



**BISMUTH TRIFLATE CATALYZED ECOFRIENDLY AND EFFICIENT
SYNTHESIS OF BIS(INDOLYL)METHANES BY GRINDING APPROACH**

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Abstract

Bismuth triflate was found to be a mild, efficient and reusable solid acid catalyst in electrophilic substitution reaction of indoles with different aldehydes and ketones to give the corresponding bis(indolyl)methanes by using clean and environmentally benevolent grinding method. The significant sorts of this method are excellent yields of the products under solvent-free conditions, mild and inexpensive catalyst.

Keywords: Bismuth triflate, aldehydes, indoles, grinding method.

Introduction

Indole moieties are featured in a variety of pharmacologically and biologically active compoundsⁱ which makes it the current interest of organic synthesis. Particularly, bis(indolyl)methanes are known to enhance estrogen metabolism in humans and is likely to be drug of choice for breast cancer and also it exhibits antibacterial activities. In particular, bis(indolyl)methanes are the most active cruciferous substances for promoting beneficial estrogen metabolism and including apoptosis in human cancer cells^{ii-iv}.

Numerous methods for synthesis of this has been developed including use of Lewis acid^v, protic acid^{vi}, PPA/SiO₂^{vii}, silica sulfuric acid^{viii}, In(OTf)₃^{ix}, I₂^x, PCl₅^{xi}, ionic liquid^{xii}, citric acid^{xiii}, cellulose perchloric acid^{xiv} and silica gel^{xv} were found to promote the reaction. Therefore, there is a great deal of interest in the synthesis of these classes of compounds.

One of the ultimate goals for organic reactions is to reduce the use of harmful organic solvents. For this reason, over the last few years enormous advances have been made to achieve the environment friendly chemical processes. One way for this purpose is carrying out the reactions in solvent-free conditions^{xvi}. In view of green chemistry utilization of solid state grinding technique is becoming much significant in organic synthesis^{xvii}. There

are several reports on the use of organo-bismuth compounds as catalysts in organic synthesis possibly due to the unstable nature of Bi-C bonds. Keeping the importance of green and sustainable chemistry in mind, we aimed to develop bismuth catalyzed eco-friendly protocol for the synthesis of bis(indolyl)methanes.

Experimental section

Material and methods: All chemicals were purchased from Thomas beaker Ltd, India and used without any further purification. Melting points were recorded on Electro thermal MEL-TEMP apparatus and are uncorrected. Conventional mortar and pestle was used for grinding the reaction mixture. Infrared spectra were recorded on Bruker spectrophotometer in a KBr disc and the absorption bands are expressed in cm^{-1} . ^1H NMR spectra were recorded on NMR spectrometer AC200 in CDCl_3 .

Typical experimental procedure: To the mixture of indole **1** (2.0 mmol) and aromatic aldehyde **2** (1.0 mmol) was taken in a mortar and pulverized well in the presence of bismuth triflate (5 mol. %) using pestle and further grinding was continued until reaction was completed. Progress of the reaction was monitored by TLC (ethyl acetate: n-hexane = 2:8). After completion of reaction, reaction mixture was quenched with 5ml water to get product **3**. Then it was collected by simple filtration. Thus obtained product was crystallized with aqueous ethanol to afford pure product without need of any further purification. The spectral data of selected bis(indolyl)methanes given below.

Spectroscopic data for selected compounds

3, 3'-Bis(indolyl) phenylmethane (Entry 3a)

IR (KBr): 3470, 3015, 1600, 1518, 1451, 1414, 1209, 1090, 1013, 754, 667 cm^{-1} ; ^1H NMR (CDCl_3 , δ ppm): 5.87 (1H, s), 6.64 (2H, s), 7.05-7.52 (13H, m), 7.91 (2H, bs, NH)

3, 3'-Bis(indolyl)-4-methylphenylmethane (Entry 3b)

IR (KBr): 3475, 3017, 1604, 1513, 1456, 1415, 1218, 1095, 1019, 755, 669 cm^{-1} ; ^1H NMR (CDCl_3 , δ ppm): 2.29 (3H, s), 5.81 (1H, s), 6.63 (2H, s), 6.81-7.36 (12H, m), 7.92 (2H, bs, NH)

3, 3'-Bis(indolyl)-3,4-dimethoxyphenylmethane (Entry 3d)

IR (KBr): 3470, 3015, 1603, 1517, 1453, 1409, 1331, 1211, 1095, 1029, 752 cm^{-1} ; ^1H NMR (CDCl_3 , δ ppm): 3.72 (3H, s), 3.83 (3H, s), 5.79 (1H, s), 6.62 (2H, d), 6.75 (2H, d), 7.09 (3H, t), 7.14 (2H, t), 7.26-7.41 (4H, m), 7.87 (2H, bs, NH)

3, 3'-Bis(indolyl)-4-chlorophenylmethane (Entry 3e)

IR (KBr): 3465, 3009, 2920, 1594, 1520, 1448, 1405, 1210, 1090, 1002, 750, 661 cm^{-1} ; ^1H NMR (CDCl_3 , δ ppm): 5.83 (1H, s), 6.61 (2H, bs), 7.03-7.69 (12H, m), 7.90 (2H, bs, NH)

3, 3'-Bisindolyl(2-furfuryl)methane (Entry 3j)

IR (KBr): 3475, 3011, 2388, 1596, 1448, 1417, 1211, 1092, 1023, 757, 672 cm^{-1} ; ^1H NMR (CDCl_3 , δ ppm): 5.91 (1H, s), 6.01 (1H, d), 7.24 -7.43 (5H, m), 6.27 (1H, d), 6.83 (1H, d), 7.01 (2H, t), 7.12 (2H, t), 7.92 (2H, bs, NH)

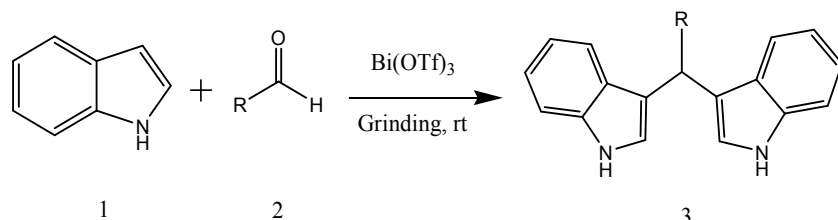
Result and discussion

For our initial study, reaction of indole and benzaldehyde for the synthesis of bis(indolyl)methanes various attempts were made under grinding technique by using mortar and pestle. In this regard, different catalysts such as sulphamic acid, oxalic acid, citric acid and bismuth triflate were utilized for this reaction. When citric acid and sulphamic acid were employed, product was obtained in low yields (**Table-1**). Furthermore, use of oxalic acid as catalyst resulted into moderate yield, whereas intervention of bismuth triflate delivered fascinating results with very high yield up to 92%. Finally, as a matter of fact, bismuth triflate stood out as an excellent catalyst furnishing high product yield within much shorter reaction time (**Table-2**).

Table-2 shows a major difference in the yield and reaction time for different substrates. Aromatic aldehydes having an electron withdrawing substituent undergo reaction at a much faster rate as compared to electron releasing groups attached, and gave bis(indolyl)methanes in excellent yields.

It is noteworthy to point out that, reaction mixture on pulverization in mortar immediately turns into sticky mass, which on further grinding for appropriate time affords the desired product in excellent yield and purity. To further establish the scope of optimized reaction conditions and in order to generalize the synthetic procedure, variety of electronically divergent aryl aldehydes were treated indole and all these substrates were found to be equally amenable to these conditions. Interestingly, some heteryl aldehydes also underwent the reaction efficiently. Representative results are summarized in **Table-2**. Formation of the products was confirmed on the basis of spectroscopic data.

In particular, this success of bismuth triflate under grinding technique could be attributed to the facts that the grinding of organic reactants causes multiple particle ruptures, which results in their size reduction and a simultaneous generation of large new surfaces and surface energy within the system. Thus, newly formed large surfaces during grinding come in close contact by their collision and results in the interaction of fractional and impact forces, releasing high dynamic energy. At this stage, hot point is formed where the molecules reach very high vibrational excitation leading to bond breaking and making. Consequently, the chemical reactivity of reactants considerably increases, which results in significant acceleration of chemical reaction leading to the formation of desired product within short reaction times avoiding undesirable products.



Scheme1: Reaction of indole with various carbonyl compounds in presence of Bi(OTf)₃.

Table-1: Effect of Catalysts on the synthesis of Bis(indolyl)methanes by grinding method.

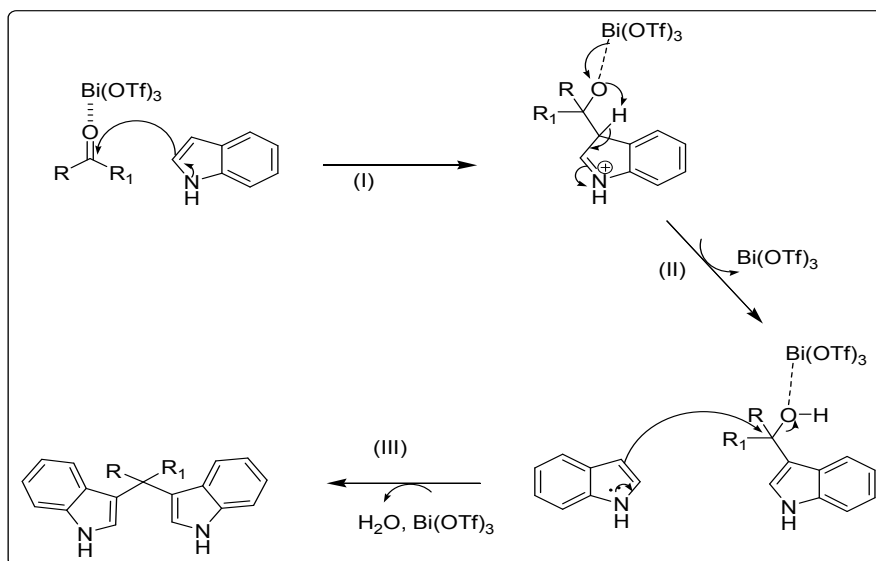
Entry	Catalyst	Time (min)	Yields (%)
1	Citric acid	60	21
2	Sulphamic acid	60	19
3	Oxalic acid	60	55
4	Bismuth triflate	8	92

Table-2: Synthesis of bis(indolyl)methanes derivatives using the bismuth triflate as a catalyst.

Entry	R	Time (min)	Yield (%)	Melting Point* (°C)
3a	C ₆ H ₅	8	92	145-147
3b	4-Me-C ₆ H ₄	13	93	93-95
3c	4-F-C ₆ H ₄	5	90	191-193
3d	3,4-di-MeO-C ₆ H ₃	23	94	220-222
3e	4-Cl-C ₆ H ₄	6	90	104-105
3f	4-OH-C ₆ H ₄	21	75	123-125
3g	3-NO ₂ -C ₆ H ₄	8	79	221-223

3h	3-MeO, 4-OH-C ₆ H ₃	28	86	111-113
3i	2-NO ₂ - C ₆ H ₄	7	91	137-139
3j	2-Furyl	18	79	319-321
3k	2-Piperonyl	17	90	98-99

*Melting points matched with physical data in literature.



Scheme 2: A possible mechanism for the preparation of bis(indolyl)methanes

Conclusion

In summary, we have developed a new and clean synthetic protocol for using mild and inexpensive catalyst under grinding technique. This technique overcomes some of the problems associated with excessive or wasteful heating. Remarkable advantages of this synthetic strategy over others are decreased reaction times, omission of solvents, simplified work-up procedure, ambient reaction temperature, consumption of low amount of catalyst in view of atom economy, and better energy balance in comparison with those of classical performance.

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