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BISMUTH NITRATE-CATALYZED MICHAEL REACTION OF INDOLES AND SEQUENTIAL REACTIONS IN A ONE-POT METHOD

Indrani Banik,[1]Ram Naresh Yadav,[2]Md. Firoj Hossain,[3] Neeta Srivastava,[1]and Bimal Krishna Banik[4]*

[1]Department of Molecular Pathology, The University of Texas-M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, Texas 77030, USA;[2]Department of Chemistry, Faculty of Engineering & Technology, Veer Bahadur Singh Purvanchal University, Jaunpur-222003(UP), INDIA;[3]Department of Chemistry, University of North Bengal, Raja Rammohunpur, Darjeeling-734013,West Bengal, India; [4]Department of Mathematics and Natural Sciences, College of Sciences and Human Studies, Prince Mohammad Bin Fahd University, Al Khobar, Kingdom of Saudi ArabiaEmail: bimalbanik10@gmail.com; bbanik@pmu.edu.sa

Abstract:

Bismuth nitrate-catalyzed Michael reaction of indoles with α β–enones followed by a series of nucleophilic reactions performed through sequentially one-pot process. This method has produced numerous functionalized indole derivatives as a privileged scaffold found in various biologically relevant pharmaceuticals and natural products.

Key Words:

Bismuth Nitrate, Michael reaction, Sequential reaction, One-pot method

Introduction:

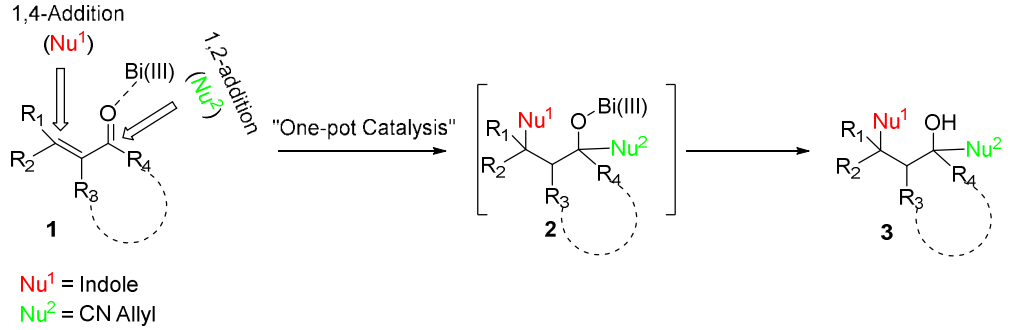
Michael reaction of indoles with α β-unsaturated carbonyl compound is an important objective and one of the most important C-C bond forming reaction in domain of synthetic organic chemistry. Significant progress has been made in these areas to develop sustainable catalytic procedure. The most notable catalysts are Lewis acid,[1,2]Bronsted acid,[3,4]organocatalysis,[5,6]iodine,[7,8]and bismuth (III) triflate.[9,10]However, either these catalytic methods are corrosive or cannot be applied in large scale synthetic practices. Therefore, it is obvious to identify a cost-effective, low toxic and environmentally benign catalytic system for this study. In this connection, our research on bismuth nitrate-catalyzed reactions have shown to be successful in the preparation of diverse organic molecules.[11–16]Our group previously reported a study on Michael addition reaction of indoles with bismuth nitrate as a catalyst. We herein report on one-pot sequential 1,4-conjugate addition and 1,2-nucleophilic

addition of diverse nucleophiles onto Michel adduct generated *in situ.* After careful examination of the reaction conditions and the structure of the Michael adducts have prompted us to design a sequential reaction that can be performed in a single-pot operation. In this communication, a series of Michael addition adduct and their transformation into diverse functionalized important precursors for the advanced synthesis has been achieved. The representative examples include Michael reaction-cyanide addition to the ketone. The noteworthy point of this study is an exclusive substitution at C3-position of the indole ring. There are no N-substituted products has been observed. This methodology discloses a green approach for the synthesis of diverse biologically relevant 3-substituted indole derivatives under mild reaction condition all through a sequentialone- potoperation in good to high yield.

Result and Discussions:

It is well established that the regioselectivity in Michael reaction is greatly controlled by the medium of the reaction. The N-nucleophilic conjugate addition of indole could achieve under alkaline condition[17] while C-3 substitution is generally achieved under acid-catalyzed conditions.[18] Thus, in the last few years, extensive reports are published on Lewis acid-catalyzed C-3 substitution of indole with unsaturated enones.[1] This reaction either uses stoichiometric amounts or excess reagents, and therefore, the side reactions can also take place if the reactants are not precisely controlled.[19,20]Catalytic Michael reaction is an excellent in circumventing the numerous problems.[21–23]The success of the reaction depends on the nature of the catalyst, substrate, and solvent. For instance, indium salts are helpful for Michael reactions of indoles[1,24] and pyrroles.[25] But, they are not considered to be the best alternative for the carbamates. Platinum salts are excellent catalysts for carbamates.[26]
Synthesis of highly functionalized indole derivatives is an important objective because of the indole nucleus found in numerous pharmacologically and biologically active molecules.[27–32]
We demonstrated an efficient bismuth nitrate-catalyzed Michael reaction of indoles with α,β-unsaturated ketones.[11,33]This method became striking because of the development of a new catalytic environmentally benign procedure and the huge scope of the process. Considering the conditions of this method and analyzing the structure of the products, it appears that the development of sequential reactions in one-pot is conceivable. This idea is further reinforced because of our series of successful results based on bismuth salt-derived reagents in numerous organic transformations.
In general, 1,4-conjugate addition of nucleophile (Nu^1: Indole) to α,β-unsaturated carbonyl (acceptor) furnished the β-indoyl ketone that subsequently reacts with various other nucleophilic reagents to form diverse products (Scheme 1).

SCHEME 1



Bismuth nitrate-catalyzed Michael reaction of indoles withα, β-unsaturated ketones:

Lewis acid-mediated functionalization of the indole nucleus at the C-3 position is a well-established reaction. The 3-substituted indoles played an important role in the synthesis of organic molecules of diverse interest. In fact, 3-oxo-alkyl indole obtained by this method served as a potential synthetic precursor for the synthesis of natural products.In a preliminary investigation, α β-unsaturated enone**1a** was treated with indole **4a** (1:1 molar ratio) in presence of 5 to 10 mol % of bismuth (III) nitrate pentahydrate as a catalyst, in moist THF solution (3:1) at room temperature. We found that indole react smoothly with α β-unsaturated enones, affording the conjugate adduct β-indoyl ketone **5a** in good yield (85%) without formation of any unsolicitedby products (Table 1, Scheme 2).

With this encouraging result, we next focused to investigate the effect of solvents' choice on the fate of the reaction. We carried the reaction in high polar solvents like DMSO and DMF, but the reaction did not proceed well since only a trace amount of products were isolated along with unidentifiable polymeric materials. We further investigate this reaction using an aprotic and protic solvent combination with water likely MeOH/H_2O, EtOH/H_2O, THF/H_2O, dichloromethane and chloroform. After a considerable investigation, we found that a mixture of THF/H_2O (3:1) is the best choice of solvent for the reaction. It is worth mentioning that in the case of liquid Michael acceptor the reaction proceeded greatly without using any solvent.

SCHEME 2

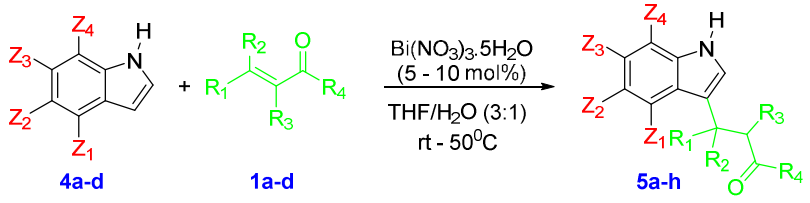


TABLE 1. Michael addition of Indoles to acyclic α, β-unsaturated enones catalyzed by Bismuth (III) nitrate pentahydrate[a]

Entry	Enone(s) **[1a→d]**				Indole(s) **[4a→c]**				Product(s) **[5a→h]**	Time **[h]**	Yield **[%]** [b]
	R^1	R^2	R^3	R^4	Z^1	Z^2	Z^3	Z^4			
1	H	H	H	Ph	H	H	H	H	**5a**	12	85
2	H	H	H	Ph	H	H	CN	H	**5b**	15	70
3	H	H	H	Ph	H	H	OBn	H	**5c**	12	72
4	H	H	H	Ph	H	OMe	OBn	H	**5d**	24	69
5	Me	H	Me	Me	H	H	CN	H	**5e**	35	56
6	Me	H	Me	Me	H	OMe	OBn	H	**5f**	30	73
7	Me	Me	H	Me	H	H	CN	H	**5g**	35	64
8	H	H	H	Me	H	H	CN	H	**5h**	12	76

[a]Reaction performed in presence of 5-10 mol% of Bi $(NO_3)_3.5H_2O$. [b]Yield(s) of products after column chromatographic purification.

Next, we established the catalyst loading to generalize the amount of catalysts required to accelerate the nucleophilic addition reaction. We found that our designed synthetic strategies need only 5 to 10 mol % of bismuth nitrates to catalyze the reaction of indoles with diverse Michael acceptors. During our investigation, we also perceived that the heavily substituted acyclic enones took a long time for the completion of the reaction (Table 1 entry 5, 6). It was

surprising to note that increasing the amounts of catalyst did not help to improve the yield of the products. Therefore, this method did not require the stoichiometric amount of catalysts to expediate the reaction.

To evaluate the broad scope of Michael reaction, a wide range of Michael acceptors (α,β-unsaturated enones) **1a-d** were reacted with indoles **4a-d** using 5 to 10 mol% of bismuth (III) nitrate pentahydrates in moist THF/H_2O (3:1) and the result were summarized in (Table 1). Although all Michael adducts were formed in excellent yield, but the reactivity is greatly influenced by the substitution pattern on the Michael donor and acceptor.

It is worthy to emphasize that aromatic enone**1a-b** led to the formation of corresponding Michael adducts with a high level of selectivity and excellent yield. However, the reaction time was not the same with substituted aromatic enones. The methyl group at α-position in acceptor made the reaction slow and took a relatively long time for the complete consumption of the starting materials.The substituted methyl vinyl ketone at the α and β–position further retarded the reactivity of Michael acceptor (entry 5, Table 1) and took longer reaction time to consume all the reactants in the reaction mixture that was attributed due to the deactivating effect of the methyl group and steric hindrance as well.

The effects of the groups present in the aromatic nucleus of indole were also noticed. We found that the electron-withdrawing group in indole **4b** took a relatively long time with a slightly lower yield in comparison to unsubstituted indole **4a** (entry1, 2, Table 1). This lower yield was due to lower nucleophilicity of the indole rings. Further substitution of the indole nucleus resulted in dropping the yield of the corresponding Michael adduct significantly.

Moreover, 3-Methyl indole**4e**underwent conjugate addition at 2-position (entry 9, Table 1) with a different mechanistic pathway. Initially, a usual conjugate addition took place at the C-3 position of indole ring which undergoes 1,2-shift of the carbocation intermediate and this leads to the formation of the final product.[34]

SCHEME 3

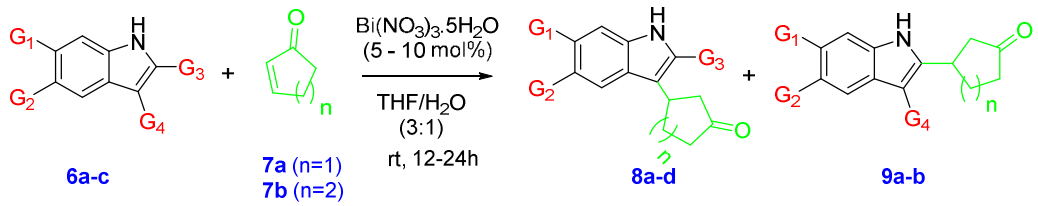


TABLE 2. Michael addition reaction to cyclic enone catalyzed by Bismuth (III) nitrate pentahydrate[a]

Entry	Indole(s) [**6a→c**]				Enone(s) [**7a→b**]	Product(s)	Time	Yield(s)
	G^1	G^2	G^3	G^4	n	**[8a→d]/[9a→b]**	[h]	[%][b]
1	H	H	H	H	**7a** (n=1)	**8a**	12	55
2	CN	H	H	H	**7a** (n=1)	**8b**	15	60
3	H	H	H	Me	**7a** (n=1)	**9a**	20	65
4	H	H	H	H	**7b** (n=2)	**8c**	15	45
5	CN	H	H	H	**7b** (n=2)	**8d**	12	79
6	H	H	H	Me	**7b** (n=2)	**9b**	24	55

[a]Reaction performed in presence of 5- 10 mol% of $Bi(NO_3)_3.5H_2O$ [b] Yield(s) of products after column chromatographic purification.

In addition, we also investigated our strategy with cyclic enones. This protocol worked effectively with lower product yield (Scheme 3, Table 2). The electronic effect of the groups

in the indole ring had no significant effects on the yield and outcome of the reactions. It was observed that cyclic Michael acceptor **7b**, furnishes the product with a lower conversion rate in comparison of **7a** (entry 4, Table 2). This was presumably due to the constraint structure of cyclopentene ring **7a.**

The success of bismuth (III) nitrate mediated 1,4-conjugate addition provoked us to design sequential 1,4-conjugate addition followed by nucleophilic 1,2-addition in one-pot operation. The optimized reaction conditions involved the initial catalytic 1,4-Michael addition of indole with α β-unsaturated enone (established by checking TLC and NMR of reaction aliquot, 12-24 h) and subsequent addition of various nucleophilic reagents to the same reaction vessel at room temperature.

The one-pot 1,4-1,2 addition of Indole(4a-d) to Michael acceptor(1a):

Cyanohydrin are potential building blocks for pharmaceuticals, agrochemicals and as a key functional group in various biologically active compounds like amino alcohols, amino acid and hydroxy acid etc..[36–38]Several synthetic methods for the cyanohydrin preparation are well exploited in the literature using diverse catalytic system.[39–42]The most common methods are Lewis acid-mediated addition of TMSCN to carbonyl functionality.[43] Classically,NaCN and KCN are very important sources of cyanide for cyanation reaction. The development of plausible synthetic methods to access α-hydroxy-α-substituted acid, ketone, and β-hydroxy amines is highly desirable which could serve as an advanced synthetic precursor in the synthesis of diverse bioactive molecules. In our efforts, we synthesized various α-hydroxy-α-cyano-O-alkyl indoles in high yield (Scheme 4, Table 3).

SCHEME 4

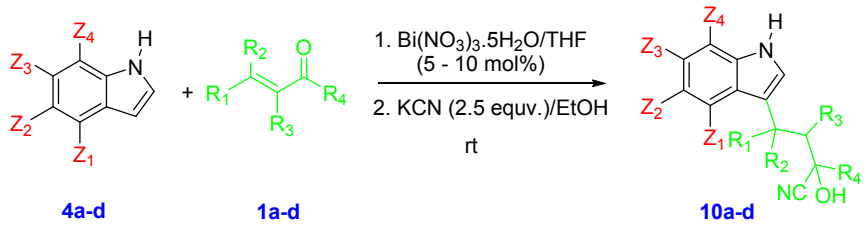


TABLE 3. Bismuth (III) nitrate catalyzedone-pot1,4-1,2-addition Indole(s) to α β-unsaturated enone (s)[a]

Entry	Indole(s) [**4a-d**]	Indole(s) $Z^1 \rightarrow Z^4$	Michael Acceptor(s)	Adduct	Time [h]	Yield [%][b]
1	**4a**	$Z^1 \rightarrow Z^4$ H	**1a** $R^1 \rightarrow R^3$ H R^4 C_6H_5/KCN	**10a**	**15**	90
2	**4b**	Z^1 Z^2 Z^4 H Z^3 CN	**1a** $R^1 \rightarrow R^3$ H R^4 C_6H_5/KCN	**10b**	**18**	80
3	**4c**	Z^1 Z^2 Z^4 H Z^3 OBn	**1a** $R^1 \rightarrow R^3$ H R^4 C_6H_5/KCN	**10c**	**15**	80
4	**4d**	Z^1 Z^4 H Z^2 OMe Z^3OBn	**1a** $R^1 \rightarrow R^3$ H R^4 C_6H_5/KCN	**10d**	**29**	70

[a]Reaction performed in presence of 5- 10 mol% of $Bi(NO_3)_3.5H_2O$ [b] Yield(s) of products after column chromatographic purification.

Towards this endeavor, a very promising result was obtained by bismuth (III) nitrate-catalyzed reaction pertaining both the cyanation and 1,4-conjugate addition reaction concomitantly encouraged us to design a one-pot protocol to execute the products of this reaction in a very efficient manner.

Initially, under optimized reaction conditions, catalytic 1,4-addition of indoles to the Michael acceptors (reaction was monitored by checking TLC and ^{1}H NMR of the reaction aliquot, 12-24h) followed by subsequent addition of potassium cyanide (2.5 equiv.) was performed. In one-pot procedure addition of KCN to the resulting β-substituted*oxa*-alkyl indole took place smoothly and the results are delineated in (Table 3). This afforded the product **10a-d**in 70-90% yield (Scheme 4, Table 3).

Conclusions:

The products from the sequential reaction as described in Schemes 2-4 can also be used for further sequential reactions to afford other indole derivatives in a one-pot method. The method described herein, and the products obtained from this procedure are highly functionalized in a simple way. The sequential method for the preparation of several indoles derivatives is simple, cost-effective and environmentally friendly. This method has the potential to combine other reactions by careful thinking about the reactivity of the functional groups and conditions used in the processes. Our research group can prepare diverse multi-functionalized molecules selecting the substrates, conditions and reagents/catalysts through the sequential one-pot process as portrayed above.

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