Microwave-Assisted Synthesis of 2-Chloroquinoline-3-Carbaldehyde on Silica Support using Mild Acidic Charcoal Catalyst

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Abstract

2-Chloroquinoline-3-carbaldehyde was synthesized using a silica-supported reaction system with a mildly acidic charcoal catalyst under microwave irradiation. The aim of optimizing the catalytic process was to improve both the yield and efficiency of the reaction. The use of microwave irradiation significantly shortened the reaction time while the mildly acidic charcoal created an effective and environmentally friendly catalytic environment.

The reaction proceeded smoothly, producing substantial amounts of the desired 2-chloroquinoline-3-carbaldehyde, which demonstrates the effectiveness of the silica-supported, charcoal-catalyzed method. This approach provides a sustainable and efficient alternative for synthesizing quinoline derivatives, which could have applications in pharmaceuticals and organic synthesis

Keyword: 2-Chloroquinoline-3-carbaldehyde**,** Silica supported acidic charcoal, Microwave irradiation.

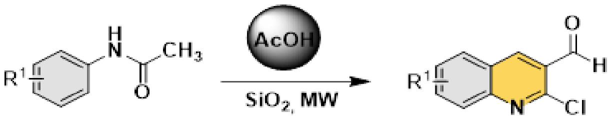
Introduction

In recent years, there has been significant interest in 2-chloroquinoline-3-carbaldehyde and their derivatives due to their remarkable biological and pharmacological activities. These compounds have demonstrated antimicrobial[3,6-9], anti-inflammatory[10,13], antimalarial agents[20] and antiviral properties[1]. The synthesis of 2-chloroquinoline-3-carbaldehydes was accomplished through the Vilsmeier Haack reaction, starting from acetanilides. This reaction pathway was carried out using traditional methods[4,5,11,12,16,17,19,21,22] as well as microwave irradiation[15] and ultrasonic irradiation[2] as shown in scheme 1.

Reagents supported by inorganic materials have been established for nearly three decades and find widespread use in laboratory and industrial-scale reactions. The reagents are anchored onto porous solid supports, allowing for excellent dispersion of active sites, greater selectivity and easier handling than traditional solution phase reactions. Additionally, some of these solid supports are recyclable, making these processes environmentally friendly and "green." To address this challenge, we investigated the use of microwave irradiation coupled with a mild acidic charcoal catalyst supported on silica for the synthesis of 2-chloroquinoline-3-carbaldehyde. Silica-based catalyst supports have gained significant attention due to their high surface area, thermal stability and ease of synthesis.

The mild acidic charcoal catalyst employed (previously reported by our research group)[18] in this study not only offers catalytic activity but also facilitates the reaction under mild acidic conditions, which is beneficial for the desired transformation. The combination of microwave irradiation and the mild acidic charcoal catalyst is expected to enhance the reaction kinetics, reduce the reaction time and improve the overall yield of 2-chloroquinoline-3-carbaldehyde. In this study, we present the optimization of the catalyst amount and reaction conditions using both conventional refluxing and microwave irradiation methods. The effectiveness of the mild acidic charcoal catalyst supported on silica was evaluated by assessing the yield and purity of the synthesized product under various reaction conditions.

In summary, the results of this study demonstrate the successful synthesis of 2-chloroquinoline-3-carbaldehyde using microwave-assisted organic synthesis with a mild acidic charcoal catalyst supported on silica. The optimized reaction conditions and catalyst amount led to satisfactory yields and purity of the desired product. This highlights the potential of microwave irradiation in conjunction with the mild acidic charcoal catalyst for efficient and environmentally friendly synthesis.



3a. R_1= H, 3b. R_1= 6-CH_3, 3c. R_1= 7-CH_3, 3d. R_1= 6-Br, 3e. R_1= 6-Cl, 3f. R_1= 6-OCH_3

Scheme 1: Microwave assisted synthesis of 2-Chloroquinoline-3-Carbaldehyde using mild acidic charcoal catalyst supported on silica

Material and Methods

Experimental: All starting reagents were commercially sourced from Loba Chemie Pvt. Ltd., Merck Specialties Pvt. Ltd., including substituted acetanilide, $POCl_3$, DMF, ethanol, ethyl acetate, petroleum ether and were used without further purification. The melting point values of the synthesized compounds were determined using the conventional method and are uncorrected. To monitor the reactions, thin-layer chromatography on silica gel 60 F254 plates was employed. For microwave irradiation, a conventional household microwave oven with a power output of 800 W was utilized. The synthesized products were identified as known compounds by comparing their melting points and spectra data with those reported in the literature. Overall, these experimental details provide insight into the methods used in this study.

Optimization of amount of Mild Acidic Charcoal Catalyst: The synthesis of 2-chloroquinoline-3-carbaldehyde was achieved by reacting substituted acetanilide with $POCl_3$ and DMF in the presence of a mild acidic charcoal catalyst. The effectiveness of the catalyst was optimized through conventional refluxing and microwave irradiation (800W). Table 1 demonstrates that using 0.2 g of the catalyst yielded satisfactory results in terms of both yield and purity under both reaction conditions. Increasing the amount of catalyst did not lead to significant improvements in yield or reaction time. Therefore, 0.2 g of the mild acidic charcoal catalyst was selected for synthesizing derivatives of 2-chloro-3-formylcarbaldehyde.

General Procedure for synthesis of 2-chloroquinoline-3-carbaldehyde: To dissolve 5 mmol of acetanilide derivatives, 33 ml of dimethyl formamide (15 mmol) was used in a 250 mL round bottom flask. Gradually add 60 mmol of phosphorus oxychloride to the solution at 0°C, then add 0.2 g mild acidic charcoal catalyst in the reaction mixture, which was then refluxed on an oil bath at 80-90 °C for 5-6 hours with the help of a reflux condenser. Upon completion of the reaction, the solution was allowed to cool to room temperature and then poured into 250 ml of ice water. The resulting precipitate was collected and dissolved in ethyl acetate and filtered to remove residual charcoal. After removing the solvent under vacuum, the product was obtained through recrystallization by using a suitable solvent.[14]

Microwave assisted synthesis of 2-chloroquinoline-3-carbaldehyde: The substrate (1 mmol) was added gradually to the Vilsmeier reagent (2 mmol) at a temperature range of 0-5 °C. Once the addition was complete, the reaction mixture was allowed to stand at room temperature for 5 minutes and then add 0.2 g mild acidic charcoal catalyst and silica gel (1.5-2 g) was added (Scheme 1). The mild acidic charcoal catalyst and silica gel was mixed thoroughly with the mixture using a glass rod until a free-flowing powder was obtained.

Table 1
Effect of catalyst amount on conventional as well as microwave assisted model reaction of 2-chloroquinoline-3-carbaldehyde synthesis

Entry	Catalyst (g)	Conventional method		Microwave irradiation	
		Time (hr)	Yield (%)	Time (hr)	Yield (%)
1	0.050	9	78	2.5	82
2	0.100	8.5	82	1.7	84
3	0.150	6	88	1.5	90
4	**0.200**	**6**	**90**	**1.5**	**94**
5	0.250	6	90	1.5	93
6	0.300	6	88	2	90

Table 2
Comparative study of 2-chloroquinoline-3-carbaldehyde synthesis under different reaction conditions

Entry	Product	R^1	Conventional		Conventional (Mild acidic charcoal catalysed)		Microwave (SiO_2)		Microwave (SiO_2 and Mild acidic charcoal catalysed)	
			Time (hrs)	Yield %	Time (hrs)	Yield %	Time (hrs)	Yield	Time (hrs)	Yield %
1	3a	H-	9-10	78	6-7	82	2.5-3	84	1.5-2	86
2	3b	6-CH_3-	8-9	74	6-7	78	1-1.5	80	1-1.2	82
3	3c	7-CH_3-	8-9	68	7-8	72	1-1.5	75	1-1.2	77
4	3d	6-Br-	8-9	42	7-8	48	1-1.5	54	1-1.2	60
5	3e	6-Cl-	8-9	44	7-8	52	1-1.5	56	1-1.2	62
6	3f	6-OCH_3-	8-9	50	7-8	58	2-2.5	62	1-1.5	66

The resulting powder was subjected to microwave irradiation for an appropriate duration as per table 2.

Results and Discussion

Table 3 presents the results of the reactions conducted using different reaction conditions, namely conventional (with and without mild acidic charcoal catalysis) and microwave-assisted with SiO_2 support and SiO_2 support with mild acidic charcoal catalysis. The product yields and reaction times are reported for each reaction condition. The experimental results indicate significant differences in the reaction time and product yield when comparing to different reaction conditions. In the conventional method without the presence of mild acidic charcoal catalyst, it was observed that the reaction time was considerably high, while the yield of the desired product was relatively low. This suggests that the conventional method alone is not efficient in promoting the desired reaction.

However, when the same reaction was conducted in the presence of a mild acidic following irradiation, cold saturated aqueous NaOAc solution (10 mL) was added, stirred and filtered. Finally, the product was extracted using dichloromethane. After removing the solvent under vacuum, the product was obtained through recrystallization using a suitable solvent. The physical properties of all products including melting point, IR, ^{1}H NMR,^{13}C NMR and LCMS were compared with those of known compounds and authentic samples to confirm their identity. Charcoal catalyst, a notable reduction in the reaction time was observed, accompanied by a slight increase in the product yield. This indicates that the mild acidic charcoal catalyst has a positive effect on the reaction, improving its efficiency by facilitating the desired transformation.

Furthermore, by utilizing SiO_2 as a support material in the microwave-assisted reaction, a significant decrease in the reaction time was observed compared to the conventional method. Additionally, an increase in the product yield was observed, suggesting that the microwave method in combination with SiO_2 support enhances the reaction kinetics and promotes a more efficient conversion of the starting material. Remarkably, when the reaction was conducted using both SiO_2 support and mild acidic charcoal catalyst, a substantial reduction in the reaction time was achieved.

Additionally, there was a further increase in the product yield compared to the individual application of either the SiO_2 support or the mild acidic charcoal catalyst. This demonstrates the synergistic effect of combining both the catalyst and support, leading to enhanced reaction kinetics and improved product yield.

Overall, the results highlight the importance of catalysts and support materials in facilitating and optimizing chemical reactions. The mild acidic charcoal catalyst and SiO_2 support play crucial roles in reducing the reaction time and increasing the product yield, providing valuable insights for further advancements in the synthesis of the desired compound.

Characterization data

2-chloroquinoline-3-carbaldehyde (3a): MP:145-146 °C; IR (KBr, cm^{-1}):.3036, 1683, 1135, 753; ^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$-*d*):10.40 (s, 1H), 8.99 (s, 1H), 8.29 (dd, *J* = 8.2, 1.4 Hz, 1H), 8.05 (dd, *J* = 8.4, 1.3 Hz, 1H), 8.00 (ddd, *J* = 8.4, 6.7, 1.5 Hz, 1H), 7.78 (ddd, *J* = 8.2, 6.6, 1.5 Hz, 1H); ^{13}C NMR (δ, ppm) (100 MHz, DMSO-*d*): 189.85, 149.45, 149.05, 141.89, 134.36, 130.68, 128.74, 128.27, 126.87, 126.83, 40.73; MS (m/z): 192 (M+1)

2-chloro-6-methylquinoline-3 carbaldehyde (3b): MP: 121-123 °C; IR (KBr, cm^{-1}): 3013, 1687, 1156, 816; ^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$-*d*):10.56 (s, 1H), 8.67 (s, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.77 – 7.67 (m, 2H), 2.58 (s, 3H); ^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$-*d*): 189.32, 149.28, 148.26, 139.55, 138.42, 135.96, 128.41, 128.26, 126.61, 126.34, 77.25, 21.57; MS (m/z): 206 (M+1)

2-chloro-7-methylquinoline-3carbaldehyde (3c): MP: 142-144 °C; IR (KBr, cm^{-1}): 2999, 1685, 1482, 1140, 860; ^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$-*d*):10.40 (s, 1H), 8.94 (s, 1H), 8.20 (dd, *J* = 8.3, 2.6 Hz, 1H), 7.86 (s, 1H), 7.67 – 7.60 (m, 1H), 2.61 (s, 3H); ^{13}C NMR (δ, ppm) (100 MHz, DMSO-*d*):189.95, 149.71, 149.52, 145.56, 141.58, 131.03, 130.45, 127.41, 126.27, 125.04, 40.83, 22.37.

6-bromo-2-chloroquinoline-3-carbaldehyde (3d): MP: 186-188 °C; IR (KBr, cm^{-1}): 3018, 1689, 1478, 1128, 825; ^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$-*d*):10.59 (s, 1H), 8.70 (s, 1H), 8.18 (t, *J* = 1.4 Hz, 1H), 7.98 (d, *J* = 1.4 Hz, 2H); ^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$-*d*):188.76, 150.48, 148.18, 139.10, 136.98, 131.51, 130.24, 127.68, 127.09, 122.17, 77.35; MS (m/z): 271 (M+1)

2,6-dichloroquinoline-3-carbaldehyde (3e): MP:158-159 °C; IR (KBr, cm^{-1}): 3056, 1663, 1418, 1133, 827; ^{1}H NMR (δ, ppm) (400 MHz, $CDCl_3$-*d*): 10.59 (s, 1H), 8.70 (s, 1H), 8.05 (d, *J* = 9.0 Hz, 1H), 8.00 (d, *J* = 2.4 Hz, 1H), 7.85 (dd, *J* = 9.1, 2.3 Hz, 1H); ^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$-*d*): 188.80, 150.36, 147.95, 139.19, 134.43, 134.13, 130.18, 128.12, 127.20, 77.23.

2-chloro-6-methoxyquinoline-3-carbaldehyde (3f): MP: 143-145 °C; IR (KBr, cm^{-1}): 3048, 1679, 1493, 1150, 858; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 10.54 (s, J = 1.8 Hz, 1H), 8.61 (d, J = 2.6 Hz, 1H), 7.94 (dd, J = 9.2, 2.1 Hz, 1H), 7.51 (dt, J = 9.3, 2.3 Hz, 1H), 7.17 (d, J = 2.7 Hz, 1H), 3.96 (s, 3H); ^{13}C NMR (δ, ppm) (100 MHz, $CDCl_3$-*d*): 189.35, 158.79, 147.63, 145.78, 138.59, 129.89, 127.74, 126.53, 126.40, 106.45, 77.39, 55.79.; MS (m/z): 222 (M+1)

Conclusion

In this study, we successfully demonstrated the microwave-assisted synthesis of 2-chloroquinoline-3-carbaldehyde derivatives using a mild acidic charcoal catalyst supported on silica. The optimized reaction conditions, including a catalyst amount of 0.2 g, provided satisfactory yields and purity for all tested compounds. The microwave-assisted synthesis showed comparable or slightly improved yields compared to the conventional refluxing method while significantly reducing the reaction time. This highlights the efficiency and time-saving advantages of microwave irradiation in organic synthesis. The results emphasize the importance of catalyst optimization in microwave-assisted reactions. Increasing the catalyst amount beyond 0.2 g did not yield significant improvements in yield or reaction time. Overall, this study contributes to the advancement of microwave-assisted organic synthesis and highlights the potential of the mild acidic charcoal catalyst supported on silica for the efficient synthesis of 2-chloroquinoline-3-carbaldehyde derivatives. The findings also provide valuable insights for the development of novel synthetic methodologies in organic chemistry, promoting more efficient and environmentally friendly approaches in organic synthesis.

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