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# ADVANCES IN CHEMISTRY OF 2-AMINO-3-CYANO-4-ARYL 4*H*-CHROMENES VIA DEHYDROGENATION REACTION

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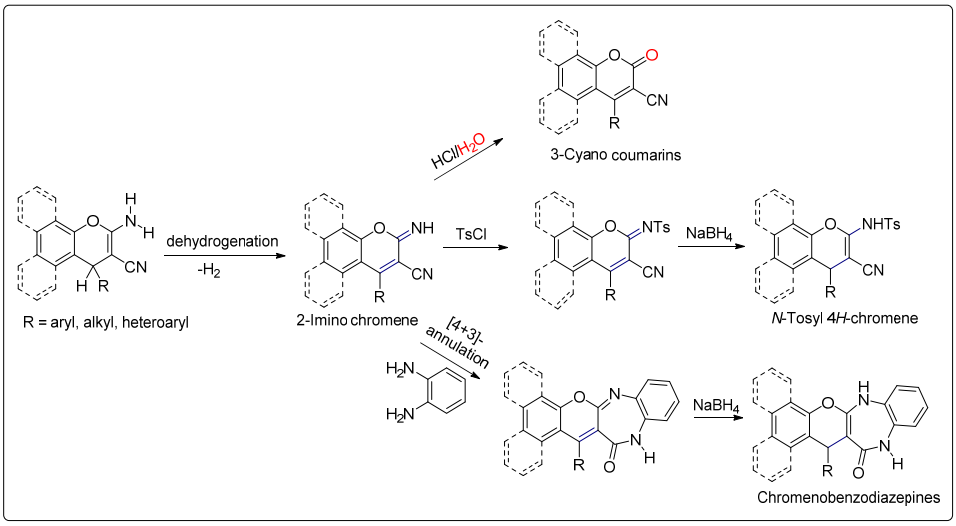
## Abstract:

2-Amino-3-cyano-4-aryl 4*H*-chromenes show wide range of biological activities including anticancer, antibacterial, antirhuematic activities. In the presence of suitable oxidants, the tautomeric form of these chromenes undergoes dehydrogenation reaction to generate 2-iminochromenes. A number of oxidants have been reported for the dehydrogenation of these chromenes. DIAD mediated selective dehydrogenation reaction provides an easy access to iminochromenes. These 2-iminochromenes can be hydrolysed to the corresponding biologically important coumarins. Exploration of the chemistry of 2-iminochromenes has enabled the synthesis of novel *N*-sulfonylchromenes. 2-Iminochromenes undergo [4+3]-annulation reactions with 1,2-diminobenzene, 2-aminophenol and 2-aminothiophenol to generate chromenobenzodiazepines and chromenobenzoazepines.

**Keywords:** 2-Amino-3-cyano-4-aryl 4*H*-chromene, dehydrogenation, 2-iminochromenes, [4+3]-annulation, chromeno-benzodiazepine.




## Contents:

## 1. Introduction:

Heterocyclic compounds constitute nearly 70% of the biologically active and drug molecules available in the literature.[1] Heterocycles that incorporate oxygen atom are naturally abundant and exhibit a broad spectrum of biological activities-some of which are pharmaceutically important.[2]Among the *O*-containing heterocycles, chromene is considered as a priviledged structural motif which is found in many biologically active natural products.[3] These natural products show a wide spectrum of biological activities such as anti-cancer,[4] antimalarial,[5] anti-tumor,[6] anti-viral,[7] anti-inflamatory,[8] anti-parkinson[9] activities (Figure 1).

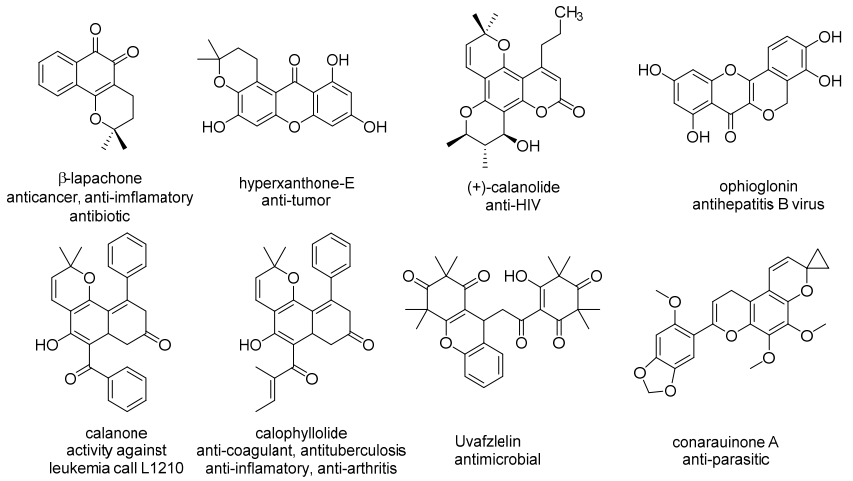



**Figure 1**: Structure and biological activity of selected chromenes isolated from natural sources.

1.2. Among the various chromene scaffolds viz., 2*H*-chromene, 4*H*-chromene, 3*H*-isochromene and 1*H*-isochromene (Figure 2), 4*H*-chromenes, in particular, have attracted much attention of medicinal chemists due to the important biological activities associated with them. A large number of 4*H*-chromenes have been synthesized for structure-activity-relationship studies.[10-31]Figure 3 depicts a few selected examples of naturally available and synthetic 2-amino-3-cyano-4-aryl 4*H*-chromenes. This article will highlight the recent advances in the chemistry of 2-iminochromenes obtained via the dehydrogenation reaction of 2-amino-3-cyano-4-aryl 4*H*-chromenes.

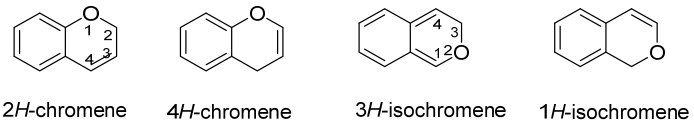



**Figure 2**: Basic structures of various chromenes

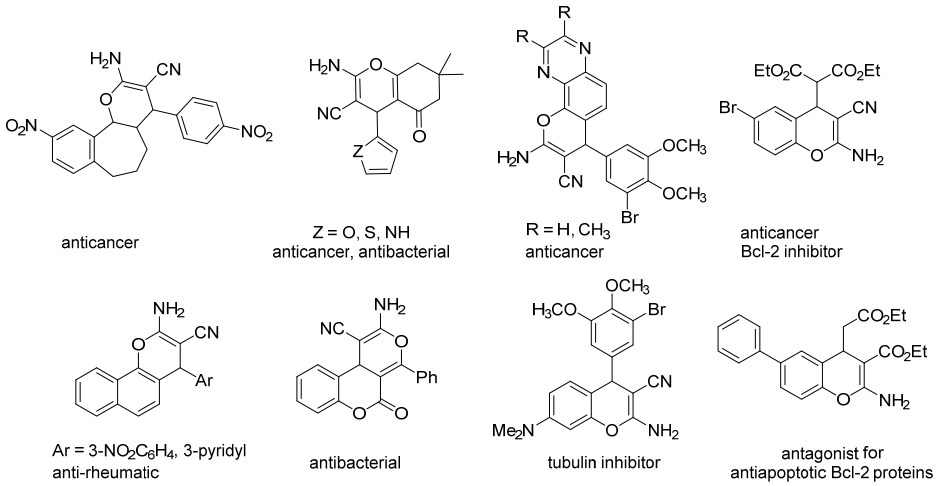
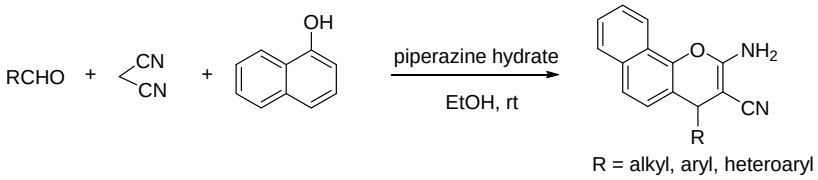


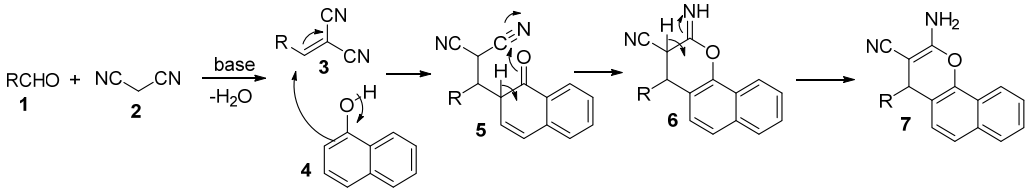

**Figure 3**: Selected examples of bioactive 2-amino-3-cyano-4-aryl 4*H*-chromenes

2. Methods of synthesis: 2-Amino-3-cyano-4-aryl 4*H*-chromenes are synthesised by a three component reaction among an aldehyde, malononitrile and a phenol (Scheme 1). Reaction is usually promoted by an organic base.[32]




**Scheme 1**: Piperazine hydrate mediated synthesis of 2-amino-3-cyano-4-aryl 4*H*-chromene

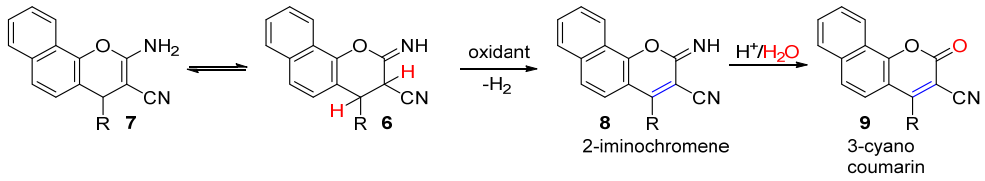
The mechanism of the condensation reaction is depicted in Scheme 2. Knoevenagel condensation between an aldehyde **1** and malononitrile **2** leads to adduct **3** which on condensation with the α-naphthol **4** generateintermediate **5**. Rearomatization and carbonyl addition to nitrile leads to intermediate **6** which undergoes 1, 3-proton shift to give rise to chromene **7**. A wide range of phenols and enols have been successfully converted to chromenes via the three component condensation reaction.




**Scheme 2**: Mechanism of synthesis of 2-amino-3-cyano-4-aryl 4*H*-chromene

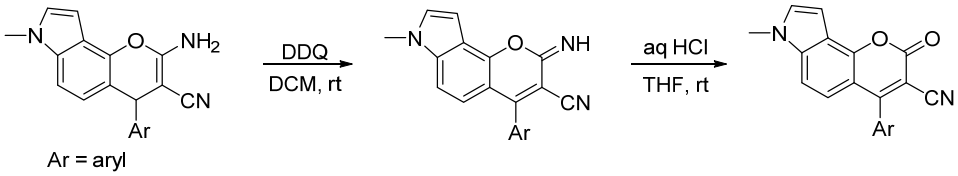
Metal oxide based nano-particles[33] and phase transfer catalyst[34] have also been utilized for the synthesis of 2-amino-3-cyano 4*H*-chromene in high yields.

3. Dehydrogenation of 2-amino-3-cyano 4*H*-chromene: In the presence of a suitable oxidant under neutral conditions, the tautomer **6** can undergo loss of a hydrogen molecule to generate highly conjugated 2-iminochromenes. Under acidic conditions 2-iminochromenes undergo hydrolysis to generate corresponding coumarins.




**Scheme 3**: Iminochromene via dehydrogenation of chromene

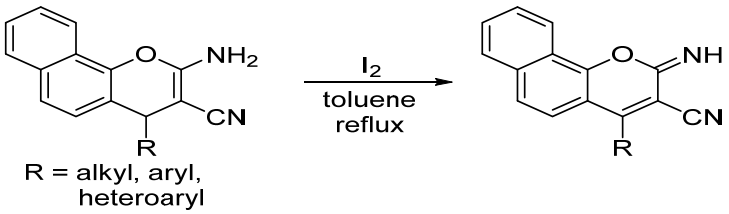
3.1. DDQ mediated dehydrogenation:During the medicinal activity studies of 2-amino-3-cyano-4-aryl 4*H*-chromenes, Cai et al. carried out the dehydrogenation of the 4*H*-chromenes using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in dichloromethane as the solvent at room temperature (Scheme 4).[35]




**Scheme 4**: DDQ mediated dehydrogenation of chromenes

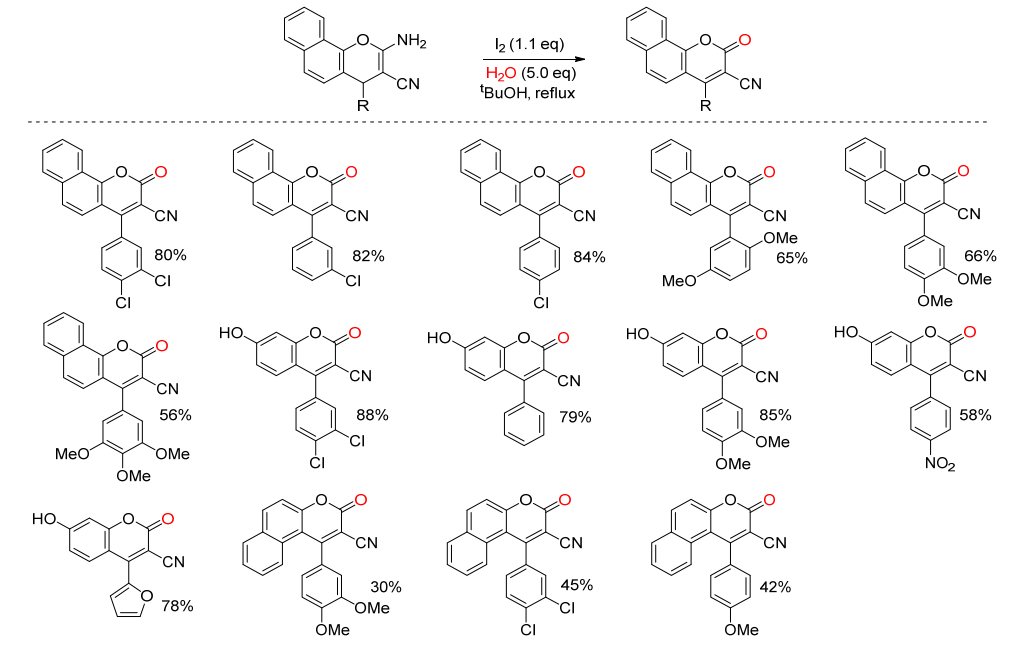
Iminochromenes were subsequently converted to the coumarins under acidic conditions. However, the exact mechanism of the reaction is not known. The reaction is believed to proceed via single electron transfer process.

3.2. Molecular iodine mediated dehydrogenation:2-Amino-3-cyano 4*H*-chromenes undergo dehydrogenation when treated with iodine under anhydrous conditions (Scheme 5).[36] Unlike DDQ, the iodine mediated dehydrogenation reaction tolerates free phenolic hydroxyl group and therefore useful for 4*H*-chromenes derived from dihydroxyphenols.



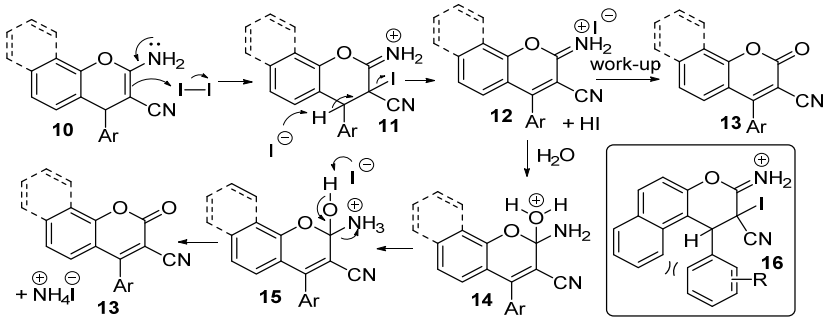

**Scheme 5**: Iodine mediated dehydrogenation of 4*H*-chromene

Iodine mediated dehydrogenation reaction was utilized by our research group to convert 2-amino-3-cyano 4*H*-chromenes into their corresponding 3-cyano chromenes by carrying out the reaction in a polar protic solvent in the presence of stoichiometric amount of water to facilitate the hydrolysis of iminochromenes in situ(Scheme 6).[36]




**Scheme 6**: Iodine mediated conversion of chromenes into coumarins

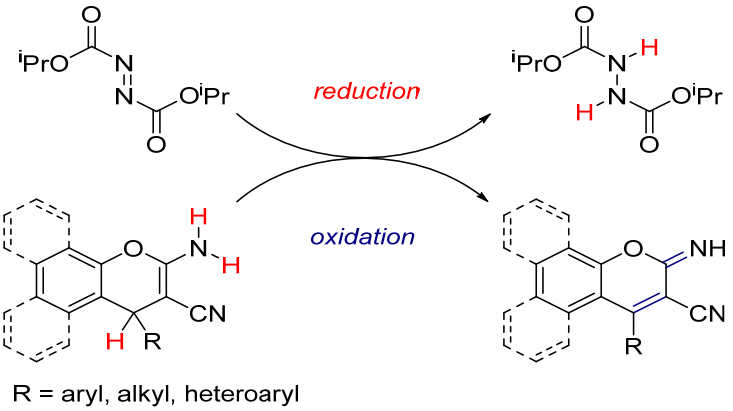
Coumarins were usually obtained in high yields in iodine mediated reactions. In some cases, the coumarins could be isolated in pure form without column chromatography. This suggests that the method could useful for large scale synthesis. The mechanism of the reaction is depicted in Scheme 7.



**Scheme 7**: Mechanism of iodine mediated conversion of chromene into coumarin

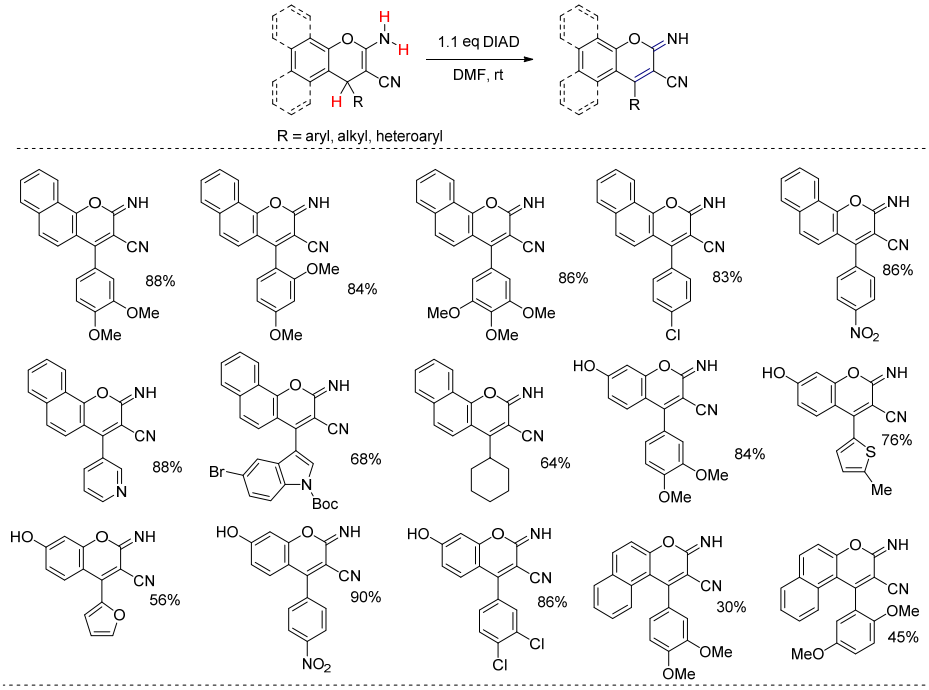
It is believed that chromene undergoes nucleophilic additionto iodine to generate intermediate **11** which on elimination give rise to intermediate **12**. Hydrolysis of the intermediate **12** generates the coumarin **13**. Under the reaction conditions, chromenes derived from β-naphthol give rise to intermediate **16**. Due to steric crowding of aryl rings in **16**, reactions of chromene derived from β-naphthol are usually slow and low yielding.

3.3. DIAD mediated dehydrogenation: Chromenes were dehydrogenated using DIAD in a polar aprotic solvent under neutral conditions to generate 2-iminochromenes in high yields (Scheme 8).[37]



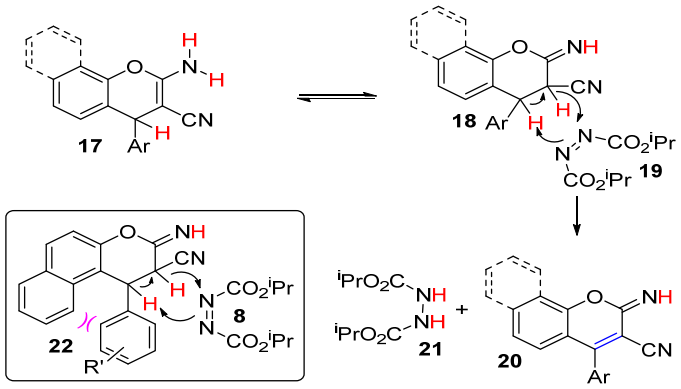

**Scheme 8**: DIAD mediated redox type reaction of chomenes

A wide range of 2-amino-3-cyano 4*H*-chromenes were dehydrogenated using DIAD in DMF at room temperature to obtain corresponding 2-iminochromenes in good yields (Scheme 9).




**Scheme 9**: DIAD mediated synthesis of 2-iminochromenes

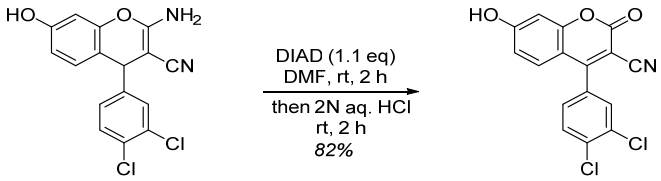
The mechanism of the reaction is depicted in Scheme 10. The tautomer of chromene is believed to undergo redox reaction with DIAD in a concerted manner to generate 2-iminochromene along with reduced form of DIAD. Due to steric crowding in intermediate **22**, chromenes derived from β-naphthol generate 2-iminochromenes in low yields. DIAD could be reduced with chromene in absence of any additives suggesting that it could be useful as a reducing agent.




**Scheme 10**: Plausible mechanism for DIAD mediated dehydrogenation of 4*H*-chromene

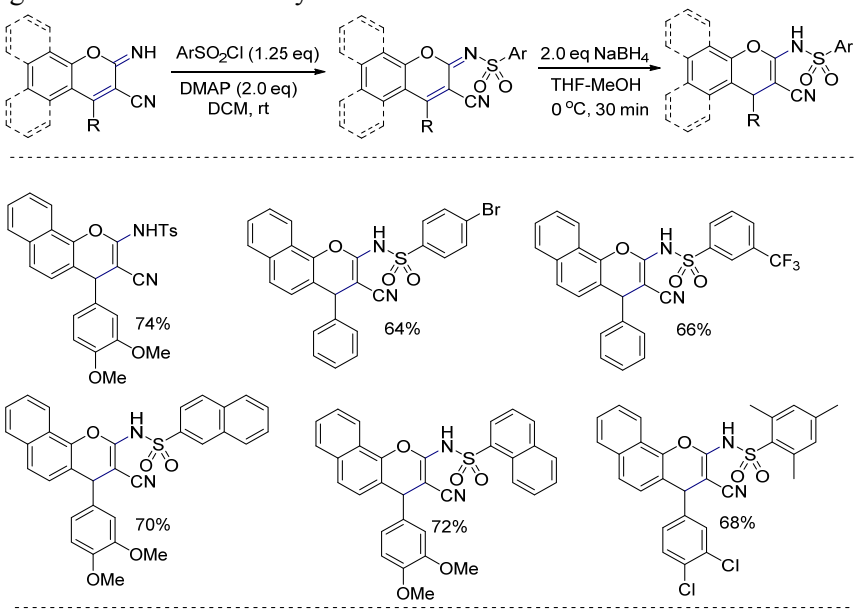
4. Reaction of 2-iminochromenes: The DIAD mediated dehydrogenation reaction provided an easy access to 2-iminochromenes. Our group explored the chemistry of 2-iminochromenes to generate novel compounds.

4.1. Hydrolysis of 2-iminochromenes: In-situ hydrolysis of 2-iminochromene were carried out using aq. HCl at room temperature to generate coumarin in high yield (Scheme 11). Aqueous HCl was added after the completion of the dehydrogenation reaction to hydrolyse the 2-imino group.[37]



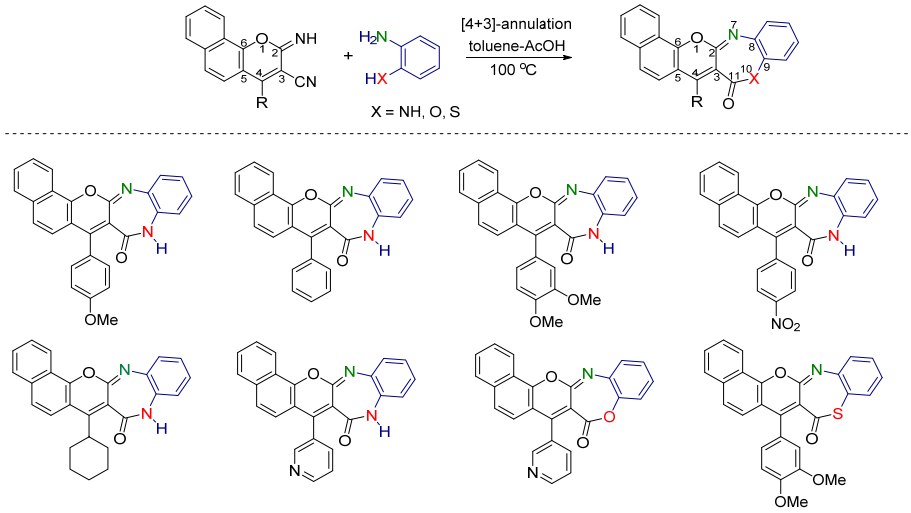

**Scheme 11**: In-situ hydrolysis of 2-iminochromene to 3-cyanocoumarin

4.2. *N*-Sulfonylation of 2-iminochromenes: Chromenes do not react with alkyl and aryl sulfonyl chloride under standard conditions. However, 2-imonochromenes readily underwent sulfonylation in presence of *N*,*N*-dimethylamino pyridine at room temperature.[37] *N*-sulfonyliminochromenes were reduced with $NaBH_4$ to generate the corresponding 4*H*-chromenes (Scheme 12). Unlike the chromenes, *N*-sulfonylchromenes do not undergo hydrolysis under acidic conditions. Moreover, *N*-sulfonylchromenes cannot be dehydrogenated under the conditions employed for the dehydrogenation of 2-amino-3-cyano 4*H*-chromenes.



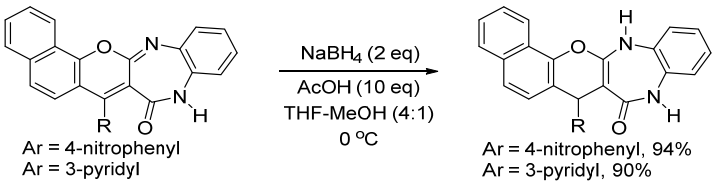

**Scheme 12**: Synthesis of *N*-sulfonylchromenes from 2-iminochromenes

4.3. [4+3]-annulation reaction: Our group developed a [4+3]-annulation of 2-iminochromenes with 1,2-diaminobenzene under mild acidic conditions in which the imino- and cyano group act as the electrophilic centres.[38] The reaction generates novel chromenobenzodiazepines in good yields. The annulation reaction was also successfully carried out using 2-aminophenol and 2-aminothiophenol to obtain corresponding chromenobenzodiazepines (Scheme 13). However, the annulation reactions are usually slow with 2-aminophenol and 2-aminothiophenol due poor nucleophilic character of O- and S-atom. The [4+3]-annulation reactions were not successful when carried out with aliphatic 1,2-diamine and 2-amino alcohol. The annulation reaction was successful under mild acidic conditions. Under strong acidic conditions, reaction failed to generate the annulation product and leads to the hydrolysis of the iminochromenes.



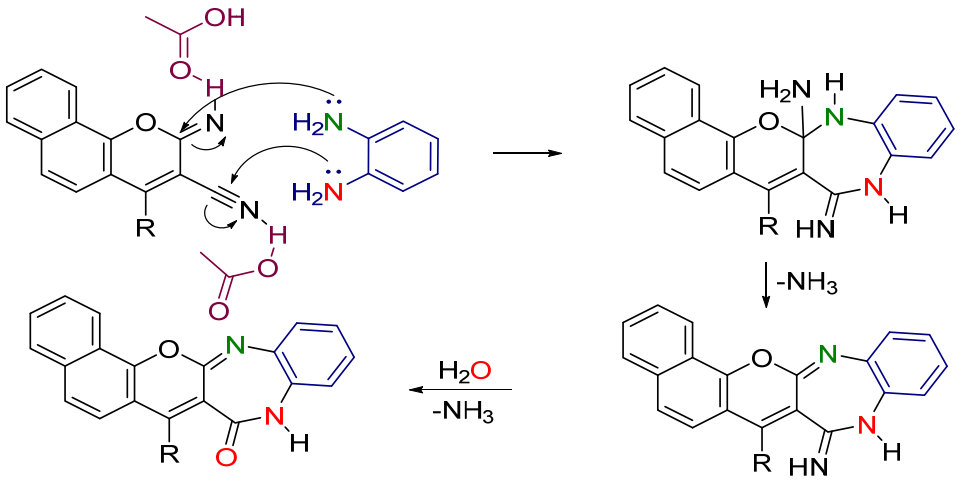

**Scheme 13**: Synthesis of chromenobenzoazepine and chromenobenzodiazepines from 2-iminochromenes.

The chromenobenzodiazepines can be effectively reduced to the corresponding 4*H*-chromenobenzodiazepine under mild acidic conditions. Screening of several conditions showed that the reduction can be performed with $NaBH_4$ in the presence of acetic acid (Scheme 14).[38]




**Scheme 14**: Synthesis of 4*H*-chromenobenzodiazepine via $NaBH_4$ reduction

The mechanism of the annulation reaction is depicted in Scheme 15. Dual activation of the imino as well as nitrile group of iminochromene by acetic acid via hydrogen bonding promotes the nucleophilic addition of the diamine. The resulting intermediate undergoes loss of ammonia molecule followed by hydrolysis during work-up to generate the chromenobenzodiazepine.




**Scheme 15**: Mechanism of [4+3]-annulation reaction of 2-iminochromenes

## 5. Conclusion:

Dehydrogenation of 2-Amino-3-cyano 4*H*-chromenes to the corresponding 2-iminochromenes provide a pathway for the generation novel chromene based compounds. Dehydrogenation reaction provides a method for the generation of *N*-sulfonylhydrazones which are more stable than the parent chromenes towards acidic conditions. This, in turn, will enable the development of novel chemistry of the *N*-sulfonylchromenes such as C-H functionalization at C-4 position. 2-Iminochromenes could be explored for novel annulation reaction to generate chromene based fused heterocyclic compounds. The rapid reduction of DIAD by 4*H*-chromenes suggests that they can be useful as an organic reducing agent under suitable conditions. The chemistry of 2-iminochromenes will attract attention of medicinal as well as synthetic organic chemists in foreseeable future.

## Acknowledgement:

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