Arabian Journal of Chemistry (2016) 9, S2004–S2010

King Saud University

Arabian Journal of Chemistry

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ORIGINAL ARTICLE

# Nafion-H® catalyzed efficient condensation of indoles with aromatic aldehydes in PEG-water solvent system: A green approach

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Received 14 December 2012; accepted 20 May 2014
Available online 2 June 2014

**KEYWORDS**

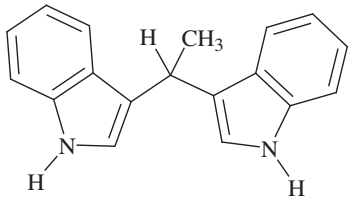
Nafion-H®;
Bis(indolyl)methanes;
Polyethylene glycol;
Green chemistry;
Heterogeneous catalysis

**Abstract** Nafion-H® has been used as an efficient and reusable catalyst for an improved and rapid synthesis of bis(indolyl)methanes from electrophilic substitution of indoles with aromatic aldehydes using PEG-400:water system as medium. This methodology offered remarkable improvements in the synthesis of bis(indolyl)methanes with regard to the yield of the products, operational simplicity and green aspects by avoiding the use of expensive, toxic catalysts and solvents. Also the catalyst could be recovered after the completion of reaction and reused several times without any significant loss in its catalytic potential.



## 1. Introduction

Indoles and their derivatives are well known as an important class of heterocyclic compounds in organic synthesis and exhibit various physiological and pharmacological activities, (Sundberg, 1970) such as beneficial estrogen metabolism promoter, (Zeligs, 1998) inhibitory of human prostate cancer cells, (Grubbs et al., 1995) and radical scavenging activities associated with cancer cells (Benabadji et al., 2004). These compounds are also used in dietary supplements which promote healthy estrogen metabolism in humans (Anderton et al., 2004). Bis(indolyl)alkanes have received considerable attention because of their occurrence in bioactive metabolites of terrestrial and marine origin (Porter et al., 1977; Osawa and Namiki, 1983). A large number of these indolyl methanes were isolated from terrestrial and marine natural sources such as tunicates and sponges, (Fahy et al., 1991; Bifulco et al., 1995; Bell et al., 1994; Garbe et al., 2000) for example, Vibrindole A (3,3′-diindolyl ethane) (**I**) exhibits antibacterial activity and 3,3′-diindolyl methanes have potent anti-carcinogenic properties (Hong et al., 2002).




Because of these significant pharmacological, industrial and synthetic applications, the synthesis of these heterocycles has become a prime focus for synthetic organic chemists

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Peer review under responsibility of King Saud University.

ELSEVIER Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.arabjc.2014.05.009
1878-5352 

(Kaishap and Dohutia, 2013). Literature reveals a number of synthetic methods for the preparation of bis(indolyl)alkane derivatives from condensation of the indole with variety of carbonyl compounds in the presence of different catalysts and reagents (Gill et al., 2010; Khaksar and Mojtaba Ostad, 2011; Mukherjee et al., 2013). Good to high yields of the desired products may be obtained using these methods but most of the reported protocols suffered from some drawbacks, such as prolonged reaction times (Tekale et al., 2013; Li et al., 2006), expensive reagents (Heravi et al., 2008), low yields of products (Kumar et al., 2012), high catalyst loading (Dabiri et al., 2007), corrosive reagents and large amounts of solid supports (Jerome et al., 2009) that could eventually result in the generation of large amount of toxic waste. Therefore, the development of simple, convenient and an eco-friendly approach for the synthesis of these pharmaceutically important compounds is still in demand.

In view of current interest in catalytic processes, there is a need for developing a more benign method for the synthesis of bis(indolyl)methanes using heterogeneous catalyst owing to the increasing environmental requirements on waste minimization. In recent years, perflourinated resin sulfonic acid Nafion-H® has received considerable attention as an eco-friendly recyclable acid catalyst for carrying out various organic transformations (Kidwai and Chauhan, 2013, Suling et al., 2012; Prakash et al., 2012; Kidwai et al., 2011; Jain et al., 2009; Varma and Polshettiwar, 2008; Narsaiah et al., 2007). The high catalytic activity of Nafion-H®, its selectivity, inertness, thermal stability and ease of separation from the reaction mixture as well as its regeneration render it a very attractive candidate for organic synthesis (Olah et al., 1986; Molnar, 2008). Reducing or eliminating the use of volatile and toxic organic solvents can minimize the generation of waste, which is a requirement of one of the principles of green chemistry (Andrade and Alves, 2005; Anastas and Warner, 1998; Deligeorgiev et al., 2010). In this context, polyethylene glycol (PEG-400) is found to be an interesting solvent system. PEG is known to be inexpensive, thermally stable, recoverable, biologically compatible and non-toxic (Lamaty et al., 2012). Recently, it has been used as a reaction medium in organic reactions (Kidwai and Chauhan, 2013; Firouzabadi et al., 2012; Fantin et al., 2011; Burley et al., 2010).

The versatility of Nafion-H® catalyst and the environmentally benign nature of solvent PEG encouraged us to couple them together and study their application for the preparation of bis(indolyl)methanes. As a part of our ongoing effort in the laboratory toward the evolution of efficient, selective and eco-friendly synthetic methods for the synthesis of pharmacologically important moieties, (Kidwai and Chauhan, 2012; Kidwai et al., 2012, 2012a,b) we herein report a Nafion-H® catalyzed simple, rapid, efficient and green synthesis of bis(indolyl)methanes in PEG-400:water as the reaction medium.

## 2. Experimental section

### 2.1. Materials and methods

All chemicals were purchased from Sigma–Aldrich and were used without further purification. All reactions and purity of bis(indolyl)methanes were monitored by thin-layer chromatography (TLC) using aluminum plates coated with silica gel $F_{254}$ plates (Merck) using hexane:EtOAc (80:20) as an eluent. The spots were detected either under ultraviolet (UV) light or by placing in an iodine chamber. Melting points were determined in open capillaries using a Thomas Hoover melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer FTIR-1710 spectrophotometer using Nujol film. $^1$H and $^{13}$C nuclear magnetic resonance (NMR) spectra were recorded on a JEOL JNM-ECX 400P FT NMR system using tetramethylsilane (TMS) as an internal standard. ESI-MS mass spectra were recorded on Waters LCT Micromass. Elemental analysis was performed on a Heraeus CHN rapid analyzer. The temperature of the reaction mixture was measured through a non-contact infrared mini gun thermometer (AZ minigun type, model 8868).

### 2.2. General procedure for the synthesis of bis(indolyl)methane derivatives

A 50 mL round-bottomed flask was filled with aromatic aldehydes **1a**–**1l** (1 mmol), indoles **2a**–**2b** (2 mmol) and Nafion-H® (1 bead, 0.3 g) along with PEG-400:water (60:40) (5 mL) solvent system. The mixture was then stirred at 80 °C until the reaction was complete. The reaction mixture was then allowed to cool to room temperature and then the product was extracted with ethyl acetate (5 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate and filtered. The solvent was evaporated under *vacuo* to give the crude product. The remaining solution of PEG-400 and water was concentrated to recover pure PEG-400 which was then reused for the subsequent reactions (Zhu et al., 2009). The crude products, thus obtained were subjected to purification through recrystallization or column chromatography on silica gel using ethyl acetate with hexane in varying proportions as an eluent to yield bis(indolyl)methane derivatives, **3a**–**3n**. The structures of all the known products were established on the basis of melting points and spectral analysis (IR, $^1$H NMR, $^{13}$C NMR, and mass spectral data) and elemental analysis.

### 2.3. Regeneration of catalyst

The catalyst was washed successively with acetone and deionized water then dried overnight at 105 °C. The obtained catalyst had almost the same catalytic activity as the fresh catalyst.

### 2.4. Spectral data for the synthesized derivatives ***3a–3n***

#### 2.4.1. Bis(3-indolyl)(phenyl)methane ***(3a)***

Pink solid; M.Pt. 128–130 °C (Kantam et al., 2004); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$: 7.91 (br s, 2H, NH), 7.36–7.55 (m, 8H, Ar–H), 7.11–7.23 (m, 5H, Ar–H), 6.52 (s, 2H), 5.83 (s, 1H, Ar–CH); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$: 40.02, 111.04, 112.67, 119.12, 121.78, 122.04, 126.11, 126.89, 128.2, 128.56, 136.45, 137.77; IR (film) $\nu_{max}$: 3431, 3057, 1601, 1490, 1336, 1093, 743 cm$^{-1}$; Anal. calcd. for $C_{23}H_{18}N_2$: C, 85.68; H, 5.63; N, 8.69; found: C, 85.51; H, 5.43; N, 8.40%; ESI-MS calcd. for $C_{23}H_{18}N_2$: 322.15, found: 322.39.

#### 2.4.2. Bis(3-indolyl)(4′-chlorophenyl)methane ***(3b)***

Pink solid; M.Pt. 78–80 °C (Hasaninejad et al., 2007); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$: 8.02 (br s, 2H, NH), 7.42–7.78

(m, 8H, Ar–H), 7.12 (d, 2H, $J$ = 7.8 Hz, Ar–H), 7.02 (d, 2H, $J$ = 7.8 Hz, Ar–H), 6.53 (s, 2H), 5.81 (s, 1H, Ar–CH); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$: 39.56, 111.03, 111.22, 119.03, 119.63, 119.78, 123.57, 126.76, 128.37, 130.14, 130.78, 131.56, 136.60, 142.55; IR (film) $\nu_{max}$: 3413, 3056, 1590, 1090, 1013, 744 cm$^{-1}$; Anal. calcd. for $C_{23}H_{17}ClN_2$: C, 77.41; H, 4.80; N, 7.85; found: C, 77.23; H, 4.55; N, 7.75%; ESI-MS calcd. for $C_{23}H_{17}ClN_2$: 356.11, found: 357.48.

### 2.4.3. Bis(3-indolyl)(4′-methylphenyl)methane (3c)

Pink solid; M.Pt. 96–98 °C (Deb and Bhuyan, 2006); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$: 7.86 (br s, 2H, NH), 7.10–7.40 (m, 8H, Ar–H), 6.98 (d, 2H, $J$ = 8.0 Hz, Ar–H), 6.94 (d, 2H, $J$ = 8.0 Hz, Ar–H), 6.63 (s, 2H), 5.84 (s, 1H, Ar–CH), 2.32 (s, 3H, $CH_3$); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$: 21.09, 39.74, 110.89, 119.10, 119.88, 121.79, 123.48, 127.11, 128.45, 128.86, 129.16, 131.92, 134.88, 135.89; IR (film) $\nu_{max}$: 3411, 3050, 1609, 1510, 1216, 1092, 742 cm$^{-1}$; Anal. calcd. for $C_{24}H_{20}N_2$: C, 85.68; H, 5.99; N, 8.33; found: C, 85.40; H, 5.73; N, 8.07%; ESI-MS calcd. for $C_{24}H_{20}N_2$: 336.16, found: 335.78.

### 2.4.4. Bis(3-indolyl)(4′-nitrophenyl)methane (3d)

White solid; M.Pt. 216–220 °C (Deb and Bhuyan, 2006); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$: 9.60 (br s, 2H, NH), 8.19 (d, 2H, $J$ = 8.0 Hz, Ar–H), 7.35–7.62 (m, 8H, Ar–H), 7.30 (d, 2H, $J$ = 8.0 Hz, Ar–H), 6.28 (s, 2H), 5.77 (s, 1H, Ar–CH); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$: 39.18, 111.23, 118.89, 120.03, 121.07, 123.24, 123.78, 124.19, 127.49, 129.11, 136.50, 147.23, 156.08; IR (film) $\nu_{max}$: 3398, 3046, 1653, 1520, 1345, 1024, 764 cm$^{-1}$; Anal. calcd. for $C_{23}H_{17}N_3O_2$: C, 75.19; H, 4.66; N, 11.44; found: C, 74.89; H, 4.35; N, 11.27%; ESI-MS calcd. for $C_{23}H_{17}N_3O_2$: 367.13, found: 367.29.

### 2.4.5. Bis(3-indolyl)(2′-hydroxyphenyl)methane (3e)

Light brown solid; M.Pt. 90–94 °C (Chakrabarty et al., 2006); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$: 9.85 (br s, 1H, OH), 7.89 (br s, 2H, NH), 7.28–7.50 (m, 8H, Ar–H), 6.67–6.83 (m, 4H, Ar–H), 6.60 (s, 2H), 5.59 (s, 1H, Ar–CH); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$: 35.77, 110.89, 116.82, 117.24, 119.44, 119.91, 121.17, 122.45, 123.67, 126.78, 129.02, 130.11, 136.75, 154.49; IR (film) $\nu_{max}$: 3410, 3057, 1591, 1337, 1092, 743 cm$^{-1}$; Anal. calcd. for $C_{23}H_{18}N_2O$: C, 81.63; H, 5.36; N, 8.28; found: C, 81.40; H, 5.21; N, 8.01%; ESI-MS calcd. for $C_{23}H_{18}N_2O$: 338.14, found: 338.29.

### 2.4.6. Bis(3-indolyl)(2′-thienyl)methane (3f)

Pale white solid; M.Pt. 186–190 °C (Wang et al., 2005); $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$: 7.91 (br s, 2H, NH), 7.12–7.38 (m, 8H, Ar–H), 6.91–7.02 (m, 3H), 6.86 (s, 2H), 6.09 (s, 1H, Ar–CH); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$: 44.27, 111.42, 118.10, 119.03, 120.78, 121.56, 122.45, 123.16, 124.78, 126.52, 132.28, 136.47, 149.44; IR (film) $\nu_{max}$: 3410, 3053, 1654, 1542, 1220, 1025, 764 cm$^{-1}$; Anal. calcd. for $C_{21}H_{16}N_2S$: C, 76.80; H, 4.91; N, 8.53; found: C, 76.64; H, 4.57; N, 8.38%; ESI-MS calcd. for $C_{21}H_{16}N_2S$: 328.10, found: 329.27.

### 2.4.7. Bis(3-indolyl)(piperonyl)methane (3g)

Pale yellow solid; M.Pt. 96–100 °C (Kamble et al., 2006); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$: 8.02 (br s, 2H, NH), 7.10–7.38 (m, 8H, Ar–H), 6.78 (s, 2H), 6.58–6.65 (m, 3H), 5.99 (s, 2H, $CH_2$), 5.83 (s, 1H, Ar–CH); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$: 44.56, 100.72, 111.03, 115.24, 116.32, 119.17, 119.78, 120.23, 121.79, 122.37, 123.50, 126.83, 130.18, 136.49, 145.67, 147.26; IR (film) $\nu_{max}$: 3414, 3057, 1681, 1501, 1256, 1038, 746 cm$^{-1}$; Anal. calcd. for $C_{24}H_{18}N_2O_2$: C, 78.67; H, 4.95; N, 7.65; found: C, 78.38; H, 4.75; N, 7.48%; ESI-MS calcd. for $C_{24}H_{18}N_2O_2$: 366.14, found: 366.36.

### 2.4.8. Bis(2-methyl-3-indolyl)(phenyl)methane (3h)

Pink solid; M.Pt. 246–248 °C (Deb and Bhuyan, 2006); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$: 8.72 (br s, 2H, NH), 6.91–7.14 (m, 8H, Ar–H), 6.66–6.75 (m, 5H, Ar–H), 5.87 (s, 1H, Ar–CH), 1.95 (s, 6H, 2 $CH_3$); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$: 13.53, 38.45, 109.92, 112.78, 118.42, 119.90, 120.33, 125.58, 127.67, 128.80, 131.89, 135.91, 143.82; IR (film) $\nu_{max}$: 3395, 3043, 1650, 1581, 1217, 1009, 743 cm$^{-1}$; Anal. calcd. for $C_{25}H_{22}N_2$: C, 85.68; H, 6.33; N, 7.99; found: C, 85.40; H, 6.10; N, 7.65%; ESI-MS calcd. for $C_{25}H_{22}N_2$: 350.18, found: 350.00.

### 2.4.9. Bis(2-methyl-3-indolyl)(4′-methoxyphenyl)methane (3i)

Red solid; M.Pt. 96–100 °C (Liu et al., 2007); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$: 7.85 (br s, 2H, NH), 6.98–7.24 (m, 8H, Ar–H), 6.90 (d, 2H, $J$ = 7.8 Hz, Ar–H), 6.77 (d, 2H, $J$ = 7.8 Hz, Ar–H), 5.93 (s, 1H, Ar–CH), 3.77 (s, 3H, $OCH_3$), 2.03 (s, 6H, 2 $CH_3$); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$: 12.35, 38.03, 55.45, 109.78, 113.34, 113.56, 199.16, 119.38, 121.56, 128.90, 130.02, 130.19, 131.69, 134.98, 157.89; IR (film) $\nu_{max}$: 3448, 3048, 1594, 1502, 1242, 1043, 735 cm$^{-1}$; Anal. calcd. for $C_{26}H_{24}N_2O$: C, 82.07; H, 6.36; N, 7.36; found: C, 81.86; H, 6.18; N, 7.19%; ESI-MS calcd. for $C_{26}H_{24}N_2O$: 380.19, found: 380.27.

### 2.4.10. Bis(2-methyl-3-indolyl)(3′-nitrophenyl)methane (3j)

Yellow solid; M.Pt. 262–266 °C (Heravi et al., 2009); $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$: 8.06 (br s, 2H, NH), 7.89 (s, 1H, Ar–H), 7.45–7.68 (m, 3H, Ar–H), 7.01–7.22 (m, 8H, Ar–H), 6.05 (s, 1H, Ar–CH), 2.16 (s, 6H, 2 $CH_3$); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$: 11.92, 33.78, 110.33, 110.67, 119.56, 120.62, 121.16, 122.89, 124.77, 127.78, 132.35, 135.02, 135.21, 137.17, 146.69, 147.72; IR (film) $\nu_{max}$: 3400, 3057, 1645, 1527, 1219, 1013, 748 cm$^{-1}$; Anal. calcd. for $C_{25}H_{21}N_3O_2$: C, 75.93; H, 5.35; N, 10.63; found: C, 75.68; H, 5.11; N, 10.37%; ESI-MS calcd. for $C_{25}H_{21}N_3O_2$: 395.16, found: 395.27.

### 2.4.11. Bis(2-methyl-3-indolyl)(2′-hydroxyphenyl)methane (3k)

Light pink solid; M.Pt. 162–166 °C; $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$: 10.13 (br s, 1H, OH), 7.86 (br s, 2H, NH), 6.80–7.04 (m, 8H, Ar–H), 6.62–6.74 (m, 4H, Ar–H), 6.10 (s, 1H, Ar–CH), 2.06 (s, 6H, 2 $CH_3$); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$: 11.13, 33.82, 109.78, 111.91, 114.63, 118.25, 119.07, 120.88, 121.00, 121.81, 125.23, 126.45, 128.67, 130.78, 131.69, 134.78, 136.03, 154.76; IR (film) $\nu_{max}$: 3426, 3052, 1655, 1532, 1271, 1086, 745 cm$^{-1}$; Anal. calcd. for $C_{25}H_{22}N_2O$: C, 81.94; H, 6.05; N, 7.64; found: C, 81.72; H, 5.92; N, 7.45%; ESI-MS calcd. for $C_{25}H_{22}N_2O$: 366.17, found: 366.25.

### 2.4.12. Bis(2-methyl-3-indolyl)(4′-bromophenyl)methane (3l)

White solid; M.Pt. 210–214 °C; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$: 9.10 (br s, 2H, NH), 7.20 (d, 2H, $J$ = 8.8 Hz, Ar–H),

6.88–7.10 (m, 8H, Ar–H), 6.65 (d, 2H, $J$ = 8.8 Hz, Ar–H), 5.76 (s, 1H, Ar–CH) 1.92 (s, 6H, 2 $CH_3$); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$: 12.14, 38.34, 109.88, 111.92, 118.41, 118.70, 119.14, 119.86, 122.26, 128.29, 130.69, 131.98, 134.86, 143.03; IR (film) $\nu_{max}$: 3382, 3047, 1634, 1571, 1245, 1010, 746 $cm^{-1}$; Anal. calcd. for $C_{25}H_{21}BrN_2$: C, 69.94; H, 4.93; N, 6.52; found: C, 69.75; H, 4.80; N, 6.38%; ESI-MS calcd. for $C_{25}H_{21}BrN_2$: 428.09, found: 427.84.

#### *2.4.13. Bis(2-methyl-3-indolyl)(2′-hydroxy-3′-methoxyphenyl)methane* ***(3m)***

White solid; M.Pt. 232–236 °C; $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$: 9.80 (br s, 1H, OH), 7.83 (br s, 2H, NH), 7.29–7.45 (m, 8H, Ar–H), 6.61–6.72 (m, 3H, Ar–H), 6.14 (s, 1H, Ar–CH), 3.84 (s, 3H, $OCH_3$), 2.05 (s, 6H, 2 $CH_3$); $^{13}$C NMR (DMSO-$d_6$, 100 MHz): δ 11.65, 39.17, 55.46, 109.78, 111.89, 112.48, 118.27, 119.13, 120.73, 121.80, 122.09, 128.56, 131.45, 134.78, 136.29, 143.56, 146.47; IR (film) $\nu_{max}$: 3401, 3011, 1654, 1542, 1217, 1072, 750 $cm^{-1}$; Anal. calcd. for $C_{26}H_{24}N_2O_2$: C, 78.76; H, 6.10; N, 7.07; found: C, 78.37; H, 5.97; N, 6.88%; ESI-MS calcd. for $C_{26}H_{24}N_2O_2$: 396.18, found: 396.34.

#### *2.4.14. Bis(2-methyl-3-indolyl)(1′-styryl)methane* ***(3n)***

Yellow solid; M.Pt. 98–102 °C; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$: 7.85 (br s, 2H, NH), 7.28–7.35 (m, 5H, Ar–H), 7.02–7.22 (m, 8H, Ar–H), 6.24 (d, 1H, $J$ = 15.4 Hz), 5.44 (m, 1H), 5.22 (m, 1H, Ar–CH), 2.22 (s, 6H, 2 $CH_3$); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$: 11.42, 32.23, 110.18, 113.33, 119.36, 120.43, 122.56, 123.22, 125.45, 127.75, 127.88, 128.02, 128.24, 131.67, 131.89, 134.93, 135.26; IR (film) $\nu_{max}$: 3411, 3057, 1620, 1536, 1271, 1095, 744 $cm^{-1}$; Anal. calcd. for $C_{27}H_{24}N_2$: C, 86.13; H, 6.43; N, 7.44; found: C, 86.04; H, 6.22; N, 7.25%; ESI-MS calcd. for $C_{27}H_{24}N_2$: 376.19, found: 376.29.

## 3. Results and discussion

In an initial attempt, a blank reaction was carried out using 1 equiv. of benzaldehyde **(1a)** and 2 equiv. of indole **(2a)** as a representative example (Scheme 1). These were stirred in ethanol. After 5 h, only 52% of the product **(3a)** was obtained. The same reaction was then conducted using Nafion-H® as a catalyst under similar conditions. Surprisingly, it was completed cleanly within 40 min and the yield was dramatically enhanced up to 78% (Table 1, entry 1).

For further improvement of product yield and to optimize the reaction conditions, the same reaction was carried out using polyethylene glycol (PEG-400) as medium. A significant improvement was observed and the yield increased up to 86% after stirring the mixture for only 30 min only (Table 1, entry 5). Encouraged by these promising results, we optimized the reaction conditions by employing different ratios of PEG-400:water solvent system. A decrease in the quantity of PEG-400 from 100% to 60% increased the product yield from 86% to 94% (Table 1, entries 6–9). But a further decrease in the ratio of PEG-400 decreased the product yield, which is attributed to the loss of solubility of the reactants in water.

**Table 1** Effect of different solvents on the synthesis of bis(indolyl)methane **3a**.[a]

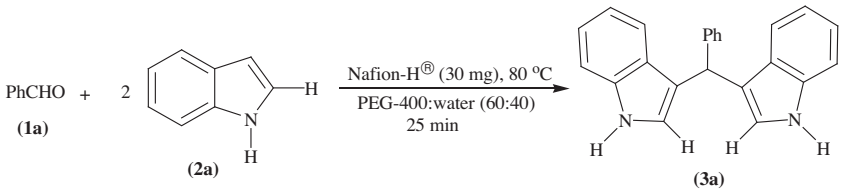
| Entry | Solvent/mL | Time/min | Yield/(%)[b] |
|---|---|---|---|
| 1 | EtOH | 40 | 78 |
| 2 | MeCN | 35 | 82 |
| 3 | THF | 50 | 66 |
| 4 | Toluene | 60 | 54 |
| 5 | PEG-400 | 30 | 86 |
| | PEG-400:$H_2O$ | | |
| 6 | 90:10 | 35 | 88 |
| 7 | 80:20 | 35 | 90 |
| 8 | 70:30 | 35 | 92 |
| 9 | 60:40 | 25 | 94 |
| 10 | 50:50 | 35 | 83 |
| 11 | 40:60 | 45 | 78 |

[a] Reaction conditions: benzaldehyde **1a** (1 mmol), indole **2a** (2 mmol); catalyst: Nafion-H® (30 mg); temp: 80 °C; solvent: x (5 mL).
[b] Isolated yields.

We also studied the influence of different solvents on the reaction rate as well as the yields of products (Table 1). Only acetonitrile afforded products in good yields with similar reaction times (Table 1, entry 2). The reason for the low yields in some solvents is due to the inability of solvent to swell Nafion-H® which resulted in its low catalytic activity. Nafion-H® being non-porous relies on the solvation of the ionic groups by an appropriate solvent to form solvents channels and clusters. The low yields were observed due to the failure of the substrate to be able to access the catalyst (Seen, 2001).

The effect of temperature was also examined for the model reaction (Fig. 1). From the point of view of maximum yield in minimum time, 80 °C was chosen as the reaction temperature.

The scope of this reaction with respect to various substituted aromatic aldehydes with indoles under these reaction conditions was also investigated (Scheme 2). The results obtained are sumarized in Table 2. The effect of electron-deficiency and nature of substituents on the aromatic ring showed little effect on this conversion. The nitro-substituted aryl aldehydes required longer reaction times to produce comparable yields than those of their simple and electron-rich counterparts (Table 2, entries 4, 10). Only aromatic aldehydes gave excellent




**Scheme 1** Nafion-H® catalyzed model reaction for the synthesis of bis(indolyl)methanes.

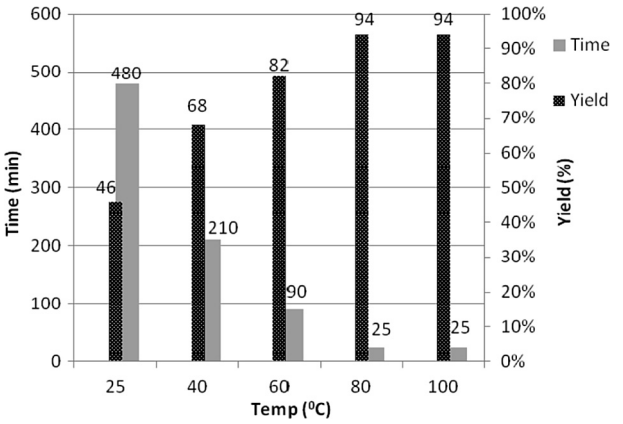



**Figure 1** Effect of temperature. Reaction conditions: benzaldehyde **1a** (1 mmol), indole **2a** (2 mmol); catalyst: Nafion-H® (30 mg); temp: x (°C); solvent: PEG-400:water (60:40) system (5 mL). Isolated yields.

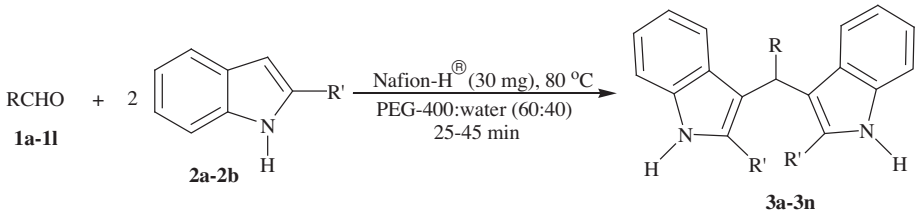
yields whereas the reaction proceeded very slowly with aliphatic substrates like butanal, propanal, heptanal *etc.* and did not even reach completion. The product yields obtained were as low as 50–55%. Hence, we proceeded with aromatic aldehydes only.

Recyclability of the Nafion-H® catalyst was checked for the model reaction of indole and benzaldehyde (Scheme 1). After completion of the reaction, a simple decantation of the organic liquid afforded the catalyst which was washed with acetone, dried and utilized for subsequent preparation of bis(indolyl)methane derivatives. The procedure was repeated four times for the reaction without any significant loss of activity as the catalyst remained active even after the fourth run with 94% yield (Fig. 2). In these experiments, while the yields and reaction times remained same up to four catalytic cycles, the reaction times were found to increase gradually with comparable yields of bis(indolyl)methanes.

A plausible mechanism for the Nafion-H® catalyzed synthesis of bis(indolyl)methanes is shown in Scheme 3. In the initial step, Nafion-H® protonates the carbonyl oxygen of aldehyde making it susceptible to attack by indole **(2a–2b)**. In this condensation reaction, indole forms an intermediate **III** with aldehydes **(1a–1l)** by loss of water, which undergo further addition with a second molecule of indole to afford intermediate **V** which then suffers a hydride shift to furnish bis(indolyl)methane derivatives **(3a–3n)**. In the entire mechanism, Nafion-H® was regenerated and reused for consecutive runs.

### 3.1. Catalytic activation of Nafion-H®

Nafion-H® is a perflouroalkyl sulfonic acid resin. Its superacidity is due to the electron-withdrawing effect of the perflouroalkyl backbone to which the sulfonic acid group is attached (Olah et al., 1986). The catalytic activa-




**Scheme 2** Nafion-H® catalyzed synthesis of bis(indolyl)methane derivatives.

**Table 2** Nafion-H® promoted synthesis of bis(indolyl)methane derivatives.[a]

| Entry | R | R′ | Product | Time/min | Yield[b]/% |
|---|---|---|---|---|---|
| 1 | Ph (**1a**) | H (**2a**) | **3a** | 25 | 94 |
| 2 | 4-Cl-$C_6H_4$ (**1b**) | H | **3b** | 30 | 94 |
| 3 | 4-Me-$C_6H_4$ (**1c**) | H | **3c** | 30 | 92 |
| 4 | 4-$NO_2$-$C_6H_4$ (**1d**) | H | **3d** | 40 | 92 |
| 5 | 2-HO-$C_6H_4$ (**1e**) | H | **3e** | 25 | 91 |
| 6 | 2-Thienyl (**1f**) | H | **3f** | 45 | 85 |
| 7 | Piperonyl (**1g**) | H | **3g** | 45 | 88 |
| 8 | Ph | Me (**2b**) | **3h** | 25 | 94 |
| 9 | 4-MeO-$C_6H_4$ (**1h**) | Me | **3i** | 25 | 94 |
| 10 | 3-$NO_2$-$C_6H_4$ (**1i**) | Me | **3j** | 40 | 90 |
| 11 | 2-HO-$C_6H_4$ | Me | **3k** | 25 | 92 |
| 12 | 4-Br-$C_6H_4$ (**1j**) | Me | **3l** | 35 | 92 |
| 13 | 2-HO-3-MeO-$C_6H_3$ (**1k**) | Me | **3m** | 35 | 90 |
| 14 | $C_6H_5CH$ = CH (**1l**) | Me | **3n** | 40 | 86 |

[a] Reaction conditions: aromatic aldehydes **1a–1l** (1 mmol), substituted indoles **2a–2b** (2 mmol); catalyst: Nafion-H® (30 mg); temp: 80 °C; solvent: PEG-400:water (60:40) system (5 mL).
[b] Isolated yields.

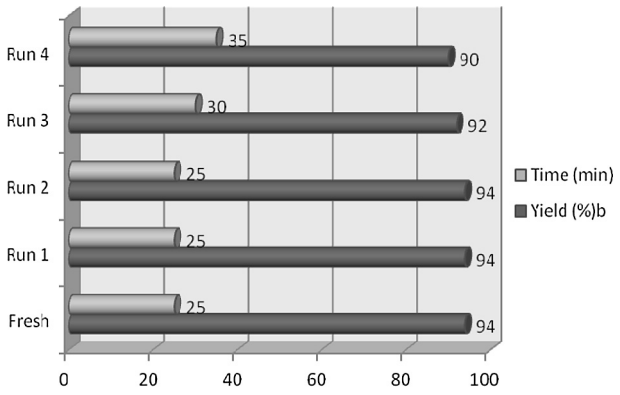
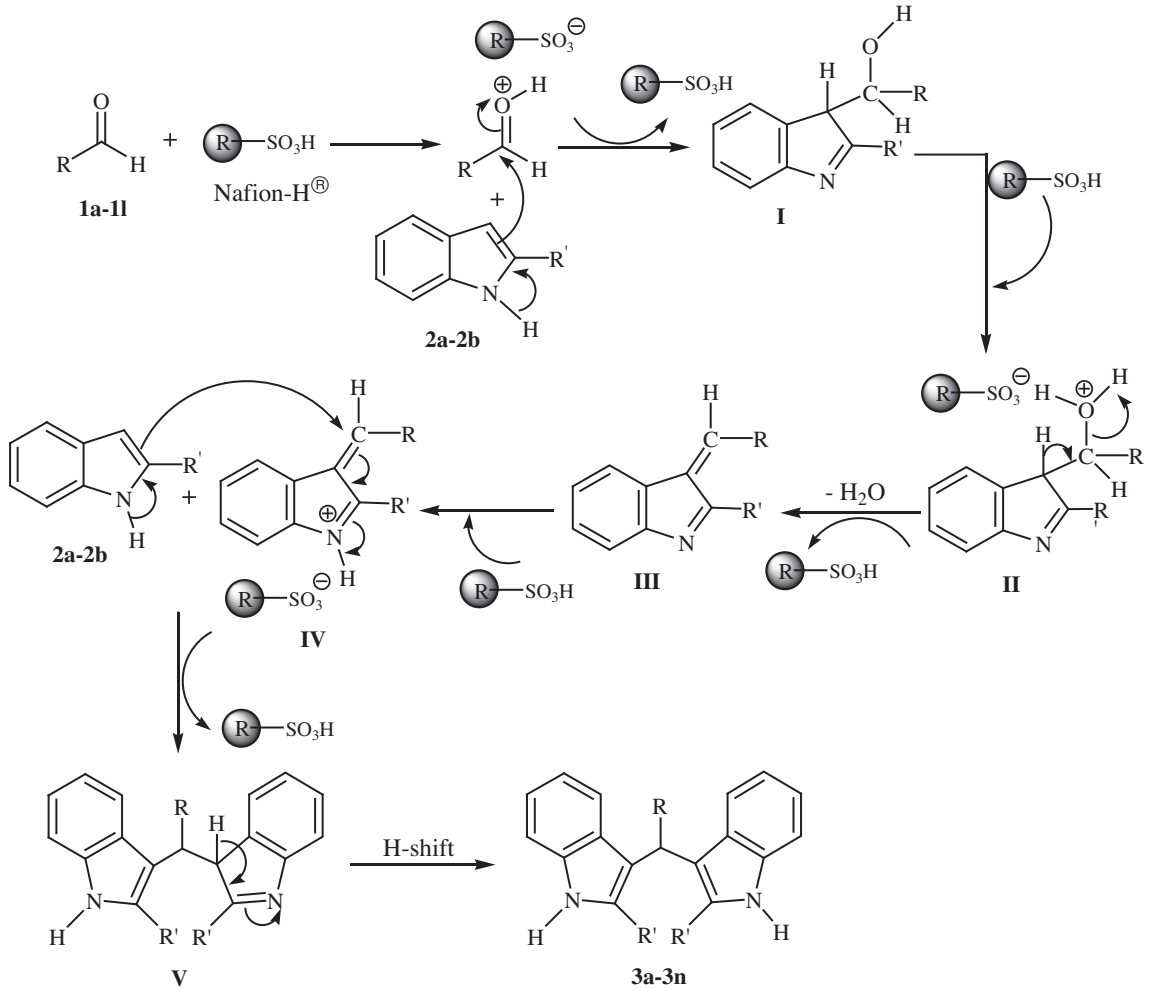



**Figure 2** Recycling studies of the catalyst. Reaction conditions: benzaldehyde **1a** (1 mmol), indole **2a** (2 mmol); catalyst: Nafion-H® (30 mg); temp: 80 °C; solvent: PEG-400:water (60:40) system (5 mL). Isolated yields.

tion of Nafion-H® resin relies on the nature of solvent used in the reaction. The $SO_3H$ groups that are responsible for its acidity are present on the catalyst surface that is kept in contact with the bulk solvent. This acid resin has inherently very low surface area unless an appropriate solvent is used to swell the polymer, thereby exposing its acid centers to the reaction (Goodwin et al., 2007). In polar solvents, bulk acidity of Nafion-H® is enhanced due to swelling which leads to better accessibility of the sulfonic acid active sites whereas its catalytic activity in non-swelling solvents is very low due to very low surface area and hence substrates are not able to access the acidic sites of Nafion-H®.

## 4. Conclusions

In summary, we have demonstrated Nafion-H® as an efficient and eco-friendly catalyst for the synthesis of these pharmacologically important moieties in PEG-400:water solvent system. The simple, cleaner reaction conditions, efficiency and cost effectiveness, shorter reaction time, easy work up and recyclability of catalyst make this method an attractive, environmentally friendly synthetic protocol for the preparation of bis(indolyl)methanes.




**Scheme 3** Plausible mechanism for the Nafion-H® catalyzed synthesis of bis(indolyl)methanes.

**Acknowledgements**

Author (R. Chauhan) is thankful to the UGC (University Grants Commission) for providing Junior Research Fellowship and also to the Director of University Science and Instrumentation Centre, University of Delhi, Delhi for providing the instrumentation facilities.

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