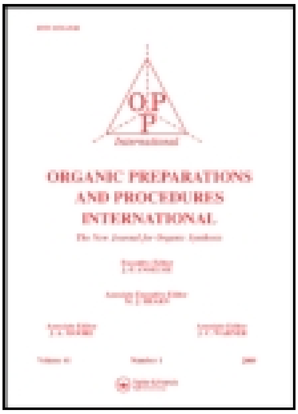


Organic Preparations and Procedures International: The New Journal for Organic Synthesis
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/uopp20

Facile and Mild Synthesis of bis(3-Indolyl)methanes

R. Ghorbani-Vaghei [a] & S. M. Malaekehpoor [b]
[a] Department of Organic Chemistry, Faculty of Chemistry, Bu-Ali Sina University, Hamedan, Iran
[b] Payame Noor University, Hamedan, Iran

To cite this article: R. Ghorbani-Vaghei & S. M. Malaekehpoor (2010): Facile and Mild Synthesis of bis(3-Indolyl)methanes, Organic Preparations and Procedures International: The New Journal for Organic Synthesis, 42:2, 175-182

To link to this article: http://dx.doi.org/10.1080/00304941003699715

Organic Preparations and Procedures International, 42:175–182, 2010
Copyright © Taylor & Francis Group, LLC
ISSN: 0030-4948 print
DOI: 10.1080/00304941003699715

Facile and Mild Synthesis of *bis*(3-Indolyl)methanes

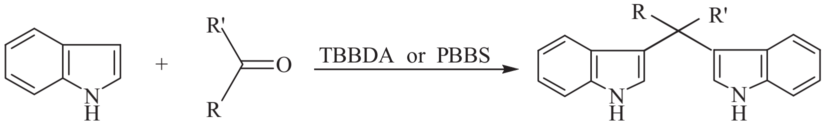
R. Ghorbani-Vaghei[1] and S. M. Malaekehpoor[2]

[1]Department of Organic Chemistry, Faculty of Chemistry, Bu–Ali Sina University, Hamedan, Iran
[2]Payame Noor University, Hamedan, Iran

bis(Indolyl)alkanes and their derivatives are of great interest and importance because of their pharmaceutical and biological applications.[1] They are the most cruciferous substances for the promotion of beneficial estrogen metabolism in women and men.[2] Therefore, the synthesis of these moieties has become of interest to organic chemists.[3] Several methodologies for their preparation have already been developed, mainly using protic or Lewis acids.[4] Recently, glacial acetic acid,[5] HBF_4-SiO_2[6] and I_2[7] have also been found to catalyze preparation of the *bis*(indolyl)methanes. However, since some procedures involve the use of microwave irradiation or heat,[5] corrosive catalysts,[7] and require tedious work-ups, and/or long reaction times,[4] new procedures that address these drawbacks seem desirable.

In continuation of our interest in the application of *N,N,N′,N′*–tetrabromobenzene-1,3-disulfonamide [TBBDA] and poly(*N*-bromobenzene-1,3-disulfonamide) [PBBS][8] in organic synthesis,[8–13] we now report a convenient method for the synthesis of *bis*(indolyl)methanes from indole with various aldehydes and ketones in the presence of TBBDA and PBBS under in solution and solvent-free conditions.

The electrophilic substitution reaction of indole with aldehydes and ketones in the presence of TBBDA and PBBS proceed smoothly at room temperature to afford the corresponding *bis*(3-indolyl)methanes (1) in good to high yields (*Scheme 1*, *Table 1*).



1

Scheme 1

It is noteworthy that neither electronic nor steric variation in the aldehydes has any effect on the yields. Functional groups such as methoxy (*Entries 3, 7, 11*), hydroxyl (*Entries 4,7,*

Submitted April 10, 2009.

Address correspondence to R. Ghorbani-Vaghei Department of Organic Chemistry, Faculty of Chemistry, Bu–Ali Sina University, Hamedan, Iran. E-mail: rgvaghei@yahoo.com

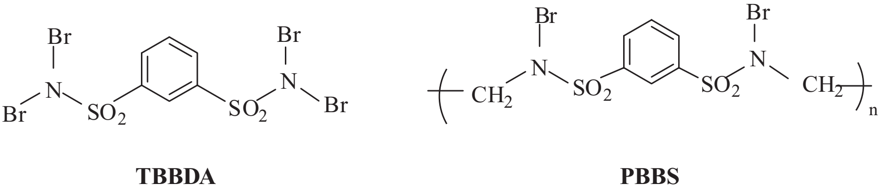
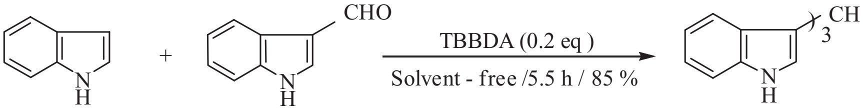


Figure 1
Structure of Reagents

13), halo (*Entries 5,12, 14*) and nitro (*Entries 9, 10*) were unchanged during the reaction. Forthermore, polycyclic aromatic aldehydes (*Entries 15, 16*), aliphatic aldehyde (*Entry 18*) and ketones (*Entries 19–21*) and *cis*-cinnamaldehyde were treated with indole in the presence of TBBDA and PBBS to give the corresponding *bis*(indolyl)methanes in good to high yields.

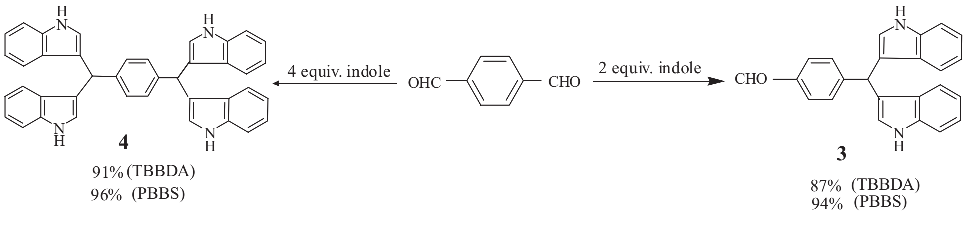
Based on these results, *tris*(indolyl)methanes[15] are also formed when three equivalents of indole are treated with 3-formylindole in the presence of TBBDA under solvent-free conditions at room temperature (2) but PBBS under these conditions and use of two equivalents of indole afforded the corresponding product in less yield (*Scheme 2*).



2

Scheme 2

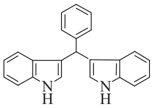
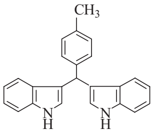
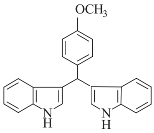
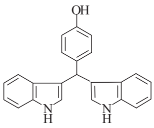
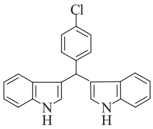
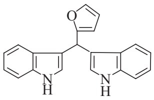
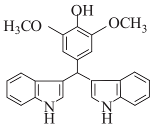
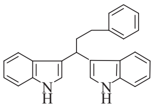
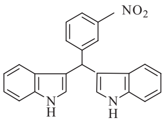
N,N,N′,N′-Tetrabromobenzene-1,3-disulfonamide [TBBDA] and poly(*N*-bromobenzene-1,3-disulfonamide) [PBBS] are also effective for the synthesis of *tetra*-3-indolyl(terephthalyl)dimethanes.[17] Thus *tetra*(2-indolyl)(terephthalyl)dimethanes[17] were obtained by controlling the molar ratio of indole. Addition of two and four equivalents of indole to terephthaldialehydehyde, gave **3** and **4** respectively at room temperature under solvent-free and solvent conditions (*Scheme 3*).



Scheme 3

Since PBBS and TBBDA contain bromine atoms which are attached to nitrogen atoms, it is possible that these reagents release Br^+ *in situ* which can act as an electrophilic

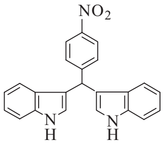
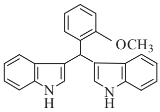
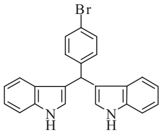
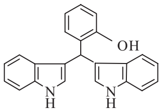
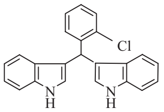
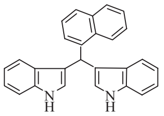
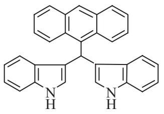
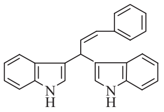
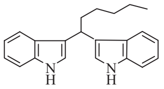
Table 1
Formation of *bis*(indolyl)methanes with Aldehydes and Ketones Catalyzed by TBBDA or PBBS Under Different Condition

		Solvent (CH_3CN)		Solvent- free			
Entry	Product	TBBDA Yield(%)/ Time(min)	PBBS Yield (%)/ Time (min)	TBBDA Yield(%)/ Time(min)	PBBS Yield (%)/ Time (min)	mp. (°C) (lit.)	Ref.
1		87 (120)	85 (65)	94 (2)	97 (10)	124–126 (125–126)	16
2		82 (180)	92 (7)	97 (5)	94 (10)	96–97 (96–98)	16
3		95 (30)	93 (102)	95 (3)	87 (110)	187–189 (187–189)	14
4		90 (180)	90 (86)	93 (60)	94 (170)	121–123 (120–122)	16
5		87 (150)	95 (10)	98 (1)	95 (163)	76–78 (76–77)	14
6		93 (3)	96 (125)	97 (1)	97 (60)	319–321 (320–322)	16
7		80 (45)	91 (8)	92 (2)	96 (6)	118–120 —	—
8		90 (45)	96 (100)	95 (5)	75 (75)	82–84 —	—
9		91 (180)	83 (177)	96 (1)	93 (68)	261–263 (260–262)	16

(Continued on next page)

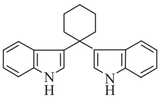
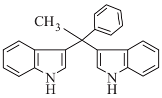
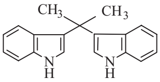
Table 1

Formation of *bis*(indolyl)methanes with Aldehydes and Ketones Catalyzed by TBBDA or PBBS Under Different Condition *(Continued)*

		Solvent (CH_3CN)		Solvent- free			
Entry	Product	TBBDA Yield(%)/ Time(min)	PBBS Yield (%)/ Time (min)	TBBDA Yield(%)/ Time(min)	PBBS Yield (%)/ Time (min)	mp. (°C) (lit.)	Ref.
10		92 (100)	90 (142)	93 (1)	89 (100)	218–220 (220–222)	16
11		95 (60)	97 (25)	94 (2)	96 (5)	134–135 (134–136)	16
12		90 (180)	96 (135)	92 (1)	98 (77)	110–112 (112–113)	19
13		95 (180)	95 (51)	92 (1)	90 (102)	340–342 (342–344)	16
14		93 (240)	96 (20)	90 (10)	90 (120)	71–73 (72–74)	14
15		90 (105)	95 (30)	87 (41)	94 (37)	218–220 (220)	18
16		79 (190)	94 (300)	84 (50)	90 (510)	236–238 (236–239)	16
17		72 (155)	85 (285)	78 (120)	60 (144)	95–97 (96–98)	16
18		94 (8)	98 (7)	95 (15)	98 (19)	67–69 (68–70)	6

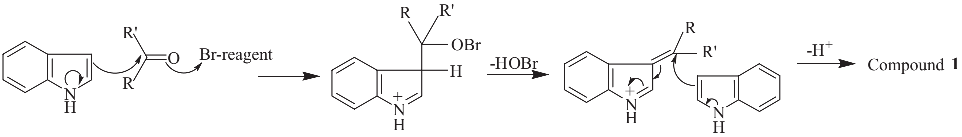
(Continued on next page)

Table 1
Formation of *bis*(indolyl)methanes with Aldehydes and Ketones Catalyzed by TBBDA or PBBS Under Different Condition *(Continued)*

		Solvent (CH_3CN)		Solvent- free			
Entry	Product	TBBDA Yield(%)/ Time(min)	PBBS Yield (%)/ Time (min)	TBBDA Yield(%)/ Time(min)	PBBS Yield (%)/ Time (min)	mp. (°C) (lit.)	Ref.
19		90 (330)	90 (305)	88 (5)	80 (50)	117–119 (116–118)	16
20		80 (15)	83 (236)	78 (60)	70 (98)	188–190 (188–190)	16
21		87 (25)	83 (46)	86 (27)	96 (30)	64–65 (64–66)	6

[a]Products were characterized from their physical properties, comparison with authentic samples and by spectroscopic methods.

species.[8,14] Therefore, the following mechanism can be suggested for the synthesis of *bis*(3-indolyl)methanes (*Scheme 4*).



Scheme 4

In summary, we have developed a simple, convenient and efficient synthetic protocol for the synthesis of *bis*(3-indolyl)methanes be used amounts of [TBBDA] and [PBBS] under solvent-free and solvent conditions at room temperature. It was found that TBBDA gives better results under solvent-free conditions than in slution but the reverse is true for PBBS. The short reaction time coupled with the simplicity of the procedure make this method one of the most efficient methods for the synthesis of this class of compounds.

Experimental Section

Substrates, solvents and other chemicals were purchased from Fluka, Merck and Aldrich chemical companies. The progress of the reaction was monitored by (TLC SiO_2-*n*-hexane:acetone). IR spectra (KBr) were conducted on Shimadzu infrared Fx-90 spectrophotometer and the nuclear magnetic resonance (NMR) spectra were recorded on a Jeol 90 MHz spectrometer using TMS as the internal standard. TBBDA and PBBS were prepared

Table 2

Elemental Analyses and Spectroscopic Data of New Compounds

$C_{25}H_{22}N_2O_3$ (*Entry 7*): Pink solid, mp 118–120°C; IR (KBr): ν 3391, 2934, 1513, 1456, 1422, 1323, 1211, 1111, 743 cm^{-1}; ^1H NMR (FT-90 MHz, $CDCl_3$): δ 7.94 (brs, 2H, NH), 7.47–7.30 (4H, m), 7.25 (2H, d, $J = 7.1$ Hz), 7.07 (2H, d, $J = 7.2$ Hz), 6.63 (2H, s), 6.58 (2H, s), 5.79 (1H, s), 3.72 (6H, s), 2.00 (1H, s); ^{13}C NMR (FT-90 MHz, $CDCl_3$): δ 40.41, 56.30, 105.8, 111.1, 119.2, 119.9, 121.9, 123.6, 127.1, 133.6, 135.5, 136.8,146.9, 148.1; MS (*m/z*) 398 (M^+).

Anal. Calcd. for $C_{25}H_{22}N_2O_3$: C, 75.37; H, 5.52; N, 7.03. Found: C, 75.20; H, 5.70; N, 7.02.

$C_{25}H_{22}N_2$ (*Entry 8*): Brown solid, mp 82–84°C; IR (KBr): ν 3389, 2928, 1494, 1455, 1337, 1226, 1094, 907, 742, 699 cm^{-1}; ^1H NMR (FT-90 MHz, $CDCl_3$): δ 8.04 (brs, 2H, NH), 7.75 (2H,d, $J = 11.6$ Hz), 7.58 (2H,d, $J = 5.3$ Hz), 7.51–7.38 (3H, m), 7.25 (2H,d, $J = 13.4$ Hz), 7.19–6.89 (4H, m), 6.49 (2H, s), 5.25 (1H, s), 4.48–4.38 (2H, m), 2.54 (2H, t, $J = 8.0$ Hz); ^{13}C NMR (FT-90 MHz, $CDCl_3$): δ 33.96, 35.87, 37.39, 111.3, 119.6, 120.0, 121.0, 122.3, 125.9, 126.3, 127.1, 128.4, 128.5, 136.6, 142.0; MS (*m/z*) 350 (M^+).

Anal. Calcd. for $C_{25}H_{22}N_2$: C, 85.71; H, 6.29; N, 8.00. Found: C, 85.71; H, 6.16; N, 7.93.

according to our previously reported procedure.[8] Elemental analyses and spectroscopic data of the two new compounds prepared are given in *Table 2*.

General Procedure for Solvent-free Synthesis of bis(3-Indolyl)methanes using TBBDA or PBBS

To a mixture of aldehyde (1 mmol) and indole (0.23 g, 2 mmol) was added TBBDA or PBBS (0.05 g, 0.1 mmol). The mixture was stirred with magnetic stirrer at room temperature for to appropriate time (*Table 1*). The progress of the reaction was monitored by TLC (8:2 *n*-hexane/acetone). After completion of the reaction, CH_2Cl_2 (20 mL) was added, and the sulphonamide was removed by vacuum filtration. Evaporation of the filtrate under reduced pressure gave generally pure products. Some of compounds (*Entries 3, 4, 10, 14, 19, 20*) were purified by thin layer chromatography (8:2, *n*-hexane/acetone).

General Procedure for the Synthesis of bis(3-Indolyl)methanes using TBBDA or PBBS in Acetonitrile

To a mixture of aldehyde (1 mmol) and indole (0.23 g, 2 mmol) was added TBBDA or PBBS (0.05 g, 0.1 mmol) in acetonitrile (2 mL). The mixture was stirred with magnetic stirrer at room temperature for the appropriate time (*Table 1*). The Progress of the reaction was monitored by TLC (8:2 *n*-hexane/acetone). After completion of the reaction, CH_2Cl_2 (20 mL) was added, and the sulphonamide was removed by vacuum filtration. Evaporation of the solvent under reduced pressure gave generally pure products. Some of compounds

(*Entries 1, 2, 4, 9, 10, 13, 17, 19, 20, 21*) were purified by thin layer chromatography (8:2, *n*-hexane/acetone).

General Procedure for Solvent-free Synthesis of tris(Indolyl)methanes using TBBDA

To a mixture of 3-formylindole (1 mmol) and indole (0.35 g, 3 mmol) was added TBBDA (0.1 g, 0.2 mmol). The mixture was stirred with magnetic stirrer at room temperature for to appropriate time (*Scheme 2*). The progress of the reaction was monitored by TLC (8:2 *n*-hexane/acetone). After completion of the reaction, CH_2Cl_2 (20 mL) was added, and the sulphonamide was removed by vacuum filtration. Evaporation of the solvent under reduced pressure and purified by thin layer chromatograghy gave generally pure products.

General Procedure for Solvent-free Synthesis of Tetra-2-indolyl(terephthalyl) dimethanes using TBBDA

To a mixture of terephthaldialdehyde (0.13 g, 1 mmol) and indole (0.23 g, 2 mmol) was added TBBDA or PBBS (0.05 g, 0.1 mmol). The mixture was stirred with magnetic stirrer at room temperature for to appropriate time (*Scheme 3*). The progress of the reaction was monitored by TLC (8:2 *n*-hexane/acetone). After completion of the reaction, CH_2Cl_2 (20 mL) was added, and the sulphonamide was removed by vacuum filtration. Evaporation of the filtrate under reduced pressure gave generally pure products.

General Procedure for the Synthesis of Tetra-2-indolyl(terephthalyl)dimethanes using PBBS in Acetonitrile

To a mixture of terephthaldialdehyde (0.13 g, 1 mmol) and indole (0.23 g, 2 mmol) was added TBBDA or PBBS (0.05 g, 0.1 mmol) in acetonitrile (2 mL). The mixture was stirred with magnetic stirrer at room temperature for the appropriate time (*Table 1*). The Progress of the reaction was monitored by TLC (8:2 *n*-hexane/acetone). After completion of the reaction, CH_2Cl_2 (20 mL) was added, and the sulphonamide was removed by vacuum filtration. Evaporation of the solvent under reduced pressure gave generally pure products.

General Procedure for Solvent-free Synthesis of Tetra-3-indolyl(terephthalyl) dimethanes using TBBDA

To a mixture of terephthaldialdehyde (0.13 g, 1 mmol) and indole (0.46 g, 4 mmol) was added TBBDA or PBBS (0.16 g, 0.3 mmol). The mixture was stirred with magnetic stirrer at room temperature for to appropriate time (*Scheme 3*). The progress of the reaction was monitored by TLC (8:2 *n*-hexane/acetone). After completion of the reaction, CH_2Cl_2 (20 mL) was added, and the sulphonamide was removed by vacuum filtration. Evaporation of the filtrate under reduced pressure gave generally pure products.

General Procedure for the Synthesis of Tetra-3-indolyl(terephthalyl)dimethanes using PBBS in Acetonitrile

To a mixture of terephthaldialdehyde (0.13 g, 1 mmol) and indole (0.23 g, 2 mmol) was added TBBDA or PBBS (0.16 g, 0.3 mmol) in acetonitrile (2 mL). The mixture was stirred with magnetic stirrer at room temperature for the appropriate time (*Table 1*). The Progress of the reaction was monitored by TLC (8:2 *n*-hexane/acetone). After completion of the reaction, CH_2Cl_2 (20 mL) was added, and the sulphonamide was removed by vacuum filtration. Evaporation of the solvent under reduced pressure gave generally pure products.

Acknowledgments

We are thankful to Bu-Ali Sina University, Center of Excellence and Development of Chemical Methods (CEDCM) for financial support.

References

1. R. J. Sundberg, *The Chemistry of Indoles*, Academic Press, New York, NY, (1996).
2. M. A. Zeligs, *J. Med. Food*, **1**, 67 (1998).
3. M. Chakraborty, B. Ramkrishna and H. Yosihiro, *Heterocycles*, **55**, 2431 (2001).
4. A. Chaterjee, S. Manna and J. Banerji, *J. Chem. Soc.*, *Perkin Trans. 1*, 553 (**1980**).
5. M. Zahran, Y. Abdin and H. Salama, *ARKIVOC*, (**xi**), 256 (2008).
6. B. P. Bandgar, A. V. Patil and V. T. Kamble, *ARKIVOC*, (**xvi**), 252 (2007).
7. B. P. Bandgar and K. A Shaikh, *Tetrahedron Lett.*, **44**, 1959 (2003).
8. R. Ghorbani-Vaghei and H. Jalili, *Synthesis*, 1099 (**2005**).
9. R. Ghorbani-Vaghei, M. A. Zolfigol, M. Chegeny and H. Veisi, *Tetrahedron Lett.*, **46**, 4505 (2006).
10. R. Ghorbani-Vaghei and S. Akbari-Dadamahaleh, *Tetrahedron Lett.*, **50**, 1055 (2009).
11. R. Ghorbani-Vaghei and E. Shahbazee, *J. Braz. Chem. Soc.*, **16**, 647 (2005); *Chem. Abstr.*, **143**, 405657z (2005).
12. M. A. Zolfigol, R. Ghorbani-Vaghei, S. Mallakpour, G. Chehardoli, A. Ghorbani-Choghamani and A. Yazdi Hosain, *Synthesis*, 1631 (**2006**).
13. R. Ghorbani-Vaghei, E. Shahbazee and H. Veisi, *Mendeleev Commun.*, 207 (**2005**).
14. J. Shun-Jun, W. Shun–Yi and L. Teck-Peng, *Tetrahedron.*, **60**, 2051 (2004).
15. J. M. Chinnian, N. Rajagopal and K. Mani, T. P. Paramasivan, *Applied Catalysis*, **266**, 1 (2004).
16. Z. H. Zhang, L. Yin and Y. M. Wang, *Synthesis*, 1949 (**2005**).
17. M. A. Zolfigol, P. Salehi, M. Shiri and Z. Tanbakouchian, *Catal. Commun.*, **8**, 173, (2007).
18. B. P. Bandgar, S. V. Bettigeri and N. S. Joshi. *Monatsh. Chem.*, **135**, 1265 (2004).
19. L. T. An, F. Q. Ding, J. P. Zou, X. H. Lu and L. L. Zhang, *Chin. J. Chem.*, **25**, 822 (2007); *Chem. Abstr.*, **148**, 585641z (2008).