Chemoselective One-pot Conversion of Primary Alcohols to their Bis(indolyl)methanes Promoted by $Bi(NO_3)_3 \cdot 5H_2O$

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A new, “green” and efficient one-pot protocol for the synthesis of bis(indoyl)methanes from primary alcohols using $Bi(NO_3)_3 \cdot 5H_2O$ is described. This procedure performs chemoselectively through a solvent-free reaction and the products are obtained in high to excellent yields.

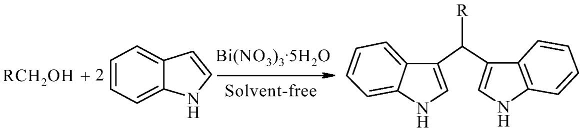
Key words: Bis(indolyl)methane, Primary Alcohol, $Bi(NO_3)_3 \cdot 5H_2O$, Solvent-free Reaction

Introduction

Indole derivatives are widely distributed in nature and are known to possess a broad spectrum of biological and pharmaceutical activities [1, 2]. In particular, bis(indolyl)methanes have received much attention in previous years [3]. Such compounds are prone to develop interesting bioactivity and could be used as antibacterial [4] and antitumor [5 – 7] agents. Thus the development of facile and environmentally friendly synthetic methods towards bis(indolyl)methanes constitutes an active area of investigation in pharmaceutical and organic synthesis. The principal approach for the synthesis of these compounds is limited to the direct condensation reaction of indoles with various aldehydes or ketones in the presence of protic or Lewis acids [8 – 16]. Then, extension of the access to new bis(indolyl)methane derivatives starting from other precursors is highly desirable.

Results and Discussion

For the first time Ireland *et. al.* reported a one-pot scheme in which an aldehyde was generated from alcohols using Swern oxidation conditions and was trapped *in situ* by a Wittig reagent [17]. This procedure alleviated the necessity of isolating the intermediate aldehyde and vastly improved the yield. These results prompted us to focus our work on the use of primary alcohols instead of aldehydes in bis(indolyl)methane synthesis. On the other hand, the development of a less toxic reaction protocol, avoiding purification steps, would extend the scope of this transformation. As part of an ongoing program in our laboratory on the ability of Bi(III) salts [18 – 20], we observed the oxidative [21, 22] and catalytic behaviors [23, 24] of $Bi(NO_3)_3 \cdot 5H_2O$ in organic transformations. Herein, we would like to report an elegant route for preparing bis(indolyl)methanes, which involves alcohols as precursors in the presence of $Bi(NO_3)_3 \cdot 5H_2O$ under solvent-free conditions (Scheme 1).



Scheme 1.

As a model system, $Bi(NO_3)_3 \cdot 5H_2O$ was added to benzyl alcohol in a mortar. The mixture was mixed and kept at 65 °C for a few seconds. When indole was mixed in at r. t., the corresponding bis(indolyl)methane resulted quantitatively. In order to establish the reaction protocol, a series of primary alcohols were applied for this synthesis without affecting other functional groups present in the alcohols and the products were also obtained in excellent yields at very short reaction times (Table 1). To the best of our knowledge using primary alcohols in a one-pot manner for this transformation has not been reported previously. This procedure alleviated the necessity of isolating the intermediate aldehyde and vastly improved the yield. The

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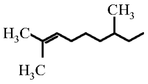
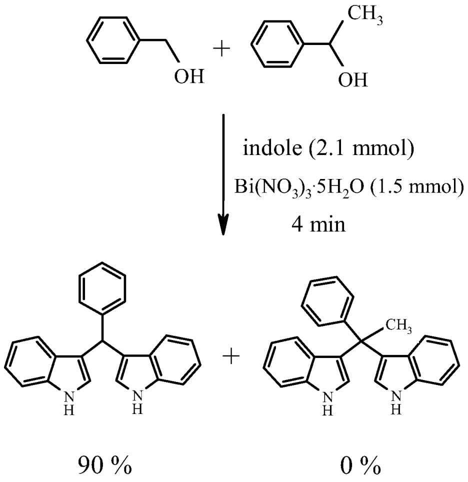
Table 1. One-pot synthesis of bis(indolyl)methanes[a] from primary alcohols promoted by $Bi(NO_3)_3{\cdot}5H_2O$ under solvent-free conditions.

R	Time [min]	Yield [%][b]
C_6H_5	4	90
$4\text{-}NO_2C_6H_4$	5	95
$2\text{-}NO_2C_6H_4$	6	95
$2\text{-}ClC_6H_4$	2	93
$2,4\text{-}Cl_2C_6H_3$	3	91
$4\text{-}FC_6H_4$	4	94
$4\text{-}CH_3C_6H_4$	4	90
$4\text{-}(CH_3)_3CC_6H_4$	5	93
$4\text{-}CH_3OC_6H_4$	2	95
$2\text{-}CH_3OC_6H_4$	4	89
$PhCH_2OC_6H_4$	3	91
	12	80

[a] The products were characterized by ^1H NMR, ^{13}C NMR and IR spectroscopy and comparison with reported data. [b] Isolated yields.



Scheme 2.

reaction proceeded efficiently at ambient pressure and the corresponding products were obtained in high to excellent yields. Additionally, our methodology avoids the use of toxic solvents or reagents.

Encouraged by these results we extended our method to secondary alcohols and carried out reactions using 1-phenylethanol or cyclohexanol. None of the secondary alcohols gave bis(indolyl)methanes even after longer reaction times, showing that the bis(indolyl)methane synthesis from primary alcohols in the presence of secondary ones is chemoselective (Scheme 2).

In conclusion, we have demonstrated a new, chemoselective, straightforward and efficient protocol for the one-pot synthesis of bis(indoyl)methanes from primary alcohols using $Bi(NO_3)_3 \cdot 5H_2O$ as a low toxic, inexpensive and oxygen and moisture tolerant reagent under solvent-free conditions. In addition to efficiency and simplicity, this procedure provides a very fast (2 – 12 min), "green" and low cost procedure for the synthesis of these products from primary alcohols.

Experimental Section

Typical procedure for the preparation of bis(indolyl) methanes

A mixture of 4-fluorobenzyl alcohol (126 mg, 1 mmol) and $Bi(NO_3)_3 \cdot 5H_2O$ (735 mg, 1.5 mmol) was stirred for a few seconds at 65 – 70 °C. When the oxidation reaction was completed, indole (117 mg, 2.1 mmol) was added and the mixture was stirred for 4 min at r. t. After completion of the reaction (monitored by TLC), ethanol (10 mL) was added and filtered. The filtrate was concentrated and purified on silica gel (*n*-heptane/ethyl acetate 4 : 1 as eluent) to afford the pure product in 94 % yield. Pink colored solid; m. p. 70 – 72 °C (lit. [5e] = 72 – 74 °C). – IR (KBr): v = 3400, 2950, 1600, 1445, 1217, 740 cm^{-1}. – ^1H NMR (200 MHz, $CDCl_3$): δ = 7.91 (br, s, 2H), 7.45 – 6.92 (m, 12H), 6.7 (s, 2H), 5.90 (s, 1H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 39.8, 111.5, 115.2, 115.6, 119.8, 120.3, 122.4, 123.9, 127.3, 130.4, 137.1, 140.1, 159.4.

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