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Natural kaolin as an efficient recyclable catalyst for the synthesis of new 2,4-disubstituted quinolines

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ABSTRACT

Substituted 2, 4- diphenyl quinolines were synthesized by a multicomponent domino reaction of anilines, aldehydes and terminal aryl alkynes. The synthetic pathway involves the formation of an imine, followed by the intermolecular addition of an alkyne to the imine. This intermediate immediately undergoes ring closure and oxidative aromatization. The reaction is catalyzed by natural kaolin, a strong, environmentally benign solid acid. In this procedure natural kaolin is used without any supporting. This catalyst- assisted microwave irradiation has oxidizing ability that leads to aromatization of final intermediate and produces the aromatic substituted quinolines without any other oxidizing agents. The multicomponent approach yields the products in excellent yields in a matter of minutes. The use of microwave activation reduces the reaction time significantly. No side-products are formed significantly. In addition one of the synthesized substituted quinolines is a new compound. However, this catalyst can be used for the synthesis of a variety of important heterocycles such as pyrrazoles, oxazolines, benzodiazepines and quinoxalines.

***Keywords**: Kaolin, Heterogeneous catalyst, 2,4-Disubstituted quinolines, Solvent-free.*

1. Introduction

The synthesis of quinolines and its derivatives has been of considerable interest to organic and medicinal chemistry for many years since a large number of natural products and drugs contain this heterocyclic nucleus [1,2]. Due to their importance, many methods have already been developed for the synthesis of quinolines. Classical example include Skraup-Doebner-Van Miller [3], Combes [4] and Friedlander [5] synthesis. 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.

One such way is to use multicomponent domino reactions that can provide structurally complex molecules in a one-pot manner, ensuring high atom economy and good overall yields [6]. Isolation and purification of intermediates at individual steps can be eliminate, thereby minimizing less and waste generation.

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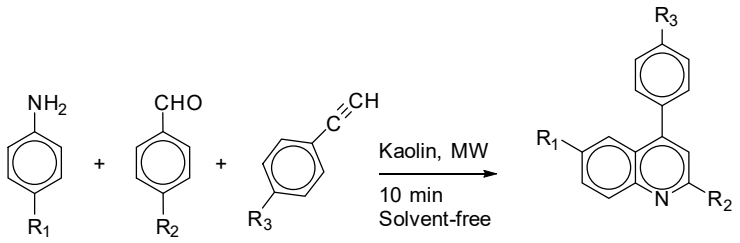
In this method multicomponent domino reactions were catalyzed by environmentally compatible catalyst can be considered a highly green synthesis design. Earlier investigations have provided evidence for the efficiency of solid acid catalysis in the synthesis and functionalization of several biologically active heterocycles [7,8]. Previous studies have also proved that the combination of solid acid catalysis with microwave assisted organic synthesis (MAOS) can lead to effective procedures for the synthesis of heterocyclic compounds and their derivatives in excellent yields and in short reaction times.

Many three-component reactions of aldehydes, anilines and terminal alkynes to give propargylamines have been widely explored [9-12].

In this study, we describe a rapid and efficient synthesis of substituted quinolines via a microwave-assisted, three-component domino reaction of aldehydes, anilines and terminal alkynes catalyzed by kaolin (Scheme 1).

Natural kaolin is a commercially available, environmentally benign solid acid [13]. It is a strong acid that is stable under high temperature and/ or microwave conditions.



R_1= H,Et

R_2= Ph, p-Me, p-OMe, p-Cl , p-NO_2 , p-OH , p-N,N-dimethyl

R_3= H

Scheme 1. The synthesis of quinolines via a microwave-assisted three component reaction.

The three-component, four-step domino sequence includes imine formation, nucleophilic attack by phenylacetylene on the imine, intramolecular cyclization and aromatization.

2. Experimental

2.1. Materials and methods

All starting chemicals were purchased from Merck and Fluka and used without further purification. Melting points were determined in an open capillary tube in an electrothermal IA9700 melting point apparatus. ^{1}HNMR spectra were recorded on a Bruker-400 MHz instrument using tetramethylsilane (TMS) as an internal standard. IR spectra were recorded on a Shimadzu-IR 470 spectrophotometer.

2.2. General experimental procedure

Aniline or its substituted derivatives (1.2 mmol), benzaldehyde or its substituted derivatives (1.2 mmol) and phenylacetylene (1 mmol=102.13 mg) were dissolved in 3 mL CH_2Cl_2 in a round bottomed flask. 500 mg of natural kaolin was mixed with the above reaction mixture. After 5 min stirring the solvent was evaporated under reduced pressure. The dry mixture was then transformed to a reaction vial and irradiated in the microwave reactor for the specified time.

After the reaction was completed (monitored by TLC), CH_2Cl_2 (10 mL) was added to the reaction mixture and filtered. The filtrate was concentrated, and the residue was subsequently purified by recrystallization from ethanol afford pure substituted quinolines in 48-98% yields.

Selected spectral data

*6-chloro 2-(4- N, N-dimethylamino phenyl)-4-phenyl quinoline (**Table 3, entry 8**)*

White solid. m.p.= 110°C. IR (KBr): $\bar{\nu}$ = 3224, 1629, 1620, 1519, 1076, 756, 663 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): δ= 8.32 (m, 3 H) , 7.80 (s, 1 H) , 7.20 (m, 5 H) 6.70 (dd, *J*= 2.4 Hz , 4H), 3.10 (s, 6H) ppm. Anal. Calcd. for $C_{23}H_{19}ClN_2$: C 76.97, H 5.35, N 7.81; Found: C 76.99, H 5.27, N 7.76.

3. Results and Discussion

In this work we selected aniline, benzaldehyde and phenylacetylenes as model substrates to optimize the condition for reaction. The reactions were carried out in a CEM Discover Benchmate microwave reactor using an open vessel technique. First, the effect of temperature, catalyst and reaction time was studied. The results are presented in Table 1.

Table 1. Synthesis of 2,4-diphenylquinoline under various experimental conditions[a].

Entry	Catalyst	Temp.(°C)	Time (min)	Conditions	Yield (%)
1	No catalyst	130	30	MW[b]	0
2	Natural kaolin	80	15	MW[b]	10
3	Natural kaolin	100	15	MW[b]	96
4	Natural kaolin	100	10	MW[b]	96
5	Natural kaolin	100	8	MW[b]	89
6	Natural kaolin	130	8	MW[b]	75
7	Nafion − H	100	10	MW[b]	72
8	$H_3[PW_{12}O_{40}]$	100	10	MW[b]	51
9	CF_3SO_3H	100	180	$ClCH_2CH_2Cl$	25
10	Natural kaolin	100	180	$ClCH_2CH_2Cl$	40

[a]1.2 mmol benzaldehyde, 1.2 mmol aniline and 1 mmol phenylacetylene.

[b]Microwave heating- solvent free.

Preliminary investigations indicated that a small excess of aniline and benzaldehyde (1.2 equivalents of both) with respect to phenylacetylene were required to obtain optimum yields of the product. The conversion was lower when equimolar amounts of all the reactants were used. A further increase in the molar amounts (1.5 equivalents) of aniline and benzaldehyde with respect to phenylacetylene did not improve the yields.

When the reaction was attempted without a catalyst, no product formation was observed (Table 1, entry 1). We tested several catalysts. In the presence of kaolin catalyst, the reaction could be completed under mild conditions in a matter of minutes. The best yield and selectivity was obtained at $100\,^{o}C$, after a 10 min reaction time (Table 1, entry 4). Longer irradiation did not increase the yield (Table 1, entry 3). Under the same conditions, other solid acids, such as Nafion-H or phosphotungestic acid ($H_3[PW_{12}O_{40}]$), resulted in lower yields (Table 1, entries 7, 8).

The trifilic acid-catalyzed reaction gave a much lower yield, which is agreement with the results of Xiao et al. (Table 1, entry 9) [12]. For comparison, reactions were also carried out with Natural kaolin and trifilic acid under conventional heating conditions in an open vessel. As expected, conventional heating required longer reaction times and resulted in a significantly lower yield (Table 1, entry 10).

A comparative Table was provided for making a comparison with the literature (Table 2). Based on these data, we concluded that the best catalyst for the reaction is Natural kaolin. Therefore, as shown in Table 3, these reactions gave the expected products in good yields. It is worth mentioning that when p-hydroxy benzaldehyde was used, the product was obtained in lower yield (Table 2, Entry 5) compared to other aldehydes. This phenomenon is probably attributed to the very strong adsorption of the hydroxyl group on the surface of kaolin. In general, methoxy-group containing substrates give moderate yields in other reactions [17].

Similarity to the studies, we chose the reaction with the simplest unsubstituted starting materials as a test reaction for our reusability studies, carrying out the reactions under identical conditions. Firstly, the catalyst-reactant mixture was prepared as mentioned in the experimental. After the reaction the product was removed from the catalyst, which was washed with hexane, dichloromethane, acetone and methanol to remove organic residues. A new catalyst-reactant mixture was then prepared using the recovered catalyst and the reaction performed under identical conditions. This cycle was repeated five times. The results of the catalyst recycling study are summarized in Table 4.

As the data show, the catalyst remained very stable during the five reactions, showing no sign of deactivation, and provided excellent yields (48-98%).

The proposed mechanism for the synthesis of 2,4-diarylquinolines from anilines, benzaldehydes and phenylacetylenes is illustrated in scheme 2 [17]. The overall mechanism involves the kaolin-catalyzed formation of an aldimine (A), which is attacked by phenylacetylene to give an aldimine (B), which undergoes cyclization followed by oxidative aromatization in presence of kaolin to give the 2,4-diarylquinoline. The authors proposed that the attack of acetylene on the in situ-generated imine A could be facilitated by a Lewis acid activation of the imine to give propargylamines B. when the imine is formed on

Table 2. The synthesis of substituted 2,4-diphenylquinoline under various experimental conditions based on literature.

Entry	Catalyst	Solvent	Temp. (°C)	Time (min)	Yield (%)[a]	Ref.
1	$Yb(Pfb)_3$	None	80	720	90	[14]
2	$Yb(OTf)_3$	None	80	720	60	[14]
3	$InCl_3$-SiO_2	None	80[b]	12	87	[15]
4	Ammonium acetate	None	80[c]	180	83	[16]
5	K-10	None	100	10	96	[17]
6	CuCl/AgOTf	$ClCH_2CH_2Cl$	100	120	95	[10]
7	$AuCl_3$/CuBr	CH_3OH	r.t.	10080	87	[11]
8	$Cu(OTf)_2$	CH_2Cl_2	r.t.	960	87	[12]
9	Natural kaolin	None	100	10	98	-[d]

[a]Isolated yields.

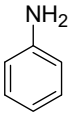
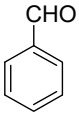
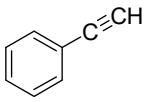
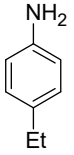
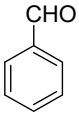
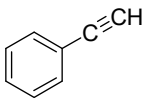
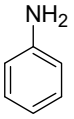
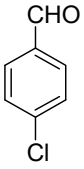
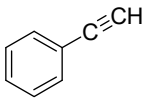
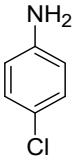
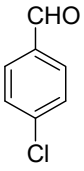
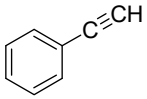
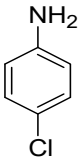
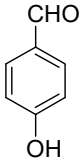
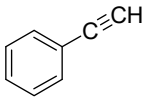
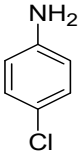
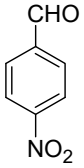
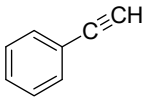
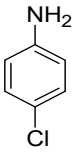
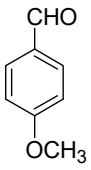
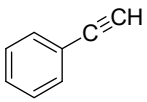
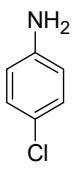
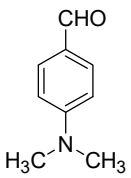
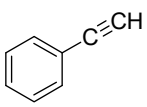
[b]MW assisted.

[c]Infrared irradiation.

[d]Our study.

the kaolin surface, it remains bound to the Lewis acid center to further exploit the reactivity of its δ+ carbonyl carbon. This is followed by the nucleophilic attack of the ortho-position of the aniline on the alkyne to close the ring, giving cyclic intermediate C. This spices undergoes rearrangement to give dihydro-quinoline intermediate D. The oxidizing ability of kaolin, mostly under microwave-assisted conditions was reported previously [7,17]. Newly formed intermediate D undergoes oxidative aromatization in presence of kaolin to give the final product (E).

Table 3. The synthesis of substituted 2, 4-arylquinolines using substituted Aniline, Aldehyde and Phenylacetylenes[a].

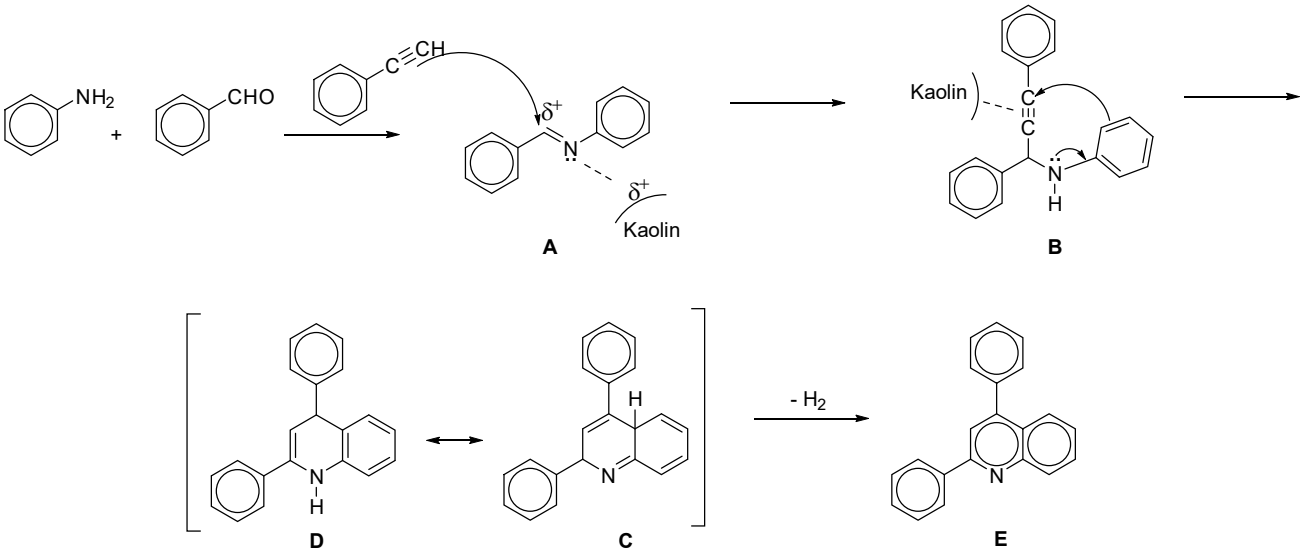
Entry	Aniline	Aldehyde	Phenylacetylene	Yield[b] (%)	m.p (°C)		Ref.
					Found	Reported	
1				90	oil		
2				94	61-62	88-89	[17]
3				92	87-88	162	[18]
4				71	92-93	132-134	[19]
5				48	111-112	114-116	[18]
6				76	131-132	218-220	[19]
7				94	68-69	117	[20]
8				98	110[c]	-	This work

[a]1.2 mmol benzaldehyde, 1.2 mmol aniline and 1mmol phenylacetylene.
[b]Isolated yields.
[c]New compound.

Table 4. The synthesis of 2, 4-diphenylquinoline using the recovered kaolin in five successive reaction cycles.

Reaction	Temp. (°C)	Time (min)	Yield (%)
1	100	10	96
2	100	10	92
3	100	10	94
4	100	10	93
5	100	10	94

[a]1.2 mmol benzaldehyde, 1.2 mmol aniline and 1mmol phenylacetylene.
[b]Isolated yields.



Scheme 2. The proposed mechanism for the kaolin-catalyzed synthesis of 2,4-diphenyl quinoline.

4. Conclusions

In summary, we have reported an ecofriendly solid recyclable catalyst for the facile one- pot synthesis of the substituted 2,4- diphenylquinolines from aldehydes, alkynes and amines under solvent- free and microwave irradiation conditions in high yields. This reaction features a short reaction time, broad scope of substrates, solvent- free conditions and easy procedure. Furthermore, a new derivative of quinoline is synthesized.

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