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Indium trichloride catalyzed three component one-pot route to 1-hydroxymethyl-3-aminomethyl indoles

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ABSTRACT

A one-pot synthesis of 1-hydroxymethyl-3-aminomethyl indoles **3** could be achieved in excellent yield by reacting indoles **1** with formaldehyde and secondary amines **2** in the presence of molecular sieves (3 Å) and catalytic amount of $InCl_3$ (10 mol %) in 1,4-dioxane at room temperature for 3–5 h.

Indole scaffolds are widespread in biologically active compounds and natural products.[1] Their main importance is in medicinal chemistry and drug discovery which has resulted in continued interest in their synthesis.[2] Indole and its synthetic analogs are known to possess important biological activities such as antipyretic,[3] analgesic[4] anticonvulsant etc.[5] Among various indole derivatives, 3-aminomethyl indoles[6,7] were found to possess inhibitory activity toward phosphorylation of kinase $pp60^{c\text{-}Src}$,[7,8] which is a non-receptor protein tyrosine kinase (PTK), participating in many cellular activities including cell adhesion, invasion, motility, differentiation, and growth factor receptor signaling.[9] Hemiaminals[10] of indoles are also reported to possess good anti-tumor activity.[11] Hemiaminals are generally used as prodrugs to increase the bioavailability[12] of drug molecules containing indole and other N-heterocyclic moieties, due to their labile nature, hemiaminals generally fragment into formaldehyde and indole or other N-heterocyclic compounds.[13] It is well known that $InCl_3$ has the ability to promote Diels-Alder,[14a] aldol,[14b] Mannich,[14c] Friedel–Crafts,[14d] and various other important organic transfomations.[14e,15]

Also indium salts have shown notable tolerance toward moisture and other co-coordinating functional groups present in the substrates.[16] We have been able to use $InCl_3$ as catalyst for the synthesis of various hetereocycles[17] of biological importance over the years. We have now observed that when indole (**1a**) was treated with formaldehyde and piperidine (**2a**) in 1,4-dioxane it resulted in the formation of 1-hydroxymethyl-3-aminomethyl indole **3a** in 15% yield as well as expected products such as 1,3-diaminomethyl indole **4a**[18a] (12%) and 1-aminomethyl indole **5a**[18] (10%) (Table 1, entry 1). When activated molecular sieves (MS) (3 Å) were added to the reaction mixture, the duration of the reaction decreased to 14 h but not much improvement in the yield and selectivity in the formation of **3a** (Table 1, entry 2). To our delight, simple addition of 10 mol % of $InCl_3$ as Lewis acid catalyst into the above reaction afforded the 1-hydroxymethyl-3-aminomethyl indole **3a** as the sole product in 84% yield in 4 h (Table 1, entry 3). The role of molecular sieves, most likely, is to absorb the water generated during the reaction. To investigate the role of solvent in the reaction, we have used various other solvents (Table 1) such as THF, MeOH, and MeCN, and it seems that 1,4-dioxane is the perfect solvent choice for this reaction (Table 1, entry 3). Then we investigated the effects of different Lewis acid catalysts in the same reaction and observed that $InCl_3$ was found to be the best among the various catalysts used to afford the desired 1-hydroxymethyl-3-aminomethyl indole **3a** (Table 2).

This optimized method was then exploited to prepare a number of substituted 1-hydroxymethyl-3-aminomethyl indoles **3b–o** by varying indoles and secondary amines. The results are summarized in the following table (Table 3).

It is pertinent to mention that when 3-methyl indole (**1f**) was reacted with formaldehyde and piperidine (**2a**) in the presence of 10 mol % of $InCl_3$ and 3 Å MS in 1,4-dioxane afforded only 1-hydroxymethyl-3-methyl indole (**6**)[10] as product in 83% yield,

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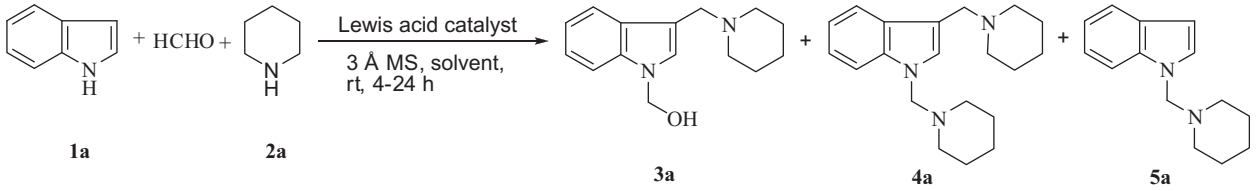
Table 1
Solvent optimization studies for the reaction of indole (**1a**), formaldehyde and piperidine (**2a**)



1a **2a** **3a** **4a** **5a**

Entry[a]	Solvent	Lewis acid catalyst	Time (h)	Yield[b] (%)		
				3a	4a	5a
1	1,4-Dioxane	No catalyst[c]	24	15	12	10
2	1,4-Dioxane	No catalyst	14	21	15	14
3	1,4-Dioxane	$InCl_3$	4	84	—	—
4	THF	$InCl_3$	13	20	23	14
5	Methanol	$InCl_3$	14	33	25	12
6	MeCN	$InCl_3$	12	62	18	9

[a] Reaction conditions: **1a** (1 mmol), formaldehyde (4 mmol), **2a** (1.5 mmol), $InCl_3$ (10 mol %), and MS (3 Å) (200 mg) in the solvent specified (10 mL) at room temperature.
[b] Isolated yield.
[c] Reaction was performed without MS (3 Å).

Table 2
The effect of Lewis acid catalysts in the reaction of indole (**1a**), formaldehyde and piperidine (**2a**)

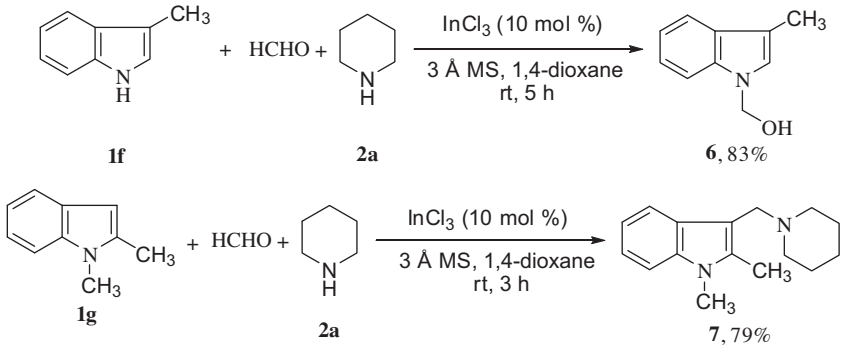
Entry[a]	Solvent	Lewis acid catalyst	Time (h)	Yield[b] (%)		
				3a	4a	5a
1	1,4-Dioxane	$InCl_3$	4	84	—	—
2	1,4-Dioxane	$FeCl_3$	5	61	17	8
3	1,4-Dioxane	$ZnCl_2$	7	48	19	8
4	1,4-Dioxane	$BF_3.OEt_2$	5	45	18	9

[a] Reaction conditions: **1a** (1 mmol), formaldehyde (4 mmol), **2a** (1.5 mmol), Lewis acid catalyst (10 mol %) and MS (3 Å) (200 mg) in 1,4-dioxane (10 mL) at room temperature.
[b] Isolated yield.

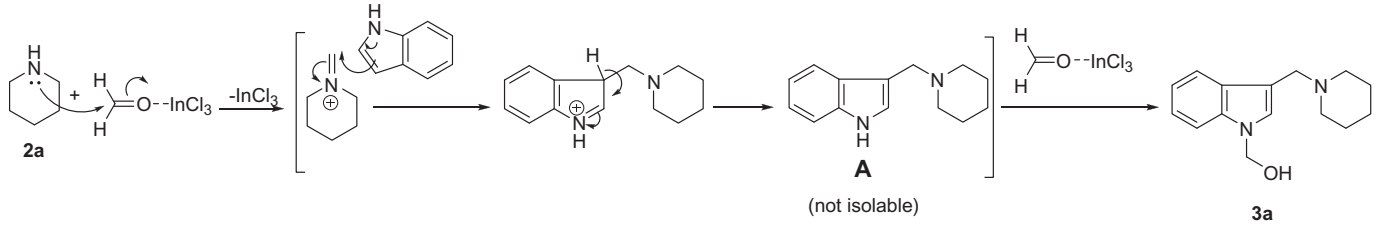
whereas 1,2-dimethyl indole (**1g**) furnished the anticipated product 3-aminomethyl-1,2-dimethyl indole **7**[19] in 79% yield (Scheme 1).

In order to investigate the mechanism of the reaction, we have performed proton NMR analysis of the crude reaction mixture (see Supplementary data) of indole (**1a**), piperidine (**2a**), and formaldehyde in the presence of $InCl_3$ and molecular sieves. It revealed that **A** (not isolable) was formed after 30 min of stirring, which on further stirring for 3.5 h was converted into product **3a** (Scheme 2). Therefore, the formation of 1-hydroxymethyl-3-aminomethyl indole **3a** may be explained as, the iminium ion generated from the reaction between formaldehyde and piperidine (**2a**) under the influence of $InCl_3$ undergoes spontaneous electrophilic substitution at C-3 of indole (**1a**) to afford 3-aminomethyl indole **A**, which further reacts with the activated formaldehyde to give **3a** (Scheme 2).

The structures of all the synthesized compounds have been deduced mainly by NMR, high resolution mass, and IR. Moreover the structure of (3-(piperidin-1-ylmethyl)-1*H*-indol-1-yl) methanol (**3a**) has been confirmed by single crystal X-ray analysis[20] (Fig. 1).

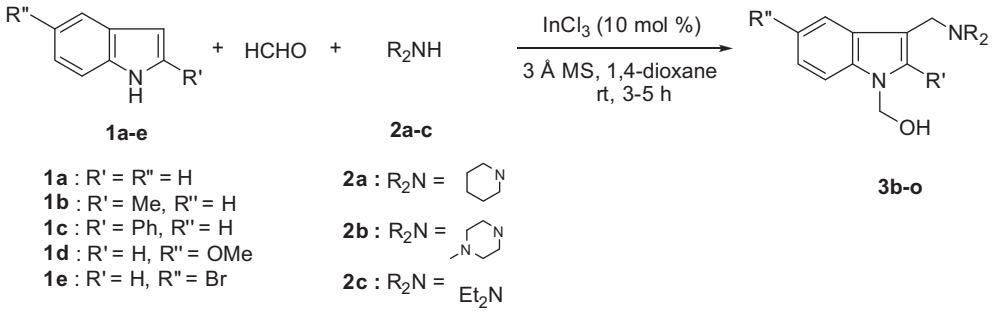


Scheme 1. Regioselectivity of the reaction.



Scheme 2. Plausible mechanism for the $InCl_3$ catalyzed formation of 1-hydroxymethyl-3-aminomethyl indole **3a**.

Table 3
$InCl_3$ catalyzed synthesis of 1-hydroxymethyl-3-aminomethyl indoles **3b–o**



Entry	Indoles **1**	Amines **2**	Time (h)	Yield of products **3b–o**[a] (%)
1	**1a**	**2b**	4.5	85 (**3b**)
2	**1a**	**2c**	3.5	83 (**3c**)
3	**1b**	**2a**	4	84 (**3d**)
4	**1b**	**2b**	4	86 (**3e**)
5	**1b**	**2c**	4.5	84 (**3f**)
6	**1c**	**2a**	3	94 (**3g**)
7	**1c**	**2b**	3.5	89 (**3h**)
8	**1c**	**2c**	4	91 (**3i**)
9	**1d**	**2a**	3	85 (**3j**)
10	**1d**	**2b**	3.5	84 (**3k**)
11	**1d**	**2c**	5	83 (**3l**)
12	**1e**	**2a**	4	88 (**3m**)
13	**1e**	**2b**	3.5	87 (**3n**)
14	**1e**	**2c**	4.5	86 (**3o**)

[a] Isolated yields.

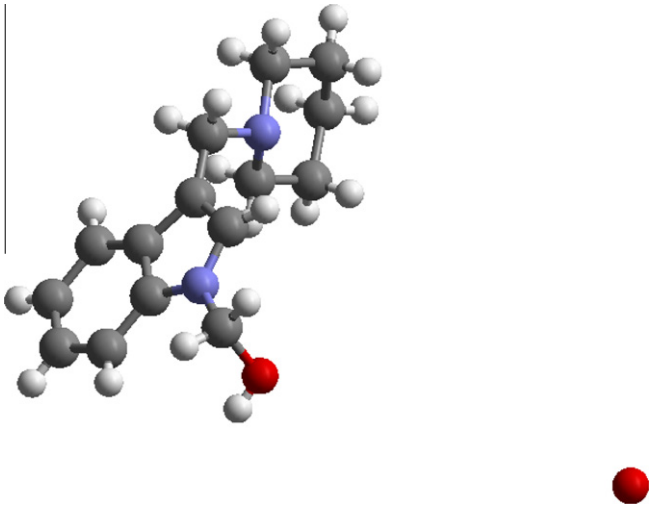


Figure 1. X-ray crystal structure of **3a** with a water molecule. The crystallographic data were collected at 298 K; hence hydrogen atoms of the water molecule could not be assigned due to thermal disorder.

In summary, an efficient Indium trichloride catalyzed one-pot synthesis of 1-hydroxymethyl-3-aminomethyl indoles[21] was achieved from the reaction of indoles, formaldehyde, and secondary amines in excellent yield. Biological activities of the synthesized 1-hydroxymethyl-3-aminomethyl indoles are underway and the results will be reported in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.08.034. These data include MOL files and InChiKeys of the most important compounds described in this article.

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20. CCDC number of **3a** is 885058. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. For details see Supplementary data.
21. *Representative procedure for the synthesis of 1-hydroxymethyl-3-aminomethyl indole* ***3a***: To a stirred mixture of 37% formaldehyde solution (w/v) (324 μL, 4 mmol) and piperidine (**2a**, 149 μL, 1.5 mmol) in 1,4-dioxane (10 mL), dry powdered 3 Å MS (200 mg) was added followed by anhydrous indium trichloride (22 mg, 10 mol %). To the above mixture, indole (**1a,** 117 mg, 1 mmol) was added and the stirring was continued for 4 h [monitored by TLC using 8% MeOH in $CHCl_3$]. Then molecular sieves were filtered off over a thin pad of celite and the filtrate was evaporated in a rotary evaporator. The residue was then diluted with water (15 mL) and extracted with $CHCl_3$ (3×25 mL). The organic layer was separated, washed with brine, and then dried over anhydrous Na_2SO_4. Removal of solvent resulted in a sticky solid which was chromatographed over silica gel [60–120 mesh] using chloroform with an increasing proportion of methanol as eluent. Elution with 5% methanol in chloroform gave compound **3a** (205 mg, 84%) as white solid. mp: 114–116 °C; FT-IR (KBr): ν_{max} 3052, 2934, 2775, 1462, 1349, 1325, 1052, 743 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.64 (d, J = 7.8 Hz, 1H), 7.49 (d, J = 7.8 Hz, 1H), 7.22 (t, J = 7.5 Hz, 1H), 7.15 (t, J = 7.3 Hz, 1H), 6.67 (s, 1H), 5.27 (s, 2H), 3.54 (s, 2H), 2.39 (br s, 4H), 1.43–1.42 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 135.76, 129.31, 127.04, 121.97, 119.87, 118.97, 111.24, 110.14, 69.62, 54.37 (2C), 53.35, 25.32 (2C), 24.19; HRMS (ESI) Calcd. for $C_{15}H_{20}N_2NaO$ $[M+Na]^+$: 267.1473, Found: 267.1489. The X-ray suitable crystals of **3a** were obtained from $CHCl_3$.