Microwave-Promoted Efficient Synthesis of Benzo[*h*]quinolines by Solvent-Free Three-Component Imino-Diels–Alder Reaction under One-Pot Conditions

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Abstract: An one-pot, solvent-free imino Diels–Alder reaction has been developed under microwave conditions using 1-naphthylamine, aldehydes, and electron-deficient terminal alkynes in the presence of a catalytic amount of $In(OTf)_3$ for construction of benzo[*h*]quinoline derivatives in short reaction times. The method is clean and operationally simple.

Key words: imino-Diels–Alder reaction, metal-catalyzed multicomponent reaction, microwave-assisted organic synthesis, benzo[*h*]quinolines

The imino-Diels–Alder (IDA) reaction is recognized as a useful approach for the construction of highly functionalized heterocycles of biological and synthetic interest and structurally diverse molecules.[1,2] During recent years, modifications of the IDA reaction have been reported.[3]

Quinolines or 1-azanaphthalenes[4] are found as building blocks in a wide variety of natural products that show activities as antimalarial,[5a] antirheumatic,[5b] antiviral,[5c] antiprotozoal,[5d] antineoplastic,[5e] antipsychotic,[5f] and antischizophrenic[5g] agents. Development of quinoline-based drugs such as haplamine,[6a] topotecan,[6b] and irinotecan[6c] has renewed interest in developing novel synthetic strategies for the synthesis of quinoline derivatives. A large number of methods for the synthesis of quinoline compounds have been reported but most of them suffer from the need for forcing reaction conditions.[7]

Metal-catalyzed multicomponent reactions (MCR)[8,9] reduce the number of operational steps.[10] Indium triflate, $In(OTf)_3$ is a Lewis acid catalyst that has become the focus of attention in several synthetic studies.[11] Previously, our group has established the catalytic activity of indium(III) salts in a range of transformations.[12]

The growing emphasis on minimizing energy consumption and elimination of harmful solvents has contributed to the extension of the range of microwave-assisted organic synthesis (MAOS).[13] Reaction under neat conditions can result in rate enhancements along with different selectivity[14] compared to conventional methodologies. Therefore, MAOS technology in dry reaction medium presents a novel protocol to carry out organic reactions which is also proved by theoretical calculations.[15]

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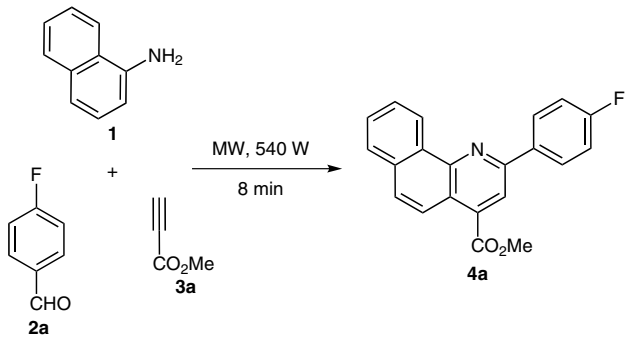
In continuation to our studies to develop microwave-assisted methodologies for the generation of nitrogen heterocycles,[16] we report herein an efficient solvent-free, one-pot IDA reaction for the synthesis of benzo[*h*]quinoline derivatives promoted by 10 mol% $In(OTf)_3$ under microwave irradiation.

Our preliminary studies were directed to investigate the reaction between 1-naphthylamine (**1**) with 1.0 equivalent of 4-fluorobenzaldehyde (**2a**) and 1.2 equivalents of methyl propiolate (**3a**) at 540 W in a microwave reactor in various solvent systems. It was observed that the reaction did not proceed in most solvents (e.g., methanol, ethanol, acetic acid, chloroform, dichloromethane, dimethylformamide, dimethyl sulfoxide, nitrobenzene, toluene, and water). However, we noticed that when the reaction was performed in toluene in the presence of 5 mol% $In(OTf)_3$ the product methyl-2-(4-fluorophenyl)benzo[*h*]quinoline-4-carboxylate (**4a**) was obtained in 50% yield (Table 1, entry 1). As we are interested in utilization of solid-state metal-catalyzed MAOS for the production of probable heterocyclic compounds we performed the reaction without any solvent and found that the product was formed in 80% yield under microwave irradiation at 540 W and 120 °C for eight minutes (Scheme 1).



Scheme 1

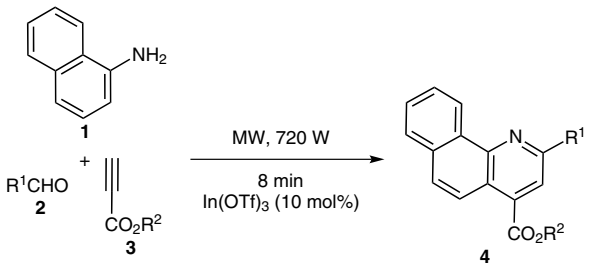
Optimization studies under various conditions revealed that $In(OTf)_3$ (10 mol%) is the best catalyst with irradiation at 720 W and 120 °C for eight minutes (Table 1, entries 2–6) Using these optimized conditions, the feasibility of the reaction scheme was then tested with the variation of different aldehydes **2** and electron-deficient terminal alkynes **3**, and the results obtained are shown in Figure 1 and Scheme 2.[17]

Table 1 Optimization for the Synthesis of **4a** under Micorwave Irradiation[a]

Entry	Solvent	Catalyst (mol%)	Yield (%)[b]
1	toluene	$In(OTf)_3$ (5)	50
2	neat	$In(OTf)_3$ (10)	90
3	neat	AgOTf (10)	82
4	neat	$Cu(OTf)_2$ (10)	84
5	neat	$Sc(OTf)_3$ (10)	78
6	neat	$Yb(OTf)_3$ (10)	79

[a] Reaction conditions: 1-naphthylamine (**1**, 1.0 mmol), 4-fluorobenzaldehyde (**2a**, 1.0 mmol), and methyl propiolate (**3a**, 1.2 mmol). Irradiation at 540 W at 120 °C for 8 min.
[b] Isolated yield.

The reaction conditions are tolerated by a range of different aromatic aldehydes and electron-deficient terminal alkynes resulting in good to excellent yields of the desired benzo[*h*]quinoline templates. It is noteworthy that aldehydes containing either electron-donating or electron-withdrawing substituents on the aromatic ring underwent the cycloaddition reaction smoothly. We also studied the effect of the positions of substituents in the aromatic ring, and we were gratified to find that the reaction was successful with aromatic aldehydes having substitutions at



Scheme 2

ortho, *meta*, and *para* positions. The reaction also proceeds with benzaldehyde, cinnamaldehyde, and heteroaromatic aldehydes such as furfuraldehyde and thiophene-2-carbaldehyde. There were no undesired side reactions, and the benzo[*h*]quinoline derivative was obtained as the only product in each instance in high yield. However, the reaction failed when aliphatic aldehydes were employed and only the naphthylimines were obtained. Increasing the reaction time or the microwave power resulted in decomposition. All of the products obtained were characterized by IR and NMR spectroscopy and mass spectrometry.

A reasonable mechanism for the formation of benzo[*h*]quinolines from the three-component reaction is outlined in Scheme 3. The sequence starts with the formation of an imine **A** from 1-naphthylamine **1** and aldehyde **2**, which then undergoes [4+2] cycloaddition with the termi-

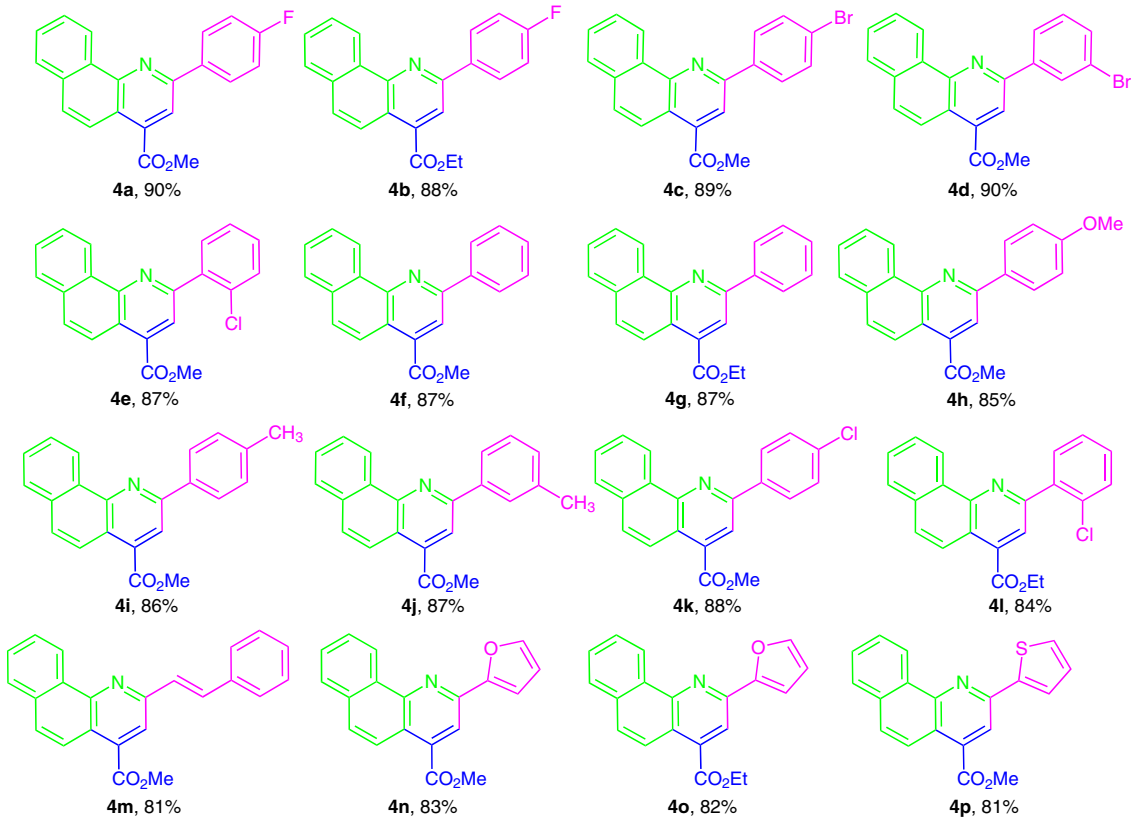
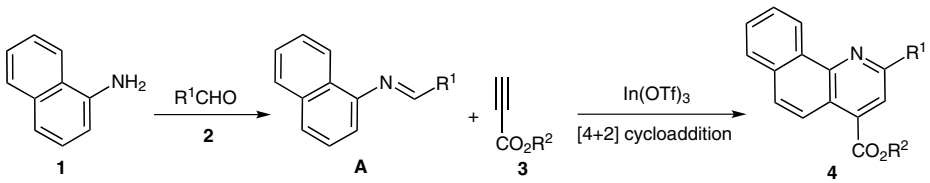


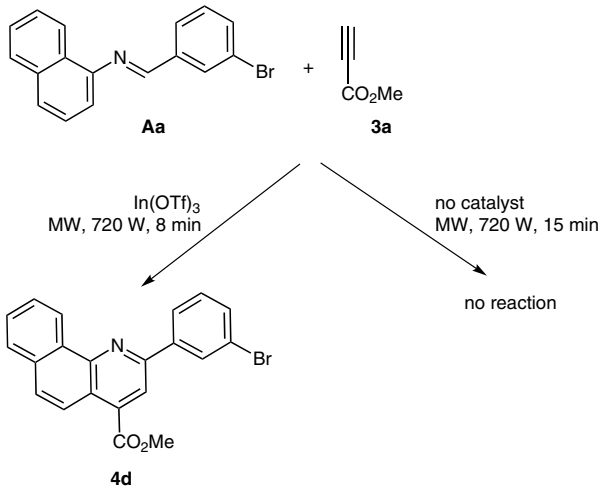
Figure 1 Direct synthesis of a library of benzo[*h*]quinoline derivatives **4a**–**p**. *Reagents and conditions*: 1-naphthylamine (**1**, 1.0 mmol), aldehydes **2** (1.0 mmol), and methyl propiolate/ethyl propiolate **3** (1.2 mmol), $In(OTf)_3$ (10 mol%), irradiation in the absence of solvent at 720 W for 8 min.



Scheme 3

nal alkyne **3** in the presence of a catalytic amount of $In(OTf)_3$ to furnish **4**.

To support our mechanistic postulate we performed a two-step reaction. First we synthesized *N*-(3-bromobenzylidene)naphthalen-1-imine (**Aa**) from 1-naphthylamine and 3-bromobenzaldehyde and this was then reacted with methyl propiolate (**3a**) under microwave irradiation in the presence of 10 mol% $In(OTf)_3$ whereby product **4d** was isolated in good yield. To confirm the role of $In(OTf)_3$ in the cycloaddition we carried out the reaction between **Aa** and **3a** without catalyst and found that there was no formation of the desired product even after prolonged irradiation (Scheme 4). This demonstrates that the formation of an indium alkynylide from In(III) catalyst and terminal alkyne[18] is essential for assembling benzo[*h*]quinoline compounds.



Scheme 4

We also set out to examine and compare the effect of the nonclassical heating procedure on the outcome of this In(III)-mediated three-component reaction. Accordingly, a mixture of 1-naphthylamine, 4-fluorobenzaldehyde, and methyl propiolate was refluxed in toluene in the presence of a catalytic amount of $In(OTf)_3$ for 10 hours to yield methyl-2-(4-fluorophenyl)benzo[*h*]quinoline-4-carboxylate in 65% yield.[19] Longer reaction times resulted in decomposition. We also carried out the reaction under neat conditions at 110 °C for 10 hours and observed that only 12% of the cyclized product was obtained.

In summary, we have demonstrated an indium triflate catalyzed imino Diels–Alder reaction which efficiently leads to the synthesis of a diverse range of benzo[*h*]quinoline derivatives. A wide variety of substituted aromatic aldehydes, cinnamaldehyde, heteroaromatic aldehydes, and electron-deficient terminal alkynes were shown to undergo the reaction with 1-naphthylamine to give the desired products exclusively. This methodology offers a new route for the synthesis of benzo[*h*]quinolines from simple starting materials with excellent atom-economy. This one-pot, three-component technique is operationally simple and provides the opportunity to remove solvent from the synthetic procedure.

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(17) **General Procedure**
1-Naphthylamine (**1**, 1.0 mmol), 4-fluorobenzaldehyde (**2a**, 1.0 mmol), and methyl propiolate (**3a**, 1.2 mmol) were irradiated in a closed vessel with $In(OTf)_3$ (10 mol%) without solvent in a Synthos 3000 microwave reactor at 720 W, 120 °C, and 10 bar for 8 min. The crude product mixture was dissolved in $CHCl_3$ and directly purified by column chromatography eluting with EtOAc–hexane (1:9) to obtain pure methyl-2-(4-fluorophenyl)benzo[*h*]quinoline-4-carboxylate (**4a**).
Compound **4a**: off-white solid; mp 116–117 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.32–9.37 (m, 1 H, arom), 8.64 (s, 1 H, $COOCH_3C$=C*H*), 7.05–7.95 (m, 9 H, arom), 3.81 (s, 3 H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.6, 155.5, 147.1, 138.6, 136.8, 136.7, 134.5, 131.07, 131.0, 130.9, 129.1, 128.6, 127.9, 127.3, 125.2, 124.8, 124.7, 123.9, 115.3, 115.0, 52.5. IR ($CHCl_3$): 1726.7, 1603.3, 1589.0, 1561.0, 1512.7 cm^{-1}. GC–MS: *m/z* = 331 $[M]^+$. Anal. Calcd for $C_{21}H_{14}FNO_2$: C, 76.12; H, 4.26; F, 5.73; N, 4.23; O, 9.66. Found: C, 76.10; H, 4.20; F, 5.69; N, 4.21; O, 9.61.

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(19) 1-Naphthylamine (**1**, 1.0 mmol), 4-fluorobenzaldehyde (**2a**, 1.0 mmol), and methyl propiolate (**3a**, 1.2 mmol) were refluxed with $In(OTf)_3$ (10 mol%) in toluene (10 mL) under air until completion (TLC), the solvent was distilled off under reduced pressure, and the product was purified by column chromatography eluting with EtOAc–hexane (1:9) to obtain pure methyl-2-(4-fluorophenyl)benzo[*h*]quinoline-4-carboxylate (**4a**).

