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Chapter 8: Applications of anthranils in the synthesis of nitrogen heterocycles

Ram Singh Jat,* M. Bhanuchandra*

Abstract: Anthranils have been extensively utilized in a variety of synthetic transformations. This chapter focuses primarily on the different transition metal-free reactions of anthranils for the formation of a wide array of nitrogen heterocycles.

Keywords: Anthranils, Quinoline *N*-oxides, Quinolines, Acridines, Nitrogen heterocycles.

1 Introduction

In recent decades, there has been a significant surge of interest in organic and medicinal chemistry regarding the synthesis of various heterocyclic frameworks that incorporated in the many biologically relevant moieties. Of these heterocycles, those containing nitrogen have garnered substantial focus because of their potential biological effects and their importance as crucial intermediates in pharmaceuticals, natural products, dyes, and agrochemicals (Appukkuttan & Van der Eycken, 2006; Joule, 2020; Katritzky, Ramsden, Scriven, & Taylor, 2008; Orru & Ruijter, 2010). In this context, anthranils have experienced remarkable advancements as a starting precursor in the past couple of decades and have found extensively used in the synthesis of numerous bioactive nitrogen heterocyclic compounds.

Ram Singh Jat

Department of Chemistry, School of Chemical Sciences and Pharmacy, Central University of Rajasthan, Ajmer, Rajasthan 305817, India. *rsjchemistry@gmail.com*

M. Bhanuchandra

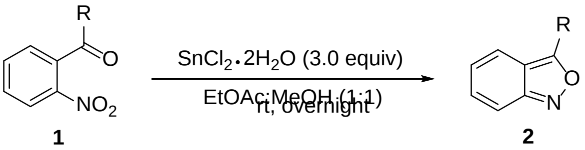
Department of Chemistry, University of Delhi, Delhi 110007, India. *bhanuchandram@chemistry.du.ac.in*

This chapter provides an overview of the progress achieved, particularly in the last decade, in the area of transition-metal-free synthesis of a wide array of nitrogen heterocycles utilizing anthranils through various annulation reactions (Fig. 1).

Fig. 1. Transition-metal-free synthesis of various nitrogen heterocycles from anthranils

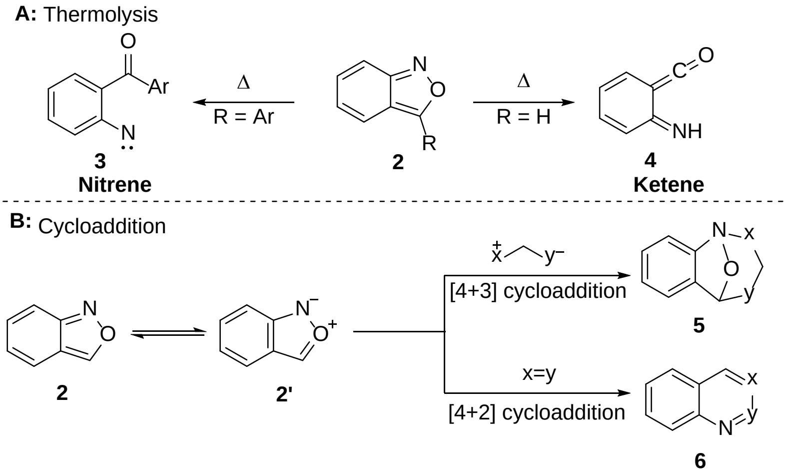
In this chapter mainly we discuss the representative synthetic procedures of anthranils and its application in various annulation reactions that lead to the creation of nitrogen heterocycles, including quinoline *N*-oxides, quinolines, and acridines.

Anthranils referred to as 2,1-benzisoxazoles, represent a significant category of readily obtainable and highly adaptable synthons that display diverse and adjustable reactivities, particularly in processes catalyzed by transition metals. They are typically stable at room temperature due to their compliance with the Hückel rule. Historically, anthranils **2** were produced by the semi-reduction of 2-nitrocarbonyls **1** using $SnCl_2$ (Chauhan & Fletcher, 2012) as shown in Scheme 1.



Scheme 1. Preparation of anthranil from 2-nitrocarbonyls

In 2019, Climent and colleagues introduced a method involving Pt-supported nanoparticle catalysis to achieve the hydrogen reduction of 2-nitrobenzaldehyde, leading to the targeted synthesis of 2,1-benzisoxazoles with favourable yields in most of the cases (Marti et al., 2017). Additionally, the targeted oxidation of 2-aminobenzophenone offers an alternative pathway for synthesizing anthranils (Zhao, Shen, & Li, 2015). However, under relatively high temperatures, anthranils can convert to aryl nitrene or ketene species *via* thermolytic cleavage of the N–O bond. The thermolytic decomposition of anthranils is primarily affected by the substituents found at the C3-position; anthranils lacking C3-substituents generates ketene intermediates **4**, whereas anthranils with C3-aryl substitutions lead to the formation of aryl nitrene intermediates **3** (Scheme 2A). Furthermore, anthranils serve as effective 1,3-dipolar synthons due to the presence of both an electrophilic formyl group and a nucleophilic amino group within a single molecule. Consequently, several significant [4+2] and [4+3] annulations of anthranils have been established to synthesize a variety of functionalized heterocycles **5-6** (Scheme 2B).



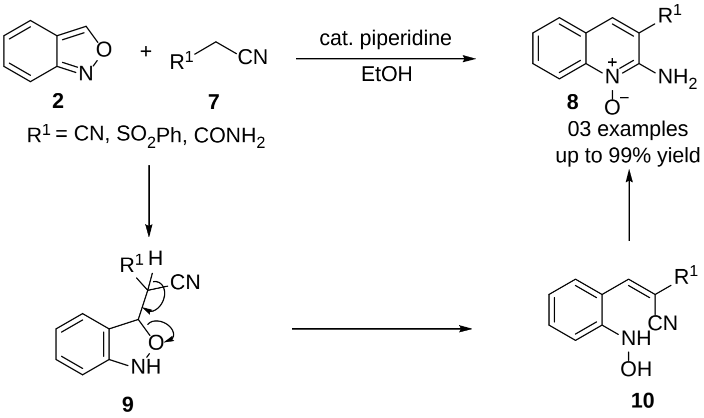
Scheme 2. Reactivity of anthranils

2 Synthesis of quinoline *N*-oxides

Quinolines and quinoline *N*-oxides represent a significant category of nitrogen-containing heterocycles, commonly found in natural products and biologically active compounds (Mfuh & Larionov, 2015; O'Donnell et al., 2009; Rajanarendar et al., 2012). Specifically, quinoline *N*-oxides are integral to the fundamental structure of quinoline alkaloids such as aurachins A, B, and L (Hattori, Yokoshima, & Fukuyama, 2017). Moreover, the cores of quinoline *N*-oxides appear in potential drug candidates involved in the activation of microsomal Na/K-ATPase (Andreev, Korvacheva, & Nizhnik, 2006), inhibition of protein kinases, treatments for cancer (Colacino, Andre, Martinez, & Lamaty, 2008), age-related ailments (Floyd, 2006), and they play vital roles in biological investigations as spin traps (H. Zhang et al., 2000). It is noteworthy that quinoline *N*-oxides are extensively used in synthetic chemistry, functioning as directing groups in C−H activation (Hwang, Kim, Jeong, & Chang, 2014; Nishida, Ida, Kuninobu, & Kanai, 2014), acting as oxidizing agents in gold-catalyzed reactions (Pagar & Liu, 2015; Y. Wang, Zheng, & Zhang, 2015), and serving either as ligands or organocatalysts in transition-metal catalysis (Malkov et al., 2003; Nakajima, Saito, Shiro, & Hashimoto, 1998; Pignataro, Benaglia, Annunziata, Cinquini, & Cozzi, 2006).

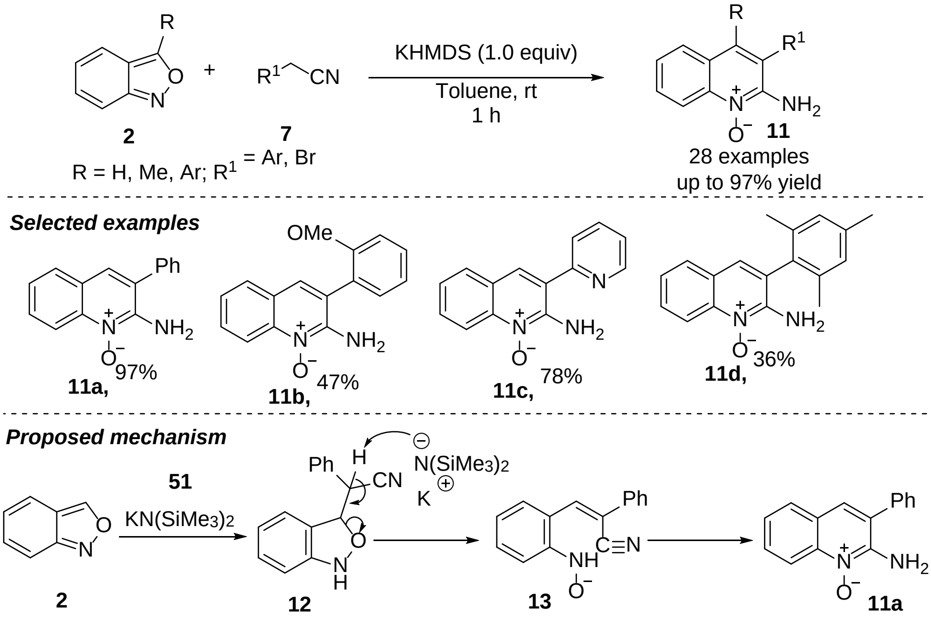
Bartulin and Taylor described a ring expansion reaction of anthranil **2** with highly activated methylene compounds **7** in the presence of piperidine as a catalyst in ethanol, resulting in the production of 2-aminoquinoline *N*-oxides **8** (Scheme 3). However, the range of this reaction is quite restricted (only 3 examples), applicable solely to reactants where the methylene group is adjacent to two activating electron-withdrawing substituents. The authors postulate that the transformation of anthranil **2** to quinoline *N*-oxides **8** begins with the addition of the anion from the active methylene component to the C3-position of anthranil, forming adduct **9**. The basic catalyst abstracts the acidic methylene proton, leading to the cleavage of the O_2-C_3 bond and producing an *o*-

hydroxylaminobenzylidene derivative **10** of the active methylene compounds. Following this, ring closure occurs through the intramolecular addition of the -NHOH group to either the -CN or -COOR group of **10**, yielding product **8** (Taylor & Bartulin, 1967).



Scheme 3. Ring expansion of anthranil to 2-aminoquinoline N-oxides

In 2024, we introduced a method for the ring-opening and reconstruction of anthranils **2** through KHMDS, which involves reacting them with arylacetonitriles **7** to produce multisubstituted 2-aminoquinoline *N*-oxides **11** (Scheme 4).



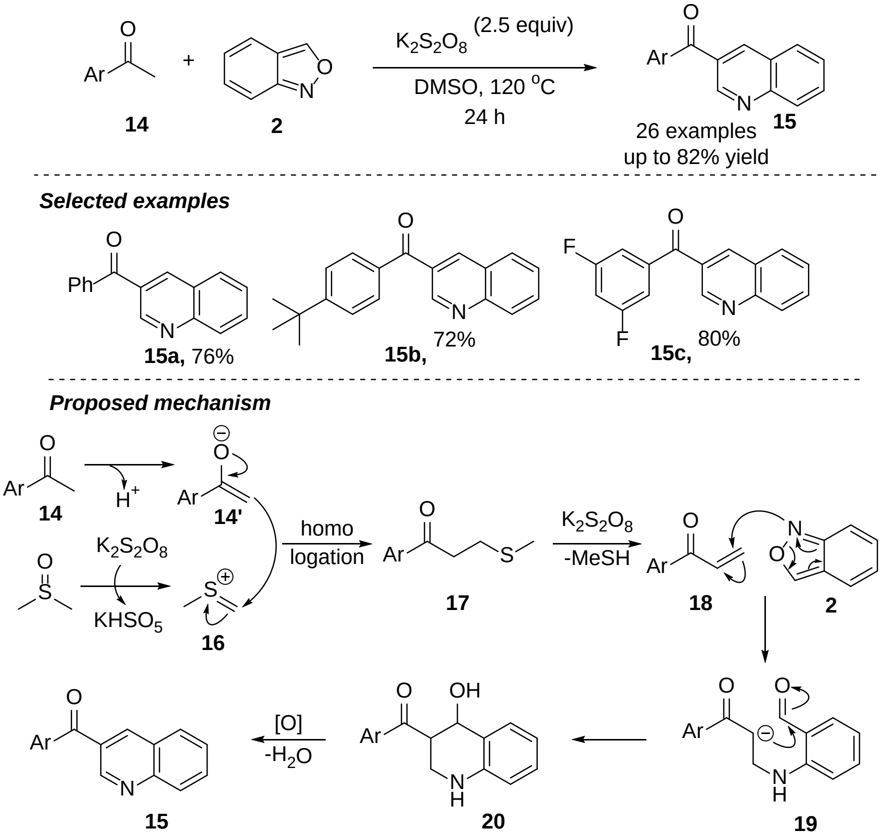
Scheme 4. Synthesis of 2-aminoquinoline *N*-oxide from anthranils

The effectiveness of the reaction concerning both starting materials is noteworthy, yielding a wide variety of densely arene-substituted quinoline *N*-oxides **11** with satisfactory yields (Jat, Singh, & Bhanuchandra, 2024). Initially, an intermolecular attack occurs when the carbanion (formed by the removal of one of the acidic methylene protons of **7** using KHMDS) targets the C3-position of anthranil **2**, resulting in the formation of species **12**. Following this, the O_2–C_3 bond cleavage and the subsequent intramolecular cyclization of the resultant species **13** into a -CN group leads to the formation of the 2-aminoquinoline *N*-oxide **11a**.

3 Synthesis of quinolines

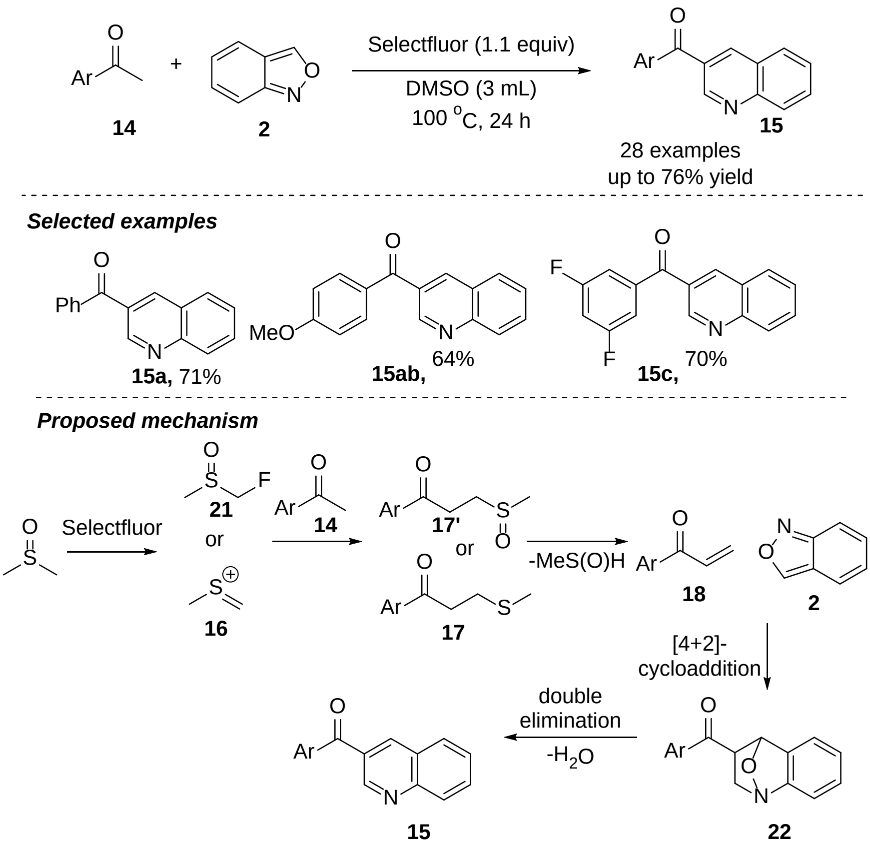
Quinolines represent one of the most prevalent structural components found in natural products, biologically active substances (Shang et al., 2018; Y. Zhang et al., 2012), and functionalized materials (H.-Y. Chen et al., 2017; Croissant et al., 2016). The synthesis of quinolines has been a topic of considerable interest for many years, resulting in the development of various efficient synthetic approaches (Xie et al., 2017; F. Zhang, Lai, Shi, & Song, 2019; X.-F. Zhu et al., 2017), such as the traditional Skraup (Jin et al., 2017; Lüdtke, Haupt, Wozniak, & Kulak, 2017) and Combes methods (Aribi et al., 2016; Selvi & Velmathi, 2018). Recently, new strategies for synthesizing quinolines, including domino cycloadditions (Kiran et al., 2017; Sanchez-Diez et al., 2016; Wan, Jing, & Wei, 2017) and methods involving transition metals (Orwat, Oh, Kubicki, & Kownacki, 2018; Xi, Zhang, Zhang, Chen, & Yu, 2015), have emerged. Nonetheless, most current methods require strong acidic or basic conditions, elevated reaction temperatures, the use of toxic or costly metal catalysts, and often rely on expensive, highly functionalized starting materials. These challenges pose significant issues from both an environmental perspective and for large-scale industrial production.

In 2017, Tiwari and colleagues presented a method for creating functionalized quinolines **15** without the use of transition metals, utilizing easily accessible acetophenones **14** and anthranils **2** (Scheme 5). This one-pot reaction method includes the *in situ* generation of α,β-unsaturated ketones **18** from acetophenones **14** *via* one-carbon homologation using DMSO, followed by the aza-Michael addition of anthranils **2** and the subsequent cyclization. In this reaction, DMSO serves as a solvent as well as a carbon source, resulting an atom-efficient and environmentally friendly approach to synthesize 3-substituted quinolines (Wakade et al., 2017). The proposed mechanism suggested that $K_2S_2O_8$ activates DMSO to produce intermediate **16**, which reacts with the enolate **14′** derived from **14** to yield intermediate **17**. Intermediate **17** undergoes $K_2S_2O_8$-mediated demethylthioation to generate α,β-unsaturated ketone **18**. Then, the aza-Michael addition of anthranil **2** to intermediate **18** produces intermediate **19**, which upon cyclization generate **20**. Finally, auto-oxidation of intermediate **20** results in the formation of 3-ketoquinoline **15**.



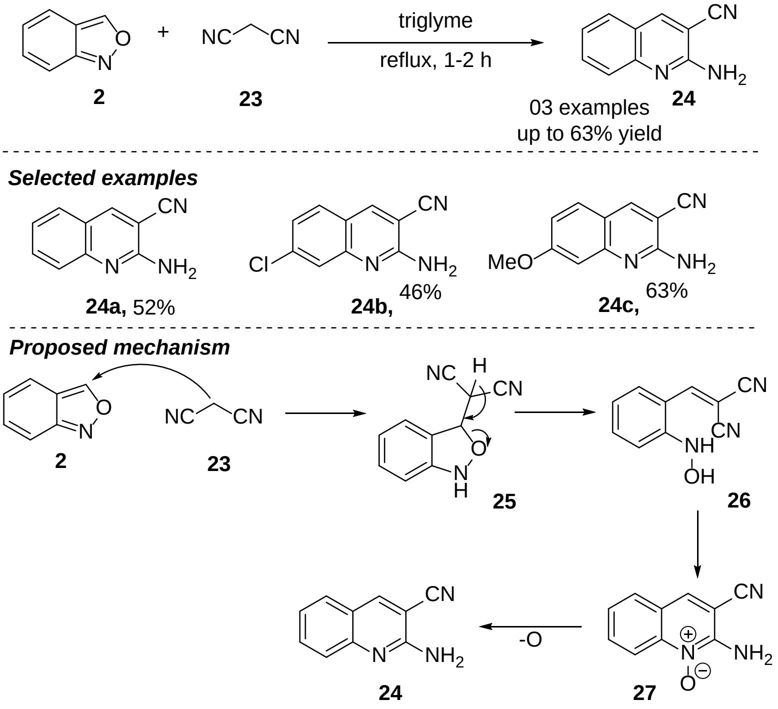
Scheme 5. Synthesis of 3-ketoquinolines from anthranils and acetophenones

In 2019, Ma and colleagues formulated an effective approach for synthesizing 3-functionalized quinolines **15** using readily available acetophenones **14** and anthranil **2** (Scheme 6). Selectfluor facilitates the activation of the C(sp^3)–H bond in acetophenones **14** and the aza-Michael addition of anthranil **2**, leading to the formation of annulated 3-acylquinolines **15** in moderate to high yields (Y. Gao, Hider, & Ma, 2019). Initially, Selectfluor activates DMSO to produce the α-fluorinated intermediate **21** or the methyl(methylene)sulfonium cation **16**, which, upon reaction with acetophenone **14**, generates intermediate **17'** or **17**, respectively. The intermediates **17'** or **17** then undergo spontaneous demethylsulfinylation or demethylthioation, resulting the formation of intermediate **18** along with the removal of MeS(=O)H or MeSH, respectively. Intermediate **18** then participates in [4+2] cycloaddition with anthranil **2** to create intermediate **22**, which subsequently undergoes dual elimination to remove water, yielding the final product **15**.



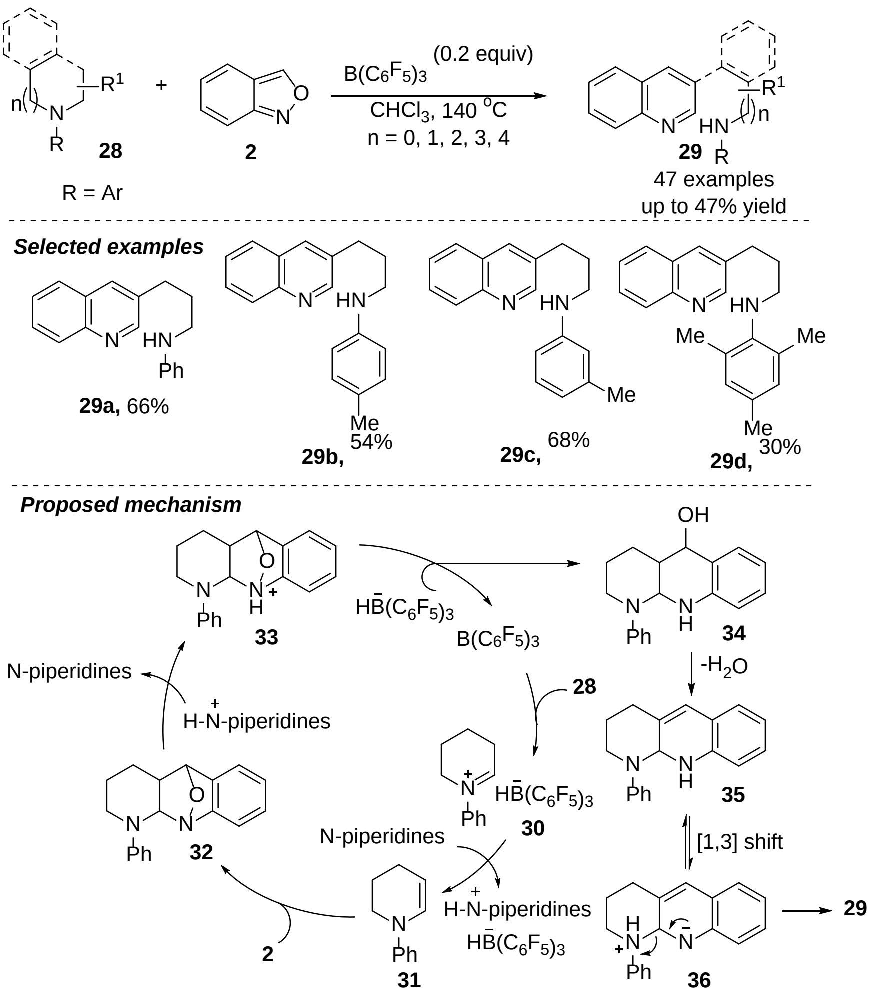
Scheme 6. Selectfluor-mediated synthesis of 3-acylquinolines from anthranils and acetophenones

In 2019, Zhang and colleagues identified an efficient and atom-economical method to convert anthranil **2** into a reactive ketene intermediate under high-temperature conditions, enabling it to directly react with malononitrile **23** without the need for any catalyst or additives, yielding quinolines **24** in moderate to good yields (Scheme 7). The authors proposed that the transformation of anthranil **2** into quinoline **24** begins with the nucleophilic addition of the anion from the active methylene component to the C3-position of the anthranil **2**, resulting in the formation of adduct **25**. The removal of the acidic methylene proton, followed by the breaking of the O_2-C_3 bond, produces an *o*-hydroxylaminobenzylidene derivative **26**. Next, the ring formation occurs through the intra-molecular addition of the -NHOH group to the -CN group of **26**, yielding the quinoline *N*-oxide **27**. Ultimately, the expulsion of one oxygen atom at elevated temperatures results in the formation of quinoline **24** (Jiang et al., 2019).



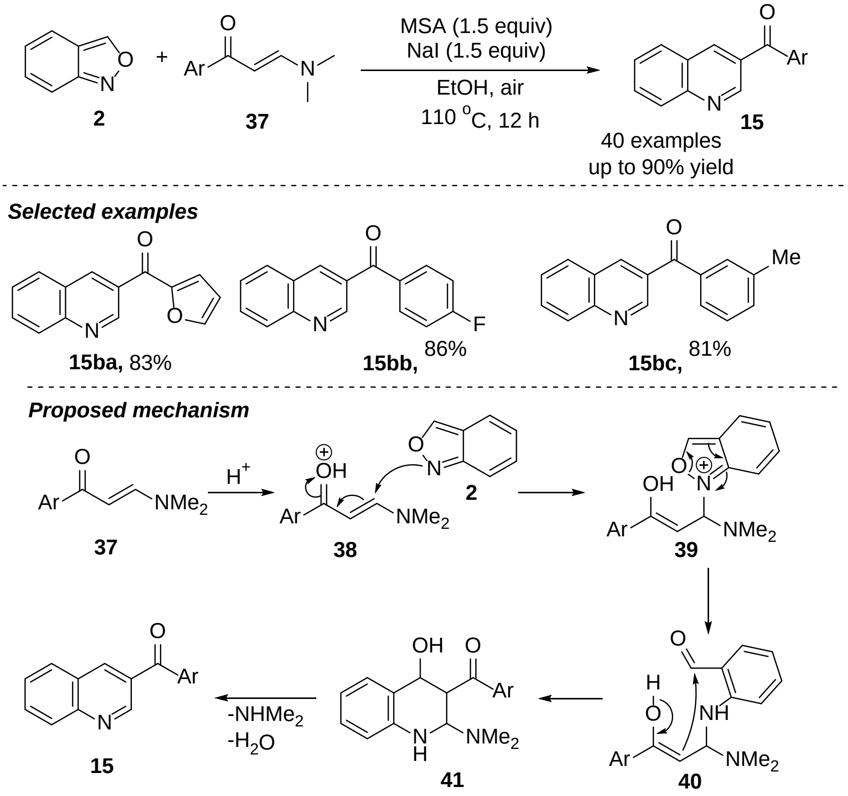
Scheme 7. Thermo-promoted formation of 2-aminoquinolines from anthranils and malononitrile

In 2022, Fan et al. demonstrated an efficient method for the α,β-difunctionalization and cleavage of C−N bond in saturated amines **28** empoying anthranil **2**, which was facilitated by $B(C_6F_5)_3$ (Scheme 8). This reaction does not need any metal catalyst or oxidant, exhibiting a high atom economy, broad functional group tolerance, and a wide range of applicable substrates. A diverse range of quinoline derivatives was synthesized easily. Mechanistic investigations suggested that the process likely involves several of hydrogen-borrowing steps followed by a [4+2] cycloaddition and successive C−N bond cleavage. The reaction begins with abstraction of hydride from **28** by $B(C_6F_5)_3$, which produce iminium borohydride salt **30**. Then, a second molecule of **28** assists in the deprotonation of the Cβ−H in **30**, resulting in the formation of the enamine intermediate **31** and yielding protonated piperidinium borohydride. Following this, the [4+2] cycloaddition of **31** with **2** produces α,β-difunctionalized piperidine **32**, which is then protonated by piperidine to generate intermediate **33**, while reforming **28**. With the presence of borohydride, **33** undergoes a ring-opening reaction that leads to the formation of intermediate **34**, releasing $B(C_6F_5)_3$ and completing the catalytic cycle. Subsequently, **34** undergoes dehydration to produce intermediate **35**, which may rearrange to intermediate **36** through a [1,3] proton shift. Subsequently, the C−N bond in **36** is cleaved to yield product **29** (He et al., 2022).



Scheme 8. $B(C_6F_5)_3$-catalyzed synthesis of quinolines from saturated amines and benzo[*c*]isoxazoles

In 2023, Zou and their research team announced the development of a mild and effective method for synthesizing a diverse array of 3-acylquinolines **15** without the use of transition metal catalysts (K.-L. Zhang, Yang, Guo, & Zou, 2023). The reaction effectively utilized various enaminones **37** and anthranils **2**, yielding numerous 3-acylquinolines **15** through aza-Michael addition and subsequent intramolecular annulation (Scheme 9). Mechanistic investigations proved that absence of radical steps involved in the process. Notably, methanesulfonic acid (MSA) and sodium iodide were essential for the successful completion of this transformation. Initially, MSA activates compound **37** to form intermediate **38**, which is attacked by compound **2** to produce intermediate **39**. The presence of sodium iodide is essential for this reaction, since it enhances the stability of intermediate **39**. Later, intermediate **40** is generated, which give rise to the formation of **41** *via* an intramolecular nucleophilic addition. Finally, compound **41** is transformed into the target product **15**.



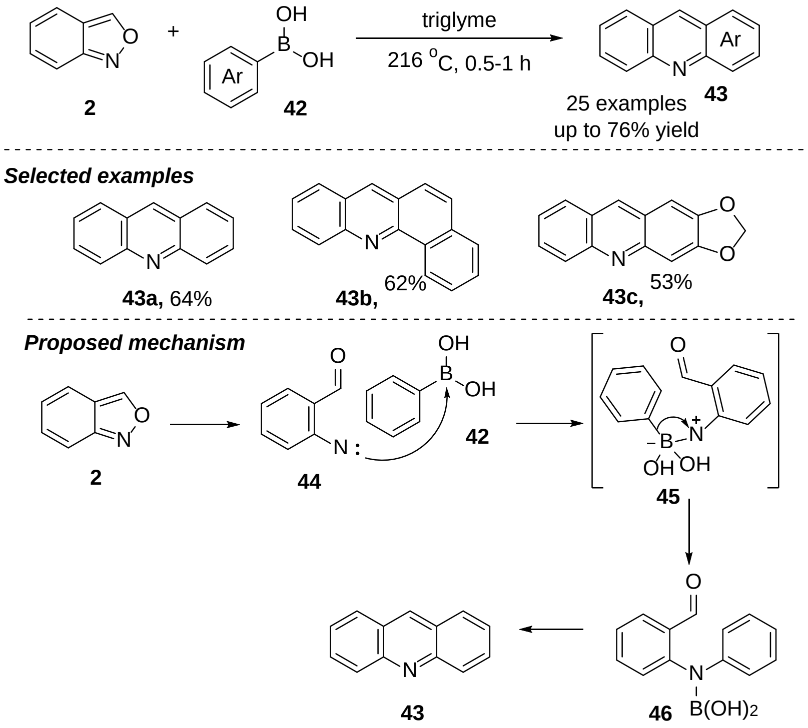
Scheme 9. Synthesis of 3-acylquinolines *via* formal [4+2] annulation of anthranils with enaminones

4 Synthesis of acridines

Acridines are important nitrogen-rich compounds which originate from anthracene and have a strong odour, ability to integrate into DNA (Belmont, Bosson, Godet, & Tiano, 2007; Denny & Baguley, 2003). Due to their distinctive aromatic framework, acridines have shown remarkable biological properties and can serve as adaptable biological probes (Gensicka-Kowalewska, Cholewiński, & Dzierzbicka, 2017; Mandal, Chhetri, Bhuyan, & Roy, 2020).

In 2024, Jiang and colleagues identified new reaction conditions for synthesizing acridines, enabling the catalyst- and additive-free direct condensation of anthranil **2** with arylboronic acids **42**, yielding acridines **43** in moderate to good yield (Scheme 10). This approach is notable for its atom economy, ease of operation, and low cost, making it particularly attractive for both academic and industrial researchers seeking new synthetic methods. A gentle and effective protocol was introduced for the synthesis of a wide variety of 3-acylquinolines under conditions that do not involve transition metals (Jiang, Xie, Gao, Wu, & Song, 2024). Through a thermolytic N–O bond cleavage at elevated temperatures, anthranils **2** can be converted into nitrenes **44**.

The nitrogen atom can subsequently attach to boric acid **42**, resulting in a zwitterionic intermediate **45**. The migration of the aryl group on **45** could then produce intermediate **46**, leading to the cyclization that forms acridine **43**.



Scheme 10. Synthesis of acridines from arylboronic acids and anthranils

Conclusions

In this chapter, we have outlined the transition-metal-free reactions involving anthranils, primarily developed over the past one decade, and their successful application in creating a wide range of nitrogen-containing heterocyclic compounds. The recent rise in the use of anthranils in transition-metal-free reactions, photoredox catalysis, and electrochemical syntheses is likely to garner significant research interest, leading to the establishment of numerous innovative synthetic methods. The current decade has seen a growing preference for green, atom-efficient, low-waste, and sustainable synthetic methods. Considering the straightforward preparation, and the potential applications of this significant category of substrates in both achiral and chiral synthesis of novel and previously known bioactive heterocyclic compounds, further developments can be anticipated.

Disclaimer (Artificial Intelligence)

Author(s) hereby declares that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during the writing or editing of this chapter.

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Competing Interests

Authors have declared that no competing interests exist.

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