



AN EFFICIENT SYNTHESIS OF BIS INDOLYL METHANE USING PMImBr

Rakesh P. Chaudhari^a, Ganesh R. Chaudhari^a, Hemant A. Mahajan^{b*}

^aDepartment of Chemistry, Arts and Science College, Bhalod, Taluka-Yawal, Dist-Jalgaon MS, India.

^bDepartment of Chemistry, MTES's Smt. G.G. Khadse College, Muktainagar, Taluka-Muktainagar, Dist-Jalgaon MS, India.

ABSTRACT:

A simple and efficient protocol has been developed for the synthesis of a series of bisindolyl methanes using an ionic liquid and a few drops of sulfuric acid. The reaction involves a three-component, one-pot condensation of two molecules of indole and aromatic aldehydes. The environmentally friendly protocol has high yields, quick reaction times, and easy product recovery.

KEYWORDS- PMImBr-1 Methyl 3 Propyl Imidazolium Bromide and PPBr- Propyl Pyridinium Bromide,

INTRODUCTION-

Indole is a crucial component of several medicinally significant natural products and has reactive sites that may be used in a range of chemical processes to produce a diversity of moleculesⁱ. Bisindolylmethanes and their derivatives are bioactive in terrestrial and marine metabolitesⁱⁱ. Bis(indole)alkaloids from the marine environment exhibit antibacterialⁱⁱⁱ, antioxidant^{iv}, cytotoxic^v, antiviral^{vi}, and anti-inflammatory^{vii} activities. In recent years, efficient and environmentally conscious Indole derivative synthesis methods have gained a lot of attention^{viii}. Bis(indolyl)methane derivatives are well known for their various biological and pharmaceutical activities. Several researchers have reported the effective synthesis of the Bisindolylmethanes derivatives utilizing ionic liquids as a catalyst such as [hmmim]Br^{ix}, [Msim]Cl^x, In(OTf)₃/[omim][PF₆]^{xi}, FeCl₃·6H₂O/[omim]PF₆^{xii}, N-ethyl pyridinium hydrogen sulfate^{xiii}, [H-Suc]HSO₄^{xiv}, Tetrabutylammonium Tribromide^{xv}, Tetramethyl guanidinium chlorosulfonate^{xvi} etc.

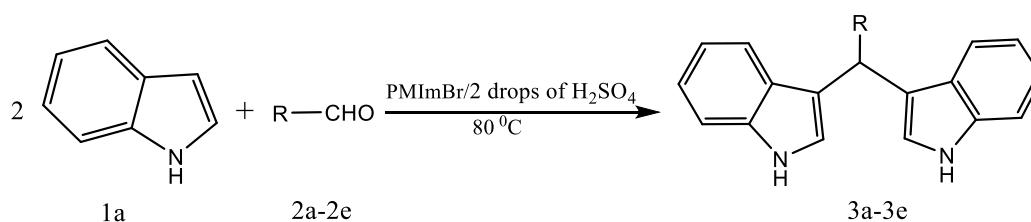
The use of ionic liquids as reaction mediums and catalysts is one prominent technique^{xvii}. Ionic liquids are organic molten salts that are liquid at or near room temperature and have distinct features that make them appealing substitutes for typical organic solvents. Because of its low toxicity, accessible availability, and cheap cost, Ionic liquid has been frequently employed as a catalyst as well as solvent in numerous chemical processes^{xviii}. Sulfuric acid accelerates the condensation of indole derivatives and substituted aldehyde to produce bis-indole. Ionic liquids improve reactant solubility, reaction speeds, and selectivity. The sulfuric acid catalyst activates

the aldehyde, followed by a nucleophilic attack of the indole on the activated carbonyl carbon in the mechanism of bis-indole synthesis in ionic liquids.

Sulfuric acid is used in ionic liquid-mediated bis-indolyl methane synthesis, which has various benefits over previous approaches, such as the reaction may be carried out under benign settings without the employment of hazardous volatile liquid. The reaction runs smoothly and efficiently, with high yields and selectivity of the ionic liquid making the process more environmentally friendly and economically feasible.

RESULTS AND DISCUSSION:

We present herein the results of the Synthesized bis(indolyl)alkanes by the Reaction of indoles with aldehydes in the presence of 2 drops of sulfuric acid in the ionic liquid PMImBr. (Scheme-1)



Our first effort included coupling two equivalents of indole with benzaldehyde at 80 °C in the presence of 10 mol% tartaric acid without using a solvent. The reaction was complete after 150 minutes, yielding product 3a at a yield of 57%. To improve the conversion, we switched to a solvent-free, 80 °C, 20 mol% tartaric acid treatment of indole (1a) with benzaldehyde (2a). This time, the reaction needed 135 minutes to complete, and a 62% yield of the desired product, 3a-3e, was obtained. (Table 1).

Table 1 Optimization of Reaction of indole with benzaldehyde under different reaction conditions.

Sr. No.	Solvent	Catalyst	Temp °C	Time	Yield %
1	-	Tartaric Acid (10%)	80	150	57
2	-	Tartaric Acid (20%)	80	135	62
3	Ethanol	Tartaric Acid (10%)	80	240	72
4	Ethanol	Tartaric Acid (20%)	80	240	82
5	PPBr	-	80	60	70
6	PMImBr	-	80	50	75
7	PPBr	Tartaric Acid (10%)	80	78	74
8	PPBr	Tartaric Acid (20%)	80	72	79
9	PMImBr	Tartaric Acid (10%)	80	70	78
10	PMImBr	Tartaric Acid (20%)	80	60	82
11	PrPyBr	H ₂ SO ₄ (2 Drops)	80	43	84
12	PMImBr	H₂SO₄ (2 Drops)	80	38	86

We then attempted the same reaction using 10% and 20% mole proportion of tartaric acid under ethanol as a solvent at 80 °C. Then, both reactions went to completion in 240 min, with yields of 72% and 85%, respectively. Additionally, we conducted the reaction without a catalyst, using propyl pyridinium bromide and 3-propyl 1 methyl imidazolium bromide, and observed a slightly higher yield (67% and 80%). When tartaric acid was added to both ionic liquids at 10% and 20%, we saw an increase in yield.

To improve the yield, we turned to strong acids such as sulfuric acid. We observed that in both ionic liquids (PPBr and PMImBr), the yield of the product increased significantly. With the addition of sulfuric acid as a catalyst, we obtained yields of 84% and 86% using PPBr and PMImBr, respectively, and we also found that the reaction time decreased from 68 min without a catalyst to 38 min with the sulfuric acid catalyst in PMImBr ionic liquid.

Encouraged by these results, we then investigated the coupling of various aromatic aldehydes with indole. We found that aromatic aldehydes with an electron-donating or electron-withdrawing group (entries 3a-3e in Table 2) could be easily coupled with indole to obtain the appropriate bis(indolyl)methanes in excellent amounts.

Table 2 Synthesis of Bis indolyl methane 3a–e catalyzed by 2 drops of H₂SO₄ in PMImBr

Sr. No.	R	Product	Time (Min)	Yield (%)	MP °C
1	C ₆ H ₅ -	3a	38	86	124-125
2	p-BrC ₆ H ₄ -	3b	36	87	110-112
3	p-ClC ₆ H ₄ -	3c	35	85	102-103
4	p-CH ₃ OC ₆ H ₄ -	3d	30	84	177-179
5	o-NO ₂ C ₆ H ₄ -	3e	31	87	88-89

EXPERIMENTAL:

All common reagents and solvents were purchased from commercial suppliers and were not purified further. These two Ionic Liquids were synthesized using some modifications previously reported in the literature^{xix}. All the experiments were carried out under neat conditions; pre-coated silica gel plates (Merck, Germany) developed with iodine were used for analytical thin-layer chromatography (TLC), and Melting points were measured using the Digital Analab Scientific Instrument. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker Advance Neo 500 MHz spectrometer in CDCl₃ or DMSO-d₆. Mass spectra were performed on a Waters Q-ToF Micro LC-MS spectrometer.

GENERAL PROCEDURE:

Preparation of PMImBr and PPBr ILs. -

Pyridine (1 mol) /1 Methyl imidazole (1 mol) was placed in a 100 mL two naked round-bottomed flask attached with a reflux condenser and stirred, to 1-bromopropane (1.1 mol) was added dropwise at 90 °C after 45 to 60 minute ionic liquid is formed. The excess starting compound was removed by extracting with 5 ml ethyl acetate. The final compound is then dried in a vacuum oven for 4 hours at 80 °C. The products were identified by ¹H NMR, ¹³C CMR, and MS data.

Synthesis of Bisindolylmethane-

A mixture of 10 mmole of Indole and 5 mmole of substituted aldehyde, 2 drops of sulfuric acid in 2 ml of PMImBr was stirred at 80 °C for 30 to 40 min. Progress of the reaction was monitored by thin-layer chromatography (TLC) (eluent ethyl acetate–hexane 80:20). After completion of the reaction, the reaction mixture was poured into crushed ice and then filtered. The product obtained was further purified by recrystallization from hot ethanol. The products were identified by melting point, ¹H NMR, ¹³C CMR, and MS data.

Spectral data of synthesized compound-

Propyl Pyridinium Bromide(PPBr):

¹H NMR (DMSO): δ (ppm) 0.23-0.26(3H,t), 1.34-1.39(2H,m), 4.22-4.25(2H,t), 8.88-8.90(2H,d), 7.93-7.97(2H,t), 8.88-8.90 (1H,t). ¹³C NMR (DMSO): δ10.11,28.90, 62.42,128.15,144.72, 145.24. Mass (m/z): 202 (M+, 100%)

1 Methyl 3 Propyl Imidazolium Bromide (PMImBr):

¹H NMR (DMSO): δ (ppm) 0.11-0.14(3H,t), 1.11-1.15(2H,m), 3.30(3H,s), 3.49-3.52(2H,t), 6.95-6.96(1H,d), 6.99-7.00 (1H,d), 9.23 (1H,s). ¹³C NMR (DMSO): δ 39.71, 111.13, 119.12, 119.39, 119.83, 119.94, 122.11, 123.62, 126.89, 130.52, 131.33, 136.71, 143.11. Mass (m/z): 205 (M+, 100%)

3-[(1H-Indol-3-yl) (phenyl)methyl]-1H-indole(3a):

¹H NMR (CDCl₃): δ (ppm) 7.83(2H,s,NH), 5.87 (1H,s), 6.61(2H,s), 6.97-7.00(2H,tri), 7.13-7.21(3H,m), 7.23-7.26(2H,m), 7.31-7.34(4H-tri), 7.37-7.38(2H,d). ¹³C NMR (CDCl₃): δ 40.22, 111.04, 119.25, 119.74, 119.96, 121.94, 123.62, 126.15, 127.10, 128.23, 128.74, 136.71, 144.02. Mass (m/z) =322(M+, 100%)

3-[(1H-Indol-3-yl) (4 bromo phenyl) methyl]-1H-indole(3b):

¹H NMR (CDCl₃): δ(ppm) 7.87(2H, s,NH), 5.82 (1H,s), 6.61(2H,s), 7.01(2H,d), 7.15-7.23(Ar-4H,m), 7.32-36 (6H,m). ¹³C NMR (CDCl₃): δ 39.71, 111.13, 119.12, 119.39, 119.83, 119.94, 122.11, 123.62, 126.89, 130.52, 131.33, 136.71, 143.11. Mass (m/z): 399(M+, 100%)

CONCLUSION:

In conclusion, the synthesis of bisindolyl methane using sulfuric acid in a Propyl methyl imidazolium ionic liquid is a very efficient and ecologically benign technique. The use of ionic liquids as a reaction medium has various benefits, including increased solubility, faster reaction rates, and less waste formation. Sulfuric acid acting as a catalyst has demonstrated its effectiveness in promoting the desired reaction resulting in the formation of bisindolyl methane with satisfactory yields.

ACKNOWLEDGEMENT:

The authors are thankful to the Principals of Arts and Science College, Bhalod and MTES's Smt. G. G. Khadse College, Muktainagar for the facility given for the present research work.

REFERENCES:

- i. Kaushik, N.; Kaushik, N.; Attri, P.; Kumar, N.; Kim, C.; Verma, A.; Choi, E. Biomedical Importance of Indoles. *Molecules* **2013**, *18* (6), 6620–6662. <https://doi.org/10.3390-/molecules18066620>.
- ii. Shirini, F.; Khaligh, N. G.; Jolodar, O. G. An Efficient and Practical Synthesis of Bis(Indolyl)Methanes Catalyzed by N-Sulfonic Acid Poly(4-Vinylpyridinium) Chloride. *Dyes and Pigments* **2013**, *98* (2), 290–296. <https://doi.org/10.1016/j.dyepig.2013.03.003>.
- iii. Gul, W.; Hamann, M. T. Indole Alkaloid Marine Natural Products: An Established Source of Cancer Drug Leads with Considerable Promise for the Control of Parasitic, Neurological and Other Diseases. *Life Sciences* **2005**, *78* (5), 442–453. <https://doi.org/10.1016/j.lfs.2005.09.007>.
- iv. Jignesh Lunagariya; Poonam Bhadja; Zhong, S.; Vekariya, R. L.; Xu, S.-H. Marine Natural Product Bis-Indole Alkaloid Caulerpin: Chemistry and Biology. *Mini-reviews in Medicinal Chemistry* **2019**, *19* (9), 751–761. <https://doi.org/10.2174/138-9557517666170927154231>.
- v. Endo, T.; Tsuda, M.; Fromont, J.; Kobayashi, J. Hyrtinadine A, a Bis-Indole Alkaloid from a Marine Sponge. *Journal of Natural Products* **2006**, *70* (3), 423–424. <https://doi.org/10.1021/np060420n>.

- vi. I Leena Gupta; Archana Talwar; Prem M.S. Chauhan. Bis and Tris Indole Alkaloids from Marine Organisms: New Leads for Drug Discovery. *Current Medicinal Chemistry* **2007**, *14* (16), 1789–1803.
<https://doi.org/10.2174/092986707781058904>.
- vii. Hwang, J.; Kim, D.; Park, J. S.; Park, H. J.; Shin, J.; Lee, S. K. Photoprotective Activity of Topsentin, a Bis(Indole) Alkaloid from the Marine Sponge Spongisorites Genitrix, by Regulation of COX-2 and Mir-4485 Expression in UVB-Irradiated Human Keratinocyte Cells. *Marine Drugs* **2020**, *18* (2), 87.
<https://doi.org/10.3390/md18020087>.
- viii. Roopa Margaret Rodrigues; Ditto Abraham Thadathil; Keerthana Ponmudi; George, A.; Varghese, A. Recent Advances in Electrochemical Synthesis of Nitriles: A Sustainable Approach. *ChemistrySelect* **2022**, *7* (12).
<https://doi.org/10.1002/slct.202200-081>.
- ix. Kumar, R.; prajapati, santosh; Rastogi, S. K.; Singh, A.; Mini Bharati; Deshmukh, M. M.; Sinha, A. K. Friedel-Crafts-Type Reaction of (Het)Arenes with Aldehydes/Ketones under Acid-Free Conditions Using Neutral Ionic Liquid: A Convenient Routes to Bis(Indolyl)Methanes and Beyond. *Asian Journal of Organic Chemistry* **2022**, *11* (3). <https://doi.org/10.1002/ajoc.202100749>.
- x. Mohammad Ali Zolfigol; Ardeshir Khazaei; Ahmad Reza Moosavi-Zare; Zare, A. Ionic Liquid 3-Methyl-1-Sulfonic Acid Imidazolium Chloride as a Novel and Highly Efficient Catalyst for the Very Rapid Synthesis of Bis(Indolyl)Methanes under Solvent-Free Conditions. *Organic preparations and procedures international* **2010**, *42* (1), 95–102. <https://doi.org/10.1080/00304940903585495>.
- xi. Ji, S.-J.; Zhou, M.; Gu, D.; Wang, S.-Y.; Loh, T.-P. Efficient Synthesis of Bis(Indolyl)Methanes Catalyzed by Lewis Acids in Ionic Liquids. *Synlett* **2003**, No. 13, 2077–2079. <https://doi.org/10.1055/s-2003-41464>.
- xii. Ji, S.-J.; Zhou, M.-F.; Gu, D.-G.; Jiang, Z.-Q.; Loh, T.-P. Efficient FeIII-Catalyzed Synthesis of Bis(Indolyl)Methanes in Ionic Liquids. *European Journal of Organic Chemistry* **2004**, *2004* (7), 1584–1587. <https://doi.org/10.1002/ejoc.200300719>.
- xiii. Mulla, R.; Arumugam Sudalai; Pathan, M. Y.; Siddique, S. A.; Inamdar, S. M.; Chavan, S. S.; Reddy, R. Efficient, Rapid Synthesis of Bis(Indolyl)Methane Using Ethyl Ammonium Nitrate as an Ionic Liquid. *RSC Advances* **2012**, *2* (8), 3525–3525. <https://doi.org/10.1039/c2ra00849a>.
- xiv. Omid Goli-Jolodar; Farhad Shirini. Succinimidinium Hydrogensulfate ([H-Suc]HSO₄) as a New, Green and Efficient Ionic Liquid Catalyst for the Synthesis of Tetrahydrobenzimidazo[2,1-b]Quinazolin-1(2H)-One, 1-(Benzothiazolylamino) Phenylmethyl-2-Naphthol, 1, 8-Dioxo-Octahydroxanthene and Bis(Indolyl)Methane Derivatives. *Journal of The Iranian Chemical Society* **2016**, *13* (6), 1077–1092. <https://doi.org/10.1007/s13738-016-0822-1>.
- xv. Shrishnu Kumar Kundu; Islam, S.; Alakananda Hajra; Adinath Majee. Tetrabutylammonium Tribromide as Efficient Catalyst in the Synthesis of Bis(Indolyl)Methanes. *Russian Journal of Organic Chemistry*, **2010**, *46* (1), 126–128. <https://doi.org/10.1134/s1070428010010136>.
- xvi. Reddi; John, J. V.; Park, H.; Kim, I. Tetramethyl Guanidinium Chlorosulfonate as a Highly Efficient and Recyclable Organocatalyst for the Preparation of Bis(Indolyl)Methane Derivatives. *Catalysis Communications*, *2014*, *57*, 55–59. <https://doi.org/10.1016/j.catcom.2014.08.003>.

- xvii. Vafaezadeh, M.; Alinezhad, H. Brønsted Acidic Ionic Liquids: Green Catalysts for Essential Organic Reactions. *Journal of Molecular Liquids* **2016**, *218*, 95–105. <https://doi.org/10.1016/j.molliq.2016.02.017>.
- xviii. Welton, T. Ionic Liquids: A Brief History. *Biophysical Reviews* **2018**, *10* (3), 691–706. <https://doi.org/10.1007/s12551-018-0419-2>.
- xix. Tong, B.; Liu, Q.-S.; Tan, Z.-C.; Welz-Biermann, U. Thermochemistry of Alkyl Pyridinium Bromide Ionic Liquids: Calorimetric Measurements and Calculations†. *The Journal of Physical Chemistry A*, *2010*, *114* (11), 3782–3787. <https://doi.org/10.1021/jp9047538>.

Received on October 31, 2023.