



Exploitation of the catalytic efficacy of Mg/Al hydrotalcite for the rapid synthesis of 2-aminochromene derivatives via a multicomponent strategy in the presence of microwaves

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ABSTRACT

Mg/Al hydrotalcite, a heterogeneous base catalyst, was found to be highly effective for the synthesis of 2-aminochromenes via a multicomponent reaction of aromatic aldehydes, malononitriles and 1-naphthol under microwaves. The reaction is rapid, clean and gives the products in high yields. The catalyst is reusable; however, there was reduction in the yield of the product.

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1. Introduction

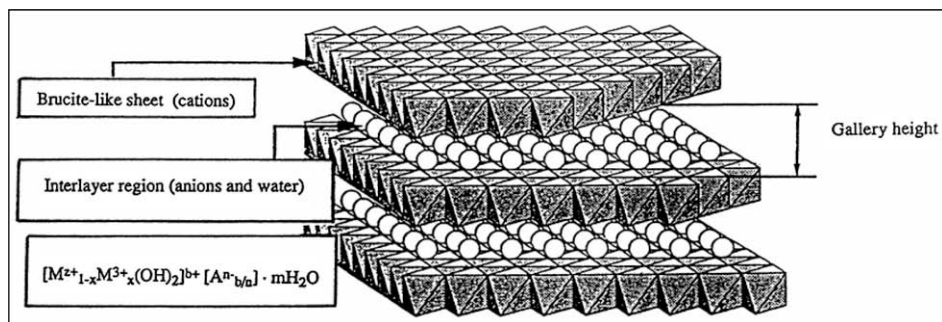
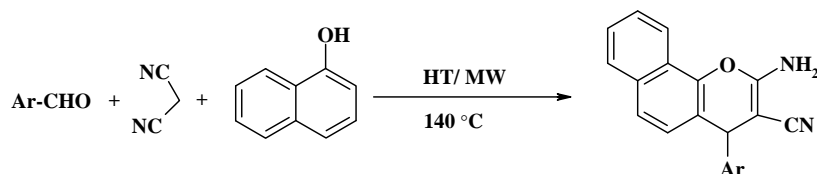
One-pot multicomponent reactions have emerged as an effective tool for atom economic and benign synthesis by virtue of their convergence, productivity, facile execution and generation of highly diverse and complex products from easily available starting materials in a single operation.¹ There has been a tremendous development in three- and four-component reactions, and efforts are still being made to find and develop new multicomponent reactions.² Multicomponent reactions are now being tailored and fine tuned for synthesizing various heterocyclic scaffolds for diverse applications. Heterogeneous catalysts are vital in green synthesis due to their easy recovery and subsequent reuse. Our research group has been developing efficient and environmentally benign protocols using various heterogeneous catalysts.^{3–6} Hydrotalcites (HTs) possess strong surface basicity and are useful catalysts for some selective oxidation reactions. HTs and modified HTs have been used for the epoxidation of olefins and α,β -unsaturated ketones using hydrogen peroxide,^{7,8} oxidation of alcohols⁹ and the Bayer–Villager reaction using peracids.¹⁰

Microwave heating has been known for long for acceleration of reactions. Cyclocondensation reactions in 'dry media' leading to heterocyclic systems have been performed under microwave irradiation. The reactions carried out in a neat or solvent-free state under microwave irradiation help to generate products not attainable through classical heating methods. A large number of heterocycles have been synthesized by this approach.¹¹ Our group recently pub-

lished the synthesis of dihydroquinazolinone derivatives using this one-pot multicomponent dry media reaction approach under microwaves.³ 2-Aminochromenes are widely employed as pigments, cosmetics, potential agrochemicals and also as components of many natural products.^{12–14} The development of an efficient methodology for the synthesis of 2-amino-chromenes is highly essential. The most straightforward synthesis of this heterocyclic system involves a three-component coupling of aromatic aldehyde, malononitrile and activated phenol. Traditionally, this condensation was catalyzed by a base such as piperidine.¹⁵ A few diverse catalysts have been employed for this multicomponent reaction. Recently, basic alumina,¹⁶ cetyl trimethyl ammonium chloride,¹⁷ NaOH,¹⁸ InCl₃,¹⁹ and I₂/K₂CO₃²⁰ have been used as catalysts for this multicomponent reaction. Very recently, nanosized magnesium oxide has also been shown as an effective catalyst for this reaction.²¹ However, all these methods include some or other drawbacks such as prolonged reaction time, tedious catalyst preparation and workup, and exhaustive usage of energy sources and solvents. The first sequential reaction in this multicomponent condensation is the Knoevenagel condensation of an aldehyde and malononitrile. Usually, this reaction is catalyzed by a mild base, and very recently it has also been shown that this reaction proceeds in water under thermal or microwave conditions.²² It appears that the catalyst does play a pivotal role in catalyzing the addition of the arylidene malononitrile intermediate to the ortho position of 1-naphthol, which is also the rate-determining step of the reaction.

In continuation of our efforts to develop efficient environmentally benign protocols for the synthesis of various heterocycles, we report herein our results with Mg/Al hydrotalcite that effi-

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ciently catalyzed the three-component condensation of aromatic aldehydes, malonitrile and 1-naphthol in a dry state under single-mode microwave irradiation (see Scheme 1).

Table 1

Effect of temperature on the synthesis of 2-aminochromene derivatives via a multicomponent condensation of benzaldehyde, malonitrile, and 1-naphthol in the presence of Mg/Al hydrotalcite under microwave irradiation

| S. no. | Temperature (°C) | Time (min) | Yield ^a (%) |
|--------|------------------|------------|------------------------|
| 1 | 90 | 14 | 34 |
| 2 | 120 | 9 | 62 |
| 3 | 140 | 7 | 84 |
| 4 | 150 | 5 | 52 |

Reaction condition: benzaldehyde (1 mmol), malonitrile (1 mmol), 1-naphthol (1 mmol), (Mg/Al = 3) HT (50% w/w of 1-naphthol), solvent-free.

Reaction attempted in a single-mode microwave reactor (Biotage).

^a Isolated yield.

Table 2

Mode in which the reaction is attempted

| Medium | Time (min) | Yield ^a (%) |
|----------------|------------|------------------------|
| Solvent-free | 7 | 84 |
| Solvated (DMF) | 21 | 60 |

Reaction condition: benzaldehyde (1 mmol), malonitrile (1 mmol), 1-naphthol (1 mmol), (Mg/Al = 3) HT (50% w/w of 1-naphthol), temp: 140 °C.

Reaction attempted in a single-mode microwave reactor (Biotage).

^a Isolated yield.

Table 3

Effect of different hydrotalcites on the three-component coupling of benzaldehyde, malonitrile, and 1-naphthol at 1400 °C under microwave irradiation

| HT | Time (min) | Yield ^b (%) |
|----------------------|------------|------------------------|
| Mg/Al: 3 | 7 | 84 |
| Mg/Al:2 ^a | 30 | 34 |
| Mg/Al: 5 | 19 | 42 |

Reaction condition: benzaldehyde (1 mmol), malonitrile (1 mmol), 1-naphthol (1 mmol), Mg/Al HT (50% w/w of 1-naphthol), temp: 140 °C.

Reaction attempted in a single-mode microwave reactor (Biotage).

^a Complete conversion of the reactants not seen on TLC.

^b Isolated yields.

2. Results and discussion

Mg/Al hydrotalcites of Mg/Al mole ratio 2, 3, and 5 were prepared by a procedure reported in the literature and were characterized by XRD and FT-IR.²³ The HTs are synthetic basic clays which contain brucite layer structure (Fig. 1).

Table 4

Reusability study

| Run | Time (min) | Yield ^a (%) |
|-----|------------|------------------------|
| 1 | 7 | 84 |
| 2 | 9 | 79 |
| 3 | 18 | 62 |

Reaction condition: benzaldehyde (1 mmol), malonitrile (1 mmol), 1-naphthol (1 mmol), (Mg/Al = 3) HT (50% w/w of 1-naphthol), temp: 140 °C.

Reaction attempted in a single-mode microwave reactor (Biotage).

^a Isolated yield.

Table 5

Synthesis of 2-aminochromenes via a multicomponent condensation of aromatic aldehydes, malonitrile, and 1-naphthol catalyzed by (Mg/Al = 3) hydrotalcite under single-mode microwave irradiation

| No. | R | Time (min) | Yield ^a (%) |
|-----|--|------------|------------------------|
| 1 | C ₆ H ₅ | 7 | 84 |
| 2 | 4-Cl C ₆ H ₄ | 6 | 88 |
| 3 | 4-F C ₆ H ₄ | 6 | 90 |
| 4 | 4-N(CH ₃) ₂ C ₆ H ₄ | 10 | 72 |
| 5 | 4-Br C ₆ H ₅ | 5 | 89 |
| 6 | 2-CH ₃ C ₆ H ₅ | 24 | 74 |
| 7 | 2-Cl C ₆ H ₅ | 8 | 76 |
| 8 | 4-OCH ₃ C ₆ H ₅ | 16 | 76 |
| 9 | 2-NO ₂ C ₆ H ₅ | 8 | 71 |
| 10 | 4-NO ₂ C ₆ H ₅ | 5 | 88 |
| 11 | 4-CH ₃ C ₆ H ₅ | 9 | 72 |
| 12 | Piperonal | 8 | 80 |

Reaction condition: aromatic aldehyde (1 mmol); malonitrile (1 mmol); activated phenol (1 mmol); (Mg/Al = 3) HT 50% w/w of 1-naphthol, temperature 140 °C, (Microwave, single mode, Biotage); solvent-free.

All products are known and are fully characterized by ¹H NMR and IR spectra.

^a Isolated yield.

Table 6

Effect on the use of different activated phenols in synthesis of 2-amino chromene derivatives via a multicomponent condensation of benzaldehyde, malononitrile an activated phenol in the presence of Mg/Al hydrotalcite under single-mode microwave irradiation

| Activated phenol | Time (min) | Yield ^b (%) |
|-------------------------|------------|------------------------|
| 1-Naphthol | 7 | 84 |
| 2-Naphthol ^a | 25 | 32 |
| Resorcinol | 9 | 61 |

Reaction condition: benzaldehyde (1 mmol), malononitrile (1 mmol), phenol (1 mmol), (Mg/Al = 3) HT (w.r.t activated phenol), temp: 140 °C.

Reaction attempted in a single-mode microwave reactor (Biotage).

^a Complete consumption of reactants not observed on TLC.

^b Isolated yields.

Table 7

Effect on the use of different active methylene compounds in synthesis of 2-amino chromene derivatives via a multicomponent condensation of benzaldehyde, malononitrile an activated phenol in the presence of Mg/Al hydrotalcite under single-mode microwave irradiation

| Active methylene compounds | Time (min) | Yield (%) ^b |
|---------------------------------|------------|------------------------|
| Malononitrile | 7 | 84 |
| Ethyl cyanoacetate ^a | – | – |
| Diethyl malonate ^a | – | – |

Reaction condition: benzaldehyde (1 mmol), malononitrile (1 mmol), 1-naphthol (1 mmol), (Mg/Al = 3) HT (50% w.r.t 1-naphthol), temp: 140 °C.

Reaction attempted in a single-mode microwave reactor (Biotage).

^a Complete consumption of reactants not observed on TLC.

^b Isolated yield.

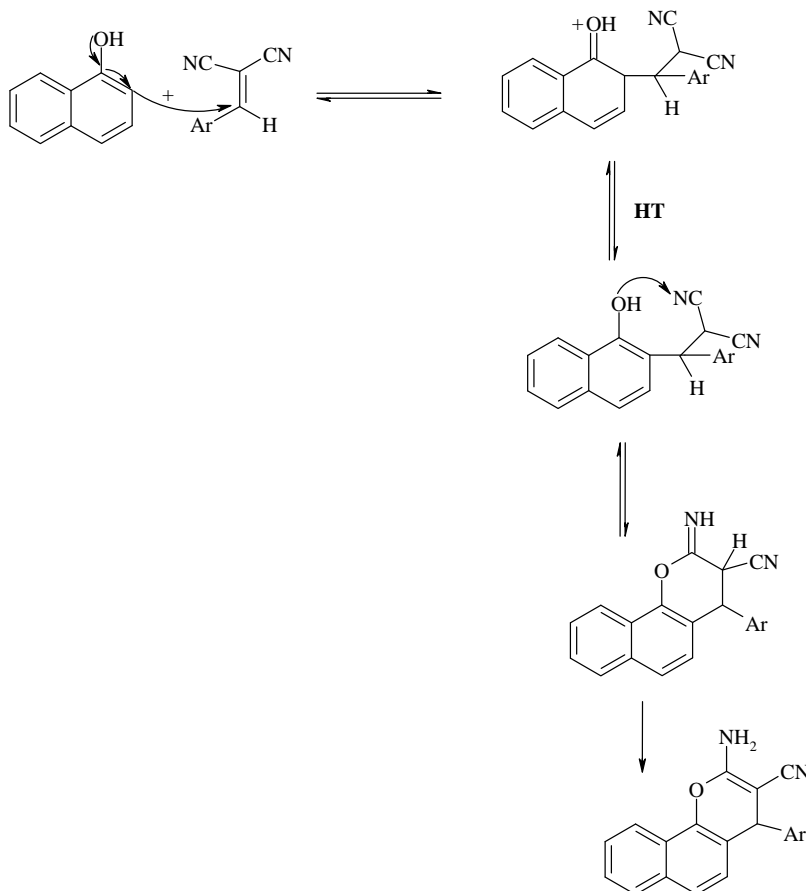
From the XRD spectrum, it was seen that the basal spacing at 7.87 Å corresponded to the HT phase. In the FT-IR of Mg/Al hydrotalcite, the absorption at 3581 cm⁻¹ corresponded to the H-bonding stretching vibration of the OH group in the brucite layer. A shoulder present at around 3000 cm⁻¹ was due to H-bonding between H₂O and the anions in the interlayer.

The reaction between benzaldehyde, malononitrile, and 1-naphthol was selected as the model reaction for optimization of various parameters. The reaction was attempted at different temperatures ranging from 90 to 150 °C (Table 1). It was found that above and below 140 °C, the yield of the product decreased. When the reaction was attempted without microwaves at 140 °C, 44% yield of the product was obtained in 4.5 h. The reaction worked best at 140 °C under microwave irradiation.

To make the reaction clean and green, the reaction was attempted under dry conditions (neat state) so that the maximum absorption of microwaves by the reactants occurs, and solvent usage is kept at a minimum. It was found that under these conditions, complete conversion occurred only in about 7 min as compared to when the reaction was attempted in the presence of a high boiling solvent like DMF (Table 2).

The reaction was carried out using different uncalcined HTs (Mg/Al = 2, 3, and 5) at 140 °C (Table 3). The uncalcined HTs (Mg/Al = 3) gave good yields of the product.

On calcination at a high temperature, the Lewis basicity of HT increases, while the Bronsted basicity decreases. The Bronsted basicity is required for the reaction. It is essentially due to hydroxyl groups in the brucite layer which are eliminated as water upon calcination. It is reported that calcined HTs contain surface basicity due to OH⁻ groups, (Mg–O) pairs, and (O²⁻) species.²⁴ The catalytic

**Scheme 2.**

activity of calcined HTs was lower than that of the corresponding uncalcined HTs. The basicity of HT is sensitive to the Mg/Al ratio. The total basicity of HT increases gradually with the Mg/Al molar ratio and comes to a maximum value at the Mg/Al ratio of 3.0. Further increase in the Mg/Al molar ratio decreases the basicity. The reaction did not take place in the absence of HT. It was found that 50% of (Mg/Al = 3) HT with respect to 1-naphthol (w/w) was required to affect the reaction.

The hydrotalcite is a heterogeneous basic catalyst and could easily be separated from the reaction mixture by simple filtration. The recovered catalyst was used for successive runs to investigate its reusability (Table 4). It was observed that there was a decrease in the yield of the product.

Under the optimized conditions, various substituted aromatic aldehydes were reacted to obtain the corresponding 2-aminochromenes in high yields (Table 5). It was observed that the aldehydes containing electron-withdrawing substituents in the para position reacted faster and gave a high yield of the product as compared to those containing electron-donating substituents.

To further extend the scope of the reaction, the reaction was attempted with various activated phenols (Table 6) as well as other active methylene compounds (Table 7). It was found that 1-naphthol and malononitrile were the best-suited reactants to bring about this condensation furnishing 2-aminochromene derivatives.

The reaction of benzaldehyde with malononitrile (Knoevenagel reaction) is reported to be catalyzed by HT.²⁵ The resulting intermediate has a highly polarized double bond which adds to 1-naphthol at the 2-position. This is followed by cyclization. The probable mechanism is given in Scheme 2.

3. Conclusion

In the present scheme, we project the importance and usefulness of cyclocondensation carried out in a 'dry state' under monomode microwave irradiation. The developed methodology is highly efficient and environmentally benign in terms of atom economy and solvent usage. In conclusion, HT and microwave is an effective combination for the synthesis of 2-aminochromene derivatives via the multicomponent condensation of aromatic aldehyde, malononitrile and 1-naphthol.

4. Experimental

4.1. Preparation of Mg/Al hydrotalcite

The Mg/Al hydrotalcites were prepared using a literature procedure.²⁴ Microwave irradiation was carried out in a microwave single-mode reactor (Biotage, Initiator). All products have been described previously and are fully characterized by IR and ¹H NMR spectra.

4.2. Typical reaction procedure

A 2–5 ml microwave reactor vial was charged with benzaldehyde (1 mmol), malononitrile (1 mmol), and 1-naphthol

(1 mmol), and Mg/Al HT (0.072 g, 50% w/w of 1-naphthol) was added. A magnetic stirrer was inserted to bring about stirring during the reaction. The vial was sealed with an aluminum cap fitted with a pressure- and temperature-calibrated Teflon seal. The vial was inserted into the cavity of the microwave reactor, and the reaction mixture was irradiated with monomode irradiation at 140 °C in a pulsed mode. The progress of the reaction mixture was monitored by TLC. After the complete consumption of the reactions, as seen on TLC, the reaction mixture was diluted with methanol (4 ml). The reaction mixture was filtered to separate the catalyst. The filtrate was concentrated under vacuum to get the solid product which was purified by recrystallizing from absolute ethanol.

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