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Synthesis of aryl/alkyl(2,2′-bis-3-methylindolyl)methanes and aryl(3,3′-bis indolyl)methanes promoted by secondary amine based ionic liquids and microwave irradiation

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ABSTRACT

Aryl/alkyl(2,2′-bis-3-methylindolyl)methanes and aryl(bis-3,3′-indolyl)methanes are synthesized in high yield using ionic liquids mediated by microwave. Reaction conditions and product recovery are simple and ionic liquids could be recycled.

Recently, the synthesis of bisheterocycles with a suitable linker has attracted considerable interest because of their unique pharmacological properties. Aryl/alkylbisindolylmethanes are compounds having symmetrical or unsymmetrical structures and are reported to be biologically important,[1–5] the bacterial metabolite vibrindole A is an example. It is reported that they inhibit bladder cancer growth, renal cell carcinoma, colon cancer, and other malignant cell growth.[6–10] Their oxidized form finds applications as dyes[11,12] and colorimetric sensors.[13,14] There are several methods for the synthesis of aryl(3,3′-bisindolyl)methanes, however, synthetic routes to aryl/alkyl(2,2′-bis-3-indolyl)methanes derived from skatole are few. Aryl(3,3′-bis-indolyl)methanes from indole are synthesized by the electrophilic substitution of indole with aldehydes or ketones in the presence of protic acid or Lewis acids[15–17] particularly lanthanide triflates,[18] zeolite (ZnY),[19] montmorillonite clay K-10.[20,21] Other catalysts that have been used include the use of lithium perchlorate,[22] I_2,[23] modified zirconia,[24] HBF_4–SiO_2,[25] ZnO,[26] trityl Chloride,[27] and a combination of $CeCl_3{\cdot}7H_2O$–NaI–SiO_2 under solvent-free conditions,[28] PEG-supported sulfuric acid[29] and a combination of glycerin and $CeCl_3{\cdot}7H_2O$[30] besides others.[31,19,32–35] In addition to the symmetrical aryl(bisindolyl)methanes, Xiao-Fei et al. have also reported the synthesis of unsymmetrical analogs using CAN and the reaction is mediated by ultrasound.[36] Ionic liquids have been used as promoters notably $FeCl_3$ based ionic liquid,[37] [bmim][BF_4]–[bmim][PF_6],[38] and [bmim][$MeSO_4$].[39] The synthesis of aryl/alkyl(2,2′-bis-3-methylindolyl)methanes,[40,41] has received very little attention, and herein the synthesis using aliphatic aldehyde as the linker has been reported.[42]

Herein we report that both the aryl/alkyl(2,2′-bis-3-methylindolyl)methanes from skatole and aryl(bis-3,3′-indolyl)methanes from indole, can be synthesized using simple ionic liquids (IL) mediated by microwave. The ILs are prepared by the action of conc. H_2SO_4 on diethyl, diisopropyl and di-*n*-propyl amines, respectively[43] and conveniently used to catalyze the reaction of indole as well as skatole with several aldehydes and ketones using microwave. Short reaction time, environmentally benign condition, simple recovery, and high yield make the procedure attractive. With indole and nitrobenzaldehyde as the substrates 100% conversion is observed and similar efficiency is observed for the reaction of 3,4-dimethoxybenzaldehyde and 2-methoxybenzaldehyde with skatole. In a typical procedure, acidic IL is mixed with two equivalents of indole (or skatole), one equivalent of the aldehyde in 1 mL of ethanol (95% v/v) and the solutions are exposed to microwave irradiation for varying duration of time.[44] The progress of the reaction is monitored by TLC in prepared silica gel plates. The products are easily isolated by dilution with water and filtration of the precipitated product leaving behind the aqueous filtrate from which IL can be completely recovered and recycled. The filtrate obtained after recovery of the product is evaporated in a rotary evaporator and the recovered IL is stored in a desiccator for reuse. The recycled catalyst can be used for three successive runs without appreciable loss in its

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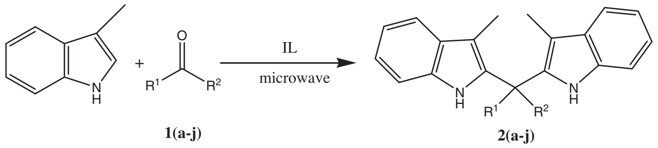
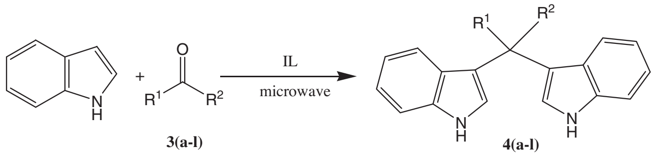


IL= $R_2NH_2^+HSO_4^-$; R = Et, n-propyl, isopropyl

R^1= H, CH_3 ; R^2= Alkyl, Aryl

Scheme 1. Synthesis of aryl/alkyl(2,2′-bis-3-methylindolyl)methanes.



R^1= H; R^2= Aryl, Cyclohexyl

Scheme 2. Synthesis of aryl(bis-3,3′indolyl)methanes.

catalytic activity. The aryl/alkyl(bisindolyl)methane derived from indole and skatole can be prepared under similar conditions. A comparative study indicates di-*n*-propylammonium hydrogensulfate and diethylammonium hydrogensulfate to be more efficient than diisopropylammonium hydrogensulfate. The effects of the three ILs are screened for their efficiency in the conversion and the results are given in Table 3. The yield of the target compound increases in the following sequence of the ILs, di-*n*-propyl > diethyl > diisopropyl. In this study 4-nitrobenzaldehyde and indole were taken as the reference reactants. In order to demonstrate the efficiency of MW technique over conventional method, the reaction of indole with 4-nitrobenzaldehyde is performed using conventional heating and the time required for complete conversion to the target molecule is found to be 25 min. The reactions are shown in Schemes 1 and 2 and the experimental results are given in Table 1 for aryl/alkyl(2,2′-bis-3-methylindolyl)methanes and Table 2 for aryl(bis-3,3′indolyl)methanes.

Table 3
Screening for efficiency of the IL

Entry	Ionic liquid	Time (min)	Yield[a] (%)
1	$[Et_2NH_2][HSO_4]$	3	91
2	$[(n\text{-propyl})_2NH_2][HSO_4]$	3	99
3	$[(\text{isopropyl})_2NH_2][HSO_4]$	3	85

[a] Yields refers to the pure isolated products.

The combined use of classical ILs and microwave offers an easy access to the aryl(3,3′-bisindolyl)methanes and aryl/alkyl(2,2′-bis-3-methylindolyl)methanes. The products can be isolated by simple filtration and the IL in the filtrate can be recovered and reused. Simple reaction conditions, absence of strong acids, high turnover

Table 1
Synthesis of aryl/alkyl(2,2′-bis-3-methylindolyl)methanes promoted by $[n\text{-}Pr_2NH_2][HSO_4]$

Entry	Aldehyde/ketone	Product	Yield[a] (%)	Mp (°C)		Time (min)
				Lit	Obs	
1	(1a) R^1 = H, R^2 = 4-NO_2-C_6H_4	**2a**	96	–	232–234	3
2	(1b) R^1 = H, R^2 = 4-CH_3-C_6H_4	**2b**[b]	95	–	154–156	5
3	(1c) R^1 = H, R^2 = 4-OH-C_6H_4	**2c**	90	–	203–205	3
4	(1d) R^1 = H, R^2 = 2-OCH_3-C_6H_4	**2d**	100	–	210–212	3
5	(1e) R^1 = H, R^2 = 3,4-$(CH_3O)_2$-C_6H_3	**2e**[b]	100	–	219–221	3
6	(1f) R^1 = H, R^2 = C_6H_5	**2f**[b]	97	–	130–132	5
7	(1g) R^1 = H, R^2 = 2,5(OH)(OCH_3)-C_6H_3	**2g**[b]	90	–	216–218	3
8	(1h) R^1 = CH_3, R^2 = CH_3	**2h**[c]	52	–	178–180	7
9	(1i) R^1 = H, R^2 = CH = CH-C_6H_5	**2i**[b]	65	–	–	5
10	(1j) R^1 = H, R^2 = CH_3	**2j**[b,d]	75	–	58–60	5

[a] Yields refers to the pure isolated products.
[b] New compounds.
[c] See Ref. 46.
[d] See Ref. 47.

Table 2
Synthesis of aryl (bis-3,3′indolyl) methanes promoted by $[n\text{-}Pr_2NH_2][HSO_4]$

Entry	Aldehyde/ketone	Product	Yield[a] (%)	Mp (°C)		Time (min)
				Lit	Obs	
1	(3a) R^2 = C_6H_5	**4a**	95	151–152[25]	152–153	5
2	(3b) R^2 = 2-NO_2-C_6H_4	**4b**	99	215–217[34]	215–217	3
3	(3c) R^2 = 3-NO_2-C_6H_4	**4c**	99	220–222[35]	221–223	3
4	(3d) R^2 = 4-NO_2-C_6H_4	**4d**	99	217–219[23]	215–218	3
5	(3e) R^2 = 3,4-$(CH_3O)_2$- C_6H_3	**4e**	90	196–198[32]	195–197	3
6	(3f) R^2 = Cyclohexyl	**4f**	95	118–120[25]	118–120	3
7	(3g) R^2 = 4-Cl-C_6H_4	**4g**	92	76–77[23]	77–78	3
8	(3h) R^2 = 4-CH_3-C_6H_4	**4h**	89	94–96[25]	93–95	5
9	(3i) R^2 = 4-OH-C_6H_4	**4i**	93	124–126[32]	124–126	5
10	(3j) R^2 = 2-CH_3O-C_6H_4	**4j**	91	134–136[33]	134–137	5
11	(3k) R^2 = Furfuryl	**4k**	85	324–326[25]	325–328	5
12	(3l) R^2 = 2,5(OH)(OCH_3)-C_6H_3	**4l**	93	112–114[32]	113–116	5

[a] Yields refers to the pure isolated products.

of products make this procedure an improved practical alternative to the conventional acid catalyzed thermal reaction.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.06.106.

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43. *Experimental procedure for the preparation of [n-Pr_2NH_2][HSO_4] & [iso-Pr_2NH_2][HSO_4]:* Under vigorous stirring, 0.05 mol sulfuric acid was added dropwise to an ice cold solution of 0.04 mol of the appropriate dialkylamine in 15 mL of chloroform. Removal of chloroform under reduced pressure gave a white solid product which was dried in vacuo.
    Di-n-propylammonium hydrogensulfate [n-Pr_2NH_2][HSO_4]: ^{1}H NMR (400 MH$_Z$, DMSO, Me_4Si) (δ_H ppm): 0.095(6H, t, *J* = 6.8 Hz, 2CH_3), 1.602(4H, sextet, *J* = 7.2 Hz, 2CH_2), 2.841 (4H, m, 2CH_2), 4.447(2H, s, NH_2), 8.297(1H, s, HSO_4); ^{13}C NMR(100 MHz, DMSO-d_6) (δ ppm): 11.349, 19.413, 48.816; HRMS (ESI): *m*/*z* = 199.0879 ([M]$^+$), calcd for $C_6H_{17}NO_4S$: 199.0878 ; The thermal decomposition point 567 K.
    Diethylammonium hydrogensulfate [Et_2NH_2][HSO_4]: prepared by reported method.[45]
44. *General procedure for the synthesis of aryl/alkyl(2,2′-bis-3-methylindolyl)methanes and aryl(bis-3,3′indolyl)methanes*: A solution of skatole or indole (2 mmol), aldehyde (1 mmol), IL (10 mol %) and ethanol (1 mL) was irradiated with microwave (560 W) for varying period of times as indicated in Table 1 and Table 2. After completion of the reaction as indicated by TLC, the reaction mixture was poured into ice and stirred for 3–4 min. The solid product was filtered and recrystallized from pet ether (60–80) and EtOAc mixture (4:1).[46,47]
    *4-nitrophenyl(2,2′-bis-3-methylindolyl)methane (**2a**)*: Orange solid; IR ν_{max} (KBr): 3437, 3390, 2916, 1593, 1516, 744 cm^{-1}; ^{1}H NMR(300 MH$_Z$, DMSO, Me_4Si)(δ_H ppm): 10.477 (2H, s, NH), 8.215 (2H, d, *J* = 8.7 Hz, ArH), 7.454–7.389 (4H, m, ArH), 7.29 (2H, d, *J* = 7.8 Hz, ArH), 7.055–6.940 (4H, m, ArH), 6.215 (1H, s, CH), 2.140 (6H, s, 2CH_3); ^{13}C NMR(75 MH$_Z$, $CDCl_3$, Me_4Si) δ : 147.77, 147.15, 135.56, 131.73, 129.43, 124.24, 122.33, 119.88, 118.78, 111.08, 109.54, 40.80, 8.74; Anal. Calcd for $C_{25}H_{21}N_3O_2$: C, 75.93; H, 5.35; N, 10.63; O, 8.09. Found: C, 75.98; H, 5.29; N, 10.65; O, 8.11. HRMS (ESI): *m*/*z* = 395.1636 ([M]$^+$), calcd for $C_{25}H_{21}N_3O_2$: 395.1634.
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46. *Synthesis of compound **2h***: A solution of skatole (2 mmol), acetone (1 mL), IL (10 mol %) irradiated with microwave (560 W) for 7 min. On cooling to ambient temperature, the IL is precipitated and filtered . The filtrate on dilution with ice cold water gave the crude product as a precipitate which is purified by column chromatography in silica gel column and EtOAc: Pet.Ether (60–80) 1:19 as the eluent.
    *Dimethyl(2,2′-bis-3-methylindolyl)methane **(2h)**: White solid; IR ν_{max}(KBr)*: 3441, 1612, 734 cm^{-1}; ^{1}H NMR (300 MH$_Z$, DMSO, Me_4Si)(δ_H ppm): 12.218 (2H, s, NH), 8.820 (2H, d, *J* = 8.4 Hz, ArH), 7.900 (2H, d, *J* = 7.2 Hz, ArH), 7.549 (2H, t, *J* = 7.2 Hz, ArH), 7.128 (2H, t, J = 7.2 Hz, ArH), 2.667 (6H, s, 2CH_3), 1.782 (6H, s, 2CH_3); ^{13}C NMR (75 MH$_Z$, $CDCl_3$, Me_4Si) δ: 202.59, 140.73, 135.02, 131.51, 122.62, 122.34, 121.07, 53.53, 28.46, 23.46; Anal. Calcd for $C_{21}H_{22}N_2$: C, 83.40; H, 7.33; N, 9.26. Found: C, 83.42; H, 7.32; N, 9.24. HRMS (ESI): *m*/*z* = 302.1785 ([M]$^+$), calcd for $C_{21}H_{22}N_2$: 302.1783.
47. *Synthesis of compound **2j***: It is carried out as per the general procedure with 0.5 mL of acetaldehyde. The crude product is purified by column chromatography in silica gel column and EtOAc: pet.ether (60–80) 1:19 as the eluent.
    *Methyl(2,2/-bis-3-methylindolyl)methane (**2j**)***:** Orange solid; IR ν_{max}(KBr): 3419, 2952, 1610, 742 cm^{-1}; ^{1}H NMR (300 MH$_Z$, $CDCl_3$, Me_4Si)(δ_H ppm): 7.758 (2H, s, NH), 7.541 (3H, d, *J* = 6.9 Hz, ArH), 7.154–7.137 (5H, m, ArH), 4.758 (1H, q, *J* = 7.2 Hz, CH), 2.269 (6H, s, 2CH_3), 1.775 (3H, d, *J* = 7.2 Hz, 1CH_3); ^{13}C NMR (75 MH$_Z$, $CDCl_3$, Me_4Si) δ :135.81, 135.09, 129.50, 121.42, 119.30, 118.30, 110.69, 107.08, 29.38, 19.28, 8.58; Anal. Calcd for $C_{20}H_{20}N_2$: C, 83.30; H, 6.99; N, 9.71. Found: C, 83.31; H, 6.97; N, 9.72. HRMS (ESI): *m*/*z* = 288.1627([M]$^+$), calcd for $C_{20}H_{20}N_2$: 288.1626.