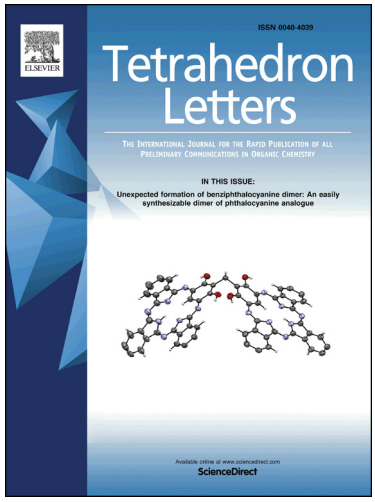

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Microwave-induced Bismuth(III)-catalyzed Synthesis of Linear Indoloquinolines

Prakash T. Parvatkar[a,b], P. S. Parameswaran[c], Debasish Bandyopadhyay[d], Sanghamitra Mukherjee[d], Bimal K. Banik[d,e]*

[a]Department of Chemistry, Goa University, Taleigao Plateau, Goa 403 206, India;
[b]Current Address: Department of Chemistry and Chemical Biology, Northeastern University, Boston, MA 02115, United States
[c]CSIR-National Institute of Oceanography, Regional Centre, Kochi 682 018, India
[d]Department of Chemistry, The University of Texas-Pan American, Edinburg, TX 78539, United States; [e]Current Address: Community Health System of South Texas, 3135 South Sugar Road, Edinburg, TX 78539, United States

Phone: +1-281-813-2104
Fax: +1-956-259-8085
Email: bimalbanik10@gmail.com

Abstract: Microwave-induced $Bi(NO_3)_3$-catalyzed one-pot synthesis of a series of linear indoloquinolines is accomplished under mild reaction conditions. While majority of these examples were carried out under solvent-free conditions, in a few cases, minimal quantity of THF is used as solvent. The methodology involves several unique reaction pathways, providing different linear indolo[2,3-*b*]quinolines in good yields from readily available starting materials and using environmentally benign $Bi(NO_3)_3.5H_2O$ as catalyst.

Keywords: Bismuth nitrate; Domino; Indoloquinoline; Microwave; Neocryptolepine

Linear indoloquinoline alkaloids have received considerable attention in recent years due to their wide range of biological activities such as antimalarial, cytotoxicity, antimuscarinic, antibacterial, antiviral, antimicotic, antihyperglycemic, antitumor and DNA interacalating properties.[1] Several linear indoloquinoline alkaloids have been isolated from the roots of *Cryptolepis sanguinolenta*,[2] a shrub indigenous to West Africa, which are being used in folk medicine in Central and West Africa for the treatment of infectious diseases, amoebiasis, fever and malaria.[1e,3] Major alkaloids reported from *C. sanguinolenta* are cryptolepine **1**[4] and neocryptolepine **2**[5a] (also known as cryptotackiene[5b]) (Fig. 1) containing linear indolo[3,2-*b*]quinoline and indolo[2,3-*b*]quinoline ring systems respectively and are being widely studied because of its biological importance. 6*H*-Indolo[2,3-*b*]quinoline **3**, an immediate chemical precursor of **2** is also been studied extensively in recent years as it shares many biological activities with cryptotackieine.[2] Compound **3**, named norcryptotackieine is also a natural product, being isolated recently from the leaves of *Justicia betonica*.[6]

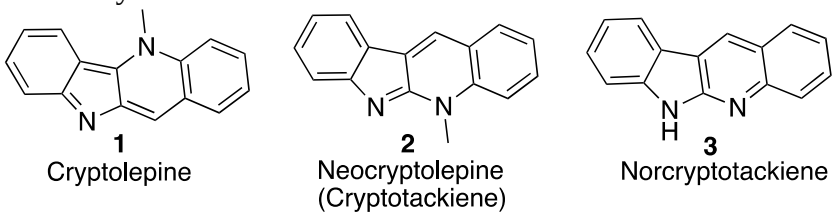
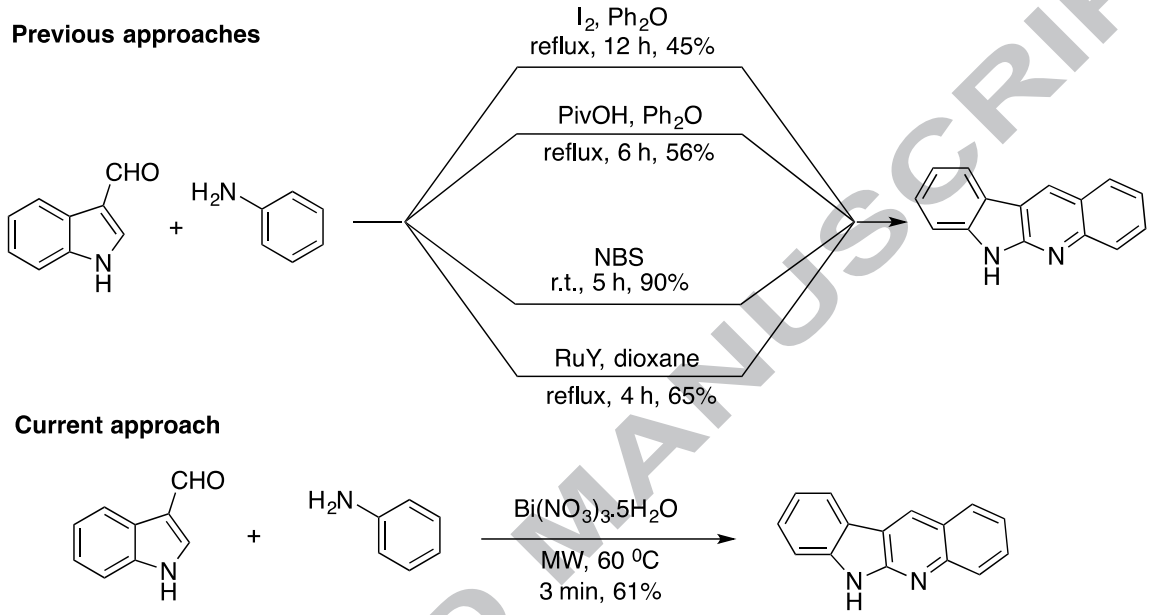


Figure 1: Naturally occurring linear indoloquinoline alkaloids

Several methods for the synthesis of **3** and its derivatives have been reported in the literature.[2] Most important among those are one-pot domino approaches (Scheme 1 - I_2 in refluxing Ph_2O,[7] RuY (Ru^{+3} ion-exchanged zeolite) in refluxing 1,4-dioxane,[8] NBS under solvent-free condition at room temperature,[9] and PivOH in refluxing Ph_2O[10]). However, most of these methodologies require higher temperature or much longer reaction times, with tedious product isolation procedures, toxicity of the catalyst or low product yields being additional impediments.

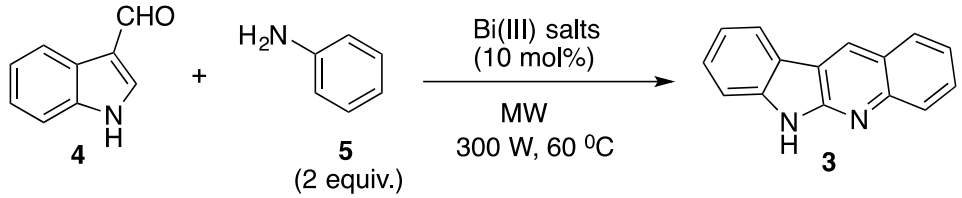


Scheme1: One-pot approaches for the synthesis of 6*H*-indolo[2,3-*b*]quinoline

Herein, we report a fast, efficient, clean and mechanistically unique microwave-mediated one-pot method for the synthesis of 6*H*-indolo[2,3-*b*]quinolines using eco-friendly bismuth-nitrate as a catalyst. In the recent years, bismuth(III) salts have attracted much attention in various organic transformations due to their low toxicity, low cost, high catalytic activity, good stability and ease of handling.[11] Furthermore, in recent years, Bi(III) compounds have been applied for efficient and atom-economic synthesis of various heterocyclic compounds in high yields and under mild reaction conditions.[12]

The mixture of indole-3-carboxyaldehyde **4** and two equivalents of aniline **5** in presence of 10 mol% of Bi(III) salt as a catalyst in tightly sealed vessel (manufactured by CEM microwave company) under solvent-free condition were irradiated in microwave at 60°C (Table 1).

Table 1: Optimization of reaction conditions[a]

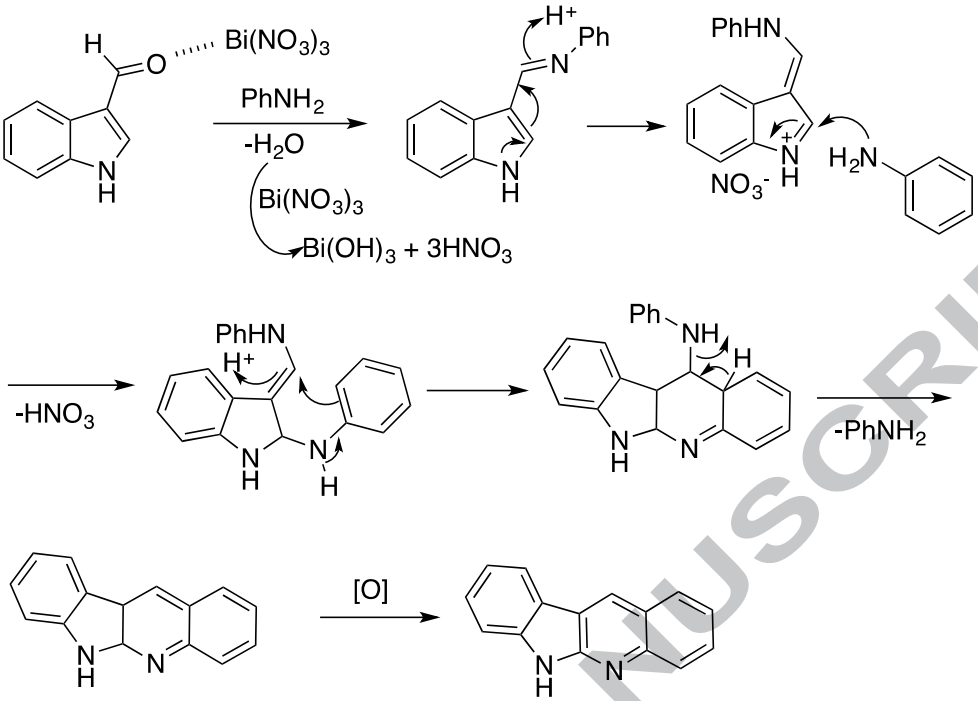


Entry	Bi(III) salt	Time (min)	Yield of 3[b] (%)
1	None	30	0
2	$Bi(NO_3)_3.5H_2O$	3	61
3	$BiCl_3$	15	10
4	BiI_3	15	10
5	Bi_2O_3	30	0

[a]Reaction conditions: **4** (1 mmol), **5** (2 mmol, 2 equiv.), catalyst (10 mol%, 0.1 equiv.). [b]Yield of the isolated product.

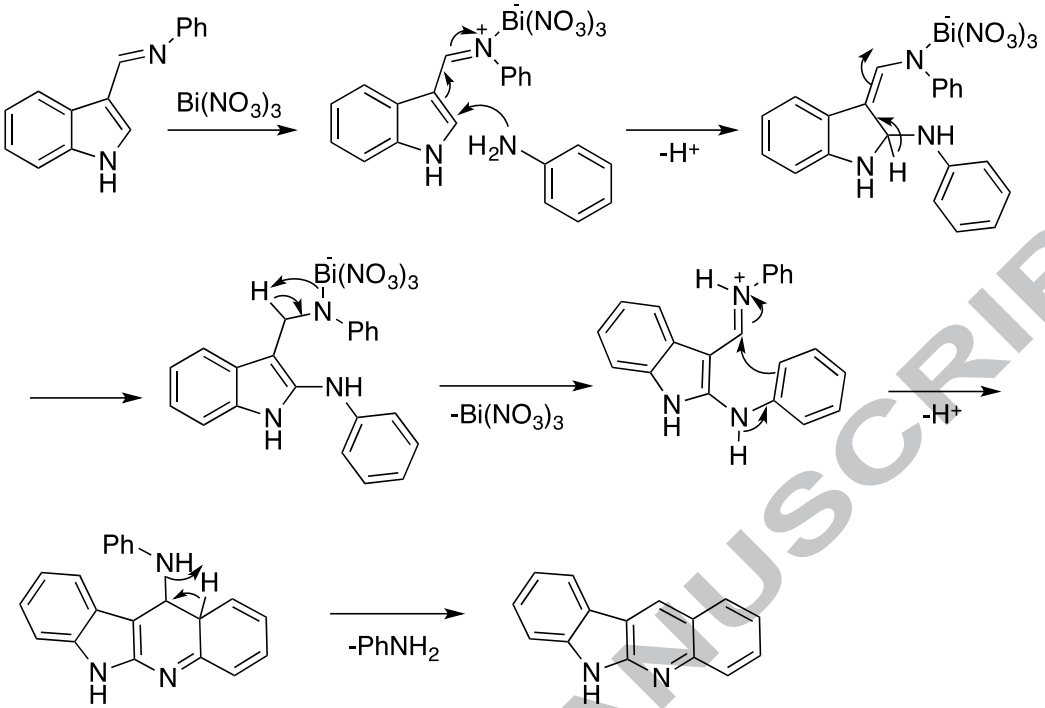
Results revealed that, in absence of catalyst (entry 1) and with Bi_2O_3 (entry 5), no product formation is observed whereas in presence of other Bi(III) salts (entry 2-4), desired product is obtained within short period of time. However, the reason for the failure of reaction with Bi_2O_3 is not known. $Bi(NO_3)_3.5H_2O$ gave the best results in terms of both yield and time. Addition of different amounts of water to the reaction mixtures of inactive bismuth salts ($BiCl_3$, BiI_3 and Bi_2O_3) did not yield the products. We have attempted to prepare anhydrous bismuth nitrate, but failed as it decomposes at high temperature and produces bismuth oxide. In order to optimize the product yield, varying percentages of $Bi(NO_3)_3.5H_2O$ (5 to 20 mol%) were studied (not shown in the table). These experiments revealed that 10 mol% loading of the catalyst furnished the highest yield of desired products in just 3 min.

We first proposed the mechanism (Scheme 2) wherein the $Bi(NO_3)_3$ acts as a Lewis acid to activate carbonyl to facilitate the imine formation through the condensation of **4** and **5**. Next step is different from the previously reported[7-9] mechanisms, wherein indole attacks the catalyst (I_2, NBS, Ru-Y) due to its electrophilic nature to form indolinium cation. However, attack of indole on the bulky $Bi(NO_3)_3$ to form indolinium cation is highly unlikely. So, we thought, water generated during the imine formation and water of crystallization present in the salt itself could have decomposed the $Bi(NO_3)_3$ under the reaction condition to form $Bi(OH)_3$ and HNO_3. In-situ generated HNO_3 then may have catalyzed the reaction further to form indolonium cation. Nucleophilic attack by another mole of aniline on indolonium cation followed by annulation and subsequent loss of aniline may have given dihydro-indoloquinoline, which may rapidly undergo oxidation to give fully aromatized indoloquinoline **3**.[7-9]



Scheme 2: Preliminary proposed mechanism catalyzed by in-situ generated HNO_3.

To test this above mechanism, we performed the reaction with catalytic amount of HNO_3. However, the reaction was very sluggish and undesired products or no products were formed. The failure of the reaction with HNO_3 indicates this transformation follows an entirely different pathway from that shown in scheme 1. This leads us to propose a new mechanism (Scheme 3), which significantly differs from the previously reported[6-8] mechanisms for this one-pot transformation. As per this postulated mechanism, $Bi(NO_3)_3$ activates the in-situ formed imine to form iminium cation.[13] 1,4-Addition of another mole of aniline **4** followed by [1,3]-hydride shift will result in 2,3-disubstituted indole derivative. Regeneration of $Bi(NO_3)_3$, subsequent ring closure and finally expulsion of aniline will lead to 6*H*-indolo[2,3-*b*]quinoline **3**.

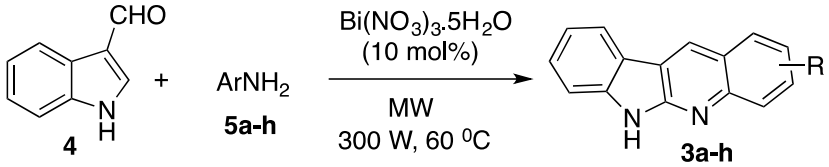


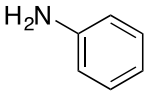
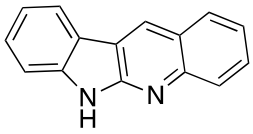
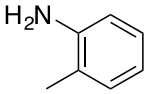
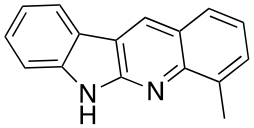
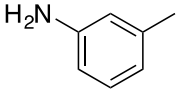
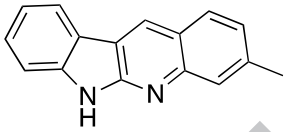
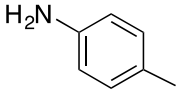
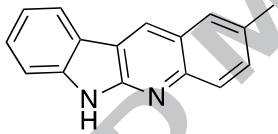
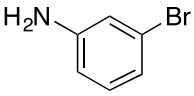
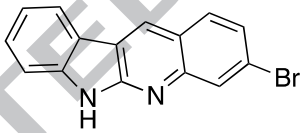
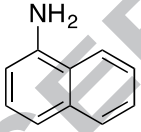
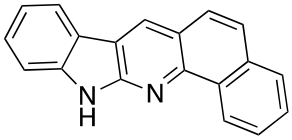
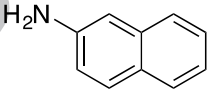
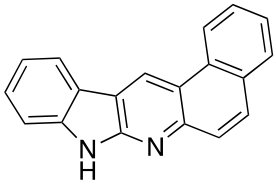
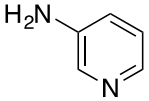
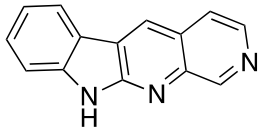
Scheme 3: Plausible mechanism catalyzed by $Bi(NO_3)_3$ through activation of imine.

After optimising the reaction conditions, we next investigated the substrate scope of this reaction with various aromatic/hetero-aromatic amines **5a-h** and indole-3-carboxyaldehyde **4** (Table 2).

In case of liquid aryl amines (entry a – e), the reaction is performed under solvent free condition while for solid aryl amines (entry f – h), THF is used as a solvent. Aryl amines containing electron-donating or electron-withdrawing groups and heteroaryl moiety are compatible with the reaction condition yielding desired products in good yields within short period of time (3-5 min). In contrast to all available methods, this is the fastest method reported so far for the synthesis of linear indoloquinolines. Mild reaction conditions, simplified reaction work-up and purification procedure, good yields and use of environmental-friendly catalyst besides interesting mechanism (different from other reported Lewis acid catalyst for this transformation) makes this methodology very attractive. While iodine can react with the aromatic amine and imine (two substrates involved in this reaction) readily, however, a similar reaction with bismuth nitrate is not possible.[7] *p*-Nitroaniline and *p*-hydroxyaniline (not shown in Table 2) did not form the product, probably due to the reduced nucleophilicity of the NH_2-group. For *p*-nitroaniline, reduced nucleophilicity is due to the presence of NO_2-substituent at 4-position whereas in case of *p*-hydroxyaniline, nucleophilicity could have reduced due to the formation of polymer hydrogen bonds between –OH and $–NH_2$ groups.

Table 2: Microwave-mediated $Bi(NO_3)_3$-catalyzed synthesis of indoloquinolines[a]



Entry	$ArNH_2$ **5**	Indoloquinolines **3**	Time (min)	Yield[b] (%)
a			3	61
b			4	56
c			4	54
d			4	55
e			4	58
f[c]			5	53
g[c]			5	55
h[c]			5	52

[a]Reaction conditions: **4** (1 mmol), **5a-h** (2 mmol), $Bi(NO_3)_3.5H_2O$ (10 mol%, 0.1 equiv.).[14] [b]Yield of the isolated product.[c]0.5 mL THF is used.

In summery, we have developed an expeditious microwave-mediated one-pot methodology for the synthesis of linear indolo[2,3-*b*]quinolines using eco- and user-friendly $Bi(NO_3)_3.5H_2O$ as catalyst. Short reaction time; use of inexpensive, non-toxic & commercial availability of catalyst; ease of product isolation; good yields and mild reaction conditions are vital advantages of this methodology. Detailed mechanistic studies of this reaction and more transformations using different substituted indole-3-carboxyaldehydes are currently underway in our laboratory. We anticipate that this methodology will find more synthetic utility in other biologically important related indoloquinolines like indolo[3,2-*b*]quinolines.

Acknowledgements:
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14. **General procedure for the synthesis of linear indoloquinolines 3a-h:** Indole-3-carboxyaldehyde **4** (1 mmol), aryl amines **5a-h** (2 mmol, 2 equiv.) and $Bi(NO_3)_3$ (10 mol%, 0.1. equiv.) were taken in a vessel, sealed tightly and irradiated at 60 ^{0}C and 300 watt power in microwave reactor (CEM Discover) for 3 - 5 min. For solid aryl amines, THF (0.5 mL) was added. Reaction mixture was diluted with THF, filtered, concentrated and purified by silica gel column chromatography using 30% EtOAc in hexanes as the eluent to afford corresponding indoloquinolines **3a-h**. All the synthesised compounds **3a-h** were characterized by ^{1}H NMR, ^{13}C NMR and confirmed by comparison with the reported NMR data.[7,9]

Highlight:

- An efficient microwave-mediated synthesis of indoloquinolines is reported.
- Reaction uses an environmentally benign bismuth nitrate as a catalyst.
- Mechanistically, this one-pot transformation is unique.
- Proposed plausible mechanism for this one-pot transformation.

Microwave-induced Bismuth(III)-catalyzed Synthesis of Linear Indoloquinolines

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