

Ultrasound assisted N-bromosuccinimide catalyzed one pot condensation approach for synthesis of Bis(indolyl)methanes from primary alcohols

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ABSTRACT

A simple, efficient protocol for one pot synthesis of bis(indolyl)methanes from primary alcohols is investigated with N-bromosuccinimide as a catalyst under ultrasound irradiation. Alcohols can be converted into carbonyl compounds by removal of hydrogen in presence of N-bromosuccinimide as an oxidant and can react *in situ* with indole to give desired bis(indolyl)methanes. In the reported one pot multicomponent condensation reaction N-bromosuccinimide promotes the oxidation of alcohol to aldehyde, facilitating the subsequent condensation with indole to afford bis(indolyl) methanes in good to excellent yields. The inexpensiveness and easy handling are some of important feature of N-bromosuccinimide. The by-product N-succinimide can be easily recovered and recycled to N-bromosuccinimide.

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1. Introduction

Indole and its derivatives are known as an important class of heterocyclic compounds which exhibit a broad spectrum of biological activities, such as antimicrobial and antifungal,¹ antibacterial,² analgesic and anti-inflammatory,³ antitumor,⁴ and anticancer⁵ etc. The most common and conventional method for the synthesis of bis(indolyl)methanes involves condensation of aromatic aldehydes or ketones with indole in presence of either Bronsted or Lewis acids.^{6,7} The major drawbacks of the methodology include use of excess of Lewis acids, expensive reagents, toxic solvents, harsh reaction conditions etc. In recent years Farhad Shirini et al.⁸ reported synthesis of bis(indolyl)methanes using aromatic aldehydes and indole with FeCl₃-RiH as a catalyst. As there is rapid progress in the fields of synthetic and catalytic chemistry, instead of conventional methodology there is great demand to the development of new protocol for environmentally benign chemical processes. Oxidation of alcohols to carbonyl compounds is an important transformation in organic chemistry which can be effected by activating C-H bond using various reagents^{9a, b}.

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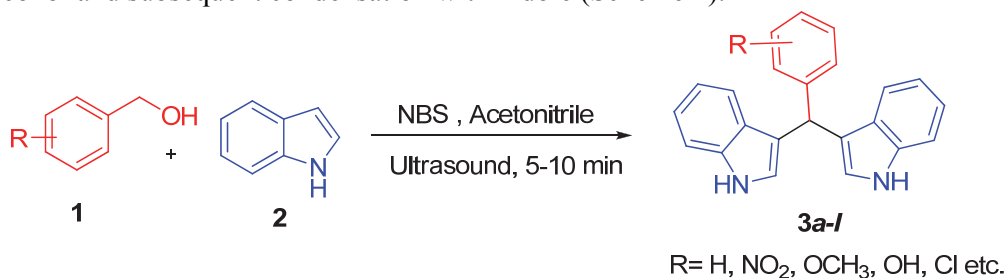
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Mohanraju et al.¹⁰ reported oxidation of primary alcohols by polymer bromide-DMSO based catalyst to afford corresponding carbonyl compounds. Various reagents have been exploited to bring about the oxidation of alcohols which includes (a) chromium based reagents, like PDC/PCC, Collins reagent ($\text{CrO}_3\text{-Py}_2$),¹¹ (b) hypervalent iodine compounds, such as 2-iodoxybenzoic acid or Dess-Martin periodinane.¹² One pot synthesis of bis(indolyl)methanes has been reported using transition metal catalysts and various oxidants such as $\text{Pd}(\text{OAc})_2/\text{Cu}(\text{OAc})$,¹³ Cu-Br/TBHP ,¹⁴ $\text{FeCl}_2/(\text{t-BuO})_2$,¹⁵ Recently Akichika Itoh et al.,¹⁶ (synlett -2012) reported one pot conversion of alcohols to bis(indolyl)methanes using iodine and molecular oxygen under visible light irradiation which required prolonged reaction time about 20 hr to complete the reaction. Very recently, Yuusaku Yokoyama and co workers¹⁷ (RSC Advances 2013) developed Palladium catalyzed synthesis of bis(indolyl)methanes which afforded 86% yield in 16 hr. The various available reports for synthesis of bis(indolyl)methanes has certain merits as well as demerits. Hence the need has been felt to develop an economically viable method having ambient reaction conditions to synthesize bis(indolyl)methanes. Furthermore, in order to enhance the yield of bis(indolyl)methanes, the various other techniques have been utilized viz, microwave^{18,19} and ultrasonication²⁰ etc. Among the studied methods ultrasound-assisted methodology has certain advantages over earlier reported methodologies. It has become useful tool in organic syntheses. The condensation proceeded under ultrasound at 40 ± 5 °C temperature and enhance the rate of reaction may be due to the cavitation and activation of catalyst by sonic waves. Use of ultrasound technique has certain advantages over conventional heating such as fast and clean reactions, simple experimental procedure and high yields of the product.²⁰ However to the best of our knowledge use of *N*-bromosuccinimide in the synthesis of bis(indolyl)methanes has not been reported earlier. In this regard herein, we report ultrasound assisted one pot multicomponent conversion of primary alcohol to afford bis(indolyl)methanes using catalytic amount of *N*-bromosuccinimide as a catalyst.

2. Results and Discussion

2.1 Synthesis and characterization

For the synthesis of bis(indolyl)methanes, optimization of the reaction conditions were carried out using various solvents, catalysts and substrate to catalyst mole ratios. The model reaction was studied with variety of catalysts like NBS, NCS, IBX, PCC, Ag_2O , ZnO , and TiO_2 for in situ oxidation of benzyl alcohol and subsequent condensation with indole (Scheme 1).



Scheme 1. Synthesis of Bis(indolyl)methanes from Primary alcohols

Within 5-10 min of ultrasound irradiation the NBS, NCS and NIS afforded corresponding bis(indolyl)methanes with 90, 70 and 20% yield respectively (Table 1, entries 1 to 3). With most of the catalyst used, reaction was either sluggish or did not proceed efficiently (Table 1 entries 4, 5, 7 and 8). Use of oxide catalysts like ZnO and TiO_2 did not show any conversion under this reaction conditions. Whereas, reaction of primary alcohols and indole with Ag_2O produced the bis(indolyl)methanes in 55% yield. (Table 1, entry 6). Among the studied catalysts, the oxidants such as NBS and NCS were found to be effective catalyst to catalyze the condensation of primary alcohols and indole for the synthesis of bis(indolyl)methanes. Considering environmentally benign approach of NBS in comparison with NCS we have chosen NBS as a milder and efficient catalyst in acetonitrile to afford corresponding product in good to high yields.

Table 1. Screening of catalysts for synthesis of bis(indolyl)methanes

Entry	Catalyst	Reaction time, min	Conversion, %
1	NBS	5	92
2	NCS	5	70
3	NIS	5	20
4	IBX	5	NR
5	PCC	5	10
6	Ag ₂ O	5 h	55
7	ZnO	4 h	NR
8	TiO ₂	5 h	NR

Reaction Conditions: 0.106 gm (1 mmol) benzyl alcohol, 0.117 gm (2 mmol) Indole, 0.178 gm (1 mmol) catalyst were stirred in 3 mL acetonitrile under ultrasound irradiation at room temperature (40 ± 5 °C), NR- no reaction.

The effect of various solvents on the yield of bis(indolyl)methanes was investigated and results are shown in Table 2. The reaction was completed in acetonitrile within 10 min with catalytic amount of NBS affording 92% yield of desired product. However the reaction was sluggish in DMSO yielding 20% yield of bis(indolyl)methanes. The extent of yield of bis(indolyl)methanes was in the order, CH₃CN>EtOH> CH₃OH>DCM>CCl₄~CHCl₃~DEE>DMF>DMSO. This observation suggests that among the studied solvents acetonitrile, being highly polar aprotic solvent enhances the activity of catalyst compared to other polar aprotic and non-polar solvents and gave the excellent yield within 10 min under ultrasound reaction condition. For further investigation we used NBS as a catalyst and acetonitrile as a solvent.

Table 2. Effect of solvent on oxidation of benzyl alcohol using NBS

Entry	Solvent	Conversion, %
1	Acetonitrile	92
2	Ethanol	90
3	Methanol	90
4	CCl ₄	88
5	CHCl ₃	80
6	Diethyl ether	80
7	DCM	85
8	1,4 Dioxane	80
9	DMF	45
10	DMSO	20

Reaction Conditions: 0.106 gm (1 mmol) benzyl alcohol, 0.117 gm (2 mmol) Indole, 0.178 gm (1 mmol) NBS were stirred in 3 mL solvent under ultrasound irradiation for 5 min at room temperature (40 ± 5 °C)

In order to find the optimum amount of NBS required for synthesis of bis(indolyl)methanes we varied the amount of NBS from 0.5 to 2.5 moles under 5 min of ultrasound irradiation and recorded the % conversion depicted in Table 3. It was found that use of 0.5 and 1 mol% NBS gave 78 and 92 % conversion respectively while further increase in the NBS mole ratio (>1 mol %) there was no significant improvement in the yield of product so we carried out reaction using 1 mol % of NBS.

Table 3. Study of effect of catalyst (NBS) concentration

Entry	Mol %	Time, min	Conversion, %
1	0.5	5	78
2	1.0	5	92
3	1.5	5	90
4	2.0	5	89
5	2.5	5	89

Reaction Conditions: 0.106 gm (1 mmol) benzyl alcohol, 0.117 gm (2 mmol) Indole, (x mmol) NBS were stirred in 3 mL acetonitrile under ultrasound irradiation for 5 to 10 min at room temperature (40 ± 5 °C).

Encouraged by these results, we studied the scope of this condensation reaction with substituted benzyl alcohols and indole under optimized reaction conditions with NBS in presence of acetonitrile as a solvent and results are tabulated in Table 4.

Table 4. Synthesis of bis(indolyl)methanes using benzyl alcohols promoted by NBS

Entry	Alcohol	Product	Time, min	Conversion, %
1		2a	10	92
2		2b	5	96
3		2c	5	95
4		2d	5	94
5		2e	5	93
6		2f	10	88
7		2g	10	85
8		2h	5	90
9		2i	5	92
10		2j	5	94
11		2k	5	90
12		2l	5	90

Reaction Conditions: 0.106 gm (1 mmol) benzyl alcohol, 0.117 gm (2 mmol) Indole, (1 mmol) NBS were stirred in 3 mL acetonitrile under ultrasound irradiation for 5 to 10 min at room temperature (40 ± 5 °C).

The objective of the present work was to minimize the problems associated with conventional condensation reaction of aldehydes with indole and to explore use of different catalyst for synthesis of bis(indolyl)methanes. The reaction of benzyl alcohol with NBS (1:1 mol) in presence of acetonitrile was proceeded cleanly and gave corresponding aldehyde within 2 min of ultrasound irradiation, which was confirmed by GC analysis. To this reaction mixture, 2 equivalent of indole was added and continued the reaction for further 5 min. The pink colored crude product was obtained within 10 min of ultrasound irradiation, which on isolation afforded corresponding bis(indolyl)-phenylmethane (**2a**) in 92% yield. (Table 4, entry 1). Several substituted benzyl alcohols carrying either electron releasing or electron withdrawing substituents afforded the desired product with good to high yield. The *ortho* and *para* nitro substituted benzyl alcohol gave more than 95% yield for corresponding product (Table 4, entry 2 and 3). Similarly, methoxy and hydroxy substituted benzyl alcohols afforded 94 and 93 % yield for the respective product (Table 4, entry 4 and 5). The condensation of methyl substituted benzyl alcohols were sluggish required higher reaction time to obtain the desired bis(indolyl)methanes. (Table 4, entry 6 and 7). The halogenated benzyl alcohols also afforded more than 90% yield for the corresponding product under similar reaction conditions (Table 4, entry 8-12). In order to illustrate the efficacy of NBS for the synthesis of bis(indolyl)methanes, we compared our obtained results with some of the best literature results (Table 5). The palladium catalyzed synthesis furnish products in 56 to 98% yield after 12 to 16 h of reaction time (Table 5, entries 1 and 3). The iodine and molecular oxygen catalyzed reaction of benzyl alcohol and indole required more than 16 h for completion of reaction in 86% yield (Table 5, entry 2). Similarly, ruthenium catalyzed reaction took about 48 h to yields 88% of

product (Table 5, entry 4). Among the studied catalysts NBS was found to be the most effective as it affords in the high yield of bis(indolyl)methanes in short reaction time (Table 5, entry 5).

Table 5. Comparison between NBS and other catalysts used to synthesis bis(indol-3-yl)methanes from benzyl alcohols

Entry	Reagent and solvent	Time	Yield, %	Reference
1	Pd(OAc) ₂ / Cu(OAc) ₂	Neat, 12 h, 70°C	up to 90	13
2	I ₂ and molecular oxygen	20 h	up to 86	16
3	Pd(OAc) ₂ , TPPMS, H ₂ O	16 h 60°C	56-98	17
4	RuCl ₃ .3H ₂ O	48 h rt	up to 88	14
5	NBS, Acetonitrile	5 to 10 min	up to 96	Present work

3. Experimental

3.1. Materials and Methods

All reagents (Aldrich, Fluka) and solvents were of commercial grade and used as received, all the products obtained were purified by column chromatography using neutral silica gel (60–120 mesh) and hexane, ethyl acetate as an eluent. ¹H NMR spectra were recorded in CDCl₃ and DMSO-d₆ using Varian 400 MHz NMR spectrometer. Proton chemical shifts (δ) are relative to TMS ($\delta = 0$) as internal standard and expressed in PPM. Coupling constants (J) are given in Hertz. The IR spectra were recorded on a FTIR spectrophotometer (Shimadzu IR affinity 1 MIRacle 10 spectrophotometer) in the range of 400–4000 cm⁻¹. Ultraviolet-visible absorption spectra of BIMs were recorded by double beam spectrophotometer (UV-3600, Shimadzu) in the range of 300–900 nm. Melting point was determined on Buchi M-560. The conversion and selectivity of the obtained product was analyzed by GC (HP 5890) using a capillary column (HP-5). GC mass spectra were taken on a Shimadzu GC-MS-QP5050A spectrometer equipped with a DB-5 column to identify the products. Reaction was monitored by thin layer chromatography (TLC) with Merck's silica gel plates (60 F₂₅₄).

3.2. General Procedure for the Synthesis of Bis(indolyl)methanes

A mixture of benzyl alcohol **1** (106 mg 1.0 mmol), and NBS (178 mg 1mmol) in acetonitrile (3 mL) was stirred in a 25 mL round bottom flask with water condenser under ultrasound irradiation for 2 min under N₂ atmosphere. The progress of the reaction was monitored by TLC (30% hexane/ethyl acetate as mobile phase, development of brown color on TLC plate with 2, 4, DNP stain). To this reaction mixture, indole **2** (117 mg 2 mmol) was added and the reaction further continued under ultrasound irradiation for 3 to 10 min. Depending on the substituent's and solvents the ultra-sonication time was varied up to 5 hrs. The formed crude product **3** was purified by silica column chromatography using hexane/ethyl acetate (90/10 v/v) as a eluent. The purified product was further characterized using UV-Vis, FTIR and NMR techniques.

3.3 Physical and Spectral Data etc.

3, 3-Bis (indolyl)-phenylmethane (2a)

IR 3469, 3371, 1595, 1507, 1330, 1012, 739 cm⁻¹ **¹H NMR** (DMSO-d₆, 400 MHz, Me₄Si): δ 5.8(1H, CH), 6.7 (2H, $J_{\text{HH}} = 2$ Hz, CH₂), 6.86 (2H, $J_{\text{HH}} = 7.6$ and 14.6 Hz, CH₂), 7.1(2H, $J_{\text{HH}} = 8$ and 14.80 Hz, CH₂), 7.02 (1H, $J_{\text{HH}} = 7.2$ and 14.40 Hz, Ph), 7.4 (4H, $J_{\text{HH}} = 8$ and 16 Hz, Ph), 7.2(4H), 10.8 (2H, br, NH); **¹³C NMR** (CDCl₃, 200 Hz): δ 144.8, 136.4, 128.19, 127.9, 126.54, 125.64, 123.41, 120.74, 118.98, 118.03, 117.97, 111.32; mp 124–126°C; m/z 321.38

3, 3-Bis (indolyl)-4-nitrophenylmethane (2b)

¹H NMR (DMSO-d₆, 400 MHz, Me₄Si): δ 6 (1H, s, CH), 6.8 (2H, d, *J*= 8.4, CH), 6.7 (2H, d), 6.84 (2H, t, *J*= 8.0 and 15.2 Hz, Ph), 7.01 (2H, t, *J*= 7.60 and 14.8 Hz, Ph), 7.1 (2H, d, *J*=8.4Hz, Ph), 7.2 (2H, d, *J* 8.0Hz, Ph), 7.3 (2H, d, *J*=8.4Hz,Ph), 10.8 (1H, bs, NH); mp 170–174°C.

3, 3-Bis (indolyl)-4-hydroxyphenylmethane (2e)

IR 3471, 3300, 1516, 1233, 1180, 747 cm⁻¹ ¹H NMR (DMSO-d₆, 400 MHz, Me₄Si): 5.6 (1H, s, CH), 6.6 (2H, d, *J*= 8.4, CH), 6.7 (2H, d), 6.84 (2H, t, *J*= 8.0 and 15.2 Hz, Ph), 7.01 (2H, t, *J*= 7.60 and 14.8 Hz, Ph), 7.1 (2H, d, *J*=8.4Hz, Ph), 7.2 (2H, d, *J* 8.0Hz, Ph), 7.3 (2H, d, *J*=8.4Hz,Ph), 9.1 (1H, bs, NH), 10.7 (2H, bs, OH); mp 170–174°C.

3, 3'-Bis (indolyl)-4-chlorophenylmethane (2j)

IR 3489, 3345, 1545, 1516, 1330, 1016, 739 cm⁻¹ ¹H NMR (DMSO-d₆, 400 MHz, Me₄Si): 5.9 (1H, s), 6.8 (2H, brs), 7.4-7.80(12H, m), 10.2(2H, bs, NH); ¹³C NMR (CDCl₃, 200 Hz.): δ 143.8,137.4, 132.15, 131.9, 127.54, 123.44, 122.41, 120.14, 118.98,118.45, 110.47, 77.22, 39.51; mp 124–126°C; m/z 321.38Mp120-122 oC; (Lit.[13] 104-105°C).

4. Conclusions

Herein, we have reported a simple, efficient methodology for the synthesis of bis(indolyl)methanes using NBS as mild and efficient catalyst under ultrasound irradiation. The reported methodology offers several advantages like inexpensiveness of the catalyst, easy availability, fast and clean reactions, simple experimental procedure and high yields of the product compared to the traditional methods of synthesis.

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