Greener one pot synthesis of 2-amino-4-arylquinoline-3- carbonitriles in neat water under microwaves

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Abstract:-A general and efficient protocol is described for one pot three component intramolecular cyclization of anilines, aldehydes and malononitrile in neat water within very shorter reaction times and higher yield. Titled compounds synthesized under both microwave irradiation and classical heating for comparison purposes. The catalytic activity of *L*-proline in these reactions was tested over a set of aldehydes and amines, demonstrating that it is reactive toward a variety of functionalities. The role of water in reaction mechanism also demonstrated. The use of a monomode oven allowed an accurate consideration of the temperature distribution in the microwave reaction vessel, which revealed a very strong and unexpected thermal heterogeneity.

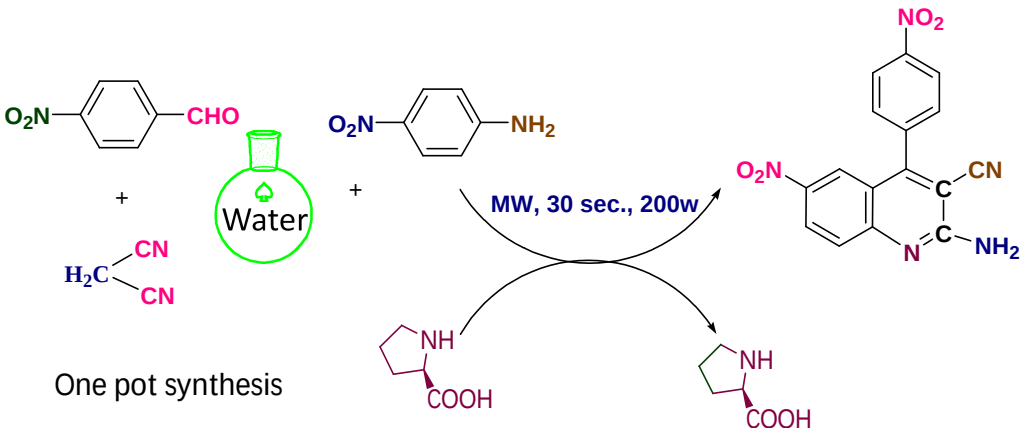
1. Introduction

The quinoline ring system is an important structural unit in naturally occurring quinoline alkaloids, therapeutics, and synthetic analogues with interesting biological activities.[1] Therefore, the development of new and efficient synthetic routes to the quinoline ring system is of interest in both synthetic organic and medicinal chemistry. Versatile methods for the synthesis of the quinoline ring system have been developed.[2] However; most of these methods are not fully satisfactory with regard to yield, reaction conditions, generality and operational simplicity. Thus, a simple, general and efficient procedure is still in demand for the synthesis of this important heterocycle.

Organocatalysts, which are metal-free organic compounds of relatively low molecular weight and simple structure, are capable of promoting a reaction in substoichiometric amounts, and have received paramount interest over the last few years.[3] In particular, the use of the amino acid proline [4] can be regarded as the simplest ‘enzyme’, and was successfully applied as a catalyst to many organic transformations.[5-6]

Multicomponent reactions (MCR-s) have recently emerged as valuable tools in the preparation of structurally diverse chemical libraries of drug-like heterocyclic compounds.[7] In view of the increasing interest for the preparation of large heterocyclic compound libraries, the development of new and synthetically valuable multicomponent reactions remains a challenge for both academic and industrial research teams. Organocatalyst-catalyzed MCRs and the use of environmentally benign solvent and reagents are particularly attractive, because they incorporate many of the green chemistry principles. Apart from this, The advantages of numerous microwave (MW) induced reactions over conventional reactions, and their utility in organic synthesis, have been fully recognized in the last two decades.[8] Well-known applications of the MW methodology involve the effective syntheses and functionalization of various and structurally diverse heterocyclic compounds.[9]

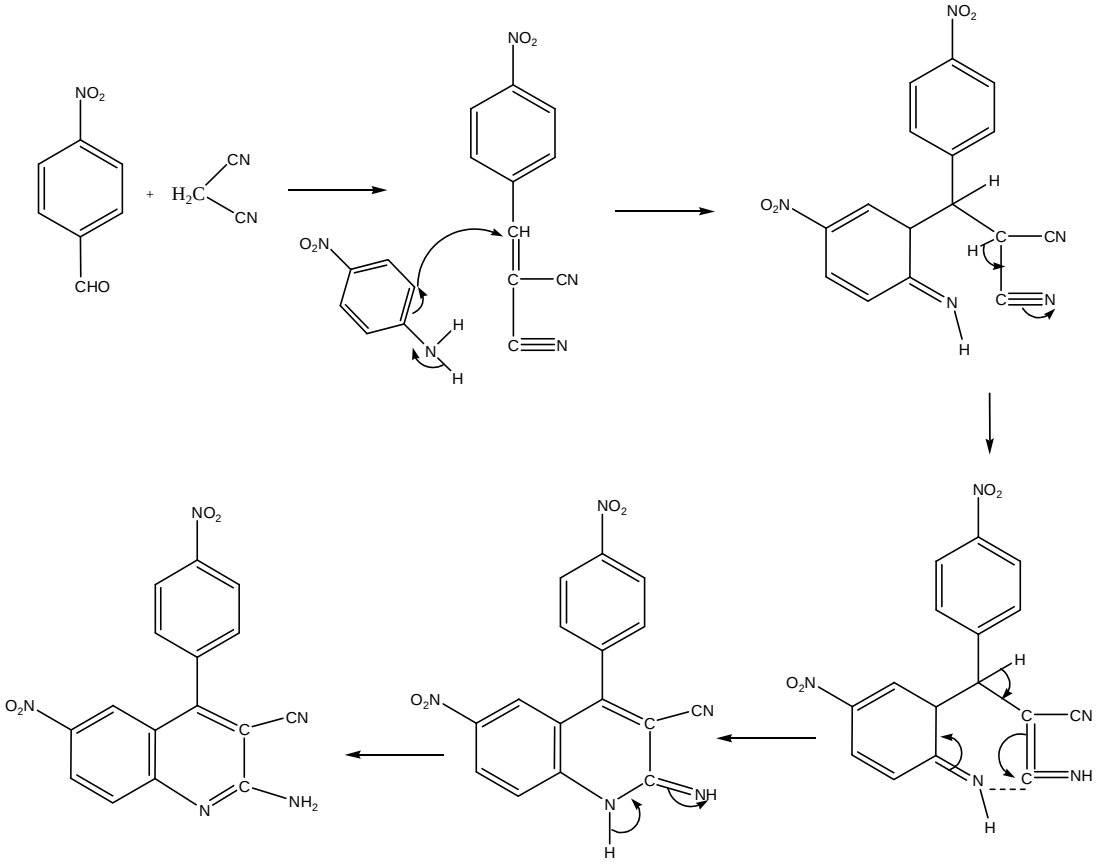
In previous study of synthesis of 2-amino-4-arylquinoline-3- carbonitriles reported by *Panahi etal.*[10] involving *L*-proline catalyzed three component reactions of anilines, aldehydes and malononitrile under water as aqueous medium. This protocol suffers several drawbacks like lesser yield, higher loading amount of organo catalyst and long heating period. Our ongoing programme to develop benign and expeditious methods for organic transformation under solvent-free conditions using microwaves irradiation,[11] and our interest in green chemistry, we planned to synthesize *L*-proline catalyzed 2-amino-4-arylquinoline-3- carbonitriles by reacting anilines, aldehydes and malononitrile under microwaves in neat water condition (**Scheme 1**).



Scheme-1

Result and discussion

The interest in ortho-aminocarbonitriles is related to the wide scope of their biological activities and applications as precursor for the synthesis of novel heterocyclic compounds.[12] So, in this part of study, we decided to investigate the reactions of malononitrile with aldehydes and anilines using L-proline as catalyst under microwave irradiation in neat condition. This reaction is resulted in the production of 2-amino-4-arylquinoline-3-carbonitrile derivatives. As a control experiment, aniline and 4-nitro-benzaldehyde were reacted with malononitrile under optimized conditions (L-proline 0.05 mol%) and 2-amino4-(4-nitrophenyl)quinoline-3-carbonitrile was produced with 99% isolated yield after 30 sec. only. As a result of this experiment it was revealed that under aforementioned conditions an oxidation process was also happened and so 2-amino-4-arylquinoline-3-carbonitrile product is obtained while the 2-amino1,4-dihydro-4-aryl-quinoline-3-carbonitrile is expected as product. According to the literature,[13] we proposed the following mechanism for the reaction (**Scheme 2).**



Scheme-2

The structure elucidation done by NMR (Fig. 1) and IR spectra. It shows peaks in NMR spectra at 2.46(s, 2 NH), 6.54(s,1H),7.89(s,1H), 8.07(s,2H), 8.30(s,2H), 8.65 (s, 1H) clearly indicate the formation of product. In IR spectra it shows band at 3477.76, 3352.49, 2216.01, 1569.03, 1479.80, 1309.30, 1175.29, 1015.49, 833.73 cm^{-1}.

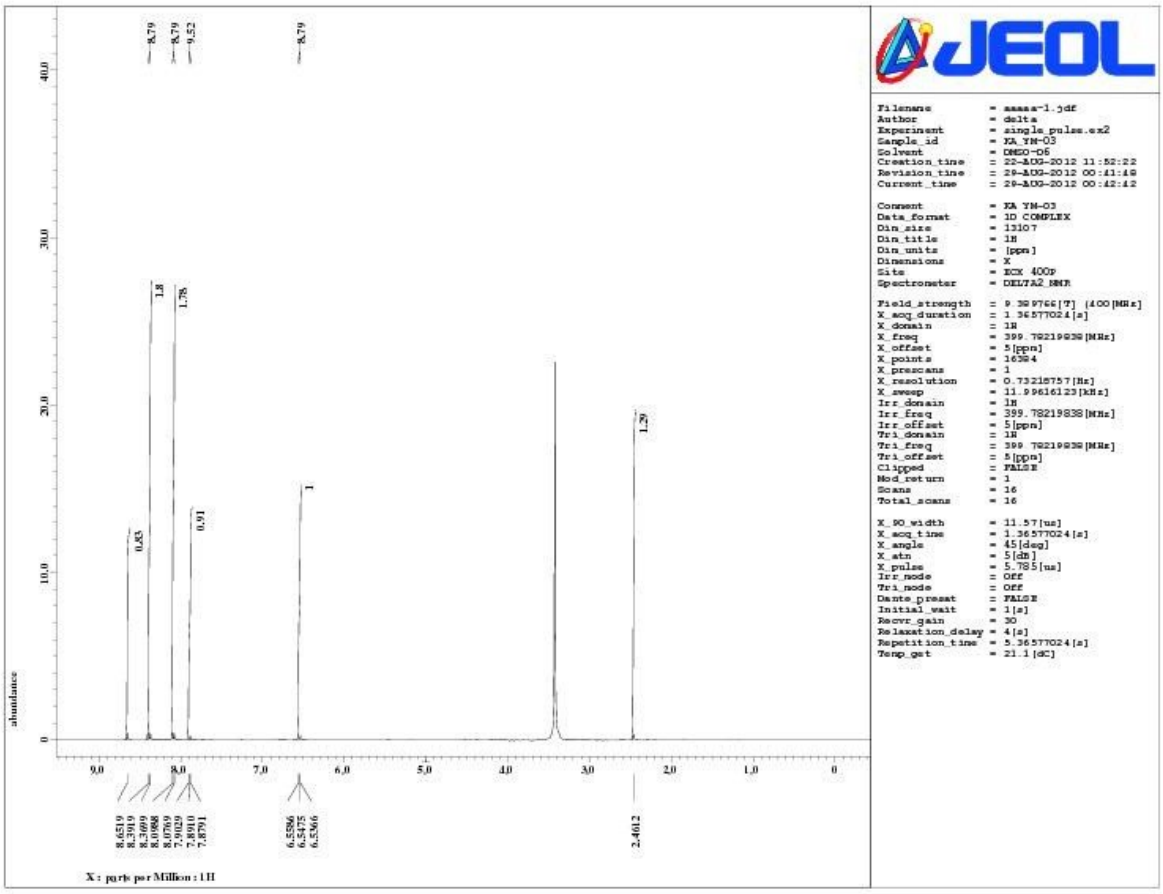


Figure-1

Regioselectivity and product selectivity of the reactions

When an aniline compound containing functional group at m-position to NH_2 is used in the reaction then it leads to the production of two product, but in MCRs only one product is obtained. In 3-aminocarbonitrile unit, basic site is the cyano group rather than amino group. The following equilibrium has been predicted for 3-aminocarbonitrile in acidic medium. The equilibrium is between nitrilium and iminium ion. This equilibrium plays an important role in

oxidation process. In the presence of *L*-proline 2-amino-1,4-dihydro-4-arylquinoline-3-carbonitrile can be protonated to produce corresponding nitrilium ion.

By varying the substituent's different quinoline derivatives are studied and the results are depicted in **Table 1.**

Table 1. Optimization of three component coupling reaction between Benzaldehyde, Aniline and Malononitrile

Entry	X	Y	Time (sec.)	m.p.(^{o}C)	Yield (%)
1.	4-NO_2	4-NO_2	30	155	99
2.	4-OCH_3	4-NO_2	34	91	96
3.	4-NO_2	4-OCH_3	45	134	98
4.	4-OH	4-NO_2	30	130	95
5.	4-NO_2	4-CH_3	45	95	97

It was observed that increasing the amount of catalyst did not have effect on the reaction progress and product. But on decreasing the amount of catalyst, the yield of the product also decreased.

Conclusion

In summary, we have developed green and efficient procedure for the regioselective synthesis of 2-amino-4-arylquinoline-3-carbonitrile using the three component reaction aldehyde, amine and malononitrile. There are variety of products synthesized in very good yield by just varying the starting materials. L-proline is used as a catalyst which is eco-friendly and the whole reaction is carried out in water as a solvent.

Experimental

Melting points were determined. Thin layer chromatography on silica gel 'G' coated glass plates using benzene, ethanol (8: 2) as eluent was used for monitoring the progress of the reactions. IR spectra (KBr) were recorded on a Magna FT IR–550 spectrophotometer, 1H NMR spectra [DMSO-d_6] were taken on a Jeol –400DX spectrometer at 400 MHz respectively, using TMS as an internal standard for PMR as external standard . Microwave assisted reactions were carried out on CEM discover monomode oven (200 W), operating 2450 MHz frequency.

General procedure for the synthesis of 2-amino-4-arylquinoline-3-carbonitrile:

Pyrex glass vial containing of mixture of 4-nitrobenzaldehyde (1 mmol), malononitrile (1 mmol), 4-methylaniline (1 mmol), water (10 ml) and a catalytic amount of (*L*)-proline (0.05 g, 5 mol %) was placed in a screw capped Teflon vessel. Microwave irradiation was applied for 30 sec. at 90°C. After the completion of reaction (TLC analysis), residue was washed with water give pure product in high yield (up to 99 %).

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