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Bismuthtriflate-catalyzed Reaction of *N*-Alkylisatins with Allyltrimethylsilane

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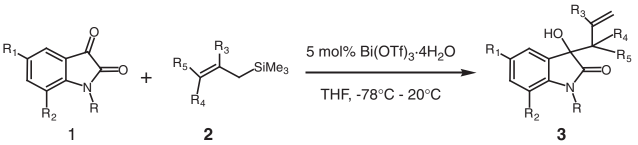
An efficient and general method has been described for the synthesis of 3-allyl-3-hydroxyoxindole by the reaction of isatins with allyltrimethylsilane in the presence of $Bi(OTf)_3 \cdot 4H_2O$. The method is catalytic and suitable for the preparation of functionalized 3-allyl-3-hydroxyoxindoles.

3-Substituted 3-hydroxyoxindoles are the core constituents of naturally occurring alkaloids and potent bioactive molecules.[1,2] Some of the bioactive molecules like convolutamydines,[3] diazonamide A,[4a] leptosin D,[4b] 30-hydroxyglucoisatisin,[4c] witindolinone C,[4d] TMC-95s,[5] celogentin K,[6] dioxibrassinine[7] as well as several other pharmaceutically active compounds[8] have a stereogenic center at the C-3 position. Particularly, chiral 3-substituted 3-hydroxyindolin-2-ones are found to be useful in medicinal chemistry as antibacterial, anti-inflammatory,[9a] laxative,[9b] growth-hormone secretagogue agents,[9c] and new targets for cancer chemotherapy.[9d] The hydroxyindolines are also useful in the synthesis of chiral ligands which are used to obtain high enantioselectivities in numerous catalytic reactions.[10] Due to their distinct biological and chemical properties, their construction has stimulated synthetic chemists,[4a] for the search of simple and efficient approaches.[5] Because of the important medicinal value of 3-hydroxyindolines, an efficient and general protocol for the synthesis of these molecules is desirable. The synthesis of 3-allyl-3-hydroxyoxindole derivatives has been reported by the reaction of isatin with allylorganometallics and allyl alcohols with palladium catalysts.[1b,11] Unfortunately, these reagents do have limitations. Since allylorganometallics are extremely strong bases as well as potent nucleophiles, their use with base-sensitive substrates is precluded. Organometallic carbon nucleophile reagents are incompatible with halo, nitro, and cyano functionalities, while allyl bromide and allylorganometallics are corrosive and toxic. In view of this, there is still need to develop a general and efficient method for the synthesis of allyloxindole derivatives.

Recently bismuth compounds have attracted attention due to their low toxicity, low cost, and high stability.[12] Bismuth salts have been reported as catalysts for opening of epoxides,[13] Mannich type reactions,[14] deprotection of acetals,[15] Friedel–Crafts reactions,[16] Fries and Claisen rearrangements,[17] and Sakurai reactions.[18] $Bi(OTf)_3$ is particularly attractive because it is commercially available or can be easily prepared from commercially available starting materials.[19] Bismuth triflate has been reported by Dubac as an efficient catalyst for the Mukaiyama aldol reaction with silyl enol ethers[20] and was recently used with a chiral ligand as reported by Kobayashi in an elegant enantioselective method.[21] Mukaiyama aldol reactions have been studied with dioxinone-derived silyl dienol ethers which proceeds regioselectively.[22] To the best of our knowledge allyltrimethylsilane has not been used for the allylation of isatin.



R = H, CH_3, Et, Bn
R1 = H, CH_3, F, Cl, Br, NO_2, OCH_3
R2 = H, Br R3 = H, CH_3
R4 = R5 = H, CH_3

Scheme 1.

Table 1. 3-Allyl-3-hydroxyoxindoles formation in different Lewis acid conditions[a]

Entry	Lewis acid (5 mol %)	Time/h	Yield/%
1	$BF_3 \cdot OEt_2$	7.4	72
2	$InBr_3$	6	65
3	$Bi(OTf)_3 \cdot 4H_2O$	4	92
4	$TiCl_4$	6.5	82
5	I_2	10	55
6	$SnCl_4$	8.9	58
7	$SnCl_2$	8.0	69

[a] All the reactions were carried out at −78–20 °C.

As a part of our ongoing research in the development of new methodologies,[23] herein we wish to report the efficient synthesis of 3-allyl-3-hydroxyoxindoles by the reaction of isatin with allyltrimethylsilane in the presence of $Bi(OTf)_3 \cdot 4H_2O$ (Scheme 1).

Initially, we explored various Lewis acids such as $BF_3 \cdot OEt_2$, $InBr_3$, $Bi(OTf)_3 \cdot 4H_2O$, $TiCl_4$, I_2, $SnCl_4$, and $SnCl_2$ for the allyloxindole reaction. Among these, $Bi(OTf)_3 \cdot 4H_2O$ was found to provide optimum conversion with good yield (Table 1). The reaction of isatin **1** with allyltrimethylsilane **2** was studied in the presence of 5 mol % of $Bi(OTf)_3 \cdot 4H_2O$ in different solvents such as DMF, toluene, THF, acetonitrile, and dichloromethane. The reaction proceeded in all the solvents with different degrees of conversion. However, THF was the solvent of choice in terms of reaction time and yield. Further, during optimization of the mole ratio of catalyst, it was noticed that the lower catalyst loading (1 mol %) did not allow the reaction to proceed; where as the higher catalyst loading (10 mol %) afforded the product in decreased yields. Encouraged by these results, we further studied the scope and limitations of this reaction with respect to the isatin (Table 2).

Generally, excellent yields of 3-allyl-3-hydroxyoxindoles were obtained with 1.5 equiv of allyltrimethylsilane **2** and 5 mol % of $Bi(OTf)_3 \cdot 4H_2O$ at −78 °C in THF. The addition of allyltrimethylsilane **2** to various isatins **1** proceeded readily and

Table 2. 3-Allyl-3-hydroxyoxindole derivative formation by using $Bi(OTf)_3 \cdot 4H_2O$ as catalyst[a] [24]

Entry	R	R_1	R_2	R_3	R_4	R_5	Time/h	Yield/%[b]
1	H	H	H	H	H	H	4	92
2	Me	H	H	H	H	H	4.5	90
3	Et	H	Me	H	H	H	4	91
4	Bn	H	H	H	H	H	3.5	88
5	Bn	Br	H	H	H	H	3	90
6	H	F	H	H	H	H	3	93
7	H	Cl	H	H	H	H	3.5	90
8	H	Br	H	H	H	H	4	87
9	H	NO_2	H	H	H	H	5	85
10	H	Me	H	H	H	H	6	86
11	H	OMe	H	H	H	H	5	88
12	H	Br	Br	H	H	H	7	70[c]
13	H	H	H	Me	H	H	6	88
14	Me	H	H	Me	H	H	5	85
15	H	H	H	H	Me	Me	7	80
16	H	Br	H	H	Me	Me	7.5	78
17	Me	H	H	H	Me	Me	6	75

[a]Reaction conditions: Isatin (1 equiv), allyltrimethylsilane (1.5 equiv), $Bi(OTf)_3 \cdot 4H_2O$ (5 mol %), in THF at −78–20 °C. [b]Isolated yields. [c]Recovered remaing starting material.

resulted in expected product.[24] Though the reaction proceeds with a 1:1 ratio of reactants, the best results were obtained with a 1.5 equiv ratio of allyltrimethylsilane. Further we extended this protocol to different substituted isatins. For example, 5-fluoroisatin reacted with allyltrimethylsilane under the optimized conditions and resulted in high yields (Table 2, Entry 6). Other 5-substituted isatins also afforded comparatively good yields of products (Table 2, Entries 7–11). In addition to this allylation, N-substituted isatins (Table 2, Entries 2–5) gave high yield of corresponding product under identical reaction conditions.[25] However, 4-substituted and 7-substituted isatins failed to participate in this allylation. Further it was observed that the reactivity can be introduced by the introduction of another substituent. For example, 5- and 7-disubstituted isatins (Table 2, Entry 12) reacted analogously under identical conditions to give corresponding product in lower yields (70%). Similarly, reaction of substituted allyltrimethylsilane (Table 2, Entries 13–17) gave expected product with good yields.

In summary, we have demonstrated the reaction of isatin with allyltrimethylsilane in the presence of $Bi(OTf)_3 \cdot 4H_2O$. This method offers several advantages such as mild reaction conditions, high yields, a highly catalytic (5 mol %) process and without formation of by-products. Moreover, this protocol may be useful for the synthesis of biologically active complex molecules.[1b,26] Other $Bi(OTf)_3 \cdot 4H_2O$-catalyzed allyllation reactions and related mechanistic studies will be reported in due course.

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26 General procedure: To a solution of isatin **1** (1 mmol) in tetrahydrofuran (2 mL) was added Bi(OTf)$_3$·4H$_2$O (5 mol %). The mixture was brought to −78 °C and stirred at this temperature for 10 min. Then a solution of allyltrimethylsilane **2** (1.5 mmol) in THF (1 mL) was added dropwise. The mixture was stirred at −78 °C for 2 h. Then the mixture was brought to 20 °C and stirred for an additional 0.5–1.5 h (Table 2). The reaction was monitored by TLC. After the completion of the reaction it was quenched with 10% aqueous HCl (1.0 mL). The mixture was stirred for 0.25 h at room temperature, neutralized by the addition of a saturated aqueous NaHCO$_3$ solution, and extracted with ethyl acetate (3 × 5 mL). The combined organic layer washed with brine solution, dried over Na$_2$SO$_4$, and concentrated under reduced pressure (rotary evaporator). The crude products were purified by silica gel column chromatography (ethyl acetate/hexane). All compounds were characterised by mp, NMR, Mass, and IR spectral data.