

## Efficient synthesis of bis(indolyl)methanes catalyzed by $(\text{PhCH}_2\text{PPh}_3)^+\text{Br}^-$ under solvent-free conditions

Farhad Shirini\*, Masoumeh Abedini, Manouchehr Mamaghani, Arman Rahmaninia

Department of Chemistry, College of Science, University of Guilan, Rasht, zip code 41335, I.R. Iran.

Received 29 November 2012; received in revised form 29 December 2012; accepted 30 December 2012

### ABSTRACT

Benzyltriphenylphosphonium bromide (BTPB) has been applied as an efficient catalyst for the preparation of bis(indolyl)methanes (BIMs) via electrophilic substitution of indoles with aldehydes in the absence of solvent.

**Keywords:** Benzyltriphenylphosphonium bromide; Aldehydes; Indoles; Bis(indolyl)methanes; Solvent-free conditions.

### 1. Introduction

Bis(indolyl) methanes (BIMs), which contain two indole or substituted indole units in a molecule, feature widely in bioactive metabolites of terrestrial and marine origin [1]. These types of compounds are also known to promote estrogen metabolism in both women and men and is expected to have an application in prevention of breast cancer [2]. Therefore, significant efforts have been directed toward the synthesis of these molecules. Synthetically, bis(indolyl) methanes are obtained via the electrophilic substitution of indoles with carbonyl compounds. To improve the rate of this type of reactions, a variety of catalysts have been reported, of them HCl [3], NBS [4], I<sub>2</sub> [5,6], KHSO<sub>4</sub> [7], NaHSO<sub>4</sub>.SiO<sub>2</sub> [8], ZrCl<sub>4</sub> [9], InCl<sub>3</sub> and In(OTf)<sub>3</sub> [10], HClO<sub>4</sub>.SiO<sub>2</sub> [11], ZrOCl<sub>2</sub>.8H<sub>2</sub>O/SiO<sub>2</sub> [12], AlPW<sub>12</sub>O<sub>40</sub> [13], H<sub>3</sub>PW<sub>12</sub>O<sub>40</sub> [14], H<sub>6</sub>P<sub>2</sub>W<sub>18</sub>O<sub>62</sub> [15], polyindole salt [16], montmorillonite K-10[17], trichloro-1,3,5-triazine [18], dodecyl sulfates [19], TPA ZrO<sub>4</sub> [20], sulfamic acid [21], aminosulfonic acid [22], RuCl<sub>3</sub>.nH<sub>2</sub>O [23], La(OTf)<sub>3</sub> [24], La(PFO)<sub>3</sub> [25], M(HSO<sub>4</sub>)<sub>x</sub> [26], V(HSO<sub>4</sub>)<sub>3</sub> [27], SiO<sub>2</sub> [28], P<sub>2</sub>O<sub>5</sub>/SiO<sub>2</sub> [29], SQ [30], HPA/TPI-SBA-15 [31], [hmim][HSO<sub>4</sub>] [32], ILIS-SO<sub>2</sub>Cl [33], [BTBAC]Cl-FeCl<sub>3</sub> [34], [bnmim][HSO<sub>4</sub>] [35], tetrabutyl ammonium tribromide (TBATB) [36], Benzyltriphenylphosphonium tribromide (BTPTB) [37] are examples. Most of the brominated catalysts which have been used, accelerate the reaction through the production of HBr [36, 37]. Despite their effectiveness, producing HBr

can cause many restrictions on their use. Moreover, disadvantages such as long reaction times, low product yields, tedious work-up procedure, use of expensive reagents, use of a larger stoichiometric amount of catalyst and use of an additional microwave or ultrasound irradiation are also reported in most of these procedures. Therefore, introduction of new methods and catalysts for the preparation of BIMs is still in demand.

### 2. Experimental

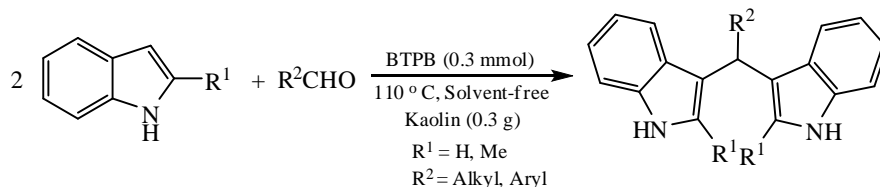
#### 2.1. General

Chemicals were purchased from Fluka, Merck, and Aldrich chemical companies. Melting points (Mp) were recorded on a Barnstead electrothermal instrument and are uncorrected. The IR and FT-IR spectra (cm<sup>-1</sup>) were recorded on Shimadzu Corporation 200-91-527 and Perkin Elmer RX1 spectrophotometers as pellets on KBr discs. The <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on Bruker AVANCEIII-400 spectrometer in CDCl<sub>3</sub> using TMS as an internal reference. The purity determination of the substrate and reaction monitoring were accompanied by TLC on silica-gel polygram SILG/UV 254 plates. All yields refer to the isolated products and the known products were characterized by their physical constants and comparison with authentic samples.

#### 2.2. General procedure

To a mixture of indole (2.0 mmol, 0.234 g) and 4-chlorobenzaldehyde (1 mmol, 0.141 g), BTPB (0.3 mmol, 0.13 g) and kaolin (0.3 g) were added. The resulting mixture was stirred at 110 °C for 20 min. The progress of the reaction

\* Corresponding author: E-mail: shirini@guilan.ac.ir.  
Tel./ Fax: +981313226232.



Scheme 1. Synthesis of bis(indolyl) methane derivatives.

Table 1 Synthesis of bis(indolyl)methanes in the absence of solvent<sup>a, b</sup>.

Entry	Carbonyl compound	R <sup>1</sup>	Time (min)	Yield (%)
1	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CHO	H	60	92 [30]
2	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CHO	H	50	95 [27]
3	2-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CHO	H	45	92 [29]
4	3,4-(MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> CHO	H	70	85 [31]
5	4-ClC <sub>6</sub> H <sub>4</sub> CHO	H	20	94 [27]
6	3-ClC <sub>6</sub> H <sub>4</sub> CHO	H	20	96 [37]
7	4-MeOC <sub>6</sub> H <sub>4</sub> CHO	H	40	90 [37]
8	4-HOC <sub>6</sub> H <sub>4</sub> CHO	H	30	95 [27]
9	3-MeC <sub>6</sub> H <sub>4</sub> CHO	H	35	95 [28]
10	4-BrC <sub>6</sub> H <sub>4</sub> CHO	Me	30	93 [37]
11	4-HOC <sub>6</sub> H <sub>4</sub> CHO	Me	30	93 [37]
12	3,4-(MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> CHO	Me	70	91 [37]
13	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> C(O)Me	H	90	-c
14	4-MeOC <sub>6</sub> H <sub>4</sub> C(O)Me	H	120	-c

<sup>a</sup>The desired products were characterized by comparison of their IR and <sup>1</sup>H NMR spectra with those of the known compounds.

<sup>b</sup>Isolated yield.

<sup>c</sup>Mixture of products.

was monitored by TLC. Upon completion of the reaction, the mixture was cooled to room temperature. Then diethylether (5 mL) was added, the mixture was filtered and filtrate was washed with diethylether (3 mL). After evaporation of the solvent under reduced pressure the crude product was obtained. For further purification the product was recrystallized from an ethanol:water solution (95:5, v/v). Pure product was obtained as a pink solid in 94% yield, m.p. 85-87 °C (lit. 87-89 °C [27]); FT-IR (KBr):  $\nu$  (cm<sup>-1</sup>): 3228, 3053, 2879, 2785, 2848, 1587, 1103. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  5.81 (s, 1H, Ar-CH), 6.61 (s, 2H), 6.93-7.71 (m, 12H), 8.51 (s, 2H, NH).

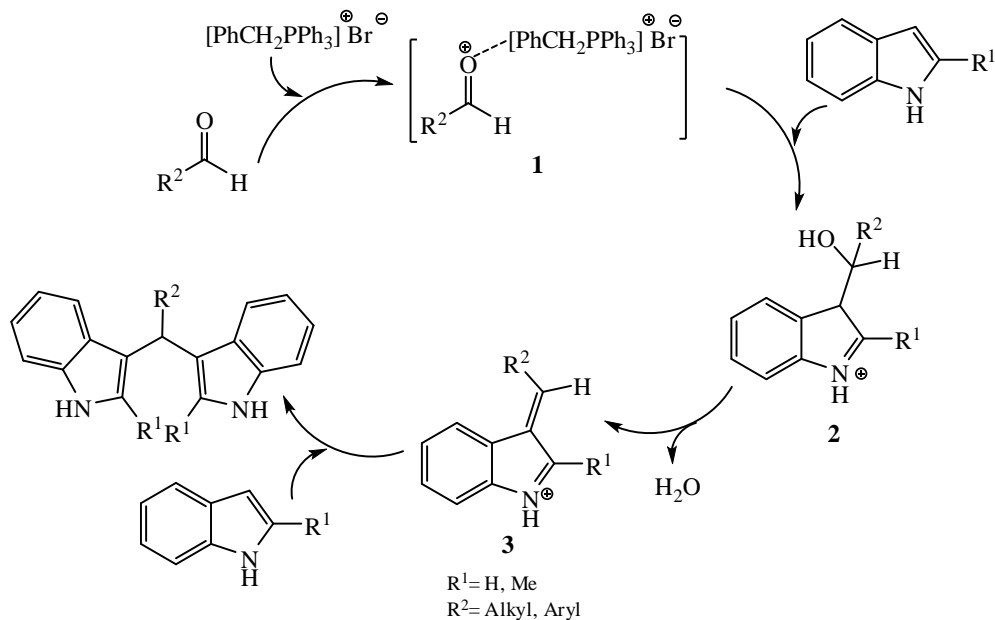
#### The selected spectral data

The physical (m.p.) and spectral data (IR, <sup>1</sup>H NMR) of some of the bis(indolyl)methane derivatives are presented below:

Table 1, entry 1: Yellow needles. m.p. 220-223 °C. IR (KBr, cm<sup>-1</sup>): 1244, 1417, 1615, 2830, 2920, 3050, 3452. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 5.99 (s, 1H), 6.68 (s, 2H), 6.99-7.70 (m, 12H), 8.03 (s, 2H, NH).

Table 1, entry 7: Red solid. m.p. 197-198 °C. IR (KBr, cm<sup>-1</sup>): 1260, 2830, 2930, 3051, 3396. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 3.78 (s, 3H), 5.84 (s, 1H), 6.65 (s, 2H), 6.80 (d, 2H), 6.97-7.03 (m, 2H), 7.13-7.41 (m, 3H), 7.93 (s, 2H, NH).

Table 1, entry 9: Yellow solid. m.p. 85-87 °C. IR (KBr, cm<sup>-1</sup>): 3400, 3047, 2964, 1591, 1253. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 3.73 (s, 3 H), 5.86 (s, 1H), 6.67-6.75 (d, 2H), 6.93-7.37 (m, 12H), 7.90 (s, 2H, NH).



**Scheme 2.** The plausible mechanism of the reaction.

### 3. Results and Discussion

In this study we wish to report the applicability of benzyltriphenylphosphonium bromide (BTPB) in the promotion of the preparation of BIMs *via* the electrophilic substitution of indoles with various aldehydes. In order to optimize the reaction conditions, we have used BTPB as a catalyst for the condensation of 4-nitrobenzaldehyde with indole at different conditions such as various molar ratios of catalyst, solvent, solvent-free and temperature. A highly sticky orange reaction mixture was obtained with the formation of the desired bis(indolyl) methane in low yield after several hours. Therefore, we studied the catalytic effect of BTPB in the presence of kaolin for the similar reaction. We have found that when the same reaction is carried out in the presence of kaolin, in addition to decreasing of the reaction time (1 h), the procedure became more easier (It should be noted that in the absence of kaolin, the mixture became very sticky, which causes the difficulty in the mixing of the reactants). These studies showed that the best result was obtained by carrying out the reaction of 4-nitrobenzaldehyde (1 mmol) with indole (2 mmol) in the presence of 0.3 mmol of BTPB and 0.3 g of kaolin at 110 °C for 60 min in the absence of solvent. These conditions were chosen as optimal (Table 1, entry 1). Also, this reaction examined in the presence of kaolin without using BTPB in which the desired product was obtained in low yield within several hours. After optimization of the reaction conditions and in order to show the general applicability of the method,

different types of aldehydes were subjected to the same reaction under the determined conditions (Scheme 1). As shown in Table 1, the corresponding BIMs were obtained during relatively short reaction times in good to high yields. Because of the formation of unidentified products, the present method is not suitable for the synthesis of BIMs from ketones (Table 1, entries 13 and 14).

A plausible mechanism of the reaction is shown in Scheme 2, based on our observations and obtained results. On the basis of this mechanism and in the first step, the carbonyl group of aldehyde is activated by BTPB as intermediate **1**. Then the reaction is followed by indole attack to **1** to give **2** and loss of H<sub>2</sub>O from **2** to afford **3**. The other indole is added to **3** in the following step to give the requested product, which can catalyze the reaction in a catalytic manner (Scheme 2).

The efficiency of the present method is shown by the comparison of the results with some of those reported in the literature (Table 2). As shown in Table 2, the corresponding reaction is also accelerated in the presence of benzyltriphenylphosphonium tribromide (BTPTB) and the reaction was completed in shorter period of time. But as mentioned in initial section, this compound, similar to most of the other brominated catalysts, produces HBr in its catalytic mechanism. This is followed by many restrictions. While our discussed catalyst (BTPB) can cause the same acceleration in higher yield without production of HBr. On

**Table 2.** Compared performance of various catalysts in bis (indolyl) methane synthesis of 4-ClC<sub>6</sub>H<sub>4</sub>CHO.

Entry	Catalyst [Ref.]	Conditions	Time (h)	Yield (%)
1	Zeokarb-225 [38]	CH <sub>3</sub> CN, r.t.	8.5	70
2	V(HSO <sub>4</sub> ) <sub>3</sub> [27]	Solvent-free, 80 °C	0.66	85
3	TBATB [36]	MeOH, r.t.	1.5	85
4	BTPTB [37]	Solvent-free, 90 °C	0.13	80
5	M(HSO <sub>4</sub> ) <sub>x</sub> [26]	EtOH, r.t.	2.5-7.5	89-91
6	P <sub>2</sub> O <sub>5</sub> /SiO <sub>2</sub> [29]	Solvent-free, r.t.	0.5	92
7	SQ [30]	H <sub>2</sub> O/r.t.	2-4	82
8	[hmim][HSO <sub>4</sub> ] [32]	EtOH, r.t.	1	93
9	ILIS-SO <sub>2</sub> Cl [33]	MeCN, r.t.	5.5	93
10	BTPB [this work]	Solvent-free, 110 °C	0.33	94

the other hand, BTPTB is synthesized from BTPB through direct increasing of Br<sub>2</sub> in a separate synthetic step. According to known chemical dangers of bromine and due to economic considerations, BTPB is more appropriate and reasonable to use than BTPTB.

#### 4. Conclusion

In conclusion, we have reported the application of BTPB in the efficient synthesis of BIMs. Relatively short reaction times, good to high yields of the products, solvent-free conditions, simple experimental procedure and lack of HBr production in acid-sensitive cases are among the other advantages of this method which make this procedure a useful addition to the available methods.

#### Acknowledgment

We are thankful to the University of Guilan and Islamic Azad University (Rasht branch) Research Councils for the partial support of this work.

#### References

- [1] T.R. Garbe, M. Kobayashi, N. Shimizu, N. Takesue, M. Ozawa, H. Yukawa, *J. Nat. Prod.* 63 (2000) 596-598.
- [2] M. Karthik, A.K. Tripathi, N.M. Gupta, M. Palanichamy, V. Murugesan, *Catal. Commun.* 5 (2004) 371-375.
- [3] M. Auria, *Tetrahedron* 47 (1991) 9225-9230.
- [4] H. Koshima, W. Matzuaka, *J. Heterocycl. Chem.* 39 (2002) 1089-1092.
- [5] B.P. Bandgar, K.A. Shaikh, *Tetrahedron Lett.* 44 (2003) 1959-1961.
- [6] S.J. Ji, S.Y. Wang, Y. Zhang, T.P. Loh, *Tetrahedron* 60 (2004) 2051-2055.
- [7] R. Narajan, P.T. Perumal, *Chem. Lett.* 3 (2004) 228-232.
- [8] C. Ramesh, J. Benerjee, R. Pal, B. Das, *Adv. Synth. Catal.* 345 (2003) 557-559.
- [9] Z.H. Zhang, L. Yin, Y.M. Wang, *Synthesis* (2005) 1949-1955.
- [10] A. Chatterjee, S. Manna, J. Benerji, C. Pascard, T. Prangé, J.N. Shoolery, *J. Chem. Soc., Perkin Trans. 1* (1980) 553-555.
- [11] V.T. Kamble, K.R. Kadam, N.S. Joshi, D.B. Muley, *Catal. Commun.* 8 (2007) 498-502.
- [12] H. Firouzabadi, N. Iranpoor, M. Jafarpour, A. Ghaderi, *J. Mol. Catal. A: Chem.* 253 (2006) 249-251.
- [13] H. Firouzabadi, N. Iranpoor, A.A. Jafari, *J. Mol. Catal. A: Chem.* 244 (2006) 168-172.
- [14] N. Azizi, L. Torkian, M.R. Saidi, *J. Mol. Catal. A: Chem.* 275 (2007) 109-112.
- [15] M.M. Hereavi, K. Bakhtiari, A. Fatehi, F.F. Bamoharrami, *Catal. Commun.* 9 (2008) 289-292.
- [16] S. Palaniappan, A. John, *J. Mol. Catal. A: Chem.* 242 (2005) 168-170.
- [17] M. Chakrabarty, N. Ghosh, R. Basak, Y. Harigaya, *Tetrahedron Lett.* 43 (2002) 4075-4078.
- [18] G.V.M. Sharma, J.J. Reddy, P.S. Lakshmi, P.R. Krishna, *Tetrahedron Lett.* 45 (2004) 7729-7732.
- [19] M.A. Zolfigol, P. Salehi, M. Shiri, Z. Tanbakouchian, *Catal. Commun.* 8 (2007) 173-178.
- [20] J.R. Satam, K.D. Parghi, R.V. Jayaram, *Catal. Commun.* 9 (2008) 1071-1078.
- [21] W.J. Li, X.F. Lin, J. Wang, G.L. Li, Y.G. Wang, *Synth. Commun.* 35 (2005) 2765-2769.
- [22] J.T. Li, H.G. Dai, W.Z. Xu, T.S. Li, *Ultrason. Sonochem.* 13 (2006) 24-27.
- [23] K. Tabatabaeian, M. Mamaghani, N. Mahmoodi, A. Khorshidi, *Can. J. Chem.* 84 (2006) 1541-1545.
- [24] D. Chen, L. Yu, P.G. Wang, *Tetrahedron Lett.* 37 (1996) 4467-4470.
- [25] L. Wang, J.H. Han, T.J. Sheng, Z. Fan, X. Tang, *Synlett* (2005) 337-339.
- [26] K. Niknam, M.A. Zolfigol, T. Sadabadi, A. Nejati, *J. Iran. Chem. Soc.* 3 (2006) 318-322.
- [27] F. Shirini, A. Yahyazadeh, M. Abedini, D. ImaniLangroodi, *Bull. Korean Chem. Soc.* 31 (2010) 1715-1718.
- [28] S.R. Mendes, S. Thurow, M.P. Fortes, F. Penteado, E.J. Lenardão, D. Alves, G. Perin, R.G. Jacob, *Tetrahedron Lett.* 53 (2012) 5402-5406.
- [29] A. Hasaninejad, A. Zare, H. Sharghi, K. Niknam, M. Shekouhy, *Arkivoc* xiv (2007) 39-50.

- [30] N. Azizi, E. Gholibeghlo, Z. Manocheri, *ScientiaIranica C* 19 (2012) 574-578.
- [31] R. Tayebee, M.M. Amini, F. Nehzat, O. Sadeghi, M. Armaghan, *J. Mol. Catal. A: Chem.* 366 (2013) 140-148.
- [32] G.D. Gong, J.I. Shun-Jun, J. Zhao-Qin, Z. Min-Feng, L. Teck-Peng, *Synlett* (2005) 959-962.
- [33] H. Hagiwara, M. Sekifuji, T. Hoshi, K. Qiao, C. Yokoyamac, *Synlett* (2007) 1320-1322.
- [34] H. Veisi, S. Hemmati. H. Veisi, *J. Chin. Chem. Soc.* 56 (2009) 240-245.
- [35] S.A. Sadaphal, K.F. Shelke, S.S. Sonar, M.S. Shingare, *Cent. Eur. J. Chem.* 6 (2008) 622-626.
- [36] X.F. Lin, S.L. Cui, Y.G. Wang, *Synth. Commun.* 36 (2006) 3153-3160.
- [37] F. Shirini, M. SafarpoorLangroodi, M. Abedini, *Chinese Chem. Lett.* 21(2010) 1342-1345.
- [38] C.J. Magesh, R. Nagarajan, M. Karthink, P.T. Perumal, *Appl. Catal. A: General* 266 (2004) 1-10.