Microwave assisted efficient synthesis of some quinoline derivatives by aza-Diels-Alder reaction strategy

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Abstract:

A catalyst and solvent free efficient three component one pot aza-Diels-Alder reaction strategy has been developed for the synthesis of some complex annelated quinolines from 1-naphthylamine, aldehyde and chalcone under microwave irradiation.

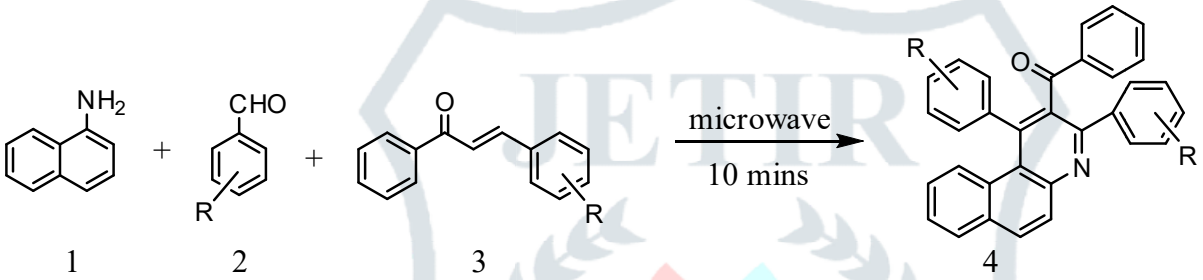
Introduction

Quinolines have been recognized as one of the most significant class of nitrogen containing aromatic heterocyclic compounds. Synthesis of the these derivatives continues to attract great attention from synthetic chemists as this ring system not only occurs in various natural products but also finds extensive utility in the pharmaceutical industry for their antibacterial, antifungal, antimalarial, anthelmintic, anticonvulsant, cardiotonic, anti-inflammatory, and analgesic activities.[1] Quinoline moiety is found in *Cinchona* alkaloids.[2] As a result, apart from various well known classical reactions[3-8] the last decade has observed significant advances towards the development of new and efficient synthetic protocols for assembling this important substructure.[9] Designing of efficient one-pot, multi-component reaction strategy to furnish the complex annulated quinolines from easily available starting material[10] is always an intriguing area as it requires coming together of the scaffolds in a desired way to obtain the target molecules. This often requires use of catalyst, solvent and tedious reaction conditions.[11] In this regard, one-pot, multi-component aza-Diels-Alder (ADA) reaction involving *in situ* generation of either the diene or dienophile can be considered a powerful alternative for assembling complex annulated quinolines. As such, new and improved methodologies, preferably performed under catalyst and solvent free conditions are still desired for construction of complex annelated quinoline structures.

In recent years, there has been a growing interest in developing microwave assisted multi component reactions (MCR)[12] under catalyst and solvent free conditions. This not only provides features like flexibility, atom economy, high yield, facile execution, environmental friendliness, but also reduces the energy requirements and reaction time. As such lots of efforts have been given to develop these methodologies to synthesize molecules of significant importance.

Result and Discussion

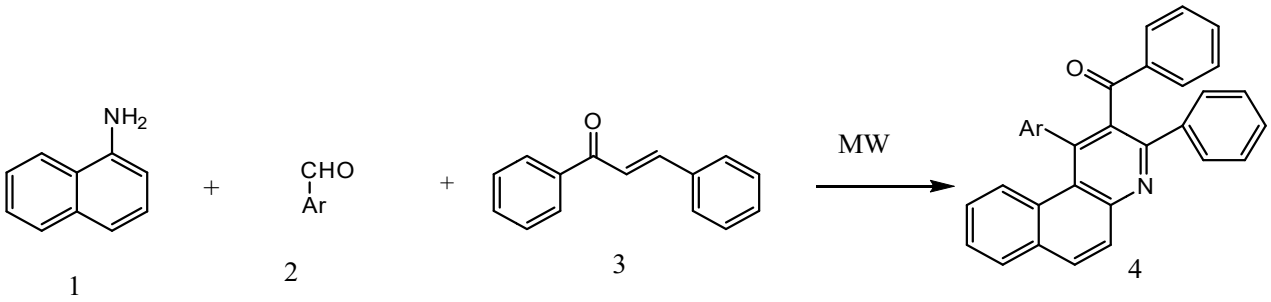
With the aim to develop more efficient synthetic processes, and reduce serious problems of prolonged reaction time, and minimize the byproducts formation, in this paper, a practical and inexpensive, method for the preparation of quinoline derivatives **4** is described (Scheme 1). Here quinoline derivatives are prepared by reacting 1-naphthylamine **1**, aromatic aldehyde **2**, and chalcone **3** in a microwave reactor.



Scheme 1

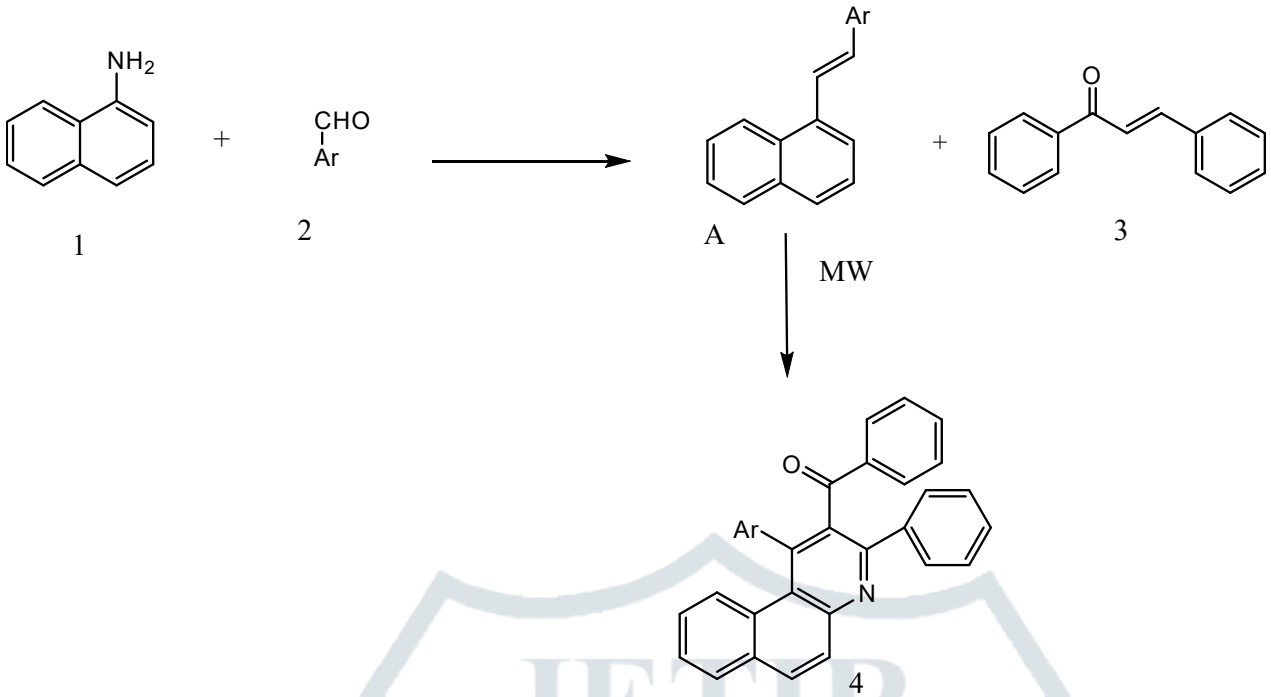
Initially, a three component reaction was performed by reacting a mixture of 1-naphthylamine, benzaldehyde and chalcone under microwave irradiation. When the reaction was carried out for 10 mins, quinoline derivatives formed at 85% yield. To explore the synthetic scope of this reaction further, various substituted aldehydes were employed under similar set of conditions[13] (Table 1). The reaction proceeds efficiently with electron-releasing or electron-withdrawing substituted benzaldehydes (78–85% yields). Results are summerised in table 1. It is pertinent to mention here that it no undesired side reaction was detected and the quinoline derivative was found as the only product. The structures of all the compounds obtained were confirmed by spectral analyses. Starting material chalcone is prepared by reacting acetophenone and benzaldehyde as per standard procedure mentioned in literature. When aliphatic aldehydes were used no desired product formation was observed. Similarly the reaction did not proceed when hetero aromatic aldehydes like furfural and thiphene aldehyde were used. When the reaction was carried out for more than 10 minutes decomposition of the quinoline derivates occurs and the desired product is obtained in low yield,

Table 1 Synthesis of complex quinoline derivatives **4a-h**



Entry	Ar	Product	Yield (%)
1	C_6H_5-	**4a**	85
2	3-Br-C_6H_4-	**4b**	83
3	2-Cl-C_6H_4-	**4c**	81
4	4-Cl-C_6H_4-	**4d**	82
5	4-Br-C_6H_4-	**4e**	82
6	4-NO_2-C_6H_4-	**4f**	80
7	3-NO_2-C_6H_4-	**4g**	78
8	2-Br-C_6H_4-	**4h**	83
9	4-F-C_6H_4-	**4i**	79
10	4-CH_3-C_6H_4-	**4j**	84
11	4-OCH_3-C_6H_4-	**4k**	82
12	3-CH_3-C_6H_4-	**4l**	83
13	2-CH_3-C_6H_4-	**4m**	80
14	2,4-Cl -C_6H_4-	**4n**	81

The formation of the observed product can be mechanistically rationalised via a formal [4+2] aza-Diels-Alder pathway. The Schiff base generated by the reaction of naphthylamine **1** and the aldehyde **2** acts as a reactive diene which reacts with the dienophile chalcone **3** to form the observed product **4** (Scheme 2). The formation of the products from the three-component reactions was further confirmed by performing the reaction stepwise. Initially, intermediate [**A**] was synthesised from the condensation of naphthylamine **1** with benzaldehyde **2a** at room temperature using ethanol as solvent. The intermediate [A] was then reacted with chalcone **3** by reacting in microwave in absence of any catalyst and solvent to get the product **4a**.



1 2 A 3 4

Scheme 2

Conclusion

In summary, a direct and economical aza Diels–Alder method is successfully demonstrated for synthesizing quinolines containing with excellent yields in a microwave-accelerated catalyst and solvent free condition. Extensive investigations are also carried out to establish actual [4+2] nature of the reaction. Overall, this methodology can relieve the problems of longer reaction time and use of toxic solvents during synthesis. Furthermore, the combination of advantages of like non generation of side products and excellent yields make this effort interesting towards formation of quinoline derivatives.

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13. Equimolar amounts of 1-aminonaphthalene **1**, benzaldehyde **2a** and chalcone **3** were mixed in a reaction vessel. The mixture is reacted in a microwave reactor for 10 mins. The crude product mixture was dissolved in ethyl acetate and directly column chromatographed using 1:9 ethyl acetate/hexane as the eluent to get pure product **4a**. Compound **4j**: White solid m.p. 209-210 ^{0}C, ^{1}H NMR (300MHz, $CDCl_3$) δ 8.90-6.87 (m, Ar, 20H), 2.32 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.5, 170.2, 165.1, 149.7, 138.2, 133.9, 132.9, 132.6, 130.6, 128.8, 128.7, 128.5, 126.3, 125.8, 125.4, 123.7, 120.3, 118.8, 117.2, 116.3, 48.4; IR ($CHCl_3$, cm^{-1}) 1706, 1605, 1509, 1381, 1229, 755. MS (GCMS, m/z) 449 $[M]^+$. Similarly, compounds all the compounds were synthesized and characterized.