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EFFICIENT MICHAEL ADDITION OF INDOLES USING BISMUTHYL PERCHLORATE AS CATALYST

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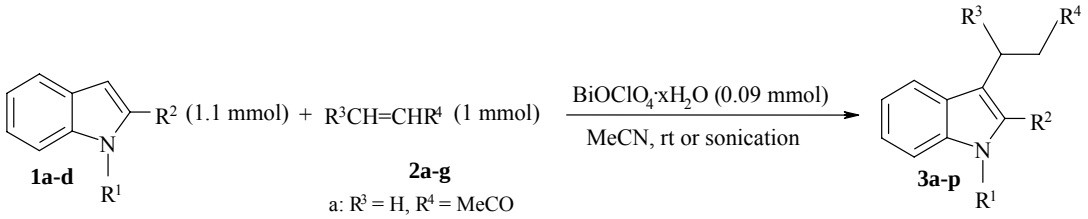
Abstract- An efficient method for Michael addition of indoles has been developed using bismuthyl perchlorate ($BiOClO_4 \cdot xH_2O$) as catalyst. The reaction proceeds to give 3-substituted indoles excellently stirring indoles and Michael acceptors in acetonitrile in the presence of the catalyst at room temperature or in much shorter reaction times under sonication at ambient temperature.

In recent years attentions have been focused particularly on 3-substituted indoles due to their various pharmacological or biological activities.[1] They have emerged as integral backbones of several antibacterial, antialgal and antimycotic agents.[2] This is an impressive profile that bodies well for the interaction of this heterocyclic building block with a variety of biological targets of interest in medicinal chemistry. Moreover, some alkaloids containing indole unit have been isolated from marine sources like *Hapalosiphon fontinalis* (a blue-green algae).[3] The scope of this has been further increased by the identification of the tri- or tetracyclic skeleton derivatives called hapalindole, as a biogenetic precursor.[4] Michael reaction of indoles with α,β-unsaturated compounds using acid catalysts has been reported.[5] Acid induced reaction of indoles requires precise control of the acidity to prevent side reactions, including dimerization and polymerization. Recently, a number of methods and reagents have been developed to overcome the problem.[6-13] However, the application of these methods suffer from some disadvantages such as the use of hazardous or expensive and or less easily available catalysts, vigorous reaction conditions, prolonged reaction times, low yields and formation of side products. Furthermore, some of these methods require strictly anhydrous conditions. Consequently, there is a need for the development of protocols using readily available and safe reagents which lead to high yields of 3-substituted indole derivatives. Recently, bismuth compounds have become attractive candidates for use as reagents in organic synthesis due to their low toxicity, ease of handling and relatively insensitivity to air and moisture.[14] Bismuth has been heralded as a green element, and the low toxicity of many bismuth

compounds is evident from their LD_{50}.[15]

Bismuthyl perchlorate ($BiOClO_4 \cdot xH_2O$) is a commercially available reagent and requires no special handling. Several organic transformations using this reagent have been reported in the literature.[16] We now report a rapid and efficient method for the Michael addition of indoles (**1a**~**d**) in the presence of catalytic amount of $BiOClO_4 \cdot xH_2O$ under two conditions: at room temperature (method A) and sonication atambient room temperature (method B) (Scheme 1).



Scheme 1

First, in order to investigate the influence of solvents on the catalyst, the addition reaction of indole (**1a**) with methyl vinyl ketone (**2a**) was carried out in hexane, chloroform, dichloromethane, 1,2-dichloroethane, dimethylformamide, methanol, and acetonitrile at room temperature. As shown in Table 1, the best result was obtained after 50 min in acetonitrile in the presence of 9 mol% of the catalyst (Entry 7). It was found that $BiOClO_4 \cdot xH_2O$ is soluble in acetonitrile, methanol and dimethylformamide, while it is slightly soluble in chloroform, dichloromethane, and 1,2-dichloroethane, while insoluble in hexane. The results indicate that the solubility of the catalyst is not an important factor for the addition reaction. It is possible that solvation of Bi atom in $BiOClO_4 \cdot xH_2O$ by the lone pairs of oxygen atom of dimethylformamide decreases the Lewis acidity of the catalyst so that the reaction does not proceed in this solvent as supported by the data in Table 1 (Entry 5). In methanol, although it is a good solvent for the catalyst, the solvation may decrease the nucleophilicity of indole and therefore results in longer reaction time and lower yield compared to acetonitrile (Entry 6). Long reaction time and low yield in hexane may be related to low solubility of substrates and possibly insolubility of the catalyst (Entry 1). On the other hand, chloroform, dichloromethane, and 1,2-dichloroethane are much better solvents for the substrates. Although, the catalyst is slightly soluble in these solvents, the reaction times and the yields indicate that the reaction may proceed via heterogeneous catalysis (Entries 2-4). We also found that the presence of water in the reaction media has no influence on the yield (Entry 8) and therefore, in contrast to some of the previous methods,[5,6a] anhydrous solvent is not necessary. The generality of this addition

reaction proceeded effectively in the reaction of indoles with a wide range of Michael acceptors in acetonitrile at room temperature without ultrasonic irradiation (Table 2, method A).

Table 1. Solvent effect on the reaction of indole (**1a**) with methyl vinyl ketone (**2a**) in the presence of $BiOClO_4 \cdot xH_2O$[a,b]

Entry	Solvent	Time (min)	Yield (%)[c]
1	Hexane	180	10
2	$CHCl_3$	90	89
3	CH_2Cl_2	75	90
4	$ClCH_2CH_2Cl$	90	82
5	DMF	240	3
6	MeOH	120	75
7	MeCN	50	97
8[d]	MeCN	50	97

[a]Without ultrasonic irradiation at room temperature. [b]In the presence of 9 mol% catalyst and 10 ml solvent. [c]Isolated yields. [d]In the presence of 2% H_2O.

However, improvement in yields and reaction times was observed under ultrasonic irradiation (Method B) (Table 2). The procedure for this reaction is remarkably simple. In a model reaction, indole (**1a**) and methyl vinyl ketone (**2a**) in acetonitrile were stirred in a container under irradiation using a laboratory sonication bath. This method allows a shorter reaction time at ambient temperature in contrast to Method A. To evaluate the use of this procedure, a variety of substituted indoles (**1b**~**d**) are reacted with Michael acceptors (**2a**~**g**). The reaction proceeds very cleanly and no undesirable side reactions were observed. On the other hand, in the absence of $BiOClO_4 \cdot xH_2O$ the reaction did not proceed even after 2 h.

According to our examination, we found that treatment of indoles (**1**), carrying either carboethoxy as an electron-withdrawing group or methyl as an electron-donating group, afforded Michael adducts (**3**) in high to excellent yields in short reaction times (Table 2). It is important to note that the protection of NH group of indole is not necessary and, under these conditions, 3-substituted indoles (**3**) were obtained without formation of any *N*-alkylation products (Entries 1-13). Another important aspect of this method is found in Entry 8. Very recently Bartoli *et al.* reported that presence of electron-withdrawing group in pyrrole ring of indole does not produce the corresponding product using cerlum (III) chloride as catalyst.[6c] However, we observed that by utilizing of our procedure, synthesis of the corresponding Michael adducts has been performed successfully (Table 2, Entry 8).

Furthermore, unlike some of the previous methods, the present protocol dose not require either strong acids or high temperatures to afford indole derivatives. Thus, this method provides an easy access to the preparation of 3-substituted indoles (**3**) without any side reactions such as dimerization, polymerization

Table 2. Reactions of indoles with Michael acceptors in the presence of $BiOClO_4 \cdot xH_2O$ under Two conditions

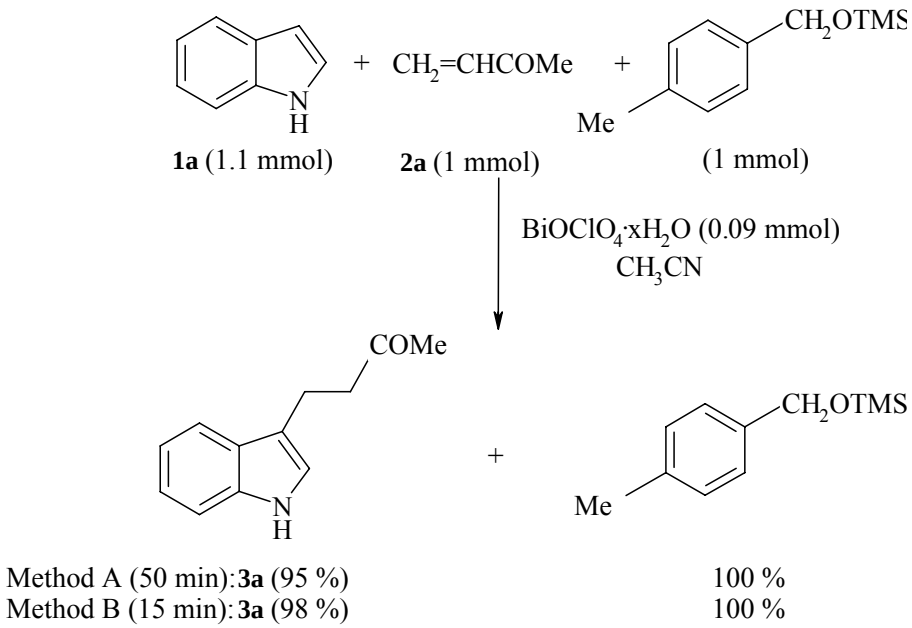
Entry	Indole	Michael acceptor	Product	Method A[a]		Method B[a]		References for known compounds
				Time (min)	Yield (%)[b]	Time (min)	Yield (%)[b]	
1	**1a**	**2a**	**3a**	50	97	15	99	10b
2	**1a**	**2b**	**3b**	90	88	60	89	6c
3	**1a**	**2c**	**3c**	120	90	45	92	10a
4	**1a**	**2d**	**3d**	105	92	60	94	5d
5	**1a**	**2e**	**3e**	120	80	60	82	6b
6	**1a**	**2f**	**3f**	60	87	30	92	13b
7	**1a**	**2g**	**3g**	90	90	45	91	10c
8	**1b**	**2a**	**3h**	45	96	15	99	-
9	**1c**	**2a**	**3i**	60	96	20	99	5b
10	**1c**	**2b**	**3j**	120	90	30	98	11
11	**1c**	**2c**	**3k**	120	89	45	93	6b
12	**1c**	**2d**	**3l**	120	90	45	92	10b
13	**1c**	**2e**	**3m**	135	85	60	87	-
14	**1d**	**2a**	**3n**	75	95	25	98	10a
15	**1d**	**2b**	**3o**	135	84	60	86	11
16	**1d**	**2c**	**3p**	135	88	45	91	10a

[a]Method A: without ultrasonic irradiation at room temperature, Method B: under ultrasonic irradiation.
[b]Isolated yields.

and *N*-alkylation and offers several advantages such as higher yields, shorter reaction times, cleaner reaction profiles with simple experimental and workup procedures.

In addition, the chemoselectivity of the present method is also demonstrated. It is interesting to note that some acid-sensitive groups such as TMS-ethers were stable under these reaction conditions. For example, when a mixture of methyl vinyl ketone and 4-methylbenzyl trimethylsilyl ether was allowed to react with indole in the presence of 9 mol% $BiOClO_4 \cdot xH_2O$ for 50 min at room temperature or 15 min under ultrasonic irradiation, the Michael acceptor was chemoselectively converted to the corresponding product but the TMS-ether remained intact (Scheme 2). It is noteworthy that deprotection of silyl ethers has been reported using this catalyst previously.[16c]

In conclusion, we have described a mild, efficient and selective procedure for the synthesis of 3-substituted indoles. No side products were observed. As this reaction is not sensitive to moisture, the solvent used and reaction conditions need not be absolutely anhydrous. Moreover, the catalyst is an inexpensive, relatively non-toxic and commercially available chemical that is commonly found in most organic laboratories.



Scheme 2

EXPERIMENTAL

All products were identified by comparison of their physical and spectral data with those of authentic samples. Melting points were determined using a Stuart Scientific apparatus and are uncorrected. IR spectra were run on a Shimadzu IR-435 spectrophotometer. ^{1}H NMR spectra were recorded in $CDCl_3$ solvent on a Bruker 500 MHz spectrometer. Yields refer to isolated products. The Bi and water contents of the catalyst were determined by atomic absorption spectrometry and Karl Fischer method respectively, which indicated the water content was about 1.7 mole per mole of the catalyst.

General procedure (Method A): To a stirred solution of indole (**1**) (1.1 mmol) in MeCN (10 ml), α,β-unsaturated compound (**2**) (1 mmol) and $BiOClO_4 \cdot xH_2O$ (0.09 mmol) were added. After completion of the reaction monitored by TLC (Table 2), the solvent was evaporated. The residue was diluted with water (10 ml), extracted with ethyl acetate (3×10 ml) and then dried over $MgSO_4$· Column chromatography of the crude residue on SiO_2 using hexane/ethyl acetate (9/1) as eluent gave the pure products (**3**) in 80-97% yields.

General procedure (Method B): A mixture of indole (**1**) (1.1 mmol), α,β-unsaturated compound (**2**) (1 mmol) and $BiOClO_4 \cdot xH_2O$ (0.09 mmol) in MeCN (10 ml) was irradiated for 15-60 min in a laboratory ultrasonic bath. After completion of the reaction (monitored by TLC), the solvent was evaporated, diluted with water (10 ml) and then extracted with ethyl acetate (3×10 ml). The combined organic layer was dried with $MgSO_4$ and after removing the solvent under vaccum, the crude product was purified by chromatography on SiO_2 using hexane/ethyl acetate (9/1) as eluent to afford pure products (**3**) in 82-99%

yields. Compound (**3h**) (Entry 8), mp 116-117 °C. IR (KBr): 3291, 2979, 1689, 1544, 1254, 1023, 738 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): 1.39 (t, *J* = 7.12 Hz, 3H), 2.13 (s, 3H), 2.79 (t, *J* = 7.86 Hz, 2H), 3.34 (t, *J* = 7.83 Hz, 2H), 4.40 (q, *J* = 7.01 Hz, 2H), 7.13 (t, *J* = 7.47 Hz, 1H), 7.30 (t, *J* = 7.07 Hz, 1H), 7.35 (d, *J* = 8.26 Hz, 1H), 7.68 (d, *J* = 8.26 Hz, 1H), 8.81 (s, 1H). EIMS: *m/z* 259 (M^+), 216, 202, 189, 170, 156, 143. Compound (**3m**) (Entry 13), mp 104-105 °C. IR (KBr): 3409, 3022, 2902, 1606, 1461, 1300, 1093, 733 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): 2.45 (s, 3H), 3.56 (dd, *J* = 15.35, 6.05 Hz, 1H), 3.75 (dd, *J* = 15.35, 8.70 Hz, 1H), 5.01 (t, *J* = 7.34 Hz, 1H), 6.61 (d, *J* = 16.19 Hz, 1H), 7.06 (t, *J* = 7.48 Hz, 1H), 7.13 (t, *J* = 7.51 Hz, 1H), 7.21 (t, *J* = 7.28 Hz, 2H), 7.28 (d, *J* = 11.32 Hz, 1H), 7.31-7.44 (m, 8H), 7.52 (d, *J* = 7.83 Hz, 2H), 7.87 (br s, 1H). EIMS: *m/z* 365(M^+), 234, 220, 204, 145, 131.

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