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Synthesis of quinolines by a solid acid-catalyzed microwave-assisted domino cyclization–aromatization approach

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ABSTRACT

A microwave-assisted solid acid-catalyzed synthesis of quinolines from anilines and cinnamaldehydes is described. Use of montmorillonite K-10 results in a one-pot process; the cyclization and oxidation steps readily take place in a domino approach. Reactions were completed in a matter of minutes and provided excellent yields. The efficient and ecofriendly catalyst and the convenience of the product isolation make this process an attractive alternative for the synthesis of these important heterocycles.

1. Introduction

The quinoline skeleton is a common structural motif in a broad range of biologically active compounds,[1] including many natural products.[2] Quinoline derivatives are utilized as antimalarial,[3] antitumor,[4] and antibacterial agents.[5]

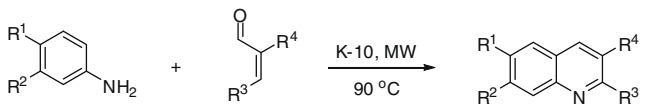
Due to their importance, the synthesis of quinolines attracted widespread attention. Several methods were developed which provide quinoline derivatives efficiently, but do so in multiple steps and using harmful reagents and harsh conditions. These procedures, including the Skraup and Doebner–Miller syntheses,[6] involve the use of a variety of Lewis[7] and Brønsted[8] acids. These traditional acids are corrosive, produce significant amount of waste, and rely on long reaction times, which do not conform to recent environmental standards. Therefore, the design of improved and environmentally benign approaches for their preparation is in great demand.

Solid acids can replace traditional mineral acids as safer alternatives. Clays, zeolites, metal oxides, and acidic ion-exchange resins have become the catalysts of choice in research laboratories and industrial processes.[9] They are also widely used in microwave-assisted organic synthesis (MAOS).[9] These catalysts are stable, easy to store and handle, and do not produce hazardous waste. Besides the potential for sustainability and improved safety, the application of heterogeneous catalysts[10] under microwave conditions includes an additional advantage; reactions can be carried out with minimum solvent use.

Based on our recent studies,[11] we have chosen montmorillonite K-10 as the catalyst. It is a commercially available, stable, inexpensive, strong solid acid, active under microwave conditions, and can be used without any pretreatment. Its features and synthetic applications have been the topic of many reviews.[12] The combination of K-10 and microwave irradiation provided an extensive number of successful processes.[13,14]

Herein, we describe an environmentally benign one-pot domino approach for the synthesis of quinolines. The major benefits of the microwave-assisted heterogeneous catalytic process are the fast reactions, solvent-free environment, and improved yields.[14]

In the reaction, the catalyst has a dual role. It ensures an effective condensation and cyclization of anilines with cinnamaldehydes and promotes the aromatization to the final product. The approach is summarized in Scheme 1.



R^1 = H, CH_3, CH_3CH_2, F, Cl, Br, CH_3O
R^2 = H, CH_3, Cl
R^3 = C_6H_5, 2-NO_2-C_6H_4, 2-CH_3O-C_6H_4, 4-CH_3O-C_6H_4, 4-NO_2-C_6H_4
R^4 = H, CH_3

Scheme 1. Synthesis of substituted quinolines from anilines and cinnamaldehydes.

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2. Results and discussion

To develop our new approach, we have chosen the cyclization of aniline with cinnamaldehyde as a probe reaction. We have observed that the catalyst yielded quinoline in a one-pot cyclization-aromatization domino sequence. The formation of dihydroquinoline was not detected. In contrast, HCl, a traditional liquid acid, while providing the intermediate dihydroquinoline, did not yield the aromatic product. In order to optimize the reaction parameters, we carried out several test reactions and studied the effect of temperature, reactant ratio, and time. Our results (Table 1) indicated that the amount of the nucleophile had a significant effect on the yield of the product. An increase in the amount of aniline from 1 to 1.5 equiv appeared to be beneficial. Further increase in the quantity of the nucleophile did not result in notable improvement. We also found that the reactions could be completed at a relatively mild temperature (90 °C) in a matter of minutes (6 min), while at higher temperatures and prolonged irradiation product decomposition and secondary reactions occurred.

For comparison, we carried out the probe reaction in a pressure vessel using conventional heating in the absence of a solvent (entries 10 and 11). The formation of the aromatic product took place very slowly. As expected, conductive heating resulted in a reaction time that was 15 times longer and provided a lower yield (entry 11). After optimization of the reaction conditions, we obtained quinoline in excellent yield and high selectivity in a short reaction time (entry 9).

To explore the scope of our methodology we used a variety of substituted anilines to synthesize quinolines. The results are summarized in Table 2.

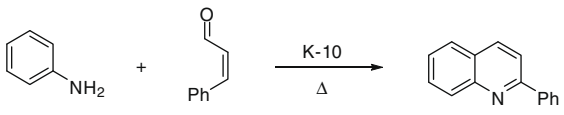
As the data indicate, almost all substituted anilines gave good to excellent yields. A minor reaction time adjustment was necessary for a couple of substrates (entries 6 and 8) to ensure the highest possible yield. In the case of the *m*-substituted anilines, a regioselective *para* cyclization occurred, yielding one product exclusively. The reactions were fast and selective with a few exceptions (entries 3, 5, and 7) when a certain amount of byproduct formed. It is worth mentioning that substrates with strong electron-withdrawing groups showed diminished reactivity, which had a negative effect on yields. Trifluoromethyl-, cyano-, and nitroaniline did not afford satisfactory yields (<20%).

To further widen the applicability of the procedure, we have selected several substituted cinnamaldehydes. The results are summarized in Table 3. As the data demonstrate, in each case the reactions took place efficiently showing a moderate substituent effect. Cinnamaldehydes readily underwent cyclization to form quinolines in moderate to excellent yields. It appears that the steric hindrance in the α-position (entry 1) and the presence of a methoxy substituent on the aromatic ring of the substrate result in moderate yields.

Overall, the reaction accommodates a variety of substituents on both rings. The reaction does not proceed with acrolein and methacrolein due to immediate polymerization of the starting materials under microwave irradiation.

The mechanism for the reaction of an α,β-unsaturated aldehyde or ketone with aniline has long been a subject of a debate. Presumably, the reaction proceeds with a Michael addition of aniline with subsequent cyclization and aromatization under the catalytic conditions.[15] Other claims suggest that the first step is a traditional condensation leading to the formation of an imine, followed by a conjugate addition of a second molecule of aniline (Scheme 2, pathway (a)).[16] A recent work proposed a fragmentation-recombination mechanism in which the intermediate formed from an initial conjugate addition undergoes fragmentation (Scheme 2, pathway (b)).[17] A corresponding ketone or aldehyde, along with an imine, is obtained before recombining to yield quinoline. Inter-

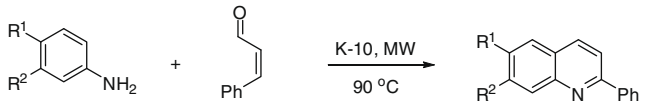
Table 1
Effect of activation method, temperature, time, and initial reactant molar ratio on the microwave-assisted K-10-catalyzed reaction of cinnamaldehyde (CN) with aniline (AN)



Entry	Method[a]	*T* (°C)	Time (min)	CN:AN	Yield[b] (%)
1	MW	80	2	1:1	25
2	MW	80	4	1:1	45
3	MW	80	6	1:1	60
4	MW	80	10	1:1	85
5	MW	90	2	1:1	35
6	MW	90	4	1:1	60
7	MW	80	6	1:1.5	60
8	MW	90	4	1:1.5	75
9	MW	90	6	1:1.5	95
10	CH	80	150	1:1.5	80
11	CH	90	90	1:1.5	70

[a] MW—microwave heating, CH—conventional heating.
[b] Determined by GC; based on cinnamaldehyde.

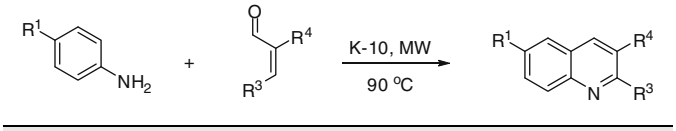
Table 2
Microwave-assisted K-10-catalyzed synthesis of quinolines from cinnamaldehyde and substituted anilines[a]



Entry	R^1	R^2	Time (min)	Yield[c] (%)
1	H	H	6	95
2	CH_3	H	6	90
3	CH_3O	H	6	40
4	CH_3CH_2	H	6	90
5	F[b]	H	6	60
6	Cl[b]	H	8	70
7	Br[b]	H	6	55
8	H	Cl	4	65
9	H	CH_3	6	90

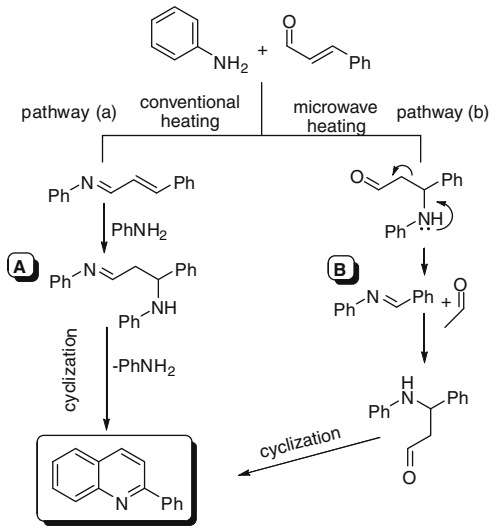
[a] Reactant ratio: aniline (1.5 mmol), cinnamaldehyde (1 mmol).
[b] Reactant ratio: aniline (2.0 mmol), cinnamaldehyde (1 mmol).
[c] Determined by GC.

Table 3
Microwave-assisted, K-10-catalyzed synthesis of quinolines from substituted cinnamaldehydes and substituted anilines[a]



Entry	R_3	R_4	R_1	Time (min)	Yield[b] (%)
1	C_6H_5	CH_3	H	6	70
2	2-$NO_2C_6H_4$	H	H	6	95
3	2-$NO_2C_6H_4$	H	CH_3	6	95
4	2-$NO_2C_6H_4$	H	CH_3CH_2	6	95
5	2-$(CH_3O)C_6H_4$	H	H	6	65
6	4-$(CH_3O)C_6H_4$	H	CH_3	6	55
7	4-$(CH_3O)C_6H_4$	H	CH_3CH_2	6	60
8	4-$(CH_3O)C_6H_4$	H	H	6	65
9	4-$NO_2C_6H_4$	H	H	6	95

[a] Reactant ratio: aniline (1.5 mmol), cinnamaldehyde (1 mmol).
[b] Determined by GC.



Scheme 2. Proposed mechanistic pathways for the K-10-catalyzed synthesis of quinolines.

estingly, we have observed, under different conditions, the formation of these distinct intermediates suggested in the two major pathways. While intermediate **A** was observed when the reaction was carried out with conventional heating, intermediate **B** formed under microwave-assisted conditions (Scheme 2).

While the reason is not clear as yet, it seems that either one of the two distinct pathways may become a major route for the reaction under different conditions. Microwave irradiation, as compared to conventional heating, initiated different pathways in reactions, even yielding different products.[18a] Local temperatures in such reactions can be significantly higher than the observed temperature of the bulk reaction mixture.[18b] Thus, it appears reasonable to propose that pathway (b) requires higher activation energy, which is available under microwave conditions.

3. Conclusion

In conclusion, a novel, solid acid-catalyzed synthesis of substituted quinolines is described. This method provides the products in good to excellent yields and selectivities in very short reaction times from commercially available and inexpensive starting materials. In addition to efficiency, the solvent-free reaction, the limited energy consumption, and waste-free nature make the process an attractive green synthesis of the target compounds.

4. General procedure

All reactants and the catalyst montmorillonite K-10 were purchased from Aldrich and used without further purification. The ^{1}H and ^{13}C NMR spectra were recorded on a 300 MHz Varian NMR spectrometer, in $CDCl_3$. Tetramethylsilane or the residual solvent signal was used as reference. The mass spectrometric identification of the products was carried out on an Agilent 6850 GC-5973 MS system (70 eV EI ionization) using a 30 m long DB-5 column (J&W Scientific). The melting points were uncorrected and were recorded on a MEL-TEMP apparatus.

4.1. One-pot microwave-assisted synthesis of quinolines—general procedure

Aniline (1.5 mmol) and cinnamaldehyde (1.0 mmol) were dissolved in 3 mL of CH_2Cl_2 in a round-bottomed flask, followed by addition of K-10 (500 mg). After 5 min stirring, the solvent was evaporated to obtain a dry mixture which was transferred into a glass reaction vessel and irradiated in the microwave reactor (CEM Discover Benchmate, 90 °C). During the optimization process, the progress of the reaction was monitored by TLC and GC. After completion of the reaction, CH_2Cl_2 was added to the mixture, and the product was separated from the catalyst by filtration. The products were isolated and purified by flash chromatography. All products showed satisfactory spectral data (MS, ^{1}H, and ^{13}C NMR). Here, the full spectral characterization is given for only the previously unknown products. Such data for the known compounds synthesized in this study are available from the authors.

4.1.1. 6-Ethyl-2-phenylquinoline (Table 2, entry 4)

Mp 40–42 °C; ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm) 8.13 (m, 4H), 7.83 (d, J = 7.2 Hz, 1H), 7.59 (m, 2H), 7.49 (m, 3H), 2.84 (q, J = 7.5 Hz, 2H), 1.34 (t, J = 7.5 Hz, 3H).

^{13}C NMR (75.474 MHz, $CDCl_3$), δ (ppm) 156.5, 146.9, 142.4, 139.7, 136.3, 130.9, 129.4, 129.1, 128.8, 127.5, 127.2, 124.9, 118.9, 28.8, 15.4.

MS-$C_{17}H_{15}N$ (233), *m/z* (%): 233 (M^+, 71), 218 (100), 204 (15).

4.1.2. 6-Ethyl-2-(2-nitrophenyl)quinoline (Table 3, entry 4)

Mp 75–77 °C; ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm) 8.16 (d, J = 8.4 Hz, 1H), 7.98 (m, 2H), 7.70 (m, 2H), 7.58 (m, 3H), 7.48 (d, J = 8.4 Hz, 1H), 2.85 (q, J = 7.5 Hz, 2H), 1.34 (t, J = 7.5 Hz, 3H).

^{13}C NMR (75.474 MHz, $CDCl_3$), δ (ppm) 154.6, 146.7, 143.2, 136.3, 135.9, 132.6, 131.6, 131.2, 129.4, 129.2, 127.2, 125.1, 124.4, 120.4, 28.9, 15.4.

MS-$C_{17}H_{14}N_2O_2$ (278), *m/z* (%): 278 (M^+, 100), 263 (19), 248 (71), 233 (42), 216 (39), 207 (67).

4.1.3. 6-Methyl-2-(4-methoxyphenyl)quinoline (Table 3, entry 6)

Mp 131–133 °C; ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm) 8.10 (m, 4H), 7.79 (m, 1H), 7.55 (m, 2H), 7.05 (m, 2H), 3.88 (s, 3H), 2.53 (s, 3H).

^{13}C NMR (75.474 MHz, $CDCl_3$), δ (ppm) 160.6, 156.1, 146.8, 135.9, 131.8, 129.8, 129.2, 128.7, 127.9, 126.3, 118.5, 114.1, 112.8, 55.4, 21.5.

MS-$C_{17}H_{15}NO$ (249), *m/z* (%): 249 (M^+, 100), 234 (38), 206 (29), 191 (22).

4.1.4. 6-Ethyl-2-(4-methoxyphenyl)quinoline (Table 3, entry 7)

Mp 101–103 °C; ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm) 8.11 (m, 3H), 7.78 (m, 2H), 7.56 (m, 2H), 7.03 (m, 2H), 3.86 (s, 3H), 2.82 (q, J = 7.2 Hz, 2H), 1.33 (t, J = 7.5 Hz, 3H).

^{13}C NMR (75.474 MHz, $CDCl_3$), δ (ppm) 160.1, 155.9, 149.8, 136.8, 131.5, 129.7, 129.2, 128.1, 127.5, 126.1, 119.5, 114.2, 113.6, 55.4, 28.8, 15.3.

MS-$C_{17}H_{17}NO$ (263), *m/z* (%): 263 (M^+, 100), 248 (95), 204 (25).

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