

Chapter 2

Sustainable Approaches Towards the Synthesis of Quinoxalines

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Abstract The quinoxaline (Qx) nucleus is present in various bioactive molecules. Thus, synthesis of Qxs continues to draw the attention of synthetic organic/medicinal chemists. The contemporary interest in search for newer synthetic methods for this privileged class of compounds remains unabated and a vast number of publications continue to appear. The focus of this chapter is on the research works published in this area after the year 2000 with the inherent objective to attain sustainability towards the synthesis. The attention will be on the key sustainable approaches of pharmaceutical industries like the solvent-free reactions, use of alternate reaction media (e.g., water, fluorous alcohols, polyethylene glycols, and ionic liquids), and alternate modes of synthesis such as microwave-assisted synthesis and flow reactions.

Keywords Quinoxaline · Bioactivity · Sustainable synthesis

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1 Introduction

Heterocyclic compounds, especially the N-heterocycles, are the most important class of compounds in the pharmaceutical and agrochemical industries. There is a strong preponderance (~60%) of N-containing heterocycles among the drug candidate molecules [1]. The 6-membered aromatic rings containing two nitrogen atoms, such as phthalazine, quinazoline, pyrimidines, and quinoxalines (Qxs), possess a broad spectrum of biological activities and are therefore of interest as target compounds in pharmaceutical and medicinal chemistry. Qx, the diazine derivative, is a heterocyclic compound comprising of a benzene ring fused with pyrazine ring. Qx and its derivatives are important nitrogen-containing heterocycles due to their broad spectrum of biological activities [2] and applications in material science [3].

2 Biological Importance of Quinoxalines (Qxs)

The Qx-based compounds exhibit versatile biological activities that include anti-cancer [4], antimicrobial/antitubercular [5], antiprotozoal [6], antiviral [7], inhibition of the enzyme phosphodiesterase [8], anti-inflammatory [9], etc.

The Qx derivatives are known for their cancer chemopreventive effect [4a]. The compounds **1–4** have been recently identified as potent and selective inhibitors of human tyrosine kinase (TRK) in liver cancer HepG2 and breast cancer MCF-7 cell lines similar to the known anticancer drug doxorubicin [4a]. The transglutaminase 2 (TGase 2) inhibitory activity has been exhibited by **5** [4b]. The TGase 2 is a cross-linking enzyme which plays an important role in oncogenesis by inducing NF- κ B activation through I- κ B α polymerization which leads to the increase of pro-survival factors and suppression of apoptosis. The Qx urea analog **6** acts on IKK β and thereby inhibits the mTOR (mammalian target of rapamycin) and NF- κ B pathways in pancreatic cancer and has shown good oral bioavailability along with *in vivo* efficacy, and being devoid of toxicities it becomes a viable cancer therapeutic [4c]. The structure–activity relationship (SAR) of these Qx ureas has been further elaborated through evaluation of a library of quinoxalin-6-amine derivatives against a panel of cancer cell lines [4e] (Fig. 2.1).

The Qx derivatives have shown interesting antimicrobial properties (antibacterial, antiviral, antifungal, antiprotozoal, etc.) and assessment of their therapeutic potential is still an active area of research in medicinal chemistry. Through the biological evaluation of a series of fluoro/trifluoromethyl quinoxalinones bearing various substituents (alkyl, haloalkyl, arylmethyl, and aryl groups) at C-3, the compounds **7** and **8** were found to have promising inhibitory activity against various strains of *Candida* [5a]. The 2,3-bis(bromomethyl)quinoxaline **9** has shown antifungal activity and the compounds **10** and **11** exhibited antibacterial activity [5b]. Substitution at the sixth position is very crucial and highest antibacterial activity was observed with CF₃ group at this position, whereas the presence of the fluoro group at this position imparted maximum antifungal activity to these compounds. Recently, 4'-acetoxybenzyl-2-quinoxalinecarboxylate **13** has been found to have antitubercular

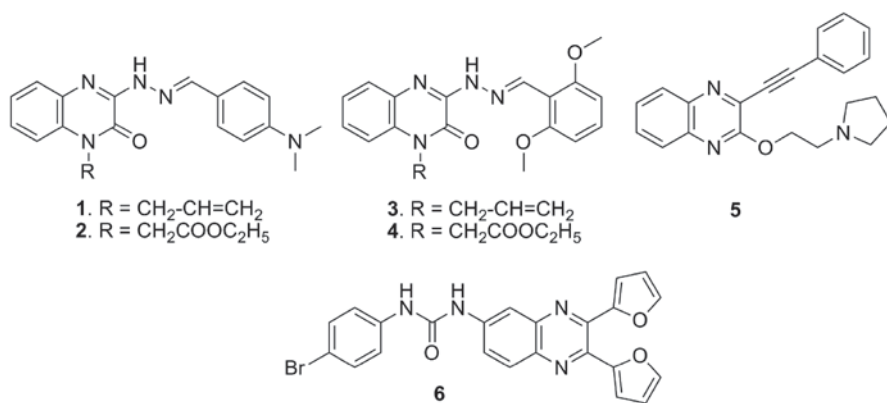
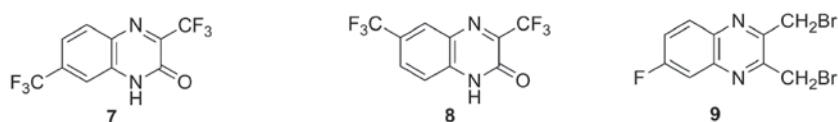
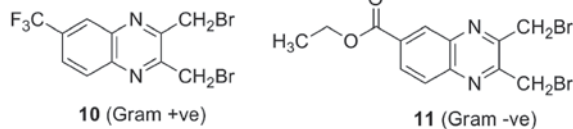


Fig. 2.1 Quinoxaline (Qx) derivatives with anticancer activity

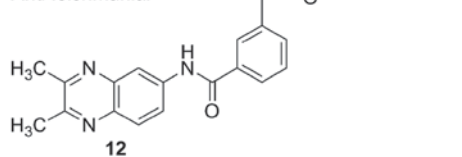
Anti-fungal



Anti-bacterial



Anti-leishmanial



Anti-tubercular

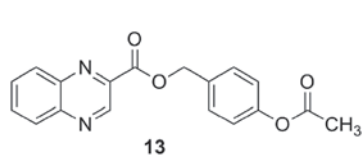


Fig. 2.2 Quinoxaline (Qx) derivatives with antimicrobial activity

activity against *M. tuberculosis* (Mtb) and *M. avium* (MAC) with minimal inhibitory concentrations (MIC) of $<1\text{--}6.25\text{ }\mu\text{g/mL}$ [5d]. Qx derivatives have been also evaluated for *in vitro* antiprotozoal (*Leishmania donovani*, *Trypanosoma brucei*, and *Trichomonas vaginalis*) activity among which the quinoxaline amide **12** has shown potent *in vitro* anti-leishmanial properties with IC_{50} of 8.2 comparable to that of miltefosine (IC_{50} 7.3) [6] (Fig. 2.2).

Fusion of the Qx moiety with another ring system and covalent attachment to other bioactive fragments led to compounds with antiviral activity. The compounds **14** and **15** with 6-(2-aminoethyl)-6*H*-indolo[2,3-*b*]quinoxaline scaffold containing

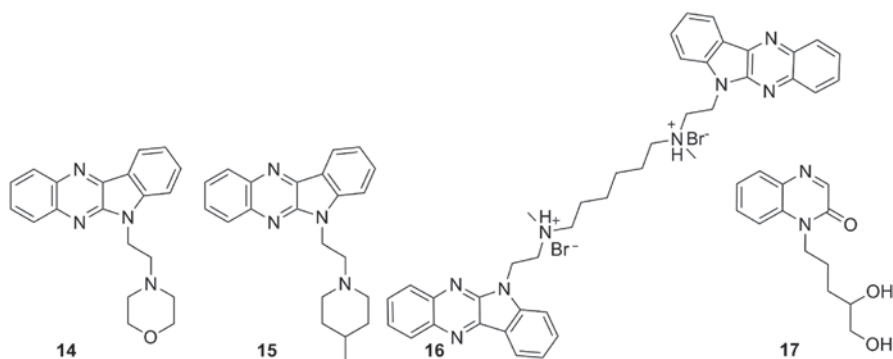


Fig. 2.3 Quinoxaline (*Qx*) derivatives with antiviral activity

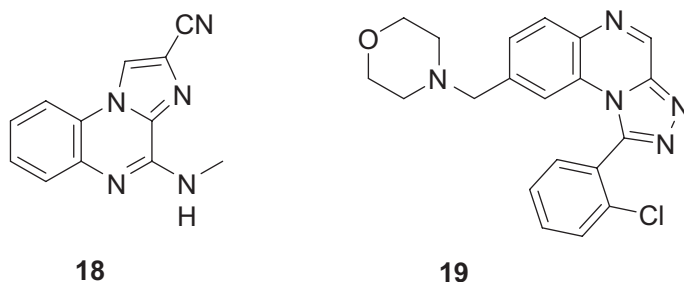


Fig. 2.4 Quinoxaline (*Qx*) derivatives with phosphodiesterase (*PDE*) inhibitory activity

morpholine and 4-methyl-piperidine moieties are potent antiviral compounds [7a]. The 2,3-dimethyl-6(2-dimethylaminoethyl)-6*H*-indolo-(2,3-*b*)quinoxaline also has shown excellent antiviral activity against human cytomegalovirus (CMV), herpes simplex virus type 1 (HSV-1), and varicella-zoster virus (VZV) [7b]. These observations led to the indoloquinoxaline derivative **16** with DNA-binding constants of ($\sim 10^9$). These findings led to the understanding of the antiviral effect of these derivatives and provided invaluable information for the future lead optimization for these kinds of compounds [7c]. The 1-(4,5-dihydroxypent-1-yn-1-yl)quinoxaline **17** has shown promising anti-HIV activity with EC_{50} value of 0.15 ± 0.1 $\mu\text{g/ml}$ and therapeutic index (SI) of 73.2 for HIV-1 of [7c] (Fig. 2.3).

The imidazo[1,2-*a*]quinoxaline derivatives are cyclic nucleotide phosphodiesterase type III (PDE-III) and type IV (PDE-IV) inhibitors with promising activity in case of 4-(methylamino)imidazo[1,2-*a*]quinoxaline-2-carbonitrile **18** [8a]. 1-Aryl-4-methyl[1,2,4]triazolo[4,3-*a*]quinoxaline **19** acts as dual phosphodiesterase II/phosphodiesterase X (PDE-II/PDE-X) inhibitor with acceptable brain uptake and high selectivity for both PDE-II and PDE-X enzymes [8b] (Fig. 2.4).

Qxs and quinoxaline-1,4-di-*N*-oxide derivatives also have anti-inflammatory and antioxidant potential [9] and provide important scavenging activities and promising *in vitro* inhibition of lipoxygenase (LOX), an enzyme which plays an important role

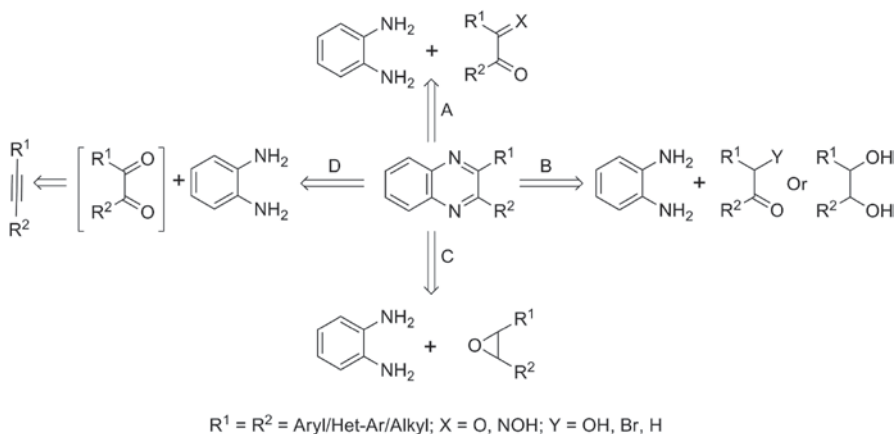
in inflammation and inflammatory process. The *in vivo* anti-inflammatory activity (41 %; carrageenin-induced edema model) was comparable with that of indomethacin (47 %) used as the reference drug.

3 Synthesis of Quinoxalines (Qxs)

The broad spectrum of biological activities of Qx-based compounds and their applications as useful materials [1–9] have inspired synthetic organic/medicinal chemists to develop new and more efficient synthetic methodologies for the preparation of Qx derivatives. Thus, search for newer and more effective synthetic methodologies for this privileged class of compounds continues to be an inspirational area of research and various reviews have been published describing the synthesis of Qxs [10, 11]. This chapter focuses on the research works involving the development of methodologies for the synthesis of aromatic Qxs (and not their reduced or polycyclic derivatives) published after the year 2000 with the inherent objective of attaining sustainability.

3.1 Sustainable Methods For Synthesis of Qxs

The various approaches (Scheme 2.1) for the synthesis of Qxs involve the Lewis/Brønsted acid or Lewis-base-promoted reaction of *o*-phenylenediamine (commercially available or prepared in situ through the reduction of the corresponding *o*-nitroaniline) with (1) 1,2-diketone/1,2-ketomonoxime (Route A) [12]; (2) α -hydroxyketone/ α -haloketone/1,2-diol or α -methylene ketone (Route B) [13]; (3) appropriately substituted epoxide (Route C) [14]; and (4) substituted alkynes (Route D) [15] under heating or microwave irradiation.



Scheme 2.1 Synthetic strategies for the construction of the Qx scaffold

The development of eco-friendly/green approaches (sustainable development) is an ongoing demand and subject of current interest due to the adverse effects of the manufacturing processes of drugs and pharmaceuticals on the environment [16]. There is considerable influence of green chemistry tools on medicinal chemistry and chemistry research-based organizations [17]. These urge for the requirement to enrich the medicinal chemist's tool box through improvement of existing transformations for more general application to make them amenable to parallel chemistry and potentially broaden the diversity of compounds for medicinal chemistry purposes [18]. There are twelve principles of green chemistry [19]; however, "It isn't expected that new chemical processes should always satisfy all 12 principles, but the check-list does provide a rough idea of whether one process is greener than the other" [16]. On a similar note, "Whether a reaction is green is highly subjective based upon the specific synthetic situation in a global context of a synthesis" [20]. The attainment of sustainability in chemical synthesis is subjected to the fulfillment of the "triple bottom-line philosophy" of green chemistry [21]. In the pharmaceutical industry, the sustainability of a chemical process is assessed by its "Green Index" determined by the following criteria:

1. Consumption of resources
2. Consumption of energy
3. Undesirable effects on human beings
4. Undesirable effects on ecosystem
5. Safety (physical, chemical, and biological)

These guidelines drive the pharmaceutical research to prioritize the R & D targets in the following aspects:

1. Stoichiometric to catalytic reactions
2. Multi- to fewer-step routes
3. Liquid acid/base to solid acid/base catalysts
4. Safer processes: avoidance of dangerous/toxic reagents and by-products
5. Improvements of reaction media: solvent free, solid state, water, supercritical media, ionic liquid (IL), etc.
6. Routes of higher atom utilization/economy

The highlight of the literature reports on Qx synthesis will be on these directives of green chemistry.

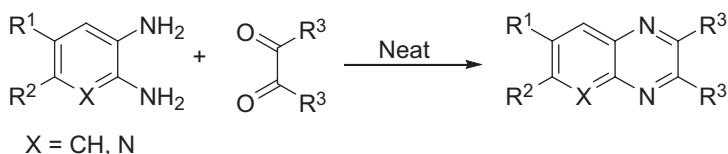
3.1.1 Solvent-Free Synthesis

The uses of volatile organic solvents (VOSs) are the major contributory factors towards environmental pollution due to their abundant use (solvents constitute more than 85 % of the total mass utilization of a chemical process) and incomplete recovery efficiency (50–80 %) [22]. Therefore, the major drive towards the initiative of sustainable development in chemical synthesis is focused on the replacement of the VOSs by solvent-free conditions [23] to reduce the waste, time period, and total

cost associated with the organic reactions. Thus, “the best solvent is no solvent” is often vouched as a good campaign for sustainability development [24]. Many reactions are known to proceed efficiently in the solid state as, in the solid-state, organic reaction occurs more efficiently and more selectively than in the solution phase [25]. This has witnessed increasing efforts for heterocyclic synthesis under solvent-free condition in the recent years [26].

However, the use and understanding of solvent-free conditions has remained underdeveloped in comparison to the solvent-based methods [27].

Synthesis using 1,2-diketones



Scheme 2.2 Synthesis of Qx from 1,2-diketone and 1,2-diamine without solvent

The Qx synthesis involves the condensation of 1,2-diamines with 1,2-diketones and require either an electrophilic activation of the diketone-coupling partner or nucleophilic activation of the diamine-reacting partner that necessitate the use of an acid and base catalyst, respectively. To achieve sustainability, the R & D priority of the pharma industry directs the use of solid acid/base catalysts to reduce waste generation as solid acid/base catalysts can be recovered and recycled. Reactions catalyzed by solid acids are by far the most important contribution of catalysis towards green chemistry [28]. Various solid acid catalysts are clay-based materials [29], silica [30], and mineral dust [31]. Although the heteropolymetallic salts are good contenders as solid acids, the solid-supported protic acids are better options for the “electrophilic activation” strategy due to their ease of preparation and cost effectiveness. Similarly, solid-supported base would also provide a better option for nucleophilic activation process. Among the solid-supported protic acids, such as $\text{H}_2\text{SO}_4\text{-SiO}_2$ [32a], $\text{HBF}_4\text{-SiO}_2$ [32b], and $\text{HClO}_4\text{-SiO}_2$ [32c], the silica-supported perchloric/fluoboric acid catalyst systems developed in this laboratory [32b–32d] have attracted the attention of synthetic chemists worldwide and appeared to be the most effective [33]. On the other hand, KF -alumina [34] has been considered as the most effective solid base as the interaction of the KF with the oxyanionic site of alumina generates the naked F^- species as a strong base which otherwise require the use of aprotic polar solvents for catalytic uses as has been demonstrated through the “demand-based thiolate anion generation” protocols [35].

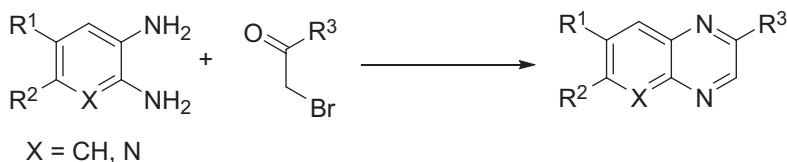
Several reports have appeared for the synthesis of Qxs using different electrophilic components like 1,2-diketones (Scheme 2.2, Table 2.1). Most of these methods [36–44] are high yielding and use different heterogeneous catalysts. The reactions can be performed at room temperature (rt) or under heating at 80 °C. The isolation/purification of the product is simple (largely nonchromatographic). The catalyst

Table 2.1 Synthesis of Qxs using 1,2-diketones

Sr. No.	Catalyst	Key features	Reference
1.	PW ₁₂ ZrO ₂	80 °C, simple workup, reusable catalyst, high yield (65–99%), 5–300 min	36
2.	TBBDA/PBBS	80 °C, excellent yield (85–98%), 3–120 min	37
3.	TSA	rt, 20–180 min and high yield, reusable catalyst	38
4.	KF/Alumina	rt, 60–150 min, 78–92%, reusable catalyst	39
5.	Acidic alumina	80 °C, good to excellent yield (45–96%), 2–90 min, reusable catalyst	40
6.	Silica gel	100 °C, 20–70 min, excellent yield, easy non-chromatographic purification	41
7.	Basic Al ₂ O ₃	rt, grinding, 10–25 min and high yield (87–99%), reusable catalyst	42
8.	Silica sulfuric acid	rt, excellent yield, reusable catalyst	43
9.	<i>p</i> -TsOH	rt, fast reaction (5–10 min), and high yield (88–99%)	44

can be easily recycled and reused. The solid-supported inorganic heterogeneous catalysts such as tungstophosphoric acid supported on zirconia (PW₁₂ZrO₂), tungstate sulfuric acid (TSA), KF/alumina, acidic alumina, silica gel, basic alumina, and silica sulfuric acid (entry 1 and 3–8, Table 2.1) are used which offer ease of handling, high reactivity and selectivity, easy separation of the product, recyclability and reusability, and economic advantage. The major drawbacks with the heterogeneous catalyst are the higher amount required than the homogenous conditions and the blocking of the pores of the catalyst during the reaction progress. However, the reusability and the other benefits offered by the heterogeneous conditions outweigh these drawbacks. The PW₁₂ZrO₂ is a heteropolyacid (HPA) modified with zirconia and has acidic strength comparable to the protic acids. Zirconia is a thermally stable material with acidic properties. KF/alumina is one of the most important basic heterogeneous catalysts having wider applications in organic synthesis. Acidic catalysts like PBBS/TBBDA and *p*-TsOH (entry 2 and 9, Table 2.1) have also been used.

Synthesis using α -bromoketones

**Scheme 2.3** Solvent-free synthesis of Qxs from α -bromoketones and 1,2-diamine

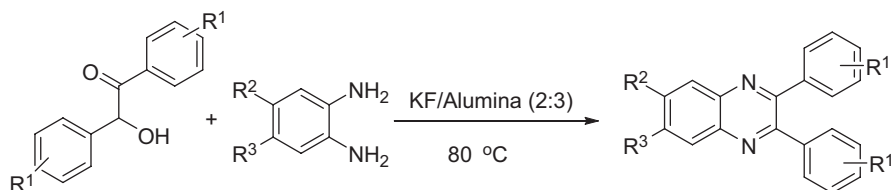
This is another strategy for the synthesis of Qxs (Scheme 2.3, Table 2.2) apart from diketones with diamine nucleophile and is based on the initial imine formation through the condensation of one of the amino groups of the diamine with the carbonyl group of the α -bromoketone. This would be followed by intramolecular

Table 2.2 Synthesis of Qxs using α -bromoketones

Sr. No.	Catalyst	Key features	Reference
1.	Cellulose sulfuric acid	rt, 20–30 min, recyclable and reusable catalyst, 89–96 %	45
2.	γ -Maghemite-silica nanocomposite	65 °C, good to excellent yield (72–93 %), recyclable catalyst, 8–30 min	46
3.	Ga(ClO ₄) ₃	rt, grinding, good to excellent yield (60–88 %), 20–60 min	47
4.	KF/alumina	rt, simple, mild condition, (1.5–5 h), 82–94 %	39
5.	HClO ₄ -SiO ₂	rt, fast reaction (15–60 min) and high yield (70–94 %), reusable catalyst	48

nucleophilic substitution of the bromine atom by the other amine group and dehydrogenation/aromatization to form the Qx. The solid/heterogeneous catalysts (e.g., cellulose sulfuric acid, γ -maghemite-silica nanocomposite, KF/Alumina, and HClO₄/SiO₂) or Lewis such as Ga(ClO₄)₃ are used to promote the imine formation (Table 2.2) and finally leading to the Qxs as the synthetic target [45–48]. However, the commercial availability of the α -bromoketone as the electrophilic partner limits the general applicability. Further, the formation of regio-isomeric Qxs would also pose problems with unsymmetrically substituted 1,2-diamine as the nucleophilic coupling partner.

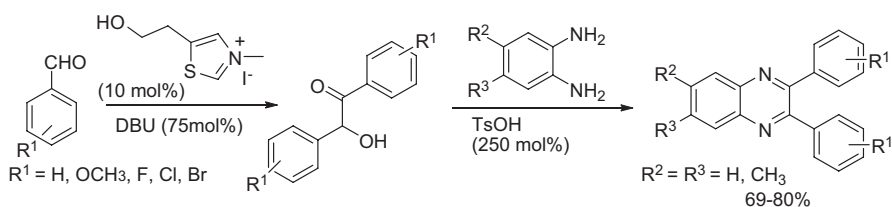
Synthesis using α -hydroxy ketone

**Scheme 2.4**

The most commonly used electrophilic coupling partner for the synthesis of Qxs is the 1,2-diketones that are usually obtained by oxidation of the precursor α -hydroxyketones, readily obtained through benzoin condensation. Thus, the direct use of benzoin would constitute a newer approach for the synthesis of Qxs as the initial reaction between the benzoin and the 1,2-diamine would form the imine which would undergo intramolecular nucleophilic substitution of the hydroxyl group by the other amine and finally would form the Qxs through dehydrogenation/aromatization. The heterogeneous solid-supported catalyst KF/alumina has been used (Scheme 2.4) for the synthesis of Qxes directly from α -hydroxyl ketenes at 80 °C [39].

Synthesis using aldehyde

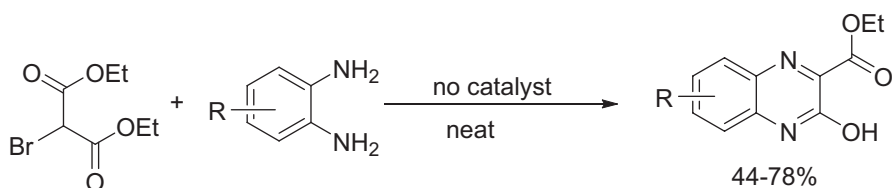
Although the need to use 1,2-diketone may be replaced by the use of benzoin, the requirement of toxic KCN to catalyze the benzoin condensation becomes detrimental in the context of sustainable/green synthesis. However, the use of N-heterocyclic carbene (NHC), generally formed in situ, would avoid the use of KCN for benzoin condensation. Thus, Qxs have been synthesized from aldehydes directly using a cascade reaction catalyzed by NHC, generated in situ from a thiazolium-based IL and diazabicycloundecene (DBU) as the base, forming an intermediate α -hydroxy ketone via the NHC-mediated benzoin condensation, which subsequently undergoes cyclocondensation with the 1,2-diamine in the presence of TsOH as the catalyst (Scheme 2.5) [49]. The inherent restriction of the use of aromatic aldehydes is the limitation of this strategy.



Scheme 2.5

Synthesis using α -bromomalonate ester

The Qx synthesis can also be performed by the reaction of 1,2-diamines with α -bromo-malonates (Scheme 2.6) [50]. The presence of the bromo group adjacent to the two ester groups makes it highly susceptible for nucleophilic substitution by the amine group of the 1,2-diamine to form the intermediate N-alkylated derivative which undergoes intramolecular cyclocondensation involving the reaction of the other amine group with one of the ester carbonyl and finally forms the Qxs via amide-imine tautomerism and dehydrogenation. Thus, the Qx formation following this procedure does not require any catalyst.



Scheme 2.6

3.1.2 Synthesis Using Innocuous Alternate Reaction Media

Although the solvent-free reaction condition offer means to avoid the detrimental VOSs, the scalability would pose problems due to lack of heat transfer. The uses of

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