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Microwave-assisted multicomponent domino cyclization–aromatization: an efficient approach for the synthesis of substituted quinolines†

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A solid acid-catalyzed microwave-assisted synthesis of substituted quinolines is described. The 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 montmorillonite K-10, a strong, environmentally benign solid acid. The multicomponent approach yields the products with nearly 90% atom economy in excellent yields in a matter of minutes. The use of microwave activation reduces the reaction time significantly.

Introduction

The quinoline moiety is present in an extensive number of naturally occurring and biologically active compounds,[1] and also shows interesting photochemical properties.[2] Due to their widespread biological activity, the synthesis of quinolines has seen extensive research over the years. Classical examples include Skraup–Doebner–Von Miller,[3] Combes[4] and Friedländer[5] syntheses. While very effective, these syntheses involve the use of a variety of traditional Lewis and Brønsted acids, which are not environmentally compatible, produce a large amount of waste and require long reaction times. Therefore, the design of improved and environmentally benign approaches for their preparation is of prime importance.

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 eliminated, thereby minimizing losses and waste generation. Multicomponent domino reactions catalyzed by environmentally compatible catalysts (natural or modified clays, metal oxides, zeolites and acidic ion-exchange resins, *etc.*) can be considered a highly green synthesis design.[7,8]

Our earlier investigations have provided evidence for the efficiency of solid acid catalysis in the synthesis and functionalization of several biologically active heterocycles.[7,9] Our 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.

A three-component reaction of aldehydes, anilines and terminal alkynes to give propargylamines has been widely explored.[10] Furthermore, the synthesis of quinolines has been reported using propargylamines catalyzed by CuCl and AgOTf.[11] These two strategies were combined to synthesize quinolines by a three-component reaction of aldehydes, anilines and alkynes *via* a multicomponent, AuCl$_3$/CuBr-catalyzed approach.[12]

However, the products were obtained in 2–12 days. Similarly, the Cu(OTf)$_2$-catalyzed synthesis of quinoline-2-carboxylates were reported in good yields (52–92%) using extended reaction times (16 hours).[13]

Continuing our efforts in sustainable synthesis development, 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 a solid acid (Scheme 1). The catalyst of choice for this study is a commercially available, environmentally benign solid acid catalyst, montmorillonite K-10.[8,14] With a Hammett acidity constant (H_0) of about −8, K-10 is a strong solid acid that is stable under high temperature and/or microwave conditions.[15] The three-component, four-step domino sequence includes imine formation, nucleophilic attack by phenylacetylene on the imine, intramolecular cyclization and aromatization.
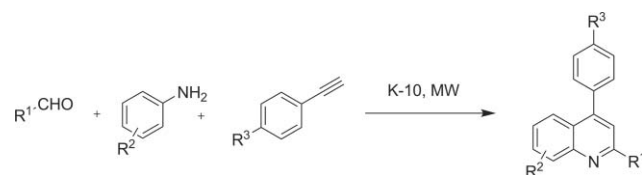
Scheme 1 The synthesis of quinolines *via* a microwave-assisted three-component reaction.

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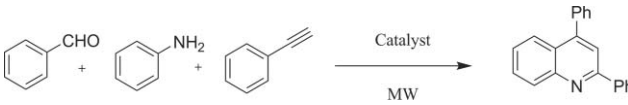
Results and discussion

Initially, we selected aniline, benzaldehyde and phenylacetylene as model substrates to optimize the conditions for our reaction. The reactions were carried out in a CEM Discover Benchmate

Table 1 The synthesis of 2,4-diphenylquinoline under various experimental conditions from aniline, benzaldehyde and phenylacetylene[a]

Entry	Catalyst	Temp./°C	Time/min	Conditions	Yield (%)[d]
1	—	130	30	MW[b]	0
2	K-10	80	15	MW[b]	10
3	K-10	90	15	MW[b]	87
4	K-10	100	15	MW[b]	96
5	K-10	100	10	MW[b]	96
6	K-10	100	8	MW[b]	89
7	K-10	130	8	MW[b]	78
8	Nafion-H	100	10	MW[b]	72
9	$H_3[PW_{12}O_{40}]$	100	10	MW[b]	54
10	CF_3SO_3H[e]	80	180	CH[c]	26
11	K-10	100	180	CH[c]	40

[a] 1.2 mmol benzaldehyde, 1.2 mmol aniline and 1 mmol phenylacetylene. [b] Microwave heating. [c] Conventional heating. [d] Determined by GC, based on phenylacetylene. [e] 1,2-Dichloroethane was used as a solvent.
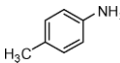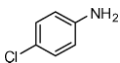
Table 2 The synthesis of substituted 2,4-diphenylquinolines using benzaldehyde, phenylacetylene and substituted anilines[a]

Entry	Aniline	Yield (%)[b]
1		96
2		92
3		81
4		83
5		92
6		76
7		72
8		88
9		74

[a] 1.2 mmol benzaldehyde, 1.2 mmol aniline and 1 mmol phenylacetylene. [b] Determined by GC, based on phenylacetylene.
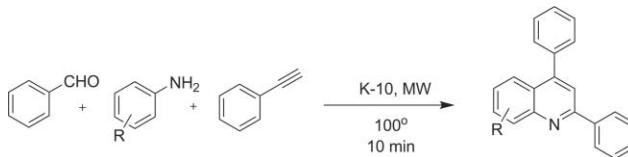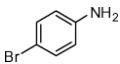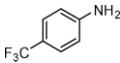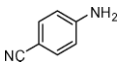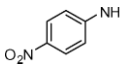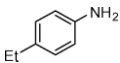
microwave reactor using an open vessel technique. First, the effect of temperature, catalyst and reaction time was studied. The results are presented in Table 1.

Our preliminary investigations indicated that a small excess of aniline and benzaldehyde (1.2 equivalent 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, but rather resulted in side reactions.

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 K-10 catalyst, the reaction could be completed under mild conditions in a matter of minutes. While the reaction occurred even at 80 °C, we obtained the best yield and selectivity at 100 °C after a 10 min reaction time (Table 1, entry 5). Longer irradiation did not increase the yield (Table 1, entry 4). Under the same conditions, other solid acids, such as Nafion-H or phosphotungstic acid ($H_3[PW_{12}O_{40}]$), resulted in lower yields (Table 1, entries 8 and 9). The triflic acid-catalyzed reaction gave a much lower yield, which is in agreement with the results of Xiao et al. (Table 1, entry 10).[12] Based on these data, we concluded that the best catalyst for the reaction is K-10. For comparison, reactions were also carried out with K-10 and triflic acid under conventional heating conditions in an open vessel. As expected, conventional heating required longer reaction times and resulted in a significantly lower yield and selectivity (Table 1, entry 11).

The selectivity decreased in certain cases mainly due to the formation of two by-products, though none were more significant than a few percent (~2–5%). These by-products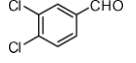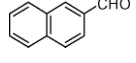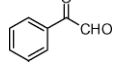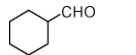 were identified by mass spectrometry as N-benzylaniline and N,N-dibenzylaniline. The formation of these by-products can be explained by ionic hydrogenation of the intermediate N-benzylideneaniline, and the further reaction and ionic hydrogenation of this product by benzaldehyde.
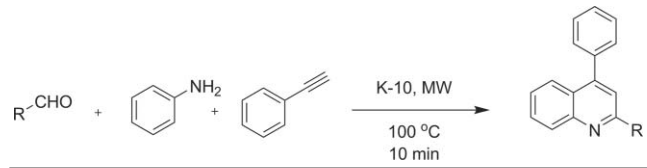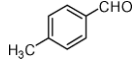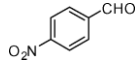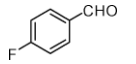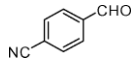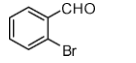
After determining the optimized conditions, we turned our attention toward studying the scope of the method. First, we used a broad variety of substituted anilines to synthesize quinolines. The results are summarized in Table 2. As the data indicate, almost all of the substituted anilines gave products in good-to-excellent yields. Both o- and p-substituted anilines readily underwent the reaction sequence, and only a moderate substitution effect was observed.

To further widen the applicability of the procedure, we also tested a variety of aldehydes. Table 3 summarizes the results for the synthesis of quinolines using aniline, phenylacetylene and different aldehydes. Most aldehydes gave products in good-to-excellent yields. Substituted benzaldehydes (Table 3, entries 1–6) reacted efficiently, again showing a moderate substitution effect. The procedure can be extended to aliphatic aldehydes, although the product was obtained in moderate yield (Table 3, entry 9) compared to aromatic aldehydes.

Encouraged by these results, we further extended the scope of our methodology with a variety of substituted anilines, benzaldehydes and terminal phenylacetylenes. The results are

Table 3 The synthesis of substituted 2,4-disubstituted quinolines using aniline, substituted aldehydes and phenylacetylene[a]
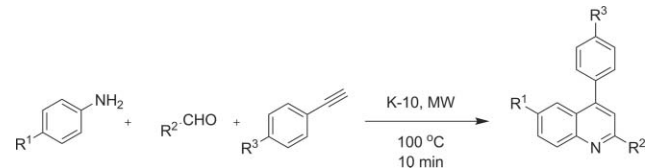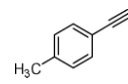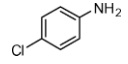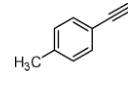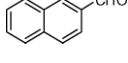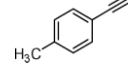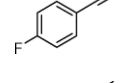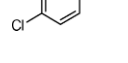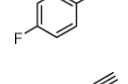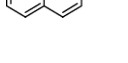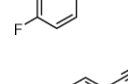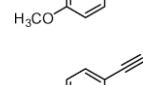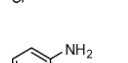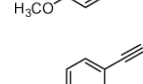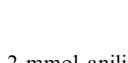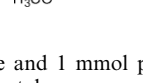

Entry	Aldehyde	Yield (%)[b]
1	(p-methyl benzaldehyde)	91
2	(p-nitro benzaldehyde)	81
3	(p-fluoro benzaldehyde)	90
4	(p-cyano benzaldehyde)	79
5	(o-bromo benzaldehyde)	83
6	(3,4-dichloro benzaldehyde)	89
7	(naphthalene-2-carbaldehyde)	85
8	(2-oxo-2-phenylacetaldehyde)	73
9	(cyclohexanecarbaldehyde)	56[c]

[a] 1.2 mmol aldehyde, 1.2 mmol aniline and 1 mmol phenylacetylene. [b] Determined by GC, based on phenylacetylene. [c] The reaction was carried out for 15 min at 80 °C.

Table 4 The synthesis of substituted 2,4-arylquinolines using substituted anilines, phenylacetylenes and aldehydes[a]

Entry	Aniline	Aldehyde	Phenylacetylene	Yield (%)[b]
1	(aniline)	(benzaldehyde)	(p-methyl phenylacetylene)	89
2	(p-chloro aniline)	(benzaldehyde)	(p-methyl phenylacetylene)	83
3	(aniline)	(naphthalene-2-carbaldehyde)	(p-methyl phenylacetylene)	78
4	(aniline)	(benzaldehyde)	(p-fluoro phenylacetylene)	79
5	(p-chloro aniline)	(benzaldehyde)	(p-fluoro phenylacetylene)	94
6	(aniline)	(naphthalene-2-carbaldehyde)	(p-fluoro phenylacetylene)	86
7	(aniline)	(benzaldehyde)	(p-methoxy phenylacetylene)	75
8	(p-chloro aniline)	(benzaldehyde)	(p-methoxy phenylacetylene)	72
9	(aniline)	(naphthalene-2-carbaldehyde)	(p-methoxy phenylacetylene)	70

[a] 1.2 mmol aldehyde, 1.2 mmol aniline and 1 mmol phenylacetylene. [b] Determined by GC, based on phenylacetylene.

presented in Table 4. As shown, these reactions also gave the expected products in good yields. It is worth mentioning that when *p*-methoxyphenylacetylene was used, the products were obtained in lower yields (Table 4, entries 7–9) compared to *p*-fluoro and *p*-methylphenylacetylenes (Table 4, entries 1–6). Based on our earlier studies, we attribute this phenomenon to the very strong adsorption of the methoxy group on the surface of K-10. In general, methoxy-group containing substrates give moderate yields in other reactions, as well when K-10 catalyst is used. Nevertheless, it appears that practically any combination of the three components can be used to synthesize the corresponding 2,4-diarylquinoline.

Finally, to verify the sustainable nature of our procedure, we carried out a series of experiments on the same catalysts. Similarly to the optimization 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 5.
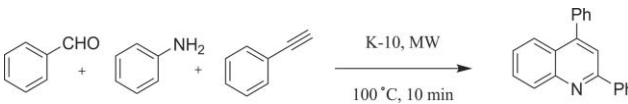
As the data show, the catalyst remained very stable during the five reactions, showing no sign of deactivation, and provided excellent yields (92–96%).

The proposed mechanism for the synthesis of 2,4-diarylquinolines from anilines, benzaldehydes and phenylacetylenes is illustrated in Scheme 2. The overall mechanism involves the K-10-catalyzed formation of an aldimine (**A**), which is attacked by phenylacetylene to give propargylamine (**B**), which undergoes cyclization followed by oxidative aromatization in presence of K-10 to give the 2,4-diarylquinoline. We propose that the attack of acetylene on the *in situ*-generated imine **A**

Table 5 The synthesis of 2,4-diphenylquinoline from aniline, benzaldehyde and phenylacetylene[a] by using the same recovered K-10 catalyst in five successive reaction cycles

Reaction	Temp./°C	Time/min	Yield (%)[b]
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 1 mmol phenylacetylene. The catalyst was filtered and washed with hexane, dichloromethane, acetone and methanol after each cycle. [b] Determined by GC, based on phenylacetylene.

could be facilitated by a Lewis acid activation of the imine to give propargylamine **B**. When the imine is formed on the K-10 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 species undergoes rearrangement to give dihydroquinoline intermediate **D**. In our earlier studies, we reported the oxidizing ability of K-10, mostly under microwave-assisted conditions.[7,16] Newly formed intermediate **D** undergoes oxidative aromatization in presence of K-10 to give the final product (**E**).
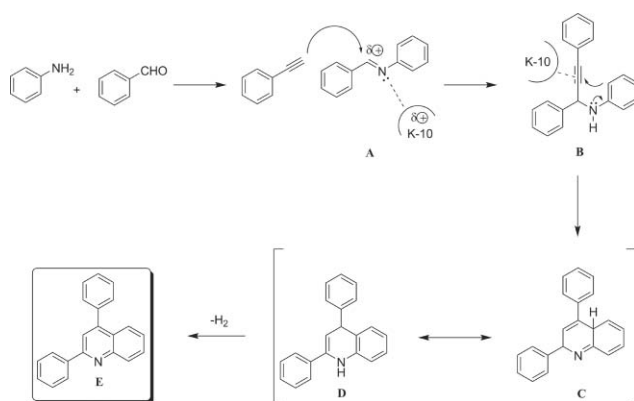
Scheme 2 The proposed mechanism for the K-10-catalyzed synthesis of 2,4-diphenylquinoline from aniline, benzaldehyde and phenylacetylene.

Conclusions

In summary, we have developed an effective and direct microwave-assisted, three-component, one-pot domino process for the synthesis of quinolines from anilines, aldehydes and terminal phenylacetylenes. The combination of solid acid catalysis, a multicomponent domino reaction approach and microwave irradiation provided the products in excellent selectivities and yields in short reaction times. In addition to efficiency and effective catalysis, the high atom economy, very limited energy consumption and its waste-free nature make the process very attractive for the environmentally benign synthesis of these important heterocycles. The application of this solid acid-catalyzed, microwave-assisted multicomponent approach could most likely be extended to the synthesis of other important medicinal scaffolds, such as pyrazoles, oxazolinones, benzodiazepines, quinoxalinones and possibly other heterocycles.

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