# SiO₂-Diphenic acid: An efficient and recyclable heterogeneous catalyst for one-pot synthesis of *bis*-(indolyl)methane derivatives in liquid phase

R VAID, M GUPTA*, O S CHAMBYAL and R GUPTA

Department of Chemistry, University of Jammu, Jammu 180006, India
e-mail: monika.gupta77@rediffmail.com

**Abstract.** An eco-friendly and expedient procedure for one-pot synthesis of *bis*-(indolyl)methane derivatives via electrophilic substitution reaction at C-3 position of indole with various aldehydes has been developed by using silica-diphenic acid as a novel heterogeneous catalyst. This method has various promising features such as short reaction time, easy work-up procedure, good yield of products and remarkable activity and selectivity of the catalyst.

**Keywords.** Heterogeneous catalysis; Indole; Aldehydes; Diphenic acid.

## 1. Introduction

Indole, the most important heterocycle present in natural compounds, has become an important structural moiety required in many pharmaceutical agents[1] due to its extensive pharmacological and biological activities.[2] One of the most important groups of indole derivatives which possess such activities and those found in cruciferous plants and marine sources are *bis*-(indolyl)methanes.[3] They exhibit different pharmaceutical activities such as anti-cancer, anti-bacterial, cytotoxic, anti-oxidative, insecticidal, anti-hyperglycaemic, anti-viral, and anti-microbial activities.[4–6] *Bis*-(indolyl)methane derivatives are also known to promote oestrogen metabolism in both men and women and are expected to have an application in the prevention of breast cancer.[7] These derivatives also possess significant anti-proliferative activity and induce apoptosis in human prostate cancer cells.[8]

Due to the unique biological properties of *bis*-(indolyl)methane derivatives, many research groups have shown interest to find feasible and efficient synthetic methods for this class of compounds. The best synthetic route towards *bis*-(indolyl)methane derivatives is the condensation reaction between indole and carbonyl compounds using different catalysts.[9,10]

In literature, a number of synthetic methods for their preparation have been reported. Of these methods, the acid catalysed electrophilic addition reaction of indole and aldehydes is one of the most simple and straightforward approaches for the synthesis of *bis*-(indolyl)alkane derivatives. Many reagents such as silica-supported boric acid,[11] [cmmim]Cl,[12] silica gel,[13] *n*-dodecylbenzene sulfonic acid (DBSA),[14] *β*-cyclodextrin sulphuric acid,[15] cyclic phosphonic acid anhydride (T3P),[16] monoammonium salt of 12-tungstophosphoric acid [(NH₄)H₂PW₁₂O₄₀],[17] nanocatalyst H₅PW₁₀V₂O₄₀/TPI-Fe₃O₄,[18] 1,3-Dibromo-5,5-dimethyl-hydantoin (DBDMH),[19] BF₃·Et₂O,[20] *N*-butyl-pyridinium bromide,[21] PEG-SO₃H,[22] triphenylphosphonium perchlorate,[23] iodine,[24] silica sulphuric acid (SSA),[25] fruit juice of citrus-lemon,[26] Ni-nanoparticles,[27] etc. Although some of these protocols are valuable, most of them suffer from one or more drawbacks, including long reaction times, low yields of products, harsh reaction conditions, and use of expensive and/or toxic catalysts and solvents. Therefore, there is a strong demand for the development of mild, clean, and highly efficient procedures for the synthesis of *bis*-(indolyl) methane derivatives.

In this context, we report here one-pot synthesis of *bis*-(indolyl) methane derivatives by reaction of indole and aromatic/heteroaromatic/aliphatic aldehydes in the presence of silica-diphenic acid as a heterogeneous and recyclable catalyst in acetonitrile at 60°C (scheme 1).

## 2. Experimental

All the chemicals and solvents were purchased from Sigma-Aldrich and Merck and were used without further purification. The mass spectra were recorded on Esquire 3000 Bruker Daltonics spectrometer (ESI). ¹H-NMR and ¹³C-NMR spectra were recorded in DMSO-*d₆* on Bruker Avance III 400 MHz spectrometer using

---

*For correspondence
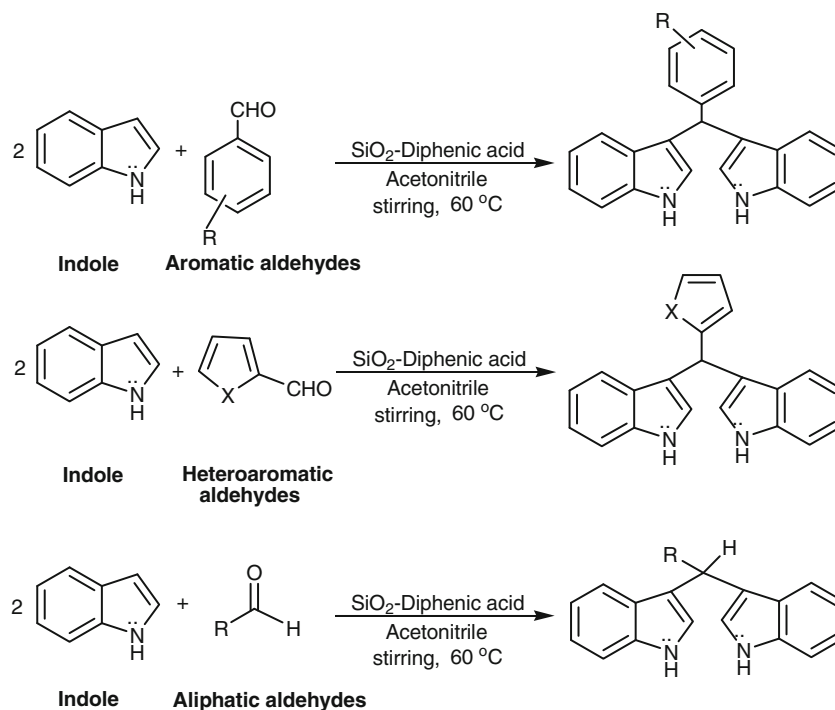
**Scheme 1.** Silica-diphenic acid catalysed synthesis of *bis*-(indolyl)methane derivatives.

TMS as an internal standard. TGA was recorded on Linesis Thermal Analyser with heating rate of 10°C/min. FTIR was recorded on SHIMADZU prestige spectrophotometer. SEM images were recorded on JSM-7600F scanning electron microscope. TEM images were recorded on CM200 PHILIPS transmission electron microscope. All physical and spectroscopic data of products were compared with those reported in the literature.

### 2.1 *Preparation of Activated Silica*

Activated silica was prepared by adding silica gel (15 g, K 60) to a solution of 1:1 HCl (150 mL) and $H_2O$ (150 mL) in a 500 mL round-bottom flask and the reaction mixture was stirred at 120°C for 12 h. The activated silica was filtered at pump, washed with water till washings were neutral, and dried in oven at 110°C for 5 h.

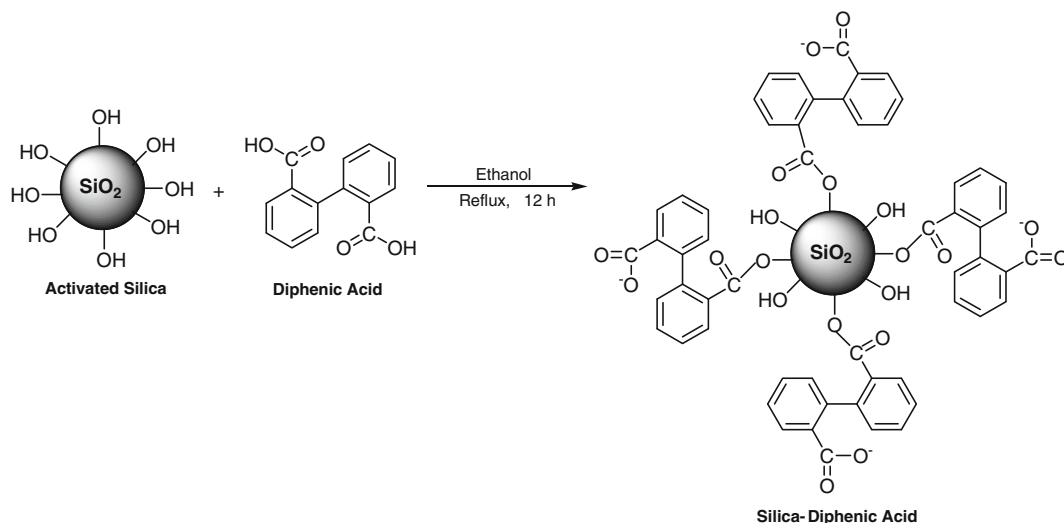### 2.2 *Preparation of silica supported diphenic acid*

In a round-bottom flask, diphenic acid (1 mmol, 0.242 g) was dissolved in ethanol (10 mL). To this solution, the activated silica gel (1 g) was added. The mixture was shaken for a few minutes and then refluxed for 12 h. After refluxing, the solvent was evaporated under reduced pressure of 250 mm Hg (333.3 mbar) for 25 h to give free-flowing powder. The complete preparation

procedure for silica-supported diphenic acid is represented in scheme 2.

### 2.3 *Characterization of Silica-Diphenic Acid*

Silica-diphenic acid was characterized by FTIR, thermal gravimetric analysis (TGA), TEM, and SEM analysis.

2.3a *FTIR*: The anchoring of diphenic acid onto the surface of silica was confirmed by FTIR spectra (figure 1) of the catalyst silica-diphenic acid. The spectra showed the characteristic absorption peaks at 1089.78 $cm^{-1}$, 800.46 $cm^{-1}$ and 466.77 $cm^{-1}$, which were assigned to asymmetric stretching, symmetric stretching, and bending modes of Si–O–Si bonds, respectively. Due to the anchoring of diphenic acid onto the surface of the activated silica through one of the carbonyl group (C=O) of diphenic acid by ester linkage, the absorption peak of carbonyl group (C=O) appears at 1720.50 $cm^{-1}$ and peaks at 1487.12 $cm^{-1}$ and 1392.61 $cm^{-1}$ were related to asymmetric and symmetric stretching vibrations of another carboxylic (-$CO_2^-$) group. The formation of ester linkage between diphenic acid and silica was further confirmed by absorption peaks at 1359.52 $cm^{-1}$ and 1151.50 $cm^{-1}$, which were attributed to Si–O–C bonds. The FTIR spectrum of the catalyst also shows the absence of characteristic –OH stretching vibration of –COOH group near 3300–3000

**Scheme 2.** Preparation of silica supported diphenic acid.



**Figure 1.** FTIR spectra of Silica-Diphenic acid.

cm$^{-1}$ and the absorption peak at 3676.32 cm$^{-1}$ may be due to the presence of some of the free Si-OH groups in the catalyst. Further, the absorption peak at 1656.85 cm$^{-1}$ corresponds to the stretching mode of vibrations of benzene rings of diphenic acid. From the above spectral data analysis of the catalyst, it has been concluded that diphenic acid was chemically adsorbed onto the surface of activated silica by forming ester linkages.

2.3b *Thermal Gravimetric Analysis*: The stability of the silica-diphenic acid was determined by thermal gravimetric analysis (figure 2). The curve showed an initial weight loss up to 90°C, which may be due to the removal of surface-adsorbed solvent and gases. The next weight loss up to 263.7°C was probably due to the loss of structural water within amorphous SiO$_2$. The weight loss up to 340.7°C may correspond to the decomposition of two benzenes of diphenic acid, followed by continuous weight loss up to 560.7°C, which may be attributed to the loss of CO and CO$_2$ groups. This thermal analysis indicates that catalyst is stable up to 100°C and hence it is safe to carry out the reaction at 60°C.

2.3c *Transmission Electron Microscopy (TEM)*: The TEM micrographs of the catalyst provide a direct
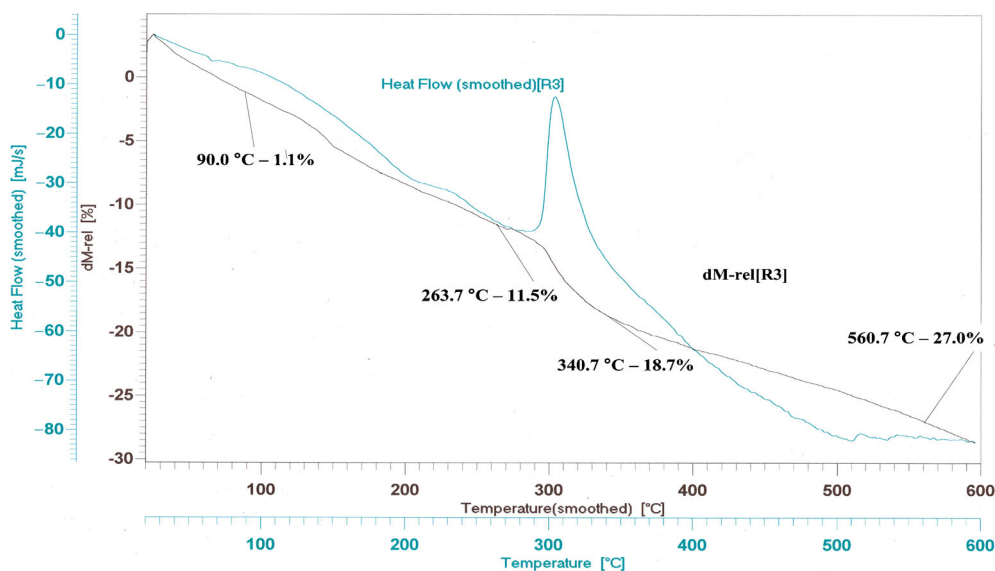
**Figure 2.** Thermal gravimetric analysis of Silica-Diphenic acid.

observation of the morphology and distribution of the diphenic acid in silica-diphenic acid catalyst. The TEM micrographs indicated that diphenic acid is uniformly distributed onto the surface of silica as shown in figure 3 and the mean diameter was found to be 5.27 nm.

2.3d *Scanning Electron Microscopy (SEM)*: The microstructure and morphology of silica-diphenic acid was studied using a scanning electron microscope (SEM). The surface of silica-diphenic acid was found to be fine homogeneous powder with porous structure and it was observed that diphenic acid particles are adsorbed onto the surface of silica as shown in figure 4.

### 2.4 *General Procedure for the One-Pot Synthesis of Bis-(Indolyl)Methane Derivatives*

To a mixture of aldehyde (1 mmol), indole (2 mmol) in a round-bottom flask (25 mL), silica-diphenic acid (0.05 g) and acetonitrile (1 mL) were added and the reaction mixture was stirred at 60°C in an oil bath for the appropriate time. On completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature and EtOAc (20 mL) was added to it. The reaction mixture was then filtered to separate the catalyst, followed by washing of filtrate with distilled water and, finally, dried over anhydrous $Na_2SO_4$. After removal of solvent under reduced pressure, the residue was purified by passing through a column of silica gel and elution with EtOAc: petroleum
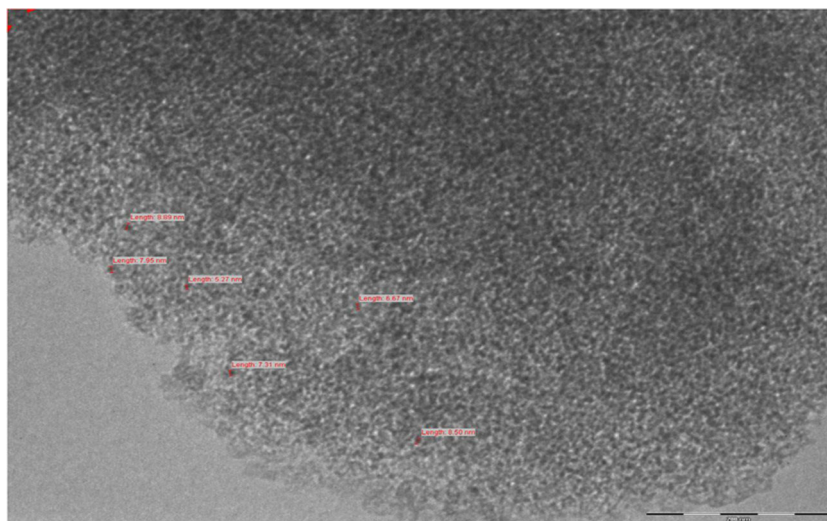


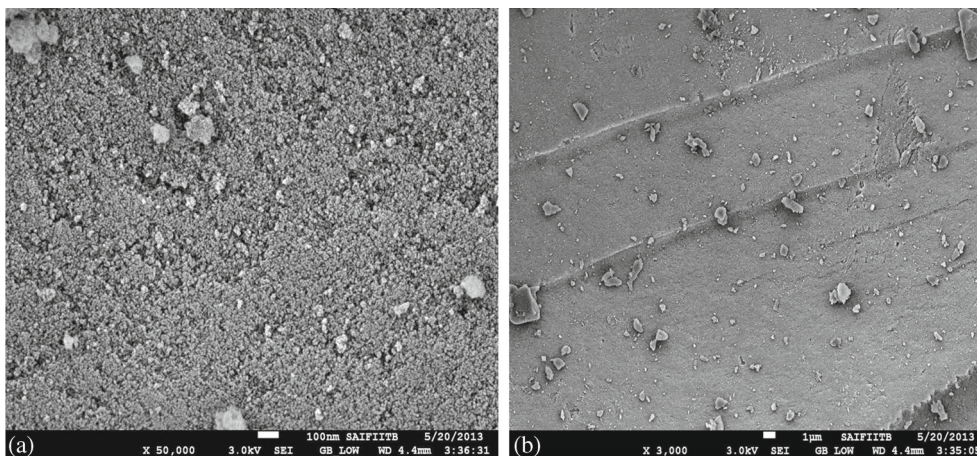**Figure 3.** TEM images of Silica-Diphenic Acid (scale bar: 200 nm).

**Figure 4.** SEM images of Silica-Diphenic Acid (a) 50,000 X; (b) 3,000 X.

ether. The products obtained from column were further recrystallized in EtOAc: petroleum ether so that these were obtained in pure form. The structures of the products were confirmed by IR, $^1$HNMR, $^{13}$C NMR and mass spectral data and compared with authentic samples available commercially or prepared according to literature methods.

### 2.5 *Spectral Data for the Synthesised Compounds*

2.5a *Phenyl-3,3′-bis-(indolyl)methane (Entry1, Table 5)*: IR ($\upsilon_{max}$ in cm$^{-1}$, KBr): 3460, 3221, 1599, 1475, 1420, 1109, 1017, 756. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 5.90 (s, 1H, methine-H), 6.67 (s, 2H), 7.12–7.56 (m, 13H), 10.13 (bs, 2H, NH). $^{13}$C NMR (400 MHz, DMSO-$d_6$): $\delta$ 51.33, 109.45, 112.12, 118.52, 120.56, 121.63, 122.46, 126.23, 127.82, 128.45, 130.31, 136.44, 139.59. MS: m/z 321 (M-1).

2.5b *3, 4-Dimethoxyphenyl-3, 3′-bis-(indolyl) methane (Entry 2, Table 5)*: IR ($\upsilon_{max}$ in cm$^{-1}$, KBr): 3480, 3020, 2928, 1629, 1556, 1445, 1029, 758. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 3.76 (s, 3H, OCH$_3$), 3.85 (s, 3H, OCH$_3$), 5.83 (s, 1H, methine-H), 6.65 (s, 2H), 6.45–6.54 (m, 3H), 7.1–7.22 (m, 4H), 7.41(d, 2H), 7.59 (d, 2H), 10.86 (bs, 2H, NH). $^{13}$C NMR (400 MHz, DMSO-d$_6$): $\delta$ 42.41, 48.64, 111.30, 112.44, 114.21, 115.46, 119.80, 120.31, 121.02, 122.10, 122.52, 122.90, 131.11, 136.82, 146.34, 148.97. MS: m/z 381 (M-1).

2.5c *4-Methoxyphenyl-3,3′-bis-(indolyl)methane(Entry 3, Table 5)*: IR ($\upsilon_{max}$ in cm$^{-1}$, KBr): 3480, 3018, 2853, 1615, 1507, 1346, 1088, 783, 742. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 3.94 (s, 3H), 5.85 (s, 1H, methine-H),

6.71 (s, 2H), 6.88–7.27 (m, 4H), 7.85–7.92 (m, 8H), 10.63 (bs, 2H, NH). $^{13}$C NMR (400 MHz, DMSO-$d_6$): $\delta$ 48.23, 51.18, 111.10, 112.53, 115.70, 119.19, 120.08, 122.19, 124.73, 127.16, 130.02, 130.90, 136.42, 148.86. MS: m/z 351 (M-1).

2.5d *4-Methylphenyl-3, 3′-bis-(indolyl) methane (Entry 4, Table 5)*: IR ($\upsilon_{max}$ in cm$^{-1}$, KBr): 3475, 3145, 3020, 2970, 1636, 1506, 1086, 736. $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 2.51 (s, 3H), 5.77 (s, 1H, methine-H), 6.79 (s, 2H), 6.85–6.87 (m, 4H), 7.22-7.39 (m, 8H), 10.8 (bs, 2H, NH). $^{13}$C NMR (400 MHz, DMSO-$d_6$): $\delta$ 39.90, 111.03, 112.23, 116.58, 117.90, 118.57, 121.33, 123.90, 128.64, 129.07, 131.21, 132.13, 135.80, 139.21. MS: m/z 335 (M-1).

2.5e *2-Flourophenyl-3, 3′-bis-(indolyl) methane (Entry 5, Table 5)*: IR ($\upsilon_{max}$ in cm$^{-1}$, KBr): 3440, 3059, 1601, 1508, 1457, 1038, 865, 738. $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 6.10 (s, 1H, methine-H), 6.83 (s, 2H), 7.03–7.09 (m, 4H), 7.24–7.26 (m, 4H), 7.35–7.37 (m, 4H), 10.87 (bs, 2H, NH). $^{13}$C NMR (400 MHz, DMSO-$d_6$): $\delta$ 49.07, 112.27, 115.55, 117.04, 118.55, 119.12, 121.76, 124.21, 124.53, 126.83, 128.35, 128.63, 130.70, 137.03, 161.74. MS(-ESI): m/z 339 (M-1), $^{19}$F NMR (400 MHz, DMSO-$d_6$): -118.65.

2.5f *2-Chlorophenyl-3, 3′-bis-(indolyl) methane (Entry 6, Table 5)*: IR ($\upsilon_{max}$ in cm$^{-1}$, KBr): 3413, 3055, 1618, 1095, 748. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 5.95 (s, 1H, methine-H), 6.88 (s, 2H), 6.6–6.7 (d, 2H), 6.91–7.05 (t, 2H), 7.10–7.21 (m, 4H, Ar-H), 7.35–7.45 (m, 4H, Ar-H), 10.98 (bs, 2H, NH). $^{13}$C NMR (400 MHz, DMSO-$d_6$): $\delta$ 39.33, 111.36, 112.21, 118.32, 118.90,

119.87, 120.23, 123.42, 126.88, 127.29, 128.90, 130.04, 134.52, 136.38, 138.49. MS: m/z 355 (M-1).

**2.5g** *4-Chlorophenyl-3, 3′-bis-(indolyl) methane (Entry 7, Table 5)*: IR ($\upsilon_{max}$ in cm$^{-1}$, KBr): 3468, 3018, 2920, 1615, 1529, 1210, 759. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 5.85 (s, 1H, methine-H), 6.82 (s, 2H), 6.8–7.05 (m, 4H, Ar-H), 7.2–7.39 (m, 8H, Ar-H), 10.87 (bs, 2H, NH). $^{13}$C NMR (400 MHz, DMSO-$d_6$): δ 40.11, 111.97, 118.01, 118.73, 119.48, 121.44, 126.91, 128.46, 129.85, 130.72, 131.67, 137.03, 144.46. MS: m/z 355 (M-1).

**2.5h** *4-Bromophenyl-3, 3′-bis-(indolyl) methane (Entry 8, Table 5)*: IR ($\upsilon_{max}$ in cm$^{-1}$, KBr): 3413, 3055, 1618, 1095, 748. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 5.83 (s, 1H, methine-H), 6.83 (s, 2H), 6.89–7.08 (m, 6H, Ar-H), 7.34–7.46 (m, 4H, Ar-H), 7.85–7.86 (d, 2H, Ar-H), 10.86 (bs, 2H, NH). $^{13}$C NMR (400 MHz, DMSO-$d_6$): δ 40.51, 111.97, 117.93, 118.74, 119.47, 121.45, 124.07, 126.90, 129.17, 131.37, 132.79, 137.03, 144.89. MS: m/z 400 (M-1).

**2.5i** *2-Nitrophenyl-3, 3′-bis-(indolyl) methane (Entry 9, Table 5)*: IR ($\upsilon_{max}$ in cm$^{-1}$, KBr): 3416, 1578, 1458, 1357, 1223. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 5.89 (s, 1H, methine-H), 6.33 (s, 2H), 6.56–6.61 (m, 4H), 7.27–7.37 (m, 4H), 7.60–7.62 (m, 3H), 8.07 (d, 1H), 10.86 (bs, 2H, NH). $^{13}$C NMR (400 MHz, DMSO-$d_6$): δ 38.54, 111.42, 112.83, 118.63, 120.30, 121.58, 122.23, 122.91, 125.80, 127.43, 130.21, 132.11, 134.22, 136.54, 148.70. MS: m/z 366 (M-1).

**2.5j** *3-Nitrophenyl-3, 3′-bis-(indolyl) methane (Entry 10, Table 5)*: IR ($\upsilon_{max}$ in cm$^{-1}$, KBr): 3405, 1526, 1459, 1352, 1049. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 5.99 (s, 1H, methine-H), 6.07 (s, 2H), 7.11–7.23 (m, 4H), 7.48–7.55 (m, 4H), 7.16 (d, 2H), 7.99–8.01 (t, 2H), 10.91 (bs, 2H, NH). $^{13}$C NMR (400 MHz, DMSO-$d_6$): δ 39.42, 111.21, 112.63, 118.92, 119.56, 120.40, 122.01, 122.80, 124.52, 127.55, 129.81, 135.41, 136.64, 139.73, 147.82. MS: m/z 366 (M-1).

**2.5k** *4-Nitrophenyl-3, 3′-bis-(indolyl) methane (Entry 11, Table 5)*: IR ($\upsilon_{max}$ in cm$^{-1}$, KBr): 3426, 1589, 1456, 1345, 1229. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 6.029 (s, 1H, methine-H), 6.58 (s, 2H), 6.89–6.91 (m, 4H), 7.27–7.37 (m, 4H), 7.62 (d, 2H), 8.16 (d, 2H), 10.94 (bs, 2H, NH). $^{13}$C NMR (400 MHz, DMSO-d$_6$): δ 40.26, 112.06, 117.12, 118.91, 119.36, 121.60, 123.90, 124.30, 126.79, 129.91, 137.02, 146.20, 153.58. MS: m/z 366 (M-1).

**2.5l** *2-Bromophenyl-3, 3′-bis-(indolyl) methane (Entry 12, Table 5)*: IR ($\upsilon_{max}$ in cm$^{-1}$, KBr): 3410, 3063, 1565, 1086, 750. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 6.02 (s, 1H, methine-H), 6.77 (s, 2H), 6.99–7.05 (m, 4H, Ar-H), 7.24–7.36 (m, 4H, Ar-H), 7.64 (d, 1H, Ar-H), 7.85–7.86 (d, 2H, Ar-H), 7.9 (d, 1H, Ar-H), 10.89 (bs, 2H, NH). $^{13}$C NMR (400 MHz, DMSO-$d_6$): δ 39.51, 111.0, 116.98, 117.74, 118.49, 121.46, 123.78, 125.91, 126.68, 128.17, 130.33, 131.79, 132.39, 135.02, 145.58. MS: m/z 400 (M-1).

**2.5m** *2-Furfuryl-3, 3′-bis-(indolyl) methane (Entry 13, Table 5)*: IR ($\upsilon_{max}$ in cm$^{-1}$, KBr): 3457, 3029, 2359, 1610, 1466, 1429, 1226, 1095, 1031, 759, 720. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 5.94 (s,1H, methine-H), 6.05 (d, 1H), 6.30(d,1H), 6.87(d, 1H), 7.08(t, 2H), 7.17(t, 2H), 7.29–7.48(m, 5H), 10.95(bs, 2H, NH). $^{13}$C NMR (400 MHz, DMSO-$d_6$): δ 42.61, 104.98, 110.32, 111.13, 112.45, 119.13, 120.16, 122.34, 122.99, 127.52, 136.55, 142.42, 152.66. MS: m/z 311 (M-1).

**2.5n** *1-Ethyl-3, 3′-bis-(indolyl) methane (Entry 14, Table 5)*: IR ($\upsilon_{max}$ in cm$^{-1}$, KBr): 3457, 3022, 3061, 1466, 1226, 1085, 1042, 766, 690. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 1.52 (d, 3H, CH$_3$), 4.66 (q,1H, methine-H), 6.81 (s, 2H), 7.18–7.22 (m,8H), 10.06 (bs, 2H, NH). $^{13}$C NMR (400 MHz, DMSO-$d_6$): δ 23.67, 39.67, 111.12, 115.98, 119.33, 120.12, 122.34, 122.67, 127.58, 136.54. MS: m/z 259 (M-1).

**2.5o** *1-Butyl-3, 3′-bis-(indolyl) methane (Entry 15, Table 5)*: IR ($\upsilon_{max}$ in cm$^{-1}$, KBr): 3466, 3019, 3052, 1501, 1196, 1079, 1038, 775, 691. $^1$H NMR (400 MHz, DMSO-$d_6$): δ 0.99 (t, 3H, CH$_3$), 1.29 (m, 2H, CH$_2$), 1.75 (q, 2H, CH$_2$), 4.66 (t, 1H, methine-H), 6.84 (s, 2H), 7.18–7.24 (m,8H), 10.59 (bs, 2H, NH). $^{13}$C NMR (400 MHz, DMSO-$d_6$): δ 14.5, 19.9, 44.5, 52.3, 111.3, 115.6, 119.7, 120.1, 122.4, 122.9, 127.8, 136.8. MS: m/z 287 (M-1).

## 3. Results and Discussion

A number of synthetic methods for the preparation of *bis*-(indolyl)methane derivatives have been reported; of these methods, the acid catalysed electrophilic addition reaction of indole with aldehydes is one of the most simple and straightforward approaches for one-pot synthesis of *bis*-(indolyl)methane derivatives.

To the best of our knowledge, the catalytic efficiency of diphenic acid in organic transformation has been less studied. According to the literature, it has been mainly explored as a ligand in inorganic chemistry[28,29] and also as co-catalyst in a few organic syntheses.[30] Therefore, we explored the catalytic efficiency of diphenic acid for one-pot synthesis of *bis*-(indolyl)methane.

### 3.1 *Optimization of the Reaction Conditions*

The reaction conditions for the synthesis of *bis*-(indolyl)methane derivatives were optimized by selecting indole and benzaldehyde as test substrates and the reaction was carried out under a different set of conditions with respect to different types of catalysts, different amounts of catalyst, temperatures and solvents. Initially, the reaction with test substrates was carried out using different types of catalysts as shown in table 1.

From the results mentioned above, we found that diphenic acid completes the reaction in less time than silica-diphenic acid. But, the use of diphenic acid as homogeneous catalyst in the above mentioned reaction of test substrates did not provide easy work-up procedure and, moreover, the selectivity of the reaction also decreases after sometime. Therefore, the use of silica-diphenic acid as a heterogeneous catalyst overcomes the disadvantages of the homogeneous conditions and provides easy work procedure and also maintains the selectivity of the reaction.

To select a proper amount of catalyst required to produce excellent yield of products, the reaction of test substrates was carried out using different amounts of silica-diphenic acid. It was found that 0.05 g of silica-diphenic acid was sufficient to carry out the reaction in lesser time with good yield of products. There was no significant change in the yield of products when large amounts of silica-diphenic acid were used instead of 0.05 g. The results are summarized in the table 2.

The reaction of test substrates was also carried out using polar and non-polar solvents like acetonitrile, methylene chloride, toluene, and water and also under solvent-free condition. It was observed that the reaction carried out in acetonitrile gave the best results in terms of yield, selectivity, and reaction time. Therefore, acetonitrile was selected as the solvent system for the synthesis of *bis*-(indolyl)methane derivatives. The results are shown in table 3.

**Table 1.** Effect of different catalysts on the synthesis of *bis*-(indolyl)methane derivatives.[a]

| Entry | Catalysts | Time (min) | Yield (%) |
|---|---|---|---|
| 1 | No catalyst | 25 | – |
| 2 | Silica | 25 | 30 |
| 3 | Diphenic acid | 15 | 80 |
| 4 | Silica-Diphenic acid | 25 | 90 |

[a]Optimized Reaction conditions: Indole (2 mmol), benzaldehyde (1 mmol), catalyst (0.05 g) and 60 °C as the reaction temperature. The reaction was carried out under air atmosphere.
[b]Yields based on separation by passing through a column of silica gel and elution with EtOAc: petroleum ether.

**Table 2.** Effect of different amounts of silica-diphenic acid.[a]

| Entry | Amounts of Silica-Diphenic acid (g) | Time (min) | Yield (%)[b] |
|---|---|---|---|
| 1 | 0.01 | 25 | 72 |
| 2 | 0.05 | 25 | 90 |
| 3 | 0.1 | 25 | 86 |
| 4 | 0.2 | 25 | 88 |

[a]Optimized reaction conditions: Indole (2 mmol), benzaldehyde (1 mmol), silica-diphenic acid (x g) and 60°C as the reaction temperature. The reaction was carried out under air atmosphere.
[b]Yields based on separation by passing through a column of silica gel and elution with EtOAc: petroleum ether.

**Table 3.** Effect of solvents/solvent-free condition on the synthesis of *bis*-(indolyl)methane derivatives.[a]

| Entry | Solvent | Time (min) | Yield (%)[b] |
|---|---|---|---|
| 1 | Water | 25 | 40 |
| 2 | Methylene chloride | 25 | 15 |
| 3 | Toluene | 25 | 12 |
| 4 | Acetonitrile | 25 | 90 |
| 5 | No solvent | 25 | 30 |

[a]Optimized reaction conditions: Indole (2 mmol), benzaldehyde (1 mmol), silica-diphenic acid (0.05 g) and 60°C as the reaction temperature in different solvents/solvent-free conditions. The reaction was carried out under air atmosphere.
[b]Yields based on separation by passing through a column of silica gel and elution with EtOAc: petroleum ether.

**Table 4.** Effect of temperature on the synthesis of *bis*-(indolyl)methane derivatives.[a]

| Entry | Temperature (°C) | Time (min) | Yield (%)[b] |
|---|---|---|---|
| 1 | 30 | 25 | 35 |
| 2 | 60 | 25 | 90 |
| 3 | 80 | 25 | 75 |
| 4 | 100 | 25 | 70 |

[a]Optimized reaction conditions: Indole (2 mmol), benzaldehyde (1 mmol) and silica-diphenic acid (0.05 g) in acetonitrile at x°C. The reaction was carried out under air atmosphere.
[b]Yields based on separation by passing through a column of silica gel and elution with EtOAc: petroleum ether.

**Table 5.** One-pot synthesis of *bis*-(indolyl)methane derivatives[a] by reaction between aromatic/heteroaromatic/aliphatic aldehydes and indole in the presence of silica-diphenic acid.
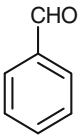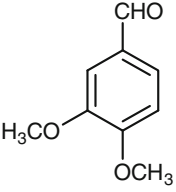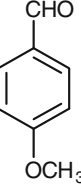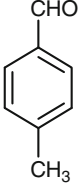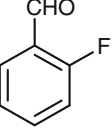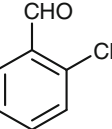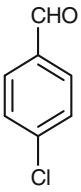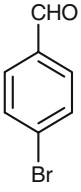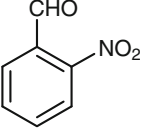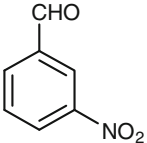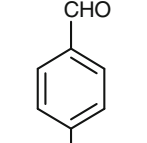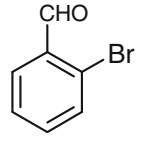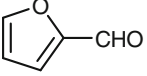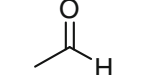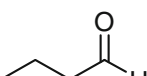
| Entry | Aldehyde | Time (min) | Yield(%)[b] | M.p. (°C) (Lit. M.p.) |
|-------|----------|------------|-------------|------------------------|
| 1 | benzaldehyde (CHO) | 25 | 90 | 87–88/93–94[31] |
| 2 | 3-methoxy-4-methoxy benzaldehyde (CHO, H₃CO, OCH₃) | 35 | 75 | 195–197/198–200[25] |
| 3 | 4-methoxybenzaldehyde (CHO, OCH₃) | 30 | 86 | 217–219/222[19] |
| 4 | 4-methylbenzaldehyde (CHO, CH₃) | 30 | 89 | 94–96/98–100[31] |
| 5 | 2-fluorobenzaldehyde (CHO, F) | 20 | 81 | 70–74/76–79[32] |
| 6 | 2-chlorobenzaldehyde (CHO, Cl) | 15 | 78 | 68–70/72–74[31] |
| 7 | 4-chlorobenzaldehyde (CHO, Cl) | 12 | 88 | 70–73/76–77[31] |
| 8 | 4-bromobenzaldehyde (CHO, Br) | 15 | 82 | 108–110/110–112[17] |
| 9 | 2-nitrobenzaldehyde (CHO, NO₂) | 10 | 78 | 94–97/98–100[31] |

**Table 5.** (continued).

| Entry | Aldehyde | Time (min) | Yield(%)[b] | M.p. (°C) (Lit. M.p.) |
|-------|----------|------------|-------------|------------------------|
| 10 | CHO, NO$_2$ (3-nitrobenzaldehyde) | 8 | 88 | 85–86/88–90[31] |
| 11 | CHO, NO$_2$ (4-nitrobenzaldehyde) | 5 | 95 | 213–215/217–219[31] |
| 12 | CHO, Br (2-bromobenzaldehyde) | 18 | 80 | 85–89/89–91[33] |
| 13 | furfural (furan-2-carbaldehyde) | 25 | 75 | 108–110/113–115[25] |
| 14 | acetaldehyde | 40 | 65 | 89–91/90–92[19] |
| 15 | butyraldehyde | 55 | 60 | 77–79/80[34] |

[a]Reaction conditions: Indole (2 mmol), aldehyde (1 mmol), silica-diphenic acid (0.05 g) and 60°C as the reaction temperature in acetonitrile. The reaction was carried out under air atmosphere.
[b]Yields based on separation by passing through a column of silica gel and elution with EtOAc: petroleum ether.

Further, to make the reaction conditions even more effective for the synthesis of *bis*-(indolyl)methanes in less time with good yields, the test reaction was also attempted at different temperatures such as 30°C, 60°C, 80°C and 100°C and it has been found that the reaction was very slow at low temperatures, whereas at higher temperatures, it becomes highly reactive but loses its selectivity and gave multiple products. Thus, 60°C was selected as the optimum reaction temperature at which the reaction proceeded effectively to give a better yield of products with good selectivity. At 60°C optimized reaction temperature, 90% yield was observed during the reaction of the test substrates, as shown in table 4.

To study the generality of the newly developed protocol, different aromatic aldehydes substituted with electron-donating and electron-withdrawing substituents and some heteroaromatic/aliphatic aldehydes were selected and good to excellent results were obtained. The results are summarized in table 5.

From table 5, the structure–activity relationship has been inferred and found that aromatic aldehydes substituted with electron-withdrawing groups undergo faster reactions than aromatic aldehydes substituted with electron-donating groups. Moreover, aliphatic aldehydes
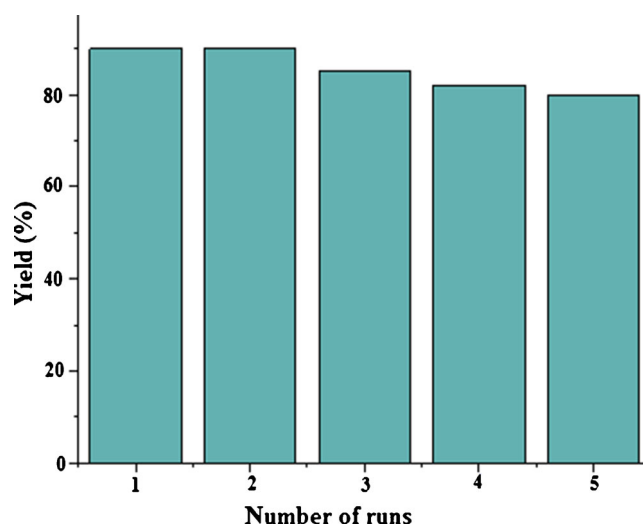


**Figure 5.** Recyclability graph of Silica-Diphenic acid in case of indole and 4-nitrobenzaldehyde.

took longer time than aromatic/hetero-aromatic aldehydes and also provide lower yield of products.

To study the effect of silica-diphenic acid as catalyst, the reaction of test substrates was also carried out in the absence of catalyst. It was found that without a catalyst, the reaction was very slow and did not proceed to completion. The reaction was also tried under microwave conditions as well as by the grinding method, but satisfactory results were not obtained as it took a very long time for completion and selectivity was also reduced.

### 3.2 *Recyclability and Heterogeneity of Silica-diphenic Acid*

To classify the catalyst as a heterogeneous catalyst, recyclability of the catalyst required to be examined. A series of five consecutive runs were carried out in case of 4-nitrobenzaldehyde and indole (Entry 11, table 5). Slight drop in the activity of the catalyst was observed. The results are shown in figure 5.

The hot-filtration test has also been performed for testing the heterogeneity of the catalyst using benzaldehyde and indole as test substrates. First, in this test, the reaction has been carried out in the presence of silica-diphenic acid in acetonitrile at 60°C. After 10 min, catalyst was filtered off from the reaction mixture and the rest of the reaction mixture was further monitored for 20 min. It was found that the reaction had not proceed further in the absence of the catalyst. Therefore, it may be concluded that there is no leaking of the diphenic acid from the silica-diphenic acid catalyst.
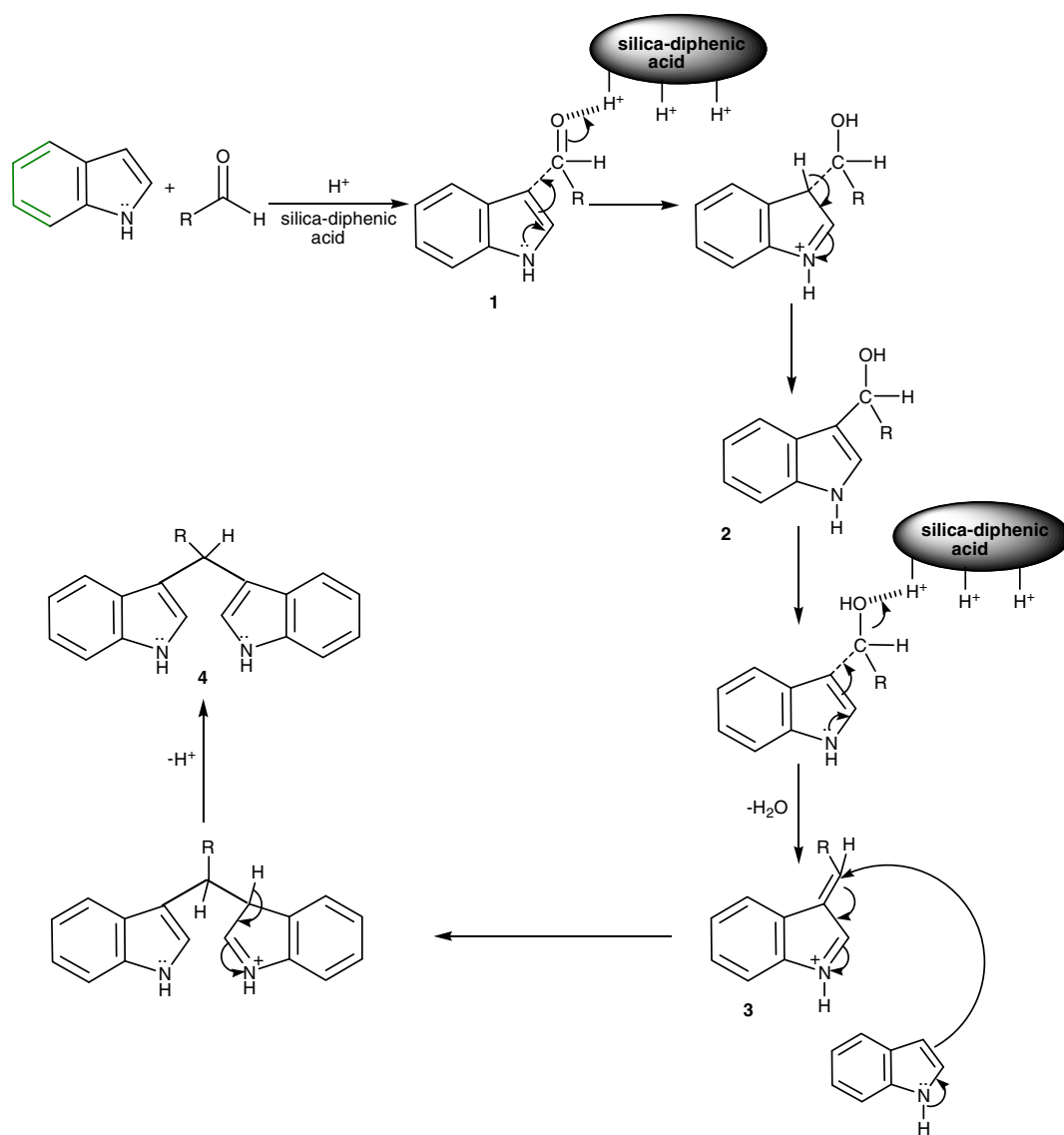


**Scheme 3.** Plausible mechanism for the reactions of indole with various aldehydes in presence of heterogeneous catalyst (silica-diphenic acid).

### 3.3 *Mechanism*

A plausible mechanism for the reaction between indole and aldehydes in the presence of a catalyst (silica-diphenic acid) has been proposed, as shown in scheme 3. In the first step, an aldehyde was protonated by the acid catalyst (silica-diphenic acid) and an electrophilic substitution reaction at the C-3 position of indole was carried out to give an intermediate (**1**) which undergoes proton rearrangement to give intermediate (**2**). After loss of water from an intermediate (**2**) activated by proton, an intermediate (**3**) was obtained, which serves as an electrophile to be attacked by a second molecule of an indole to form the corresponding *bis*-(indolyl)methane derivatives (**4**).

## 4. Conclusions

Silica-diphenic acid was found to be an effective catalyst for the electrophilic substitution reactions of indole with aldehydes, giving selectively *bis*(indolyl)methane derivatives in good to excellent yields. The use of this inexpensive, heterogeneous and recyclable catalyst under mild conditions provides short reaction time, greater selectivity, easy work-up and ecologically clean selective procedure which make this protocol practical and economically attractive.

## Supplementary Information

The $^1$H-NMR, $^{13}$C-NMR, and mass spectra of 2-Flourophenyl-3, 3′-bis-(indolyl) methane have been shown in the supplementary information available at www.ias.ac.in/chemsci.

## Acknowledgements

## References

1. Kaishap P and Dohutia C 2013 *Int. J. Pharm. Sci. Res.* **4** 1312
2. Lounasmaa M and Tolvanen A 2000 *Nat. Prod. Rep.* **17** 175
3. Garbe T R, Kobayashi M, Shimizu N, Takesue N, Ozawa M and Yukawa H 2000 *J. Nat. Prod.* **63** 596
4. Hong C, Firestone G L and Bjeldance L F 2002 *Bio. Chem. Pharmacol.* **63** 1085
5. Hibino S and Choshi T 2001 *Nat. Prod. Rep.* **18** 66
6. Povszsz L, Katakin G P, Foleat S and Malkovics B 1996 *Acta. Phys. Acad. Sci.* **29** 299
7. Karthik M, Tripathi A K, Gupta N M, Palanichamy M and Murugeson V 2004 *Catal. Commun.* **5** 371
8. Marrelli M, Cachet X, Conforti F, Sirianni R, Chimento A, Pezzi V, Michel S, Statti G A and Menichini F 2013 *Nat. Prod. Res.* **27** 2039
9. Tayebee R, Amini M N, Nehzat F, Sadeghi O and Armaghan M 2013 *J. Mol. Catal. A: Chem.* **366** 140
10. Shirini F and Khaligh N G 2013 *Chin. J. Catal.* **34** 1890
11. Kumar V, Singh C, Sharma U, Verma P K, Singh B and Kumar N 2014 *Ind. J. Chem.* **53B** 83
12. Zarea A R M, Borazjanib M P and Nazb Z 2014 *Iran. Chem. Commun.* **2** 34
13. Mendes S R, Thurow S, Fortes M P, Penteado F, Lenardao E J, Alves D, Perin G and Jacob R G 2012 *Tetrahedron Lett* **53** 5402
14. Pawar B, Shinde V and Chaskar A 2013 *Green Sustainable Chem* **3** 56
15. Alinezhad H and Haghighi A H 2012 *Caspian J. Chem.* **1** 1
16. Prasanna T S R and Raju K M 2012 *J. Korean. Chem. Soc.* **56** 74
17. Giri B Y, Devi B L A P, Vijayalakshmi K, Prasad R B N, Lingaiah N and Prasad P S S 2012 *Ind. J. Chem.* **51B** 1731
18. Tayebee R and Razib M K 2014 *Res. Rev: J. Mater. Sci.* **2** 13
19. Hojati S F, Zeinali T and Nematdoust Z 2013 *Bull. Korean Chem. Soc.* **34** 117
20. Xu X F and Xiong Y 2014 *Chin. Chem. Lett.* **25** 406
21. Gupta G, Chaudhari G, Tomar P, Gaikwad Y, Azad R, Pandya G, Waghulde G and Patil K 2012 *Eur. J. Chem.* **3** 475
22. Hasaninejad A, Shekouhy M, Zare A, Ghattali S M S H and Golzara N 2011 *J. Iran. Chem. Soc.* **8** 411
23. Nagarajan R and Perumal P T 2002 *Synth. Commun.* **32** 105
24. Bandgar B P, Bettigeri S A and Joshi N S 2004 *Monatsh. Chem.* **135** 1265
25. Pore D M, Desai U V, Thopate T S and Wadgaonkar P P 2006 *ARKIVOC* **xii** 75
26. Pal R, Khannobis S and Sarkar T 2013 *Chem. J.* **3** 7
27. Olyaei A, Vaziri M, Razeghi R, Shams B and Bagheri H 2013 *J. Serb. Chem. Soc.* **78** 463
28. Prats A E P, Bernini M C, Medina M E, Torres E L, Puebla EG, Monge M A and Snejko N 2011 *Cryst. Eng. Comm.* **13** 4965
29. Dietzel P D C, Bloma R and Fjellvag H 2006 *Dalton Trans* 586
30. Kour G, Gupta M, Paul S, Rajnikant and Gupta V K 2014 *J. Mol. Catal. A: Chem.* **392** 260
31. Li J T and Sun S F 2010 *Eur. J. Chem.* **7** 922
32. Kaishap P P, Dohuti C and Chetia D 2012 *Int. J. Pharm. Sci. Res* **3** 4247
33. Qu H E, Xiao C, Wang N, Yu K H, Hu Q S and Liu L X 2011 *Molecules* **16** 3855
34. Behbahani F K and Sasani M 2012 *J. Serb. Chem. Soc.* **77** 1157