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ORIGINAL PAPER

Efficient solvent-free synthesis of bis(indolyl)methanes on SiO_2 solid support under microwave irradiation

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An efficient synthesis of bis(indolyl)methanes was developed. Bis(indolyl)methanes were synthesized starting from various aromatic aldehydes with indole under microwave irradiation and solvent-free conditions (85–98 %). Solid support SiO_2 was found to possess favorable catalytic and dispersancy parameters for the condensation reaction. Moreover, novel bis(indolyl)methanes containing an isoxazole ring were synthesized via this method in excellent yields (> 94 %) using 3-substituted isoxazole-5-carbaldehydes and indole.

Keywords: bis(indolyl)methanes, microwave synthesis, bis(indolyl)methanes containing isoxazole-ring, SiO_2 solid support, solvent-free

Introduction

Indole and isoxazole moieties have been found in a wide variety of pharmacologically and biologically active compounds (Houlihan et al., 1992; Wagner et al., 2004; Pastor et al., 2004; Basappa et al., 2004). Bis(indolyl)methanes, which contain two indole or substituted indole units in a molecule, are recognized as one of the rapidly growing groups of sponge metabolites because of their broad spectrum of biological properties (Sundberg, 1996; Casapullo et al., 2000; Bao et al., 2005; Skibo et al., 2001; Gupta et al., 2007; Kaniwa et al., 2007). Therefore, synthesis of these compounds has attracted much attention of synthetic organic chemists and biologists. Bis(indolyl)methanes are synthetically obtained from condensation of indole with aldehydes or ketones in the presence of protic acid: HCl (Zhang et al., 2009; Roomi & Macdonald, 1970; D'Auria, 1991) or Lewis acids: $AlCl_3$, BF_3, $ZnCl_2$, etc. (Chatterjee et al., 1980; Noland et al., 1961; Babu et al., 2000; Wang et al., 1998; Yadav et al., 2001). However, most of these methods require rather harsh acidic conditions, which are often incompatible with other sensitive components present in the substrates. Recently, many milder procedures based on the use of catalytic amounts of Lewis acids have been reported. Particularly, electrophilic substitution reactions of indoles with various aldehydes or ketones have been carried out using different catalysts, such as Fe^{3+} (Wang & Ji, 2008), I_2 (Bandgar & Shaikh, 2003), montmorillonite K-10 (Chakrabarty et al., 2002), *N*-bromosuccinimide (NBS) (Koshima & Matsuaka, 2002), zeolite (Karthik et al., 2004), Al_2O_3/microvawe (MW) (Sadaphal et al., 2010), P_2O_5/SiO_2 (Hasaninejad et al., 2007), benzyltriphenylphosphonium tribromide (BTPTB)/SiO_2 (Shirini et al., 2010), SiO_2 (Mendes et al., 2012), $In(OTf)_3$ (Ji et al., 2003) and $La(PFO)_3$ (Yadav et al., 2003; Ji et al., 2004; Bandgar & Shaikh, 2003; Chakrabarty et al., 2002; Koshima & Matsuaka, 2002; Chen et al., 1996; Nagarajan & Perumal, 2002; Mi et al., 2004; Wang et al., 2005; Reddy et al., 2003).

Nowadays, the development of environmentally friendly, green techniques is one of the most important goals of chemical research. Although the acid-catalyzed condensations of indole with aldehydes is an effective route for the preparation of bis(indolyl) methanes, many of these methods suffer from draw-

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backs such as the use of expensive reagents (Yadav et al., 2001), excess of catalyst (Kamal & Qureshi, 1963), or long reaction times (Yadav et al., 2001; Kamal & Qureshi, 1963; Bandgar et al., 2004). MW irradiation has been increasingly used in organic synthesis in the last two decades. Compared with the traditional methods, a large number of organic reactions can be carried out at shorter reaction time and higher yields using MW irradiation. In order to find a new method for the synthesis of bis(indolyl)methanes, to minimize the adverse effects of organic solvent on the environment and to avoid long reaction times and unsatisfactory yields. The use of Al_2O_3 or SiO_2 in solvent-free environment was attempted leading to significant simplification of the work up procedures. Here, the synthesis of bis(indolyl)methanes where indole is attacked by the electrophile substituted benzaldehyde under MW irradiation using SiO_2 as the solid support under solvent-free conditions was attempted. The method was also extended to synthesize bis(indolyl)methanes containing an isoxazole ring starting from 3-substituted isoxazole-5-carbaldehydes. The desired new products were also obtained in almost stoichiometric yield. To the best of our knowledge, the MW-assisted process in the presence of SiO_2 only and starting from substituted benzaldehyde and 3-substituted isoxazole-5-carbaldehydes has not been reported. Although other MW-assisted syntheses of bis(indolyl)methanes with benzene rings have been presented, the desired results were not obtained by repeating the procedure introduced in literature (Sadaphal et al., 2010). In addition, in the previous literature (Ramesh et al., 2003; Kamble et al., 2007; Firouzabadi et al., 2006), SiO_2 used to synthesize bis(indolyl)methanes plays only the role of a support in the traditional methods.

Experimental

General

Aromatic aldehydes of analytical-reagent grade used in the study were purchased from Alladdin reagent (China) and used without further purification. Solvents and reagents used were supplied by Tianjin Tiantai Chemical (China). (3-Phenylisoxazol-5-yl)methanols were prepared according to the reported procedure (Shen et al., 2011). 3-substituted isoxazole-5-carbaldehydes were synthesized from (3-phenylisoxazol-5-yl)methanols by the method reported by Miller and Hoerrner (2003) and Angelin et al. (2006). All melting points were determined on an XT–4 melting point apparatus (Beijing Tech Instrument, China) and were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were measured using a Varian Mercury-300 (Germany) NMR spectrometer or a Bruker AVANCE-500 (USA) NMR spectrometer and with TMS as the internal standard. Chemical shift is given in δ relative to TMS. MS was collected on an Agilent HP1100/ 6890 LC/ MS spectrometer (USA) and an Agilent1290-micrOTOF Q II spectrometer, respectively. FT-IR spectra were collected as KBr pellets using an Shimadzu IRAffinity-1 instrument (Japan) in the range of 500–3500 cm^{-1}. An MCL-3-type MW reactor (Sichuan University, Sichuan, China) with a thermometer for MW application was used in all experiments.

General synthesis produce for 3-substituted isoxazole-5-carbaldehydes

3-substituted isoxazole-5-carbaldehydes were synthesized according to reported procedures (Miller & Hoerrner, 2003; Angelin et al., 2006). (3-phenylisoxazol-5-yl)methanols (5.0 mmol) were charged into a 100 mL round-bottom flask equipped with a magnetic stir bar. The solid was then slurried in toluene (10 mL) at room temperature. An aqueous solution of sodium bicarbonate (13 mL; 1.2 mol L^{-1}) was added into the toluene slurry at room temperature. Then, the mixed solid 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO; 0.5 mmol) was added and solid iodine (10 mmol) dissolved in alcohol was added into the reaction mixture. The reaction mixture was then aged for 10–12 h at room temperature; the reaction was monitored by TLC. The crude product was diluted with ethyl acetate (15 mL). The batch was washed with NaS_2O_3 and transferred to a separatory funnel, and the aqueous layer was extracted with ethyl acetate (2×10 mL). The organic layers were mixed and dried over anhydrous sodium sulfate for 30 min, filtrated and evaporated under vacuum to give the crude product which was purified by column chromatography (silica gel, 200–300 mesh; Qingdao Haiyang Chemical, China) using petroleum ether/ethyl acetate ($\varphi_r = 5 : 1$) to furnish the product. The yields of obtained 3-substituted isoxazole-5-carbaldehydes products were 44–92 %.

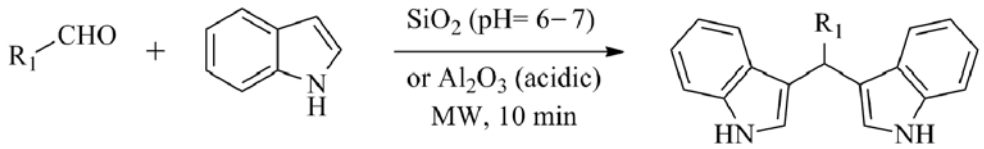
General synthesis produce for bis(indolyl) methanes with benzene-ring

SiO_2 (1.0 g, 200–300 mesh, pH 6–7) or acidic Al_2O_3 (1.0 g, 200–300 mesh) was added to a mixture of aldehyde (1.0 mmol) and indole (2.0 mmol). The reaction mixture was irradiated in a MW at 90 ℃ for 10 min; the reaction was monitored by TLC. The crude products were purified by column chromatography using petroleum ether/ethyl acetate ($\varphi_r = 4 : 1$) to afford *Ia–Ig*.

General synthesis produce for bis(indolyl) methanes with 3-substituted phenyl isoxazole-ring

SiO_2 (1.0 g) was added to a mixture of 3-

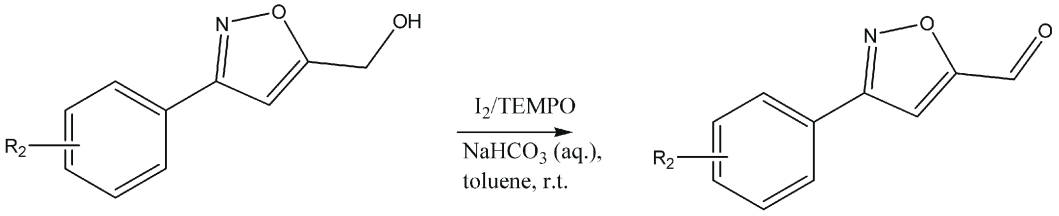
Table 1. Condensation of indole with aromatic aldehydes using two solid supports: SiO_2 and Al_2O_3



Entry	Compound	Aldehyde	Product[a]	Temperature/ °C	Time/min	Yield[b]/%		M.p./ °C
		R_1	R_1		SiO_2/Al_2O_3	SiO_2	Al_2O_3	
1	*Ia*	C_6H_5	C_6H_5	90	10	65[h]		150–152[c]
2	*Ia*	C_6H_5	C_6H_5	90	10	93	70	150–151[c]
3	*Ib*	4-Cl-C_6H_4	4-Cl-C_6H_4	90	10	98	80	78–80[d]
4	*Ic*	2-OCH_3-C_6H_4	2-OCH_3-C_6H_4	90	10	96	81	132–134[e]
5	*Id*	4-OCH_3-C_6H_4	4-OCH_3-C_6H_4	90	10	67	59	196–198[f]
6	*Ie*	4-OH-C_6H_4	4-OH-C_6H_4	90	10	85	70	116–118[g]
7	*If*	4-tBu-C_6H_4	4-tBu-C_6H_4	90	10	90	79	136–138
8	*Ig*			100	10	96	82	118–119
9	*Ih*	3-NO_2-C_6H_4	3-NO_2-C_6H_4	90	10	98	85	263–265[e]
10	*Ii*	4-CH_3-C_6H_4	4-CH_3-C_6H_4	90	10	85	76	96–98[e]
11	*Ib*	4-Cl-C_6H_4	4-Cl-C_6H_4	90	5	82	63	78–79[d]
12	*Ib*	4-Cl-C_6H_4	4-Cl-C_6H_4	90	8	93	76	78–80[d]
13	*Ib*	4-Cl-C_6H_4	4-Cl-C_6H_4	90	12	94	79	78–80[d]
14	*Ib*	4-Cl-C_6H_4	4-Cl-C_6H_4	90	15	91	78	78–80[d]

MW power was 250 W. Synthesized compounds were reported in literature. *a*) In = 3-indolyl, *b*) isolated yields, *c*) 149–150 °C, reported by Deb and Bhuyan (2006); *d*) 78–80 °C, reported by Sadaphal et al. (2010); *e*) 134–136 °C, reported by Ghorbani-Vaghei et al. (2010); *f*) 197–199 °C, reported by Zhang and Du (2009); *g*) 119–121 °C, reported by Sadaphal et al. (2010); *h*) no added SiO_2 or Al_2O_3.

Table 2. Synthesis and yield of 3-substituted isoxazole-5-carbaldehydes



Entry	Compound	R_2	Time/h	Yield[a]/%	M.p./ °C
1	*IIa*	H	9	81	62–63
2	*IIb*	4-*t*-Bu	9	92	120–122
3	*IIc*	2-Cl	9	89	36–38
4	*IId*	4-Cl	9	72	126–128
5	*IIe*	2-OCH_3	12	44	74–76
6	*IIf*	4-OCH_3	12	56	72–74

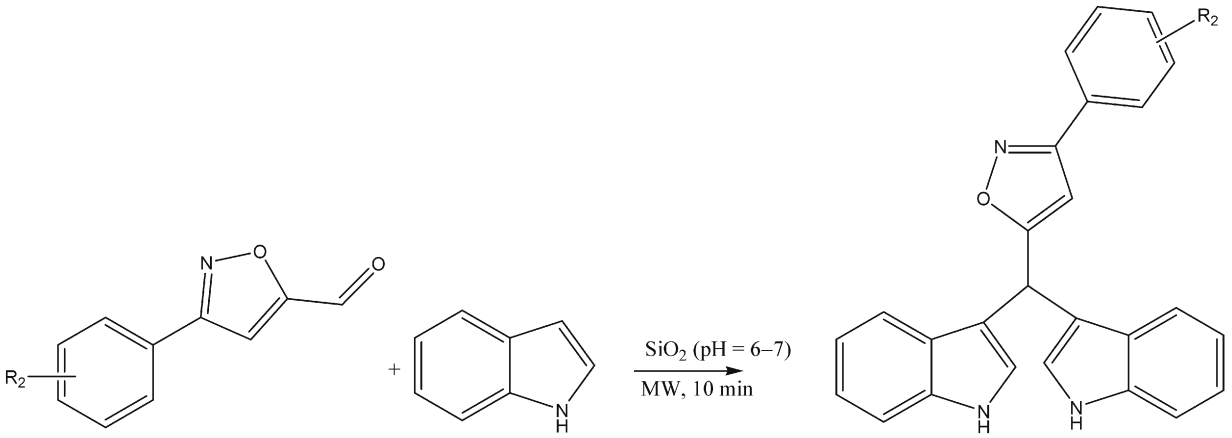
a) Isolated yields.

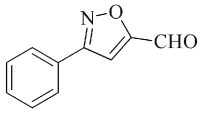
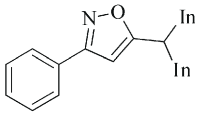
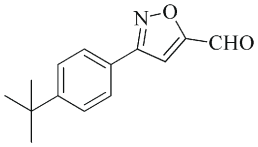
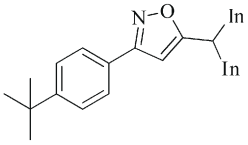
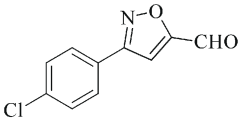
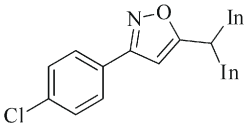
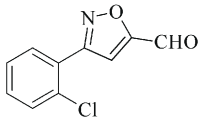
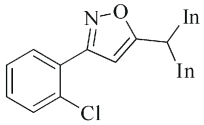
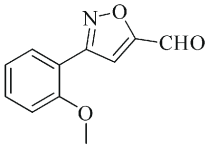
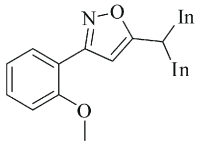
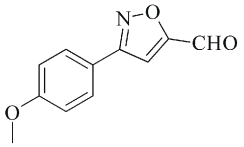
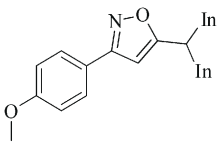
substituted isoxazole-5-carbaldehydes (1.0 mmol) and indole (2.0 mmol). The reaction mixture was irradiated in a MW at 90 °C for 10 min; the reaction was monitored by TLC. The crude products were directly purified by column chromatography using petroleum ether/ethyl acetate (φ_r = 4 : 1) to afford *IIIa–IIIf*.

Results and discussion

At the beginning of our investigation, the synthesis of bis(indolyl)methanes was carried out by treating various aromatic aldehydes with indole or employing equal amounts of SiO_2 and Al_2O_3 as solid supports under MW irradiation and solvent-free conditions (Table 1, Entries 2–10). Also, under other-

Table 3. Condensation of indole with 3-substituted isoxazole-5-carbaldehydes



Entry	Compound	Aldehyde	Product[a]	Temperature/ ℃	Time/min	Yield[b]/%	M.p./ ℃
1	*IIIa*			90	10	97	214–216
2	*IIIb*			90	10	99	222–224
3	*IIIc*			90	10	94	220–222
4	*IIId*			90	10	95	146–148
5	*IIIe*			100	10	95	82–84
6	*IIIf*			100	10	95	246–248

MW power was 250 W; *a*) In = 3-indolyl; *b*) isolated yields.

wise similar experimental conditions, the effect of MW irradiation time on the product was investigated starting from 4-chlorobenzaldehyde on SiO_2 (Table 1, Entries 3 and 11–14). It was observed that the yield of 3-((4-chlorophenyl)(3a,7a-dihydro-1*H*-indol-3-yl)methyl)-1*H*-indole (*Ib*) substantially increased under MW irradiation for 10 min compared with that observed at shorter irradiation times. However, the yield was slightly decreased when the reaction time was further increased to 12 min and 15 min. This is probably due to the carbonization of a little amount of the product. Consequently, the desired products were synthesized for 10 min in a MW at 90 ℃.

As shown in Table 1, equal loadings of Al_2O_3 and SiO_2 as the solid support (Table 1, Entries 2–10) were used to synthesize the desired products in higher yields than those obtained without solid support (Table 1, Entry 1), which implied that solid supports Al_2O_3 and SiO_2 possess good dispersancy and catalytic characteristics. The yields of bis(indolyl)methanes synthesized were excellent when SiO_2 (85–98 %) was used as

Table 4. Spectral data of newly prepared compounds

Compound	Spectral data
Ia	IR (KBr), $\tilde{\nu}$/cm^{-1}: 3390, 3050, 2360, 1600, 1450, 1330, 1220, 1090, 1010, 748, 594, 498 ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.92 (s, 2H, indole NH), 7.37 (dd, J = 10.0 Hz, 7.1 Hz, 7H, indole H4, H7, phenyl H3, H4, H5), 7.24–7.13 (m, 4H, indole H5, H6), 7.00 (t, J = 7.5 Hz, 2H, phenyl H2, H6), 6.67 (d, J = 1.5 Hz, 2H, indole H2), 5.89 (s, 1H, CH) ^{13}C NMR ($CDCl_3$, 125 MHz), δ: 144.4 (phenyl C1), 137.1, 129.2 (indole C), 128.6, 127.5, 126.6, (phenyl C2, C3, C4, C5, C6), 124.0, 122.4, 120.4, 120.1, 119.7, 111.5 (indole C), 40.6 (CH)
Ib	IR (KBr), $\tilde{\nu}$/cm^{-1}: 3410, 3050, 2360, 1620, 1450, 1340, 1210, 1090, 1010, 744, 598, 482 ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.95 (s, 2H, indole NH), 7.36 (d, J = 8.3 Hz, 8H, indole H4, H6, H7, phenyl H3, H5), 7.21–7.14 (m, 2H, indole H5), 7.01 (t, J = 7.6 Hz, 2H, phenyl H2, H6), 6.64 (s, 2H, indole H2), 5.86 (s, 1H, CH) ^{13}C NMR ($CDCl_3$, 125 MHz), δ: 143.0 (phenyl C1), 137.1, 132.2 (indole C), 130.5, 128.8, 127.3, (phenyl C2, C3, C4, C5, C6), 124.0, 122.5, 120.2, 119.8, 119.6, 111.5 (indole C), 40.0 (CH)
Ic	IR (KBr), $\tilde{\nu}$/cm^{-1}: 3410, 3050, 2930, 2360, 1740, 1600, 1460, 1340, 1240, 1100, 876, 744, 486 ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.87 (s, 2H, indole NH), 7.38 (dd, J = 18.8 Hz, 8.0 Hz, 4H, indole H4, H7), 7.15 (d, J = 11.7 Hz, 4H, indole H5, H6), 7.02–6.91 (m, 3H, phenyl H4, H5, H6), 6.81 (t, J = 7.3 Hz, 1H, phenyl H3), 6.67 (s, 2H, indole H2), 6.36 (s, 1H, CH), 3.82 (s, 3H, OCH_3) ^{13}C NMR ($(CD_3)_2SO$, 125 MHz), δ: 157.2 (phenyl C2), 137.5, 133.5 (indole C), 130.0, 127.9, 127.6 (phenyl C1, C4, C6), 124.4, 121.6 (indole C), 120.9 (phenyl C5), 119.8, 119.0 (indole C), 118.7 (phenyl C3), 112.3, 111.7 (indole C), 56.4 (CH), 32.3 (OCH_3)
Id	IR (KBr), $\tilde{\nu}$/cm^{-1}: 3400, 3060, 2950, 2360, 1610, 1510, 1460, 1340, 1240, 1170, 1090, 852, 744, 490 ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.90 (s, 2H, indole NH), 7.44–7.32 (m, 4H, indole H4, H7), 7.24 (d, J = 5.9 Hz, 2H, indole H6) 7.16 (t, J = 7.6 Hz, 2H, indole H5), 7.00 (t, J = 7.4 Hz, 2H, phenyl H2, H6), 6.82 (d, J = 8.4 Hz, 2H, phenyl H3, H5), 6.66 (s, 2H, indole H2), 5.84 (s, 1H, CH), 3.78 (s, 3H, OCH_3) ^{13}C NMR ($(CD_3)_2SO$, 125 MHz), δ: 158.2 (phenyl C4), 137.8, 137.5 (indole C), 130.1, 127.5, 124.3 (phenyl C1, C2, C6), 121.7, 120.0 (indole C), 119.3 (phenyl C3, C5), 119.0, 114.2, 112.3 (indole C), 55.8 (CH), 39.7 (OCH_3)
Ie	IR (KBr), $\tilde{\nu}$/cm^{-1}: 3410, 3050, 2920, 2360, 1610, 1510, 1450, 1340, 1260, 1210, 1090, 845, 744, 494 ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.92 (s, 2H, indole NH), 7.82 (d, J = 8.4 Hz, 1H, phenyl OH), 7.37 (d, J = 15.5 Hz, 4H, indole H4, H7), 7.21–7.10 (m, 4H, indole H5, H6), 7.00 (t, J = 7.5 Hz, 2H, phenyl H2, H6), 6.75 (d, J = 8.4 Hz, 2H, phenyl H3, H5), 6.67 (s, 2H, indole-2-CH), 5.83 (s, 1H, CH) ^{13}C NMR ($(CD_3)_2SO$, 125 MHz), δ: 156.1 (phenyl C4), 137.4, 136.1 (indole C), 123.0, 127.5, 124.2 (phenyl C1, C2, C6), 121.6, 120.0 (indole C), 119.5 (phenyl C3, C5), 118.9, 115.6, 112.2 (indole C), 39.7 (CH)
If	IR (KBr), $\tilde{\nu}$/cm^{-1}: 3410, 3060, 2960, 2360, 1620, 1510, 1450,1340, 1210, 1090, 744, 602, 482 ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.89 (s, 2H, indole NH), 7.38 (dd, J = 17.2 Hz, 8.0 Hz, 4H, indole H4, H7), 7.27 (d, J = 3.8 Hz, 4H, indole H5, H6), 7.16 (t, J = 7.5 Hz, 2H, phenyl H3, H5), 7.00 (t, J = 7.4 Hz, 2H, phenyl H2, H6), 6.68 (s, 2H, indole H2), 5.86 (s, 1H, CH), 1.29 (s, 9H, $C(CH_3)_3$) ^{13}C NMR ($CDCl_3$, 125 MHz), δ: 148.6, 140.7 (phenyl C1, C4), 137.5, 136.6, 128.2 (indole C), 127.1 (phenyl C3, C5), 125.0 (indole C), 123.5, 121.8 (phenyl C2, C6), 119.9, 119.1, 110.9 (indole C), 39.6 (CH), 31.4 ($C(CH_3)_3$) MS, m/z: 377.2 $[M - H]^+$ (calc. 377.2)
Ig	IR (KBr), $\tilde{\nu}$/cm^{-1}: 3410, 3160, 2360, 1720, 1580, 1450, 1340, 1100, 741, 509 ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.65 (d, J = 2.2 Hz, 1H, pyridyl H2), 8.51–8.43 (m, 1H, pyridyl H4), 8.03 (s, 2H, indole NH), 7.64 (d, J = 7.9 Hz, 1H, pyridyl H6), 7.37 (dd, J = 7.8 Hz, 4.3 Hz, 4H, indole H4, H7), 7.23–7.14 (m, 3H, pyridyl H5, indole H6), 7.02 (ddd, J = 8.1 Hz, 7.1 Hz, 1.0 Hz, 2H, indole H5), 6.68 (s, 2H, indole H2), 5.93 (s, 1H, CH) ^{13}C NMR ($(CD_3)_2SO$, 125 MHz), δ: 150.5, 148.0, 141.1, (pyridyl C2, C4, C6), 137.5, 136.4 (indole C), 127.3, 124.5, (pyridyl C1, C5), 124.1, 121.9, 119.8, 119.2, 118.0, 112.4 (indole C), 38.0 (CH) MS, m/z: 324.2 $[M + H]^+$ (calc. 324.15)
Ih	IR (KBr), $\tilde{\nu}$/cm^{-1}: 3420, 3060, 2850, 1920, 1620, 1520, 1350, 1220, 1160, 1090, 899, 791, 733, 602, 474 ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.21 (s, 1H, phenyl H2), 8.08 (d, J = 8.7 Hz, 1H, phenyl H4), 7.99 (s, 2H, indole NH), 7.70 (d, J = 7.9 Hz, 1H, phenyl H6), 7.41 (dt, J = 17.6 Hz, 8.4 Hz, 5H, phenyl H5, indole H4, H7), 7.20 (t, J = 7.5 Hz, 2H, indole H6), 7.02 (t, J = 7.5 Hz, 2H, indole H5), 6.68 (s, 2H, indole H2), 6.00 (s, 1H, CH) ^{13}C NMR (DMSO, 125 MHz), δ: 148.7, 148.3 (phenyl C1, C3), 137.5 (indole C), 136.0, 130.4 (phenyl C5, C6), 127.2 (indole C), 124.7 (phenyl C2), 123.5, 122.0, 119.8, 119.3, 117.8, 112.5 (indole C), 40.0 (CH)
Ii	IR (KBr), $\tilde{\nu}$/cm^{-1}: 3410, 3048, 2862, 1910, 1717, 1616, 1508, 1454, 1339, 1215, 1092, 845, 741, 579, 474 ^{1}H NMR (600 MHz, $CDCl_3$), δ: 7.79 (s, 2H, indole NH), 7.38 (d, J = 7.9 Hz, 2H, indole H4, H7), 7.30 (d, J = 8.2 Hz, 2H, indole H4), 7.23–7.20 (m, 2H, phenyl H3, H5), 7.14 (t, J = 7.5 Hz, 2H, phenyl H2, H6), 7.07–7.05 (m, 2H, indole H6), 6.98 (t, J = 7.5 Hz, 2H, indole H5), 6.59 (d, J = 1.8 Hz, 2H, indole H2), 5.83 (s, 1H, CH), 2.30 (s, 3H, CH_3) ^{13}C NMR ($CDCl_3$, 125 MHz), δ: 141.0 (indole C), 136.7, 135.5, 129.0, 128.6 (phenyl C1, C2, C3, C4, C5, C6), 127.1, 123.6, 121.9, 120.0, 119.9, 119.2, 111.1 (indole C), 39.8 (CH), 21.1 (CH_3)

Table 4. (continued)

Compound	Spectral data
IIIa	IR (KBr), $\tilde{\nu}$/cm^{-1}: 3420, 3050, 1600, 1410, 1210, 1130, 1100, 922, 748, 478 ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.05 (s, 2H, indole NH), 7.75 (dd, J = 6.5 Hz, 3.1 Hz, 2H, phenyl H2, H6), 7.50 (d, J = 7.9 Hz, 2H, phenyl H3, H5), 7.38 (dd, J = 5.7 Hz, 2.5 Hz, 5H, phenyl H4, indole H5, H7), 7.20 (t, J = 7.6 Hz, 2H, indole H6), 7.06 (t, J = 7.5 Hz, 2H, indole H2), 6.97 (s, 2H, indole H4), 6.32 (s, 1H, isoxazole H4), 6.11 (s, 1H, CH) ^{13}C NMR ($(CD_3)_2SO$, 125 MHz), δ: 176.8 (isoxazole C3), 162.5 (isoxazole C5), 137.3 (indole C), 130.9 (phenyl C3, C5), 129.9, 129.7, (phenyl C1, C4), 127.4 (phenyl C2, C6), 127.0, 124.5, 122.0, 119.7, 119.4, 114.8, 112.5 (indole C), 100.6 (isoxazole C4), 33.6 (CH) MS, m/z: 389.5 $[M + H]^+$ (calc. 389.5)
IIIb	IR (KBr), $\tilde{\nu}$/cm^{-1}: 3410, 2960, 1620, 1430, 1100, 914, 744, 474 ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.04 (s, 2H, indole NH), 7.68 (d, J = 8.3 Hz, 2H, phenyl H2, H6), 7.49 (d, J = 7.4 Hz, 2H, phenyl H3, H5), 7.40 (t, J = 8.2 Hz, 4H, indole H5, H7), 7.19 (t, J = 7.0 Hz, 2H, indole H6), 7.05 (t, J = 7.8 Hz, 2H, indole H2), 6.98 (d, J = 2.0 Hz, 2H, indole H4), 6.30 (s, 1H, isoxazole H4), 6.10 (s, 1H, CH), 1.32 (s, 9H, $C(CH_3)_3$) ^{13}C NMR ($(CD_3)_2SO$, 125 MHz), δ: 176.6 (isoxazole C3), 162.3 (isoxazole C5), 153.6 (phenyl C4), 137.3, 127.2 (indole C), 127.0, 126.6, 124.5 (phenyl C1, C2, C3, C5, C5), 122.0, 119.7, 119.4, 114.8, 112.5 (indole C), 100.6 (isoxazole H4), 33.6 (CH), 31.8 ($C(CH_3)_3$) MS, m/z: 446.2 $[M + H]^+$ (calc. 446.2)
IIIc	IR (KBr), $\tilde{\nu}$/cm^{-1}: 3410, 1600, 1430, 1340, 1210, 1090, 1010, 930, 837, 744, 494 ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.05 (s, 2H, indole NH), 7.70–7.66 (m, 2H, phenyl H2, H6), 7.49 (d, J = 7.9 Hz, 2H, phenyl H3, H5), 7.38 (dd, J = 11.3 Hz, 4.6 Hz, 4H, indole H5, H7), 7.20 (t, J = 7.1 Hz, 2H, indole H6), 7.06 (t, J = 7.5 Hz, 2H, indole H2), 6.99 (d, J = 1.7 Hz, 2H, indole H4), 6.29 (s, 1H, isoxazole H4), 6.11 (s, 1H, CH) ^{13}C NMR ($(CD_3)_2SO$, 125 MHz), δ: 177.1 (isoxazole C3), 161.6 (isoxazole C5), 137.3 (indole C), 135.6, 130.0, 129.2, (phenyl C2, C3, C4, C5, C6), 128.6 (indole C), 127.0 (phenyl C1), 124.6, 122.0, 119.7, 119.4, 114.7, 112.5 (indole C), 100.8 (isoxazole C4), 33.6 (CH) MS, m/z: 424.1 $[M + H]^+$ (calc. 424.1)
IIId	IR (KBr), $\tilde{\nu}$/cm^{-1}: 3410, 3050, 1600, 1450, 1210, 1100, 1050, 926, 741, 590, 471 ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.05 (s, 2H, indole NH), 7.73–7.67 (m, 1H, phenyl H6), 7.52 (d, J = 7.7 Hz, 2H, phenyl H3, H5), 7.45–7.30 (m, 5H, phenyl H4, indole H5, H7), 7.20 (t, J = 7.6 Hz, 2H, indole H6), 7.07 (t, J = 7.5 Hz, 2H, indole H2), 7.01 (d, J = 1.9 Hz, 2H, indole H4), 6.50 (s, 1H, isoxazole H4), 6.14 (s, 1H, CH) ^{13}C NMR ($CDCl_3$, 125 MHz), δ: 174.3 (isoxazole C3), 160.9 (isoxazole C5), 136.5 (indole C), 132.9, 130.9, 130.5, 130.2, 128.6, 126.9 (phenyl C1, C2, C3, C4, C5, C6), 126.4, 123.2, 122.2, 119.6, 119.4, 115.2, 111.2 (indole C), 103.7 (isoxazole C4), 33.3 (CH) MS, m/z: 446.1 $[M + Na]^+$ (calc. 446.1)
IIIe	IR (KBr), $\tilde{\nu}$/cm^{-1}: 3420, 2360, 1730, 1600, 1510, 1470, 1250, 1020, 744, 667, 474 ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.05 (s, 2H, indole NH), 7.85 (dd, J = 7.7 Hz, 1.8 Hz, 1H, phenyl H6), 7.53 (d, J = 7.9 Hz, 2H, indole H7), 7.37 (d, J = 8.2 Hz, 3H, phenyl H4, indole H5), 7.19 (dd, J = 11.1 Hz, 4.1 Hz, 2H, indole H6), 7.10–6.91 (m, 6H, phenyl H3, H5, indole H2, H4), 6.55 (s, 1H, isoxazole H4), 6.12 (s, 1H, CH), 3.79 (s, 3H, OCH_3) ^{13}C NMR ($(CD_3)_2SO$, 125 MHz), δ: 175.3 (isoxazole C3), 160.1 (isoxazole C5), 157.7 (phenyl C2), 137.3 (indole C), 132.3, 129.6 (phenyl C4, C6), 127.0, 124.5, 122.0 (indole C), 121.6 (phenyl C5), 119.8 (indole C), 119.4 (phenyl C1), 118.4, 114.9, 113.1 (indole C), 112.5 (phenyl C3), 103.8 (isoxazole C4), 56.5 (CH), 33.6 (OCH_3) MS, m/z: 420.2 $[M + H]^+$ (calc. 420.2)
IIIf	IR (KBr), $\tilde{\nu}$/cm^{-1}: 3410, 2360, 1610, 1430, 1390, 1250, 1100, 918, 837, 744, 474 ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.03 (s, 2H, indole NH), 7.67 (d, J = 9.0 Hz, 2H, phenyl H2, H6), 7.49 (d, J = 8.0 Hz, 2H, indole H7), 7.37 (d, J = 8.2 Hz, 2H, indole H5), 7.23–7.15 (m, 2H, indole H6), 7.09–6.99 (m, 4H, phenyl H3, H5, indole H2), 6.93–6.87 (m, 2H, indole H4), 6.25 (s, 1H, isoxazole H4), 6.09 (s, 1H, CH), 3.81 (s, 3H, OCH_3) ^{13}C NMR ($(CD_3)_2SO$, 125 MHz), δ: 176.4 (isoxazole C3), 162.1 (isoxazole C5), 161.4 (phenyl C4), 137.3 (indole C), 128.9 (phenyl C2, C6), 127.0, 124.5, 122.1 (indole C), 122.0 (phenyl C1), 119.7, 119.4 (indole C), 115.2 (phenyl C3, C5), 114.8, 112.5 (indole C), 100.4 (isoxazole-4-CH), 56.1 (CH), 33.6 (OCH_3) MS, m/z: 420.2 $[M + H]^+$ (calc. 420.2)

the solid support compared with those obtained with Al_2O_3 (70–82 %) both in 10 min. A possible reason is that specific gravity of Al_2O_3 is higher that of SiO_2, which results in the specific surface area of SiO_2 larger. Therefore, the catalytic activity and dispersancy of SiO_2 are higher than those of Al_2O_3, which proves that SiO_2 is an efficient solid support and catalyst for the reaction. Besides, the results presented in Table 1 indicate that high yields were obtained when the benzene ring of R_1 was substituted by an electron-donating group (Table 1, Entries 5–7 and 10) and even higher yields were obtained when the benzene ring of R_1 was substituted by an electron-withdrawing group (Table 1, Entry 9). However, higher yield can also be achieved when the reaction starts from 2-methoxyl benzaldehyde, probably because the tar-

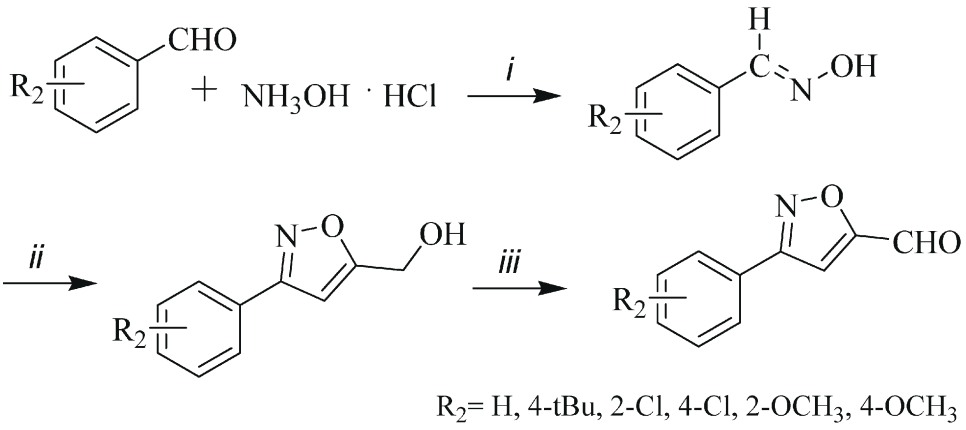


Fig. 1. Synthetic pathway of 3-substituted isoxazole-5-carbaldehydes: *i*) 6 M NaOH, EtOH, reflux; *ii*) 1 – NCS, DMF; 2 – propargyl alcohol, NEt_3; 3 – utrasonication or conventional heating; *iii*) I_2/TEMPO, $NaHCO_3$ (aq.), toluene, r.t.

get product 3-((4-methoxyphenyl)(3a,7a-dihydro-1*H*-indol-3-yl)methyl)-1*H*-indole (*Ic*; Table 1, Entry 4) revealed higher stabilization of the stable resonance structure comprising a lone electron pair of oxygen, benzene ring and methylene formed in an acidic medium.

It is known that isoxazoles are versatile scaffolds for the synthesis of a wide variety of complex natural products, and functionalized isoxazole derivatives are active pharmacophores in many pharmacologically important molecules (Wagner et al., 2004; Pastor et al., 2004; Basappa et al., 2004), e.g. bis(indolyl)methanes with 3-substituted phenyl isoxazole-ring which may extend the application of bis(indolyl)methane derivatives. Herein, six 3-substituted isoxazole-5-carbaldehyde derivatives were synthesized via a 1,3-dipolar cycloaddition reaction from substituted benzaldehyde oximes in moderate to excellent yields (44–92 %) (Fig. 1, Table 2) according to literature (Miller & Hoerrner, 2003; Angelin et al., 2006).

Further, six novel bis(indolyl)methanes containing an isoxazole ring were synthesized in 94–99 % yields from 3-substituted isoxazole-5-carbaldehydes in the presence of SiO_2 solid support under MW irradiation and solvent-free conditions (Table 3). Moreover, the substituted groups on benezene-ring showed less impact on the yields of the desired products.

Conclusions

In conclusion, a method for the synthesis of bis(indolyl)methanes under solvent-free conditions using MW irradiation has been presented. SiO_2 has been proved to be an efficient dispersant and a favorable catalyst for the reaction as it is inexpensive, easy-to-handle, and commercially available. The desired products were obtained in excellent yields. Therefore, the method is an important contribution to the bis(aryl)methane compounds synthesis pathways. The synthesis of more bis(aryl)methane compounds is being studied in our laboratory. Moreover, the method provides relevant information on the synthesis of relevant compounds.

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