

Conjugate Addition of Indoles to α,β -Unsaturated Ketones Using Bismuth (III) Bromide

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Abstract

An efficient method for the conjugate addition of indoles to a variety of chalcones using BiBr_3 in ethanol (190 proof) is reported. Products are isolated by a simple procedure that avoids an aqueous work up and extensive chromatography, thus minimizing waste. Bismuth (III) compounds are especially attractive from a green chemistry perspective because they are remarkably nontoxic, non-corrosive and relatively inexpensive.

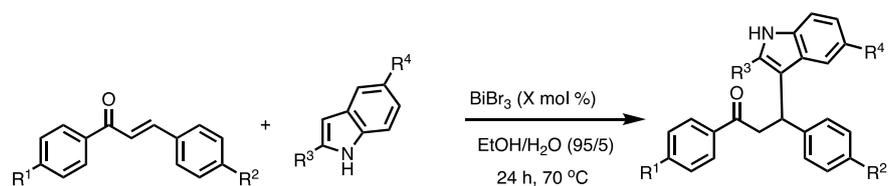
Keywords

Bismuth, Bismuth Bromide, Conjugate Addition, Green Chemistry, Indoles

Indoles and their derivatives are of considerable interest in medicinal chemistry due to the wide range of biological activity they exhibit. Indoles undergo electrophilic substitution at the 3-position and hence a variety of methods have been developed for the synthesis of 3-substituted indoles [1]-[8]. The conjugate addition of indoles to chalcones (substituted phenyl styryl ketones) leads to 3-indolyl ketones, compounds that exhibit biological activity [9]. Hence a variety of catalysts have been used to catalyze such additions. Some examples include FeCl_3 [10] [11], cesium salt of tungstophosphoric acid [12], cellulose sulfuric acid [13], KHSO_4 [14], potassium superoxide- Et_4NBr [15], poly{N, N'-dibromo-N-ethylbenzene-1,3-disulfonamide} [16], silica sulfuric acid [17], CuCl_2 [18], cyanuric chloride [19], Bu_4NHSO_4 [20], GaCl_3 [21], Br_2 [22] and I_2 [23] [24] [25]. Enantioselective conjugate addition of indoles to chalcones have also been developed using $\text{Zr}(\text{O}^t\text{Bu})_4$ -BINOL and N, N'-dioxide- $\text{Sc}(\text{OTf})_3$ complexes [26] [27]. The

conjugate addition of indoles to simple enones (but not chalcones) has been reported using $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ as a catalyst [28] [29]. The conjugate addition of indole to chalcone has also been reported with $\text{Bi}(\text{OTf})_3$ as a catalyst in CH_3CN as the solvent [30] [31]. These bismuth salts-catalyzed methods involve product isolation *via* an aqueous work-up followed by chromatographic purification that generates significant solvent waste. In an effort to develop a method in a green solvent that would eliminate waste from aqueous work-up and extensive column chromatography, we investigated the utility of BiBr_3 as a catalyst in ethanol (190 proof) for the addition of indoles to chalcones. Bismuth compounds are remarkably nontoxic, relatively stable to moisture and air, and easy to handle. As a result there has been considerable interest in the use of bismuth compounds in organic synthesis in the last two decades [32] [33] [34] [35] [36]. Herein we report the conjugate addition of indoles to a variety of chalcones using bismuth bromide, BiBr_3 , in a relatively green and inexpensive solvent, ethanol (190 proof). The product was isolated by evaporation of the solvent, filtration of the residue (using minimal CH_2Cl_2) through a short plug of silica to remove the catalyst, and concentration of the filtrate followed by trituration of the residue with $\text{CH}_3\text{CH}_2\text{OH}$ (190 proof). This method avoids the use of elaborate chromatography for product purification and also eliminates an aqueous waste stream. During optimization of the reaction conditions we found that both 2-propanol ($^i\text{PrOH}$) and absolute ethanol are also suitable solvents, but we chose $\text{CH}_3\text{CH}_2\text{OH}$ (190 proof) as it was easier to remove than $^i\text{PrOH}$, and is considerably cheaper and easier to obtain than absolute ethanol. The results are summarized in **Table 1**. Electron withdrawing groups on the phenyl ring proximal to the carbonyl required a higher catalyst loading for optimal reaction time and yield (entries 8, 9, 11 and 12). Similarly, a strongly electron donating group on the phenyl group distal to the carbonyl (entry 4) required a higher catalyst loading. When the nucleophilicity of the indole was lowered by an electron withdrawing group (entry 3) a higher catalyst loading was required. A solution of BiBr_3 in $\text{CH}_3\text{CH}_2\text{OH}$ (190 proof) has a pH of ~ 3.0 , suggesting that some HBr is generated by hydrolysis. Hence, Bronsted acid catalysis by HBr cannot be ruled out. When the conjugate addition of indole to 4'-methylchalcone (**Table 1**, entry 6) was attempted in the presence of Proton-Sponge® [37], 1,8-bis(dimethylamino) naphthalene, (0.60 equivalents) no product formed, and the starting materials were recovered. Similarly, no product was formed when the same reaction was carried out in the presence of solid K_2CO_3 . Both these results suggest that the primary role of BiBr_3 is to act as a convenient source of HBr [22]. Aqueous HBr is very corrosive and difficult to handle unlike BiBr_3 , which is an air stable and easy to handle solid.

A representative procedure is given here: A mixture of 4-methylchalcone (0.5000 g, 2.2493 mmol) and indole (0.3162 g, 2.6992 mmol, 1.2 equivalents) in $\text{CH}_3\text{CH}_2\text{OH}$ (190 proof, 10.0 mL) was stirred at room temperature as BiBr_3 (0.2018 g, 0.4497 mmol, 20.0 mol%) was added. The mixture was then heated at 70°C (temperature controlled hot plate), and the reaction progress was monitored

Table 1. Addition of indoles to chalcones using BiBr₃.

	R ¹	R ²	R ³ and R ⁴	Time (h) ^b	BiBr ₃ (X mol%)	Yield (%) ^c
1	H	H	H	24	20	72 [22]
2	H	H	R ³ = CH ₃ R ⁴ = H	24	20	73 [22]
3	H	H	R ³ = H R ⁴ = Br	25	50	78 [22]
4	H	OCH ₃	H	7	50	65 [27]
5	OCH ₃	H	H	24	20	84 [22]
6	H	CH ₃	H	26	20	85 [22]
7	CH ₃	H	H	26	20	88 [27]
8	F	H	H	24	50	67 [27]
9	Cl	H	H	24	50	67 [22]
10	H	Cl	H	24	20	77 [22]
11	Br	H	H	6.5	100	76 [38]
12	NO ₂	H	H	24	100	45 [22]

^aChalcones were purchased commercially or synthesized in lab using standard procedures [39]. ^bReaction progress was monitored using TLC and spots were visualized under UV light, and by spraying with phosphomolybdic acid followed by heating. ^cRefers to yield of isolated product that was deemed to be $\geq 98\%$ by ¹H and ¹³C NMR spectroscopy. All products have been previously reported in the literature. Superscript against yield refers to literature reference for spectral data.

by TLC (20/80, EtOAc/heptane). After 26 h, the reaction was cooled to room temperature, and concentrated on a rotary evaporator to yield a pale red solid. The solid was filtered through a plug of silica gel (7.00 g, 20 mL of CH₂Cl₂). The filtrate was concentrated on a rotary evaporator to yield a pale-yellow oily residue that was triturated with CH₃CH₂OH (190 proof, 6 mL) to yield 0.6500 g (85%) of a pale-pink solid. The product was characterized by comparison of ¹H and ¹³C NMR spectral data to literature data and deemed to be $>98\%$ pure.

In summary, a new procedure for the conjugate addition of indoles to a variety of chalcones using BiBr₃ has been developed. The low toxicity of bismuth salts, and a product isolation method that avoids waste generated from an aqueous work up and elaborate column chromatography, make this procedure particularly attractive from a green chemistry perspective.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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