Bis(indolyl)methanes Synthesis Through Sodium Iodate and Sodium Hydrogen Sulfite in Water

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Summary: An effective and eco-friendly method for the *bis*(indolyl)methanes synthesis has been developed. A successive methodology involving sodium iodate/sodium hydrogen sulfite catalyzed reaction of indole with many aldehydes gave the resultant *bis*-indol in good yield. This method offers synthetically inexpensive alternate to the previously developed procedures for the *bis*-indol synthesis. The use of a low-cost and straightforwardly accessible catalyst, improved yields and a simple reaction process are the salient features of the current method.

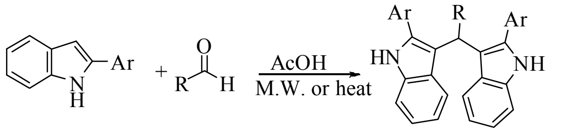
Keywords: *bis*(indolyl)methanes, water, environmentally friendly synthesis

Introduction

Bis-indol establish a imperative class of heterocyclic compounds. The parent compound 1-*bis*(3′-indolyl)methane is derived from indole-3-carbinol and exhibits estrogenic, anti-estrogenic, anti-androgenic and Ah receptor agonist activity [1, 2]. Compounds of this class also inhibit the propagation of estrogen dependent and independent cultured breast tumor cells [3, 4]. *Bis*(indolyl)methanes and their analogs are present in terrestrial and marine organism [5]. *Bis*(indolyl)alkanes also help in drug design, as some *bis*indole alkaloids possess significant *in vitro* antiprotozoal activity against *Plasmodium falciparum* and *Entamoeba histolytica* [6]. The synthesis of indoles and their derivatives have gain more consideration as a number of their synthetically transformed compounds find uses in various fields. For example, the *bis*-indole alkaloid indirubin occasionally present in human urine was amongst the initial cyclin-dependent kinase inhibitor [7]. These compounds have application in treatment of numerous diseases, like chronic myelocytic leukemia [8]. They also target glycogen synthase kinase-3 [9], aurora kinases, and to act as dioxin receptors [10-12] and are reported as potent *β*-glucuronidase inhibitors [13]. Some *Bis*(indolyl)alkanes are used as PPARr agonists and in cancer chemotherapy [14].

For the *bis*(indolyl)methanes synthesis numerous methods have been reported *i.e.* by using glacial acetic acid under microwave (M.W) Scheme-1, *bis*(indolyl)methanes synthesis have been carried out by reacting 2-arylindole derivatives with variety of aldehydes in glacial acetic acid as a catalyst under microwave irradiation [15]. Other methods using zirconyl (IV) species [16], oxalic acid [17], Cu(OTf)$_2$ [18] and zeolite [19] as catalysts are also known.

Herein we wish to report a new protocol for the *bis*-indol derivatives synthesis by using a (10 mol% of sodium iodate and sodium hydrogen sulfite) in water. Water utility as a solvent makes it ecologically friendly. To the best of our knowledge this is new protocol for the *bis*(indolyl)methanes synthesis.



Scheme-1: Synthesis of *bis*indole analogs through microwave.

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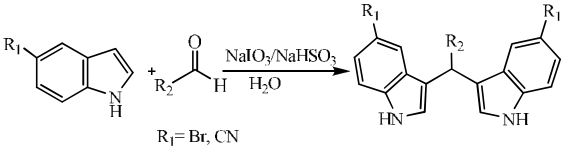
Results and Discussions

The $NaBrO_3/NaHSO_3$ has been used as an effective bromohydroxylation reagent for synthesis of olefins [20], alkynes and allylic alcohols [20], as an oxidizing agent for diols, ethers [22], and for primary alcohol [23], and for alkyl benzenes as an α-brominating reagent [24]. Previously, our research group has published the *o*-alkylbenzoic acids conversion into γ-lactones [25], disulfides synthesis [26], and the conversion of aromatic carboxylic acids into the esters [27] by the use of same reagent. In recent past, we have reported synthesis of disulfides by using periodic acid and sodium hydrogen sulfite mixture [28] in a biphasic CCl_4/H_2O mixture. In short this reagent has a wide range of applications.

In an extension of our work on the bioactive compounds syntheses [29-32] as well as new synthetic protocol development [33-36], we have now found that *bis*-indoles can be synthesized in good to excellent yields by a reaction between indole and benzaldehyde using the $NaIO_3/NaHSO_3$ reagent in water at room temperature (Scheme-2, Table-1). No need of high temperatures or toxic organic solvents is the salient features of this new protocol.



Scheme-2: Synthesis of various *bis*(indolyl)methane derivatives by sodium iodate and sodium hydrogen sulfite and comparison of yields with the previously developed method [13].

During the study on hydroxylation of indoles with numerous benzaldehydes, we found that an increase in the concentration of this catalyst from 10 to 20 mol% does not increase the yields and not effected the reaction time. Additional increase in concentration results in decreas in yields, so the optimized condition for this protocol is 10 mol% of this catalyst, and lowering or icreasing the concentration harshly affects the yields (Table-2).

The mechanism shown in Scheme-3 is proposed for this transformation. The reaction commences with the activation of carbonyl by iodine generated *in situ.* The indole ring attacks on the carbonyl carbon to form a tetrahedron intermediate (**a**) and eliminates HOI to form intermediate (**b**). In the mean time second indole ring attacks on the double bond between indole ring and aldehyde to form final product (**c**).

Table-1: Synthesis of various *bis*(indolyl)methane analogs.

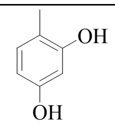
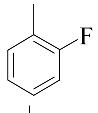
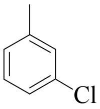
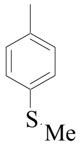
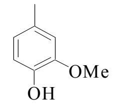
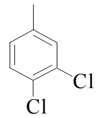
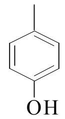
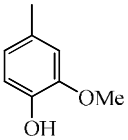
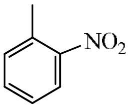
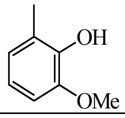
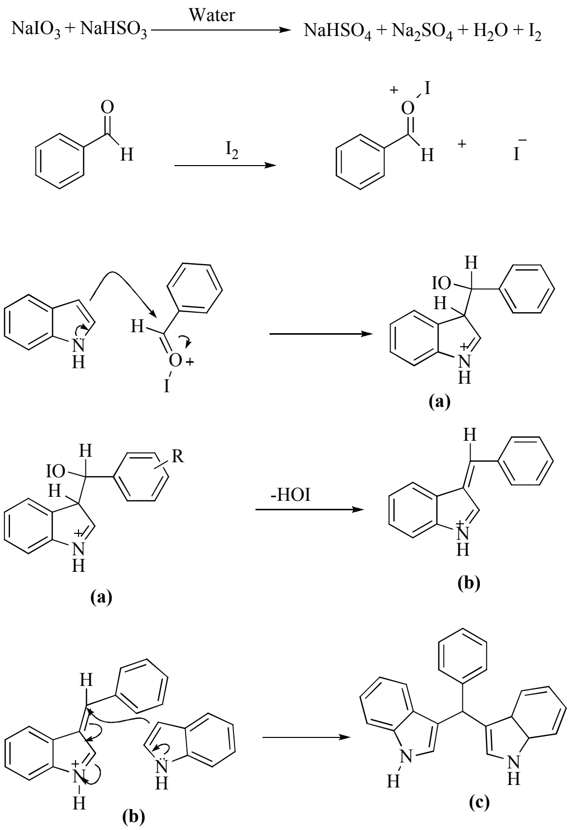
Entry	R1	R2	Time (min)	Yield	Yield [13]
1	Br		80	86	84
2	Br		85	86	82
3	Br		83	77	75
4	CN		90	76	55
5	CN		85	86	50
6	CN		81	85	59
7	Br		85	80	80
8	Br		86	85	51
9	CN		83	83	81
10	CN		80	87	78

Table-2: Different mol% of sodium iodate and sodium hydrogen sulfite comparison and their effect on compound 5 yields.

Mol%	Reaction Time (min)	Yield (%)
10	116	75
20	110	78
30	92	63
40	85	56
50	72	50



Scheme-3: Proposed mechanism for *bis*(indolyl) methane formation.

Experimental

General Information

The experiments for NMR were done on a 300 MHz Bruker FT-NMR instrument (Bruker BioSpin AG, Fällanden, Switzerland), CHN study was done on a Carlo Erba Strumentazione-Mod-1106. EI-MS were recorded on a Finnigan MAT-311A (Breman, Germany). TLC was carried out on aluminum plates pre-coated with silica gel (Kieselgel 60, E. Merck, Darmstat, Germany). UV at 254 and 365 nm is used for chromatograms visualization.

Representative Experimental Procedure

Sodium hydrogen sulfite and sodium iodate solutions (10 mol%, 0.2 mmol in 15 mL water) were prepared separately. Both solutions were mixed and stirred for ten minutes then an aldehyde (2 mmol) and indole (4 mmol) were added. The reaction completion was checked by periodical TLC. When reaction completed, then the product was isolated with extraction with ethyl acetate, was dried over sodium sulphate, filter and then evaporated. Then the pure products were got by column chromatography using ethyl acetat:*n*-hexane as elent to give pure *bis*(indolyl)methanes. The structures were elucidated by spectroscopic methods. All compounds furnished satisfactory elemental analyses.

Representative analytical data of 4-[bis(5-bromo-1H-indol-3-yl)methyl]-1,3-benzendiol (**1**).

Yield: 0.43 g (84%); ^{1}H-NMR(300 MHz, acetone-d_6): δ 10.19 (s, 2H, -NH),7.75 (s, 1H, -OH), 7.52 (d, 2H, $J_{4,6}$ = 1.8 Hz, 2 x H-4), 7.36 (d, 2H, $J_{7,6}$ = 8.4 Hz, 2 x H-7), 7.16 (, 2H, $J_{6,4}$ = 1.8, $J_{6,7}$ = 8.4 Hz, 2 x H-6), 6.87 (d, 2H, $J_{2,CH}$ = 2.1 Hz, 2 x H-2), 6.76 (d, 1H, $J_{6',5'}$ = 8.4 Hz, H-6'), 6.55 (m, 2H, H-3'/5'), 6.23 (s, 1H, Ar_3CH); MS *m/z* (rel. abund. *%*): 512 (M^+, 1), 316 (100), 194 (41), 116 (46), Anal. calcd. for $C_{23}H_{16}Br_2N_2O_2$ (512.19); C, 53.93; H, 3.15; Br, 31.20; N, 5.47; O, 6.25, Found: C, 53.91; H, 3.12; Br, 31.17; N, 5.46; O, 6.23.

Conclusions

Herein, we have established a new method which is cost-effective and environmental friendly for the *bis*(indolyl) methanes synthesis by sodium iodate and sodium hydrogen sulfite and water as a solvent.

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