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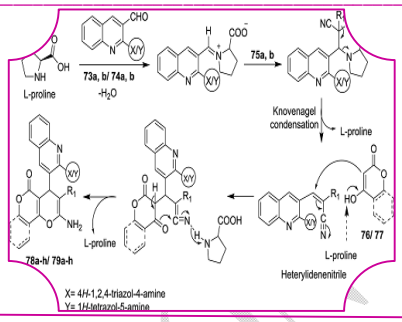
CHEMISTRY OF DERIVATIVES OF Q-2-CARBALDEHYDE WITH MALONONITRILE AND CREATION OF INDOLIZINES



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ABSTRACT

The quinoline-5,8-diones are an important class of compounds with a wide spectrum of biological activites. Over the past three decades many variously substituted derivatives of quinoline-5,8-diones have been synthesized and reported. Our lab has developed several procedures for the Knoevenagel condensation and reduction of aldehydes and ketones with malononitrile. When this reductive alkylation procedure was attempted with quinoline-2-carboxaldehyde, a crude product was observed by NMR spectroscopy. This product rearranged upon attempted purification via recrystallization or column chromatography.

KEYWORDS: *Quinoline derivatives, quinoline-5,8-diones, biological activites, Knoevenagel condensation, reduction.*

INTRODUCTION:

Cancer consists of a large group of diseases characterized by uncontrolled growth and spread of abnormal cells. If the spread is not controlled, it can result in death. It may be caused by both external internal and factors.

Certain cancers are related to infectious agents, such as hepatitis B virus (HBV), human papillomavirus (HPV), human immunodeficiency virus (HIV), Helicobacter pylori (H. pylori), and others, and could be prevented through behavioral changes, vaccines, or antibiotics.

There are different methods available to treat cancer such as Surgery, Chemotherapy, Radiation Therapy, Hormonal Therapy, Immunotherapy, Bone Marrow Transplantation etc. In most cases, a combination of several treatments is utilized to aggressively treat the cancer.

Most commonly, chemotherapy acts by killing cells that divide rapidly. This means that it also harms cells that divide rapidly under normal circumstances: cells in the bone marrow, digestive tract and hair follicles; these results in the most common side effects of chemotherapy.

The mitomycins are a family of aziridine-containing natural products isolated from Streptomyces caespitosus or Streptomyces lavendulae. One of these compounds, mitomycin C, finds use as a chemotherapeutic agent by virtue of its antitumour antibiotic activity.

Doxorubicin is a drug used in cancer chemotherapy. It is an anthracycline antibiotic, closely related to the natural product daunomycin, and like all anthracyclines, it works by intercalating DNA. Doxorubicin is commonly used in the treatment of a wide range of cancers, including hematological malignancies, many types of carcinoma, and soft tissue sarcomas.

As we observe, the compounds presented above possess a quinone structure. The quinone group may undergo oxidoreduction reactions to yield oxygen free radicals, mainly O_2- and $OH^{\cdot}$; these oxy radicals have been reported to be cytotoxic.

STUDY OF QUINOLINE-5,8-DIONES

The study of quinoline-5,8-diones derived from the highly antibacterial 8-hydroxyquinoline was first undertaken in order to determine the effect of this structural alteration on the biological activity of the latter compound. It was prepared by Fischer and Renouf by oxidation of 5-amino-8-hydroxyquinoline with chromic acid and is weakly basic.

Over several decades the synthesis and the biological activities of variously substituted derivatives have been reported and the majority of these reports have dealt with the chemistry and/or bioassays of the C-6 and/or C-7 substituted quinolone-5,8-diones.

The C-6 and C-7 substituents mainly include functionalities such as amino, hydroxyl, thiol, and their derivatives, as well as alkyl, halogen, and nitro groups. Few examples of drugs that contain quinoline-5,8-diones are lavendamycin, streptonigrin and streptonigrone.

Synthetic approaches to Lavendamycin Methyl Ester

The Bischler-Napieralski Approach

This approach relied on an eight step sequence from 8-methoxyquinaldic acid including the construction of the C ring by means of a Bischler-Napieralski type cyclization reaction. Shown in Scheme, the AB ring precursor was prepared in an overall yield of 78% from 2-amino-3-methoxybenzaldehyde via a Friedlander condensation with pyruvic acid followed by nitration. It was then coupled with the methyl ester of the β- methyltryptophan, followed by a Bischler-Napieralski cyclisation.

Finally, the fully aromatic pentacyclic ester was converted to the methyl ester of lavendamycin in an overall yield of 2.65%.In the above approach, the main drawback was the introduction of the C-7 amino group in the quinoline ring after the CDE ring formation which proved to be problematic and low yielding. In order to avoid this problem, Behforouz opted for the introduction of the protected C-7 amino group prior to the CDE ring formation.

DOEBNER-MILLER MODIFICATION

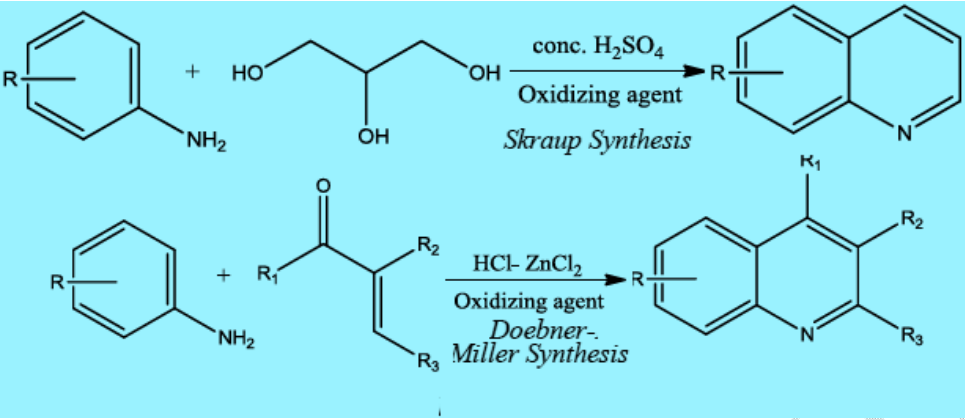
To synthesis the quinone drugs, Doebner-Miller modification is one of the suitable syntheses to produce variously substituted quinolines. Doebner-Miller reaction is the organic reaction of an aniline with α,β-saturated carbonyl compound to form quinolines.

It is the modification of Skraup procedure where in the latter uses glycerol instead of an α,β-saturated carbonyl compound. The modification takes place in the presence of HCl and zinc chloride.

This synthesis allows introduction of substituents on the pyridine ring as well while the Skraup procedure gives easy access only to quinolines substituted on the benzene ring containing only those components which were on the aniline component.

However, the method does suffer from some major disadvantages. The yields reported are usually low owing to the many by-products formed in the reaction. Depending upon the particular conditions employed, a typical product mixture obtained from the reaction of an aniline with crotonaldehyde in strongly acidic solution consists of the desired quinaldine contaminated with varying amounts of unreacted aniline, various N-alkylanilines and 1,2,3,4-tetrahydroquinaldine.

Isolation and purification of quinaldines from such reaction mixtures is often hard and tedious and many manipulations involved tend to lower the recovery of the desired product.



The mechanism of Doebner-Miller synthesis of quinaldines has been the subject of many investigations, leading to the mechanism which involves aldol condensation forming an α,β-unsaturated carbonyl compound followed by Michael addition of the aromatic amine.

Knoevenagel Condensation

Homogeneous and heterogeneous catalysis come across extensive applications in 'fine chemicals' manufacturing industries. It has been newly reviewed that in comparison with the homogenous catalysts, heterogeneous catalysts generally offer more advantages and hence is an area of growing interest.

In recent years, various environmentally unsupportive processes in synthesis of bulk and fine chemical industries are being replaced with cleaner catalytic processes. Several studies have been reported on the base-catalyzed reactions such as condensation reaction, alkylation of toluene with methanol, alkylation of alkylbenzenes, alkylation of hetroaromatics, hydrogenation-dehydrogenation reactions, Michael addition, Henry reaction, and many others.

They are paying huge attention in the fine chemical manufacture industries owing to their special features like shape selectivity, reusability and eco-friendly nature in many industrial processes.

The synthesis of industrially applicable intermediates by using mesoporous zeolites in large scale opened a wide spread applications in pharmaceuticals, agricultural chemicals, rubber chemicals, water treatment chemicals and solvents, petro-chemistry and in the synthesis of organic chemicals, which sought for in green chemistry.

KNOEVENAGEL CONDENSATION REACTION (KCR):

The Knoevenagel condensation reaction (formation of C-C bond) is an organic reaction with a modification of the aldol condensation (involving two C=O bonds), named after Emil Knoevenagel. A Knoevenagel condensation is a nucleophilic addition of an active hydrogen compound to a carbonyl group followed by a dehydration reaction in which a molecule of water is eliminated (hence condensation).

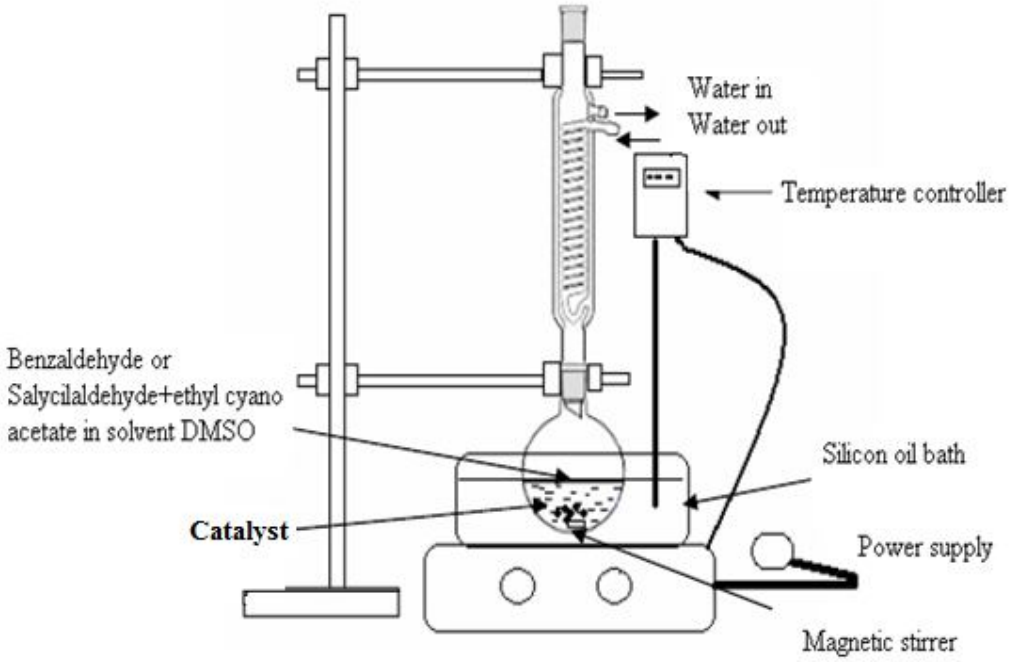
Oftenlly, the product is α, β conjugated enone which are important key products that include nitriles used in anionic polymerization, the α,β-unsaturated ester intermediates are employed in the synthesis of several therapeutic drugs and pharmacological products (e.g. calcium antagonists and antihypertensives).

The reagents such as Benzaldehyde, Salycilaldehyde, Ethyl cyano acetate (ECA) and solvent Dimethyl sulfoxide (DMSO) were used as procured from the supplier. The details of their properties are tabulated in Table. Benzaldehyde was dried and then kept under the nitrogen on basic Alumina in order to trap acid impurities, essentially benzoic acid.

Table: Reagents used for KCR and their specifications.

No.	Reagent	Manufacturer	Analysis
1.	Benzaldehyde	Aldrich, Mumbai	99.98%
2.	Salycilaldehyde	Aldrich, Mumbai	99.99%
3.	Ethyl cynoacetate(ECA)	Aldrich, Mumbai	99.98%
4.	DMSO (solvent)	Acros, Mumbai	99.99%

The experimental set up (Fig.) and flow chart for favorable condition of KCR between Benzaldehyde or Salycilaldehyde with ECA in the medium of a solvent DMSO is summarized in Fig.



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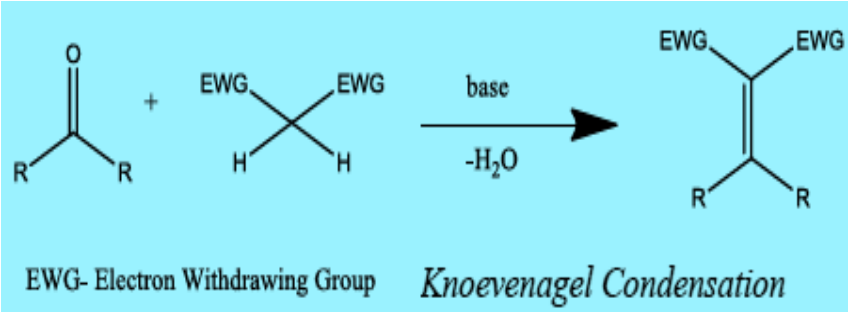
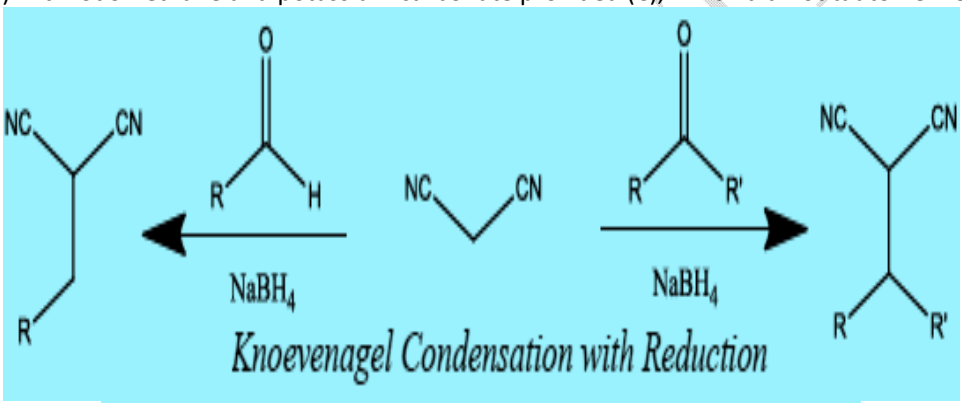
Synthesis of monosubstituted malononitriles via C-C bond formation has been a challenging problem for organic chemists. The most direct route to monosubstitued malononitriles is the alkylation of malononitrile, but this method generally produces various amounts of disubstituted malononitriles from overalkylation.

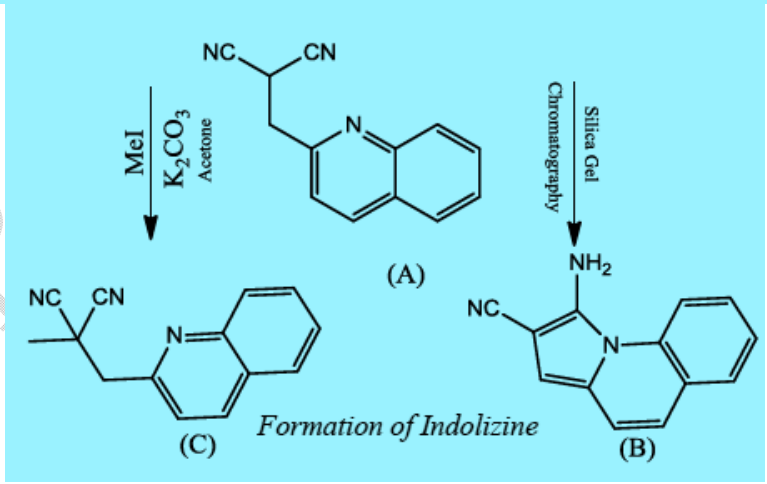
The first step usually involves a Knoevenagel condensation between malononitrile and an aldehyde or ketone. In the second step, the intermediate dicyanoalkene is reduced in a single step to afford the desired monosubstituted malononitrile. Two independent reports have recently shown that the Knoevenagel condensation step between malononitrile and aromatic aldehydes can simply occur in ethanol or water with no added catalysts. In most cases, 93% ethanol was used. Dilution of the resultant mixture with additional ethanol and cooling the reaction in an ice-water bath preceded sodium borohydride reduction.



When this procedure was attempted with 2-quinolinecarboxaldehyde, a crude product was observed but it 'decomposed' upon attempted purification via recrystallization or column chromatography. When the reaction and the entire workup were carried out at 273K, pure product was obtained.

But later, it rearranged on TLC and created a single fluorescent spot with an Rf value greater than expected for the quinoline substituted malononitrile. The nucleophilic attack of the quinoline N on the C of the nitrile followed by a proton transfer and a tautomerization resulted in the creation of indolizine. Treatment of (A) with iodomethane and potassium carbonate provided (C), which did not tautomerize.



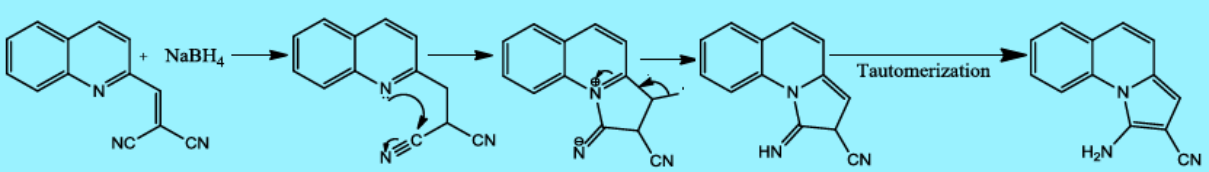


Chemistry of Indolizines

Indolizine is a heterocyclic aromatic organic compound that is an isomer of indole. The nitrogen containing heterocyclic systems have been widely distributed in nature. These compounds are interesting for their wide spectrum of biological properties. Derivatives of indolizine were investigated for potential mutagenicity and anti-mutagenic activity using Ames test.

Synthetic indolizines are important as potential central nervous system depressants, calcium entry blockers, cardiovascular agents, spectral sensitizers, and novel dyes. They are also used for the treatment of angina pectoris or as testosterone reductase inhibitors.

As mentioned above in the Knoevenagel Condensation, when the reaction is carried out with 2-quinolinecarbaldehyde and the entire workup was carried out at 273K, pure product (substituted malononitrile) was obtained. But later, it rearranged on TLC and created a single fluorescent spot with an Rf value greater than expected for the quinoline substituted malononitrile. The nucleophilic attack of the quinoline N on the C of the nitrile followed by a proton transfer and a tautomerization resulted in the creation of indolizine.



Mechanism of formation of Indolizine

CONCLUSION:

In this article we have described a rapid, efficient, environmentally and economically benign method for the synthesis of quinoline derivatives by the condensation under solvent-free conditions with the excellent yields.

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