

Rapid Communication

Bismuth(III) nitrate pentahydrate — An efficient catalyst for the synthesis of bis(indolyl)methanes under mild conditions

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Bismuth (III) nitrate pentahydrate **BN** has been used successfully for the electrophilic condensation of indole with a wide range of aldehydes to obtain bis(indolyl)methanes at ambient temperature. The methodology has the advantages of usage of inexpensive catalyst, short reaction time and mild reaction work up.

Keywords: Aldehydes, bis(indolyl)methane, indoles, bismuth(III)nitrate pentahydrate

Developments in medicinal chemistry highlight the use of indoles and its derivatives as antibiotics in the field of pharmaceuticals¹. Bis(indolyl)alkanes and their derivatives constitute an important group of bioactive metabolites of terrestrial and marine origin². Bis(indolyl)methanes are receiving increasing attention for promoting beneficial estrogen metabolism in men and women³. These compounds also exhibit beneficial effects on proliferation and induction of apoptosis in human prostate⁴. Bis(indolyl)methanes also find useful applications as a breast cancer preventive⁵. Therefore, the synthesis of these compounds has become an interesting target for synthetic chemists to pursue.

The electrophilic substitution of indole with aldehydes/ketones affording bis(indolyl)methanes is known in the literature using Lewis and Brønsted acids^{6,7}. Synthesis of bis(indolyl)methanes has been reported using VCl_3 (Ref. 8a), CuBr_2 (Ref. 8b), ZrCl_4 (Ref. 8c), KHSO_4 (Ref. 8d), InCl_3 and $\text{In}(\text{OTf})_3$ (Ref. 8e,8f), $\text{Dy}(\text{OTf})_3$ in ionic liquid^{8g}, $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ in ionic liquid^{8h}, Ionic liquid⁸ⁱ, $\text{CeCl}_3 \cdot 7\text{H}_2\text{O-NaI-SiO}_2$ (Ref. 8j), I_2 (Ref. 8k), zeokarb-225 (Ref. 8l), HMTAB^{8m}, bis(cyclopentadienyl)zirconium dichloride⁸ⁿ, sulfated zirconia^{8o}, trichloro-1,3,5-triazine^{8p}, and LiClO_4 (Ref. 6f). The use of zeolites^{7b}, montmorillonite clay^{7f}, sulphamic acid⁹, have been reported as an inexpensive and easily available catalysts for the preparation of bis(indolyl)methanes.

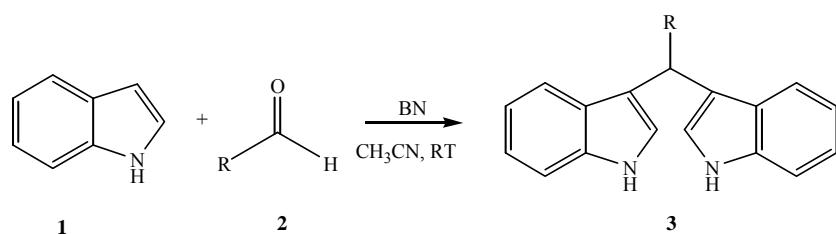
The substitution reaction using conventional Lewis acids requires stoichiometric or excess amount of the catalyst^{7g}. Moreover, in many cases, decomposition of the catalyst occurs due to the nitrogen containing reactants. In spite of having potential utilities, many of these methods involve the use of toxic and expensive reagents^{8e}, longer reaction time^{8d,8f}, strongly acidic condition and high temperatures^{8m}. Moreover, the preparation of some of these catalysts is a tedious process⁸ⁿ.

In organic synthesis, increasing attention is being paid to green reactions utilizing environmentally benign reagents and conditions. In this respect, it is of prime importance to discover a simple, green and inexpensive catalyst for the preparation of bis(indolyl)methanes. Bismuth salts have attracted much attention nowadays due to their low cost and good stability¹⁰. Bismuth(III) nitrate pentahydrate, $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ (**BN**) has specifically gained importance due to its economy, air insensitivity and safe handling. Recently, organic transformations like *O*-glycosylation^{11a}, Michael reaction^{11b} and aromatic iodination^{11c} have been reported using **BN**. It has been reported very recently that **BN** acts as an efficient catalyst for the Pechmann condensation of phenols and β -keto esters¹². Herein is reported an efficient condensation of indole with a wide range of aldehydes using **BN** as a mild and economic catalyst (**Scheme I**).

Results and Discussion

The procedure involved the reaction between indole and aldehyde using **BN** (20 mol% of catalyst) at temperature 26-28°C. After the complete consumption of the aldehyde, the reaction mixture was poured into water to separate the catalyst and extracted with ethyl acetate. Organic layer was concentrated to get a solid which on purification by recrystallization gave the pure product.

In order to explore the scope of the methodology, a wide range of aldehydes have been condensed with indole to obtain the corresponding bis(indolyl) methanes. The electron withdrawing groups did not show any influence in the course of the reaction since almost the same yields were obtained in their absence (**Table I**). One of the major advantages of this methodology was that the α,β -unsaturated aldehyde



Scheme I — Condensation of indole with aldehydes using BN

Table I — BN catalyzed synthesis of bis(indolyl)methanes derivatives^[a]

Entry	1	2	3	Time (min)	Yield (%) of 3 ^[b,c]	m. p.
a			3a	70	87	124-26 (Ref. 6g)
b			3b	60	85	76-78 (Ref. 8k)
c			3c	30	76	141-42 (Ref. 6g)
d			3d	30	84	261-62 (Ref. 8c)
e			3e	40	81	217-18 (Ref. 6g)
f			3f	55	79	94-96 (Ref. 8k)
g			3g	40	86	150-51 (Ref. 6g)
h			3h	25	74	98-99 (Ref. 8q)
i			3i	50	85	137-39 (Ref. 8c)
j			3j	55	81	291-93 (Ref. 8l)
k			3k	35	82	322-24 (Ref. 6g)
l			3l	50	84	72-74 (Ref. 8c)
m			3m	30	86	99-100 (Ref. 6g)

Contd

Table I — BN catalyzed synthesis of bis(indolyl)methanes derivatives^[a]. — *Contd*

Entry	1	2	3	Time (min)	Yield (%) of 3 ^[b,c]	m. p.
n			3n	45	83	186-88 (Ref. 8k)
o			3o	65	78	348-49 (Ref. 8r)

^[a]Indole: 2 mmol, Aldehyde: 1 mmol, BN: 0.2 mmol, Solvent: Acetonitrile (5 mL), Reaction temperature: 28-30°C. ^[b] Isolated and unoptimised yields. ^[c] Products were characterized by IR and ¹H NMR spectroscopy and comparison with reported data.

2h underwent reaction smoothly to produce the desired product selectively (without undergoing Michael addition). The reaction was feasible with heterocyclic aldehydes as well **2g**, **2j**, **2k**. Indole-3-carboxaldehyde **2j**, reacted smoothly with indole to produce tris(indolyl)methane in excellent yield. Also, benzene-1,4-dicarboxaldehyde **2i** reacted with four equivalents of indole to obtain tetrakis(indolyl)methane. It is noteworthy to mention that **3i** is obtained as the sole product without having any side reactions unlike in the case of previously reported procedures^{8c}. The methodology has several advantages like shorter reaction time (25-70 min) compared to many reported procedures (> 6hr) and ambient reaction temperature unlike reported procedures (75°C)^{8m}. A notable feature of the present methodology is that it avoids the use of tedious purification procedures like column chromatography.

Experimental Section

General Experimental Procedure: A mixture of aldehyde (1 mmol), indole (2 mmol) and bismuth (III) nitrate pentahydrate (**BN**) (0.2 mmol) in acetonitrile (5 mL) was stirred at RT (26-28°C). Progress of reaction was monitored by TLC. After the completion of the reaction, the mixture was treated with water (2×10 mL) followed by aq. Na₂CO₃ solution (10%, 1×10 mL) and the product was extracted with ethyl acetate (2×10 mL). The combined organic layer was dried over anhyd. Na₂SO₄, and concentrated *in vacuo* to afford the crude product. This was then purified by recrystallization from hexane:ethyl acetate (9:1, v/v) solvent.

3f: IR (KBr): 3455, 3145, 3020, 2970, 1625, 1525, 1180, 770 cm⁻¹; ¹H NMR (CDCl₃): δ 2.32 (s, 3H), 5.85 (s, 1H), 6.66 (d, 2H, *J* = 2.4 Hz), 6.99 (t, 2H, *J* = 8.1 Hz), 7.08 (d, 2H, *J* = 7.8 Hz), 7.3-7.4 (m, 6H), 7.45 (d, 2H, *J* = 8.0 Hz), 7.89 (br, s, 2H, NH).

Conclusion

In conclusion, a methodology has been developed involving **BN** as a mild and economic catalyst for the condensation of indole with aldehydes to obtain bis (indolyl) methanes. The protocol has the advantages like short reaction time, better yield of products, ambient reaction temperature, cleaner reaction, mild reaction work up, applicability towards a wide range of aldehydes and, above all, the usage of mild and cheap catalyst.

References

- (a) Sundberg R J, *The Chemistry of Indoles*, (Academic Press, New York), **1970**; (b) Kaon T S, *In Alkaloids, Chemical and Biological perspective*, Vol. 4 edited by Peuetier S W, (Pergamon press, Amsterdam), **1999**, 285; (c) Lounasmaa M & Tolvanen A, *Nat Prod Rep*, **17**, **2000**, 175.
- (a) Morris S A & Anderson R J, *Tetrahedron*, **46**, **1990**, 715; (b) Bifulco G, Bruno T, Riccio R, Lavayre J & Bourdy G, *J Nat Pro*, **58**, **1995**, 1254; (c) Porter J K, Bacon C W, Robins J D, Himmelsbach D S & Higman H C, *J Agric Food Chem*, **25**, **1977**, 88; (d) Osawa T & Namiki M, *Tetrahedron Lett*, **24**, **1983**, 4719; (e) Garbe T R, Kobayashi M, Shimizu N, Takesue N, Ozawa M & Yukawa H, *J Nat Prod*, **63**, **2000**, 596.
- Zeligs M A, *J Med Food*, **1**, **1998**, 67.
- (a) Kedmi M N, Yannai S, Haj A & Fares F A, *Food Chem Toxicol*, **41**, **2003**, 745; (b) Hong C, Firestone G L & Bjeldanes L F, *Biochem Pharmacol*, **63**, **2002**, 1085.
- Michnovicz J J & Bradlow H L, *Proc Roy Soc, Edinburgh*, **12**, **1989**, 1571.
- (a) Wayland E N, Venkiteswaren M R & Richards C G, *J Org Chem*, **26**, **1961**, 4241; (b) Banerji J, Chatterjee A, Manna S, Pascard C, Prange T & Shoolery J, *Heterocycles*, **15**, **1981**, 325; (c) Chatterjee A, Manna S, Benerji J, Pascard C, Prange T & Shoolery J, *J Chem Soc Perkin Trans 1*, **1989**, 553; (d) Earle M J, Fairhurst R A & Heaney H, *Tetrahedron Lett*, **32**, **1991**, 6171; (e) Babu G, Sridhar N & Perumal P T, *Synth Commun*, **30**, **2000**, 1609; (f) Yadav J S, Reddy B V S, Murthy C V S R, Kumar G M & Madam C, *Synthesis*, **2001** 783; (g) Nagrajan R & Perumal P T, *Tetrahedron*, **58**, **2002**, 1229.
- (a) Kobayashi S, Araki M, Yasuda M, *Tetrahedron Lett*, **36**, **1995**, 5773; (b) Karthik M, Magesh C J, Perumal P T,

Palanichamy M, Banumathi A & Murugesan V, *Applied Catalysis, A General*, 286(1), **2005**, 137; (c) Ramesh C, Banerjee J, Pal R & Das B, *Adv Synth Catl*, 345, **2003**, 557; (d) Mahadevan A, Sard H, Gonzalez M & McKew J C, *Tetrahedron Lett* 44, **2003**, 4589; (e) Reddy A V, Ravinder K, Reddy V L N, Goud T V, Ravikanth V & Vekateswarlu Y, *Syn Commun* 33, **2003**, 3687; (f) Chakrabarty M, Ghosh N, Basak R & Harigaya Y, *Tetrahedron Lett*, 43, **2002**, 4075.

8 (a) Rajitha B, Reddy P N, Kumar B S, Sreenivasulu N & Reddy Y R T, *J Chem Res* 4, **2005**, 222; (b) Mo L P, Ma Z C & Zhang Z H, *Syn Commun* 35, **2005**, 1997; (c) Zhang Z H, Yin L & Wang Y M, *Synthesis*, **2005**, 1949; (d) Nagarajan R & Perumal P T, *Chem Lett*, 33, **2004**, 288; (e) Ji S J, Zhou M F, Gu D G, Wang S Y & Loh T P, *Synlett*, **2003**, 2077; (f) Kumar S, Kumar V & Chimni S S, *Tetrahedron Lett*, 44, **2003**, 2101; (g) Chen D, Yu L & Wang P G, *Tetrahedron Lett*, 37, **1996**, 4467; (h) Ji S J, Zhou M F, Gu D G, Jiang Z Q & Loh T P, *Eur J Org Chem*, 7, **2004**, 1584; (i) Gu D G, Ji S J, Jiang Z Q, Zhou M F & Loh T P, *Synlett*, **2005**, 959; (j) Bartoli G, Bosco M, Foglia G, Giuliani A, Marcantoni E & Sambri L, *Synthesis*, **2004**, 895; (k) Ji S J, Wang S Y, Zhang Y & Loh T P, *Tetrahedron*, 60, **2004**, 2051; (l) Magesh C J, Nagarajan R, Karthik M & Perumal P T, *Appl Catal, A, General* 266, **2004**, 1; (m) Teimouri M & Mivehchi H, *Syn Commun* 35, **2005**, 1835; (n) Kantam L M, Khathija A & Likhar P R, *Catal Lett* 98, **2004**, 117; (o) Reddy B M, Sreekanth P M & Lakshmanan P, *J Mol Catal A, Chemical*, 237, **2005**, 93; (p) Sharma G V M, Reddy J J, Lakshmi S P & Krishna R P, *Tetrahedron Lett*, 45, **2004**, 7729; (q) Deb M L & Bhuyan P J, *Tetrahedron Lett*, 47, **2006**, 1441; (r) Kamal A & Quireshi A A, *Tetrahedron*, 19, **1963**, 513.

9 Singh P R, Singh D U & Samant S D, *Syn Commun* 35, **2005**, 2133.

10 Komatsu N, in *Organobismuth Chemistry*, edited by Suzuki H, Matano Y, (Elsevier, Amsterdam) **2001**, 371.

11 (a) Naik P U, Nara S J, Harjani J R & Salunkhe M M, *J Mol Catal A Chemical*, 234, **2005**, 35; (b) Srivastava N & Banik B K, *J Org Chem*, 68, **2003**, 2109; (c) Alexander V M, Khandekar, A C & Samant S D, *Synlett* **2003**, 1895.

12 Alexander V M, Bhat R P & Samant S D, *Tetrahedron Lett*, 46, **2005**, 6957.