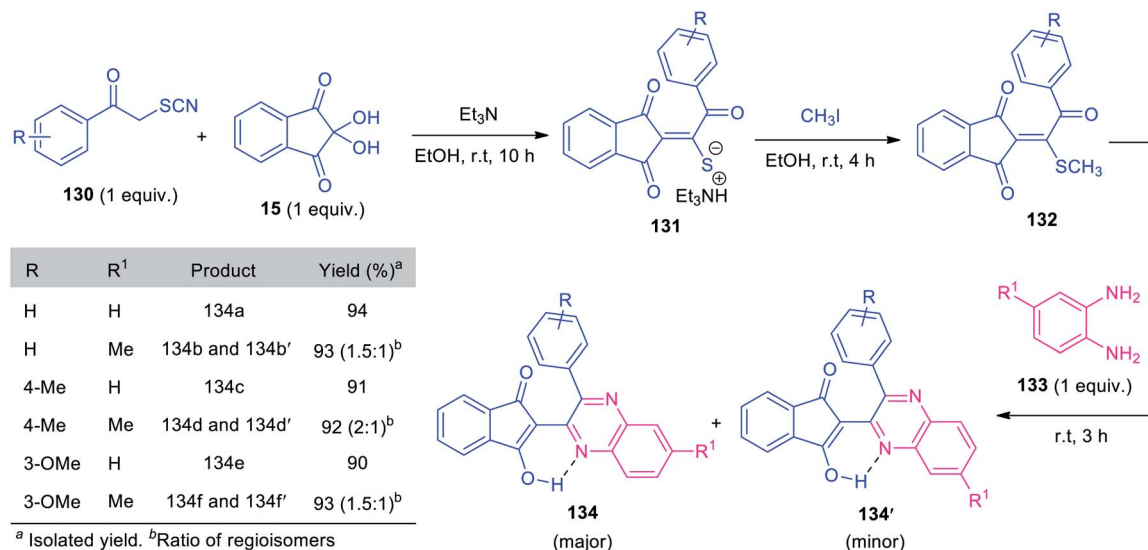
The development of an efficient concise route that provides easy access to highly functionalized and value-added compounds by fulfilling the criteria of green and sustainable chemistry has emerged as a most significant goal and formidable challenge for the synthetic chemist. Compared to synthetic step-wise process which deals with a number of limitations in the product development as well as in consistent with green chemistry principles, multicomponent reactions (MCRs) has recently come to receive widespread global acceptances as the most valuable choice of synthetic routes in industry and academia.^{118–121} Multicomponent reactions (MCRs) provide a clean and safe platform for multiple-bond forming events to occur in a single one-pot operation from more than two starting materials without separation and purification of the intermediates. Consequently, this reaction increases the product development rates by shortening the reaction steps, and also by reducing waste formation, utilizing inexpensive easily accessible reagents and reactants, *etc.*

As a consequence of these tremendous academic, economic and ecological interests, an isocyanide-based multicomponent approach¹²² for the synthesis of highly functionalized quinoxalines has been realized by Rouhani and Ramazani in 2018 (Scheme 38).¹²³

By using perlite-SO₃H nanoparticles as the catalyst, the three-component reaction of *o*-phenylenediamine **35**, aldehydes **121**, and cyclohexyl isocyanide **128** under ultrasonic irradiation were found to take place smoothly within a very short reaction time to provide the easy access of corresponding quinoxaline



Scheme 38 Ultrasound-assisted isocyanide-based multicomponent approach for the synthesis of quinoxalines **129**.



Scheme 39 Application of triethylammonium thiolate salts as efficient reagents for the multicomponent synthesis of quinoxalines **134**.

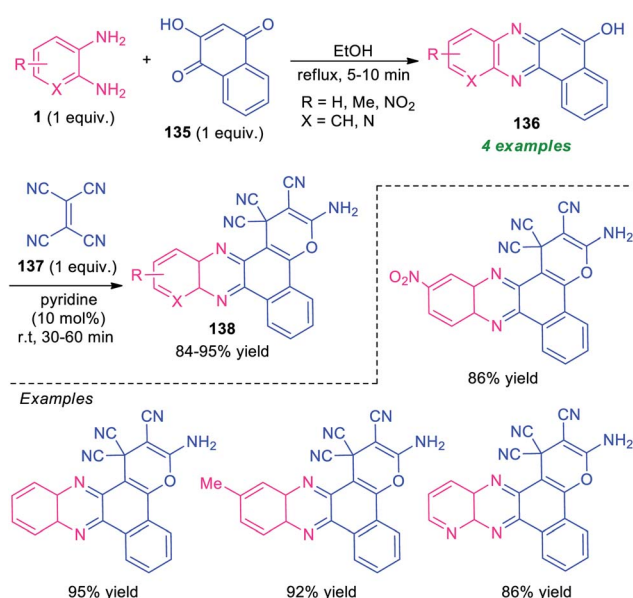
derivatives **129** in 91–94% yields. A variety of electron-withdrawing, as well as electron-donating groups present on the aryl ring of aldehydes, were well tolerated by this methodology. The exploitation of ultrasonic technology provides a clean synthesis of the desired quinoxaline products within a very short reaction time as compared to the conventional method which takes lots of time for the completion of the reaction.

In 2019, Alizadeh and co-workers synthesized triethylammonium thiolate salts **131** based on a formal [3 + 2] cycloaddition, followed by subsequent ring-opening reaction of phenacyl thiocyanate **130** with ninhydrin **15** and has been demonstrated as an efficient reagent for the synthesis of quinoxalines. Under metal-free reaction conditions, a one-pot sequential three-component reaction of triethylammonium thiolate salts **131**, with methyl iodide and *o*-phenylenediamines **133** was found to proceed smoothly to deliver several quinoxalines **134** bearing indandione framework, in high yields (Scheme 39).¹²⁴ Compound **131** containing various electron-rich groups efficiently participated in this reaction. Similarly, simple *o*-phenylenediamine **133a** (R¹ = H) selectively afforded **134** as the major products. However, when methyl-substituted diamine **133b** (R¹ = Me) was employed as the substrates, two regioisomeric products (**134** and **134'**) were achieved. Despite the remarkable advantages including mild condition, high yield, operational simplicity, and eco-benign, the limited substrate scope represents a limitation of this approach and calls for further developments.

6. Synthesis of fused quinoxalines based on metal-free multicomponent reactions

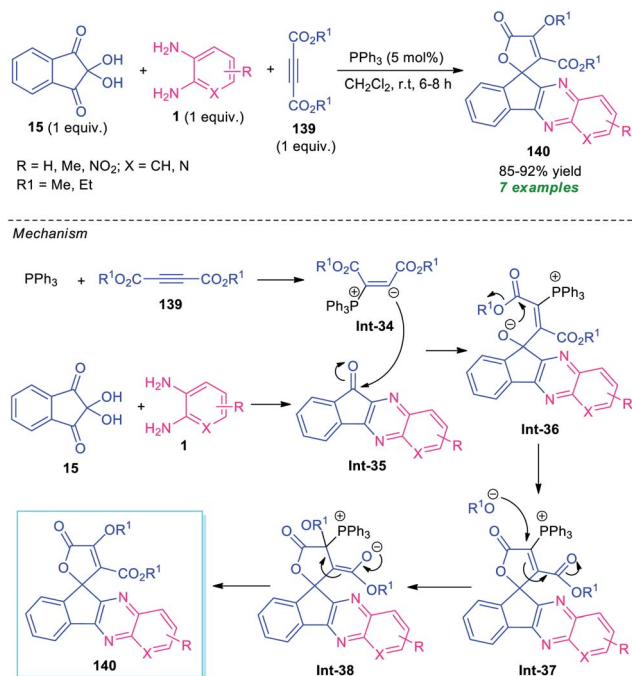
A novel one-pot three-component domino reaction between *o*-phenylenediamine **1**, 2-hydroxynaphthalene-1,4-dione **135**, and tetracyanoethylene **137** using pyridine as a catalyst in ethanol at

room temperature was presented by Mohebat and co-authors for the efficient synthesis of pyrano-fused quinoxalines **138** (Scheme 40).¹²⁵ The resulting quinoxalines **138** were obtained in good to high yields. The initial step involving the reaction of **1** with **135** takes place within 5–10 minutes under reflux condition in ethanol to form benzo[*a*]pyrano[2,3-*c*]phenazine **136**, which on treating with **137** under the influence of 10 mol% of pyridine afford the final products **138**. The products were simply isolated by recrystallization techniques that do not require further conventional purification procedures. Although the presented approach provides several key features like short reaction time, cost-effectiveness, operation simplicity, however, the narrow



Scheme 40 One-pot two-step three-component synthesis of pyran-fused quinoxalines.





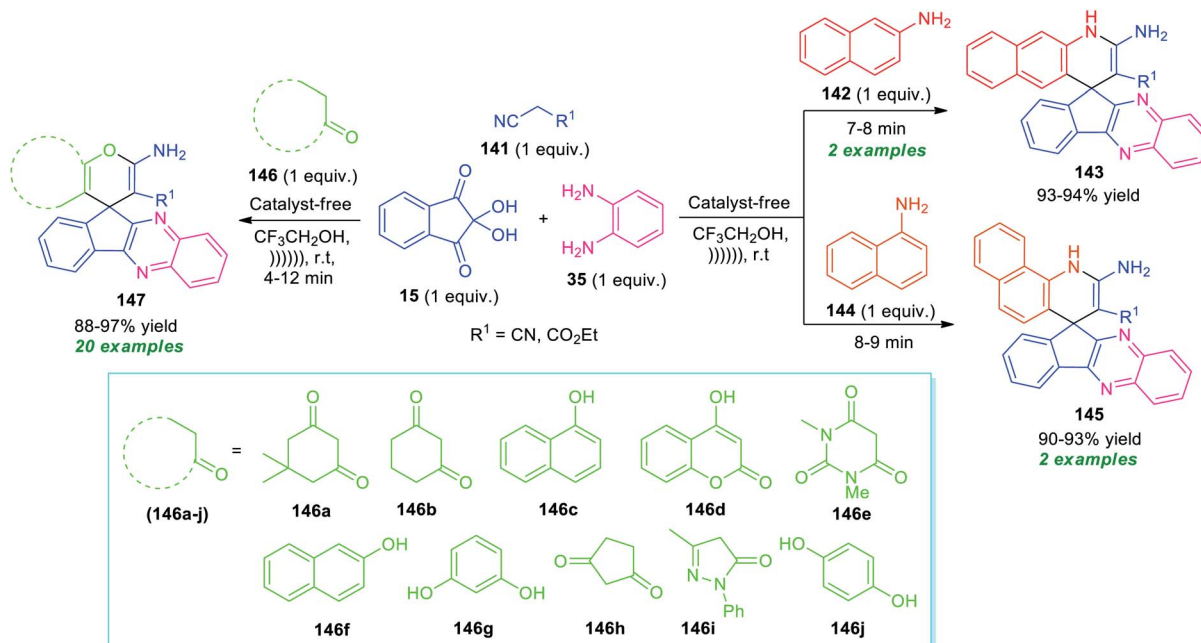
Scheme 41 PPh₃ catalyzed one-pot domino reaction to access spiro-fused quinoxaline **140**.

substrate scopes again constitute a limitation toward this method and calls for further development.

For the construction of diverse annulated quinoxalines, ninhydrin was employed as a versatile and easily accessible starting material. In this regard, Maghsoudlou and co-workers in 2017, disclosed a one-pot multicomponent domino protocol under the metal-free condition to access a variety of

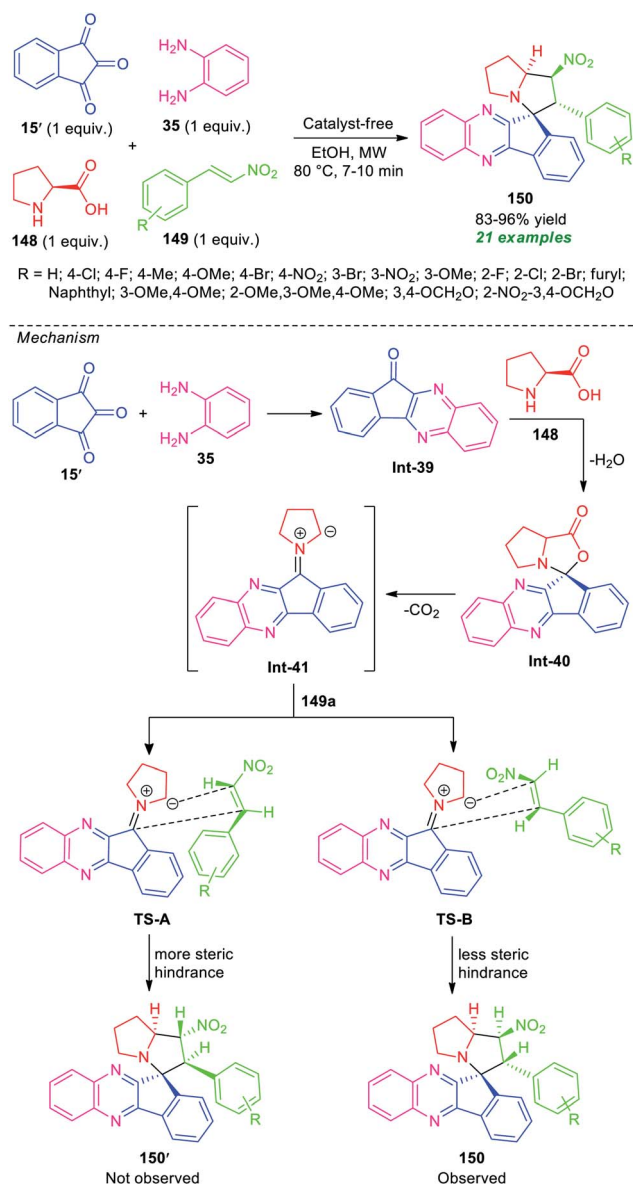
spiro-furan-indeno[1,2-*b*]quinoxalines in 85–92% yields by employing ninhydrin **15** as the starting material, alongside *o*-phenylenediamine **1**, and dialkyl acetylene dicarboxylate **139** (Scheme 41).¹²⁶ The reaction was performed in presence of 5 mol% of triphenylphosphine (PPh₃) in CH₂Cl₂ at ambient temperature that could be completed within 6–8 hours. In this transformation, PPh₃ reacts with **139** to produce 1,3-dipolar intermediate **Int-34**, which eventually attacks the C=O of spiro-indeno[1,2-*b*]quinoxaline **Int-35** formed *in situ* from the condensation of **15** and **1**. The resulting zwitterionic intermediate **Int-36** underwent intramolecular cyclization to form an intermediate **Int-37**, which is followed by subsequent rearrangement to yield the desired products **140**.

Around the same time, Heravi and Norouzy showed the successful application of ninhydrin in the multicomponent reactions for the synthesis of a library of fused quinoxaline derivatives by employing ultrasonic techniques as a non-conventional strategy (Scheme 42).¹²⁷ With the catalyst-free condition, treatment of ninhydrin **15** with *o*-phenylenediamine **35**, active methylene compound **141**, and amines **142** or **144** in presence of trifluoroethanol (TFE) under ultrasound irradiation at room temperature provides easy access of spiro [benzo[*g*]quinoline-4,10'-indeno[2,3-*b*]quinoxaline] **143** and spiro[benzo[*h*]quinoline-4,10'-indeno[2,3-*b*]quinoxaline] **145** in high yield respectively. On the other hand, the same reaction condition was found to be very suitable for various CH-activated acidic compounds **146** that react with ninhydrin **15**, *o*-phenylenediamine **35**, and active methylene compound **141** to form various spiro-fused quinoxalines **147** in good to excellent yield. All the tested CH-activated acidic compounds efficiently worked well under this condition. A comparative study for both conventional and ultrasonic methods revealed that the

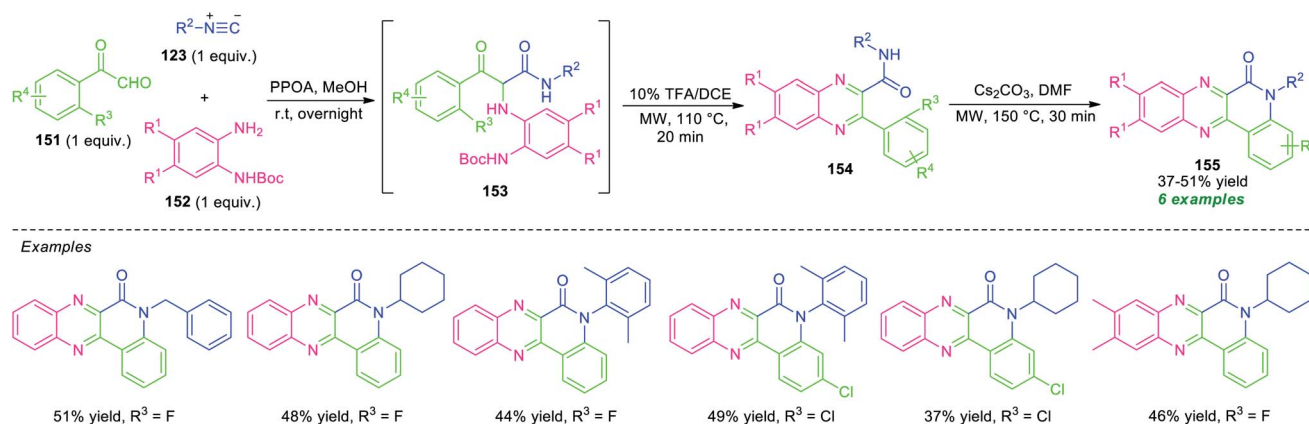


Scheme 42 Ultrasound irradiated one-pot construction of several fused quinoxaline derivatives under metal-free condition.





Scheme 43 Microwave-assisted regio- and stereoselective one-pot four-component synthesis of spiro-fused quinoxalines.



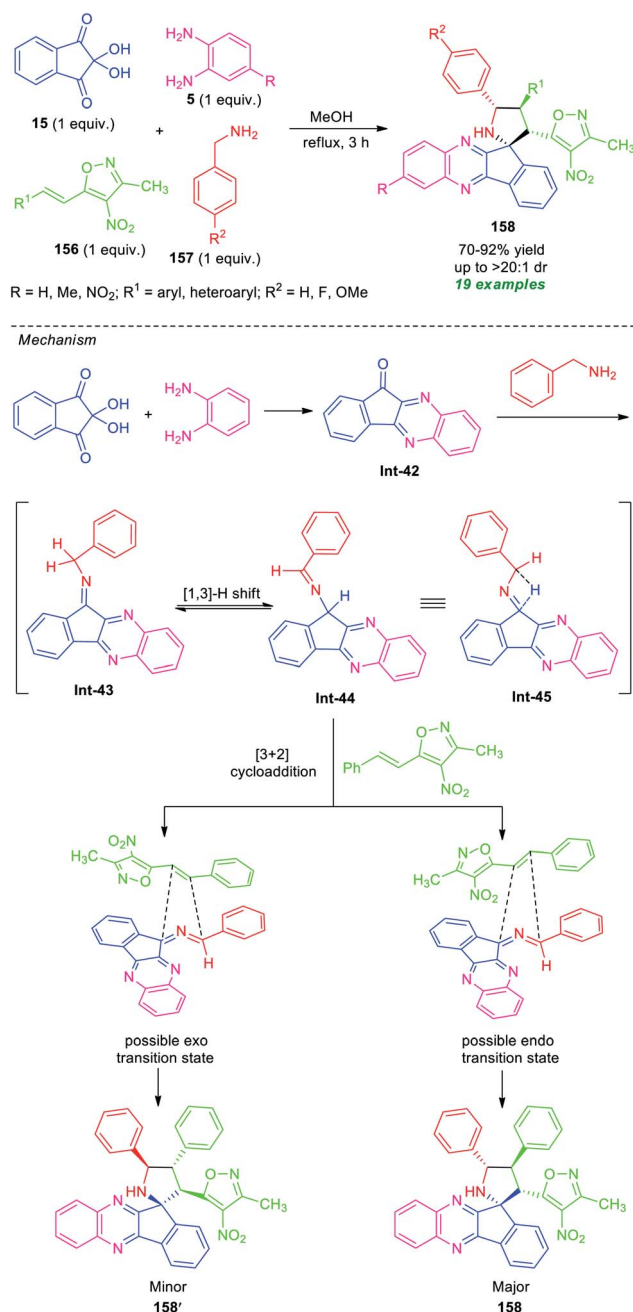
Scheme 44 Acid-less Ugi-deprotection-cyclization-substitution sequence for the synthesis of quinolinone-fused quinoxalines.

conventional method utilized a higher amount of energy, as well as a long reaction time as compared to ultrasonic conditions. Conversely, the exploitation of ultrasound not only shortened the reaction time but also improves the yield of the products.

Unlike ultrasonic techniques,¹²⁸ the attractiveness of microwaves¹²⁹ for the synthesis of promising molecular structures has recently gained favour due to its remarkable advantages associated with the synthetic practitioner like mild-condition, reduces reaction times, enhances product yield, and provides high purity of products as well as green chemistry point of view.

In 2017, Kantam, Trivedi, and co-authors introduced a microwave technique to develop a convenient strategy for the four-component synthesis of spiro-indeno[1,2-*b*]quinoxaline-11,3'-pyrrolizines derivative **150** based on an azomethine ylide 1,3-dipole mediated [3 + 2]-cycloaddition reaction (Scheme 43).¹³⁰ The synthesis starts with the treatment of ninhydrin **15**, *o*-phenylenediamine **35**, L-proline **148**, and β-nitrostyrene **149** in microwave heating at 80 °C in ethanol, to form the corresponding products **150** as single regio- and diastereomer in good to high yield. Not only aryl-substituted β-nitrostyrene bearing various electron-rich and electron-poor substituents but also heteroaryl as well as alkyl-substituted β-nitrostyrene were well tolerated by this method. The use of conventional heating conditions instead of microwave techniques required a longer reaction time for the completion of the reaction and also a slightly lower yield of the product was observed. The exploitation of microwaves provides a clean reaction profile, shortened the reaction time, and increases the product yield. Other salient features of this approach included broad functionality, eco-friendly, and environmentally benign nature.

To rationalize the stereochemistry of this regioselective dipolar cycloaddition of azomethine ylide **Int-41** generated from **15'**, **35**, and **148** to a dipolarophile **149a**, two transition states **TS-A** and **TS-B** based on steric considerations. As shown in Scheme 43, only the *endo*-product **150** was formed. This is presumably due to the thermodynamically more stable **TS-B**, while the *exo*-product **150'** was not formed due to more steric repulsion (**TS-A**).



Scheme 45 Catalyst-free regio- and diastereoselective one-pot synthesis of spiro-fused quinoxalines.

An acid-free Ugi-deprotection-cyclization (UDC) approach toward the synthesis of quinolinone-fused quinoxalines has been demonstrated by Xu and co-workers (Scheme 44).¹³¹ The overall process starts with the initial post-Ugi three-component reactions of 2-oxo-2-phenylacetaldehyde **151**, *N*-Boc-protected *o*-phenylenediamine **152**, and isocyanide **123** under the influence of phenyl phosphonic acid (PPOA) as the catalyst in MeOH at room temperature. The resulting Ugi product **153**, on treating with 10 mol% of TFA in 1,2-dichloroethane (DCE) under microwave heating condition at 110 °C, afforded the adduct **154** *via* deprotection and cyclization sequence. Subsequently,

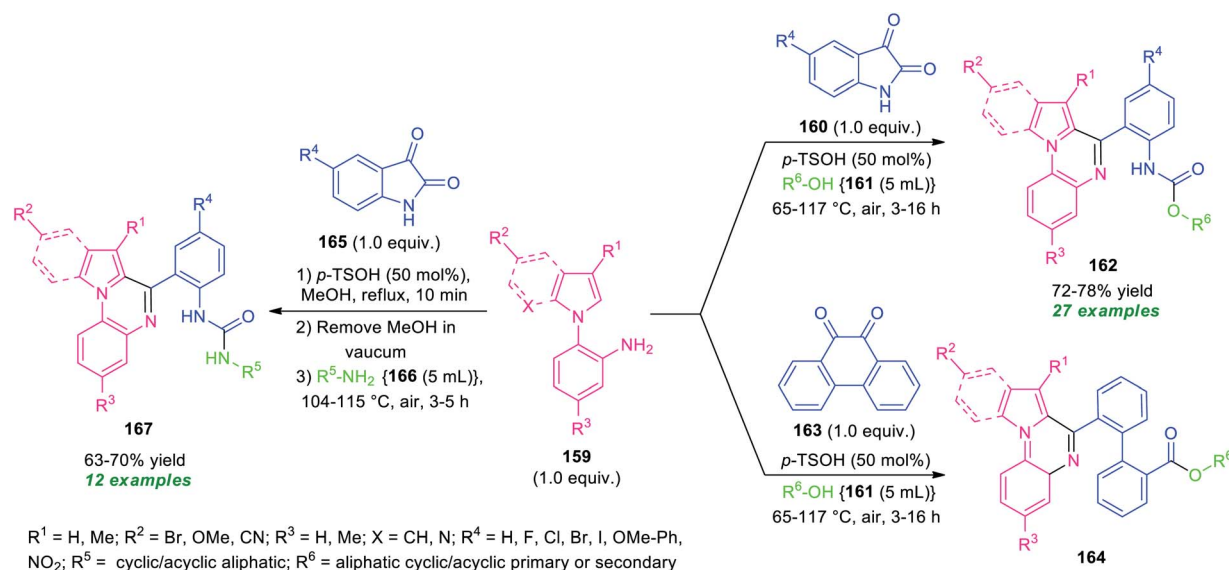
a nucleophilic substitution reaction of **154** was occurred in presence of Cs₂CO₃ in DMF in microwave condition at 150 °C to furnish the final products **155**. This multi-component reaction provides a total of six compounds in 37–51% yields from different substituted *o*-phenylenediamine, aryl as well as alkyl-substituted isocyanide and 2-oxo-2-phenylacetaldehyde.

In 2018, Chowhan *et al.* disclosed a catalyst-free four-component reaction of ninhydrin **15**, *o*-phenylenediamine **5**, 3-methyl-4-nitro-5-alkenylisoxazoles **156**, and benzylamine **157** under reflux condition in methanol for 3 hours to provide a series of spiro-indeno[1,2-*b*]quinoxaline-pyrrolidines **158** (Scheme 45).¹³² This multicomponent approach proceeds *via* an *in situ* generated azomethine ylide 1,3-dipole mediated [3 + 2] cycloaddition reaction. The resultant products were achieved in moderate to high yield with outstanding diastereoselectivity. A variety of differently substituted aryl and heteroaryl rings of **156**, as well as unsubstituted or methylated diamines **5**, were well tolerated by this method. However, nitro-substituted diamines failed to yield any product. This is presumably due to the electron-poor nature of the nitro group that makes the substrate labile.

Based on a series of observations, a mechanism and transition state to account for the stereochemistry were proposed by the authors. Initial dehydration reaction between ninhydrin, *o*-phenylenediamine, benzylamine provided the isomeric intermediate **Int-43** and **Int-44** which can be equilibrium to intermediate **Int-45**. This azomethine ylide type intermediate **Int-45**, then stereoselectively undergoes [3 + 2] cycloaddition with phenyl-isoxazole *via* two transition states. The *endo* isomer **158** was formed as the major isomer over *exo* product **158'**. This can be attributed based on the fact that in **158**, the 3-methyl-4-nitroisoxazoles core is positioned closer to the dipolar region that is opposite in **158'**.¹³²

Recently, a transition-metal-free one-pot domino process for the synthesis of diverse pyrrolo/indolo[1,2-*a*]quinoxaline derivatives has been realized by Mandal and Pramanik (Scheme 46).¹³³ By using 50 mol% of *p*-TsOH as the catalyst, a three-component reaction of *N*-(2-aminophenyl)pyrroles/indoles **159**, with various cyclic 1,2-dicarbonyl compounds **160** or **163** and alcohols **161** or aliphatic amines **166** were performed in open-air heating condition. The reactions provide a variety of different fused quinoxaline derivatives **162**, **164**, and **167** in moderate to good yields. In these reactions, aliphatic amines and alcohols were acted both as solvent as well as the reactant. To explore the generality of the developed protocol, different *N*-(2-aminophenyl)pyrroles/indoles **159** and cyclic 1, 2-dicarbonyl compounds bearing electron-withdrawing as well as electron-donating groups, and amines or aliphatic alcohols were employed. All the substrates were found to be well tolerated. However, tertiary alcohols (*tert*-butyl alcohol and 2,2,2-trifluoroethanol) failed to yield any products by this method. This is presumably due to the steric crowding and reduced nucleophilicity of the free hydroxyl group. The wide substrate scopes, mild reaction condition, metal- and oxidant-free, air as green oxidant are some of the key features of this approach.





Scheme 46 Metal-free solvent-mediated diversity-oriented one-pot domino synthesis of various fused quinoxalines.

7. Conclusion and future perspective

Considering the great importance of the quinoxaline framework in many branches of chemistry including natural products chemistry, drug discovery, medicinal chemistry, material science, and agrochemical area, tremendous efforts have been dedicated toward their synthesis. Consequently, many more useful and efficient synthetic protocol has been developed. Synthetic modifications of the classical methods for the preparation of numerous quinoxalines have also emerged. However, most of them are not clearly focused on the development of an efficient route that not only enhances the yield of the product but also reduces the cost of the reaction, provides a clean reaction profile, atom-economic, and utilized an environmentally benign pathway. Therefore, the development of novel synthetic strategies that directs the efficient synthesis of quinoxalines inconsistent with the green and sustainable chemistry principles to make a toxic and waste-free nature are highly desired.

In this pursuit, the last few years have witnessed special attention in the metal-free synthesis of quinoxalines by employing various non-metal inorganic and organic catalysts, ionic liquids, organocatalysts, molecular iodine, catalyst-free condition, green catalyst, visible-light-induced and non-conventional strategies like microwaves, and ultrasound irradiation. The exploitation of these reagents and techniques certainly makes these protocols environmentally as well as eco-friendly benign compared to those transition-metal-catalyzed routes. Despite, notable developments achieved in the transition-metal catalyzed synthesis, high cost involved in the preparation of the catalyst, toxicity, and difficulty in removing it from the final products constitutes disadvantageous effects on the atom economy and eco-friendly nature of the transformation.

In this review article, we have summarized the recent progress achieved in the synthesis of quinoxalines and various fused quinoxalines by employing two-component and multicomponent reactions under metal-free conditions and cover the reports from 2015 to date. This aspect is presented alongside the mechanistic rationalization and limitation of the reaction methodologies. The scopes of future developments are also highlighted.

As illustrated through the review, it is clear that these protocols have significant advantages such as a high level of yield, broad functional group tolerance, mild reaction condition, cost-effectiveness, *etc.* Other key features included the utilization of water as green solvents over other toxic and volatile solvents due to its remarkable properties like wide abundance, non-toxic, and inexpensive nature. Besides these, solvent-less protocols are also developed under metal-free conditions. In addition to these, the utilization of microwaves and ultrasonic techniques shortened the reaction times as well as enhanced the reactivity and selectivity of the reaction, and provides an excellent yield of the quinoxaline products.

On the other hand, the combination of the metal-free condition along with multicomponent reactions opened a new gateway for the easy access of highly functionalized quinoxalines.

Despite, notable advancement achieved in the metal-free synthesis of quinoxalines, limited substrate scopes, requirements of higher energy source, low yield of the products, longer reaction time, and high catalyst loading, constitutes the major limitations of some so far developed protocols. Therefore, ample attention needs to be paid in the upcoming days for broadening the substrate scopes with excellent yields by employing mild pathways which are safe, eco-benign, atom-economic, and provide scale-up synthesis in low catalyst loading or catalyst and metal-free condition for application to



the industrial area. Also, the biological as well as material science applications of novel quinoxaline derivatives need to be screened and should be strengthened. We hope, the present review article will help researchers working on this fascinating area for the design and developments of more precise synthetic routes for the construction of quinoxalines and for further outstanding creation of a highly functionalized novel quinoxaline framework that would find immense application in the field of medicinal chemistry and optoelectronic materials.

Conflicts of interest

"There are no conflicts to declare".

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