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Research Paper

Use of cation exchange resins for the synthesis of bis-indolylmethanes

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Abstract: Simple and highly efficient procedure for the synthesis of bis-indolylmethanes is described under both solvent and solvent-free conditions with excellent yields. This approach utilizes cation exchange resins as catalyst under mild reaction conditions.

Introduction

Indoles are found to be extremely important core component of various synthetic and naturally occurring biological active molecules. The bicyclic indole moieties are precursors of many pharmaceuticals with important therapeutic categories like antihypertensives, anticancer, antioxidants, anti-HIV, etc. Bisindole alkaloids are frequently been isolated from marine invertebrates and also found in sponges.[1] Moreover, various categories of bisindoles include antagonist and coronary dilatory activities.[2] Bisindolylmethanes can be synthesized by the electrophilic substitution reaction of carbonyl compounds and indoles. Extensive research was carried on the electrophilic substitution reaction of carbonyl compounds with indole to form bis indolylmethanes. Most of the approaches include use of acids and Lewis acids.[3,4] Some synthetic procedures involve condensation of indoles with Schiff's bases[5] and some other involve addition of indoles to appropriate nitrones or 3-indolylhydroxylamines using trimethylsilyl chloride.[6] Though initial methods require harsher conditions and long reaction times with inconsistent yields, recent methods provide simple and efficient approaches for bisindole synthesis with good to excellent yields.[7] Of these, only few procedures engage methods involving solid phase catalysts,[8] rare-earth catalysts and ionic liquids.[9] Hence, we put our efforts to extend this area of research by the use of

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Chemistry & Biology Interface, 2012, 2, 3, 199-205

solid phase catalysis for the synthesis of bis-indolylmethanes.

Results and Discussion

Through this communication, we present a novel, cost effective and efficient procedure for the synthesis of bis-indolylmethanes using cation exchange resins as catalysts under mild conditions (Scheme 1). Usually ion exchange resins are well-known for their equivalence to acid or base catalysis. This type of resins can be easily separated from the reaction mass as they are immiscible. For our studies, we chose two types of catalyst; strong cation exchange resins (supplied by Thermax-TULSION®) T63 (MP) and T57H (MP). These resins are made up with polystyrene copolymer having sulfonic functional group with high porosity. They are odorless and have excellent resistance to temperatures up to 130 °C.

In this approach our initial attempts were to use different solvents. Screening results reveal that acetonitrile is one of the best choices to achieve better quality of the product. The reaction was performed at ambient temperature. Catalyst loading was studied up to 50% w/w to the input indole and optimized conditions involve 10% w/w catalyst loading for about 8 h at ambient temperature. The used catalyst can easily be separated by filtration and can be reused for fresh reaction. The recovered catalyst was employed for further two successful recycles. However, reaction times were found to be increased while reuse of the recovered catalyst.

Apart from the solvent mediated attempts, this reaction was also studied under solvent-free conditions and the desired bis-indonylmethanes were prepared with similar yields as in presence of solvent. While this approach led to cost-effective process, it was also possible to imbibe Green components in the transformation by using traces or no solvent, low E-factor and less amount of energy.

Under optimized conditions, we examined the reaction of various aldehydes with indole in presence of two different cation exchange resins and the results are tabulated in Table 1.

The strategies described in this article have several advantages including mild reaction conditions, shorter reaction time, high yields of products, low catalyst loading, as well as simple experimental and isolation procedures. The selected catalysts are found to be highly efficient, easily available, economical, and recyclable.

Conclusions

We have successfully demonstrated that the use of both the cation exchange resins appreciably offers simple, economic and environment friendly method for the synthesis of bis-indolylmethanes.

Experimental Section

All starting materials were commercial products. LR grade solvents and commercial reagents were used without further purification. The FT IR spectra were recorded as KBr pallet using Perkin–Elmer FT IR spectrometer and only diagnostic and/or intense peaks are reported. Mass spectra (70 eV) were recorded on LC-MS spectrometer. The melting points were determined by using the capillary method on POLMON (model: MP-96-X) melting point apparatus and are uncorrected. HRMS spectra were with Waters LCT Premier XE (Micro mass Oa-TOF) instrument. ^{1}HNMR spectra were recorded in $CDCl_3$ and DMSO-d6 with Varian Mercury Plus 400 MHz

ISSN: 2249 –4820

Chemistry & Biology Interface, 2012, 2, 3, 199-205

instrument. ^{13}CNMR spectra were recorded in $CDCl_3$ and DMSO-d6 with Varian Gemini 200 MHz instrument. Signals due to the solvent (^{13}CNMR) or residual protonated solvent (^{1}HNMR) served as the internal standard. The 1H NMR chemical shifts and coupling constants were determined assuming first-order behavior. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad); the list of coupling constants (J) corresponds to the order of multiplicity assignment. TLC analyses were performed on a silica gel 60 F254 precoated-plates (250 μm layers). We note that our spectral assignments are supported by comparison with the literature.

General procedures for the synthesis of bis(indol-3-yl)methanes 3a–i;

Method a: solvent mediated: A mixture of 1*H*-indole (1, 2.34 g, 20 mmol) and aldehyde (10 mmol) in acetonitrile (10 mL) was taken in a flask along with cation exchange resin (0.1 g, 10% w/w). The reaction mass was heated at 80 °C with stirring. The progress of the reaction was monitored by thin-layer chromatography (TLC eluent: n-hexane-ethylacetate, 8:2). After the reaction was completed, the catalyst was filtered off, following by washing with ethyl acetate (3 X 10 ml). The filtrate was concentrated under reduced pressure, and the product was purified by column chromatography (silica gel, n-hexane-ethylacetate, 1:4).

Method b: solvent-free conditions: To a well-ground mixture of 1*H*-indole (1, 2.34 g, 20 mmol) and aldehyde (10 mmol) in a mortar was added cation exchange resin (0.1 g, 10% w/w) and the mixture was thoroughly mixed with pestle for about 15 minutes. Dichloromethane (10 mL) was added to the crude mixture and the mixture was filtered to separate the catalyst. The filtrate was washed with saturated sodium bisulfate (2×10 mL) to extract the unreacted aldehyde. The organic layer was dried ($CaCl_2$) and evaporated. The obtained crude product was subjected to column chromatography (silica gel, n-hexane-ethylacetate, 1:4) to obtain the pure product.

3,3'-(phenylmethylene)bis(1*H*-indole) (3a): Red colored solid. mp: 125-127 °C; IR (KBr): 747, 1007, 1091, 1335, 1455, 1541, 3051, 3398; 1H NMR (400 MHz, CDCl3): δ = 5.88 (s, 1H), 6.67 (d, 2H, J = 1.6 Hz), 7.00-7.04 (m, 2H,), 7.17-7.21 (m, 2H), 7.39-7.41 (m, 4H), 7.43 (d, 2H, J = 7.8 Hz), 7.35-7.39 (m, 5H), 7.95 (brs, 2H, NH); 13C NMR (75 MHz, CDCl3): δ = 40.2, 111.0, 119.2, 119.73, 119.9, 121.9, 123.58, 126.11, 127.0, 128.2, 128.7, 136.7, 144.0; MS (ES): m/z = 322 (M-).

3-[(1H-indol-3-yl)(3-nitrophenyl)methyl]-1*H*-indole (3b): Brick red colored solid. mp: 96-99 °C; IR (KBr): 742, 1093, 1093, 1347, 1456, 1524, 3055, 3408; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.99 (s, 1H), 6.67 (d, 2H, *J* = 1.6 Hz), 7.00-7.04 (m, 2H,), 7.17-7.21 (m, 2H), 7.39-7.41 (m, 4H), 7.43 (d, 2H, *J* = 7.8 Hz), 7.68 (d, 2H, *J* = 7.8 Hz), 7.98 (brs, 2H, NH), 8.06-8.08 (m, 1H), 8.21 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 39.98, 111.25, 118.24, 119.5, 121.47, 122.29, 123.58, 123.66, 126.6, 129.10, 134.86, 136.7, 146.35, 148.45; MS (ES): m/z = 366 (M^-); ESI-HRMS: *m/z* $[M-H]^+$ for $C_{23}H_{16}N_3O_2$ calculated: 366.1243, found: 366.1231.

4-[di(1*H*-indol-3-yl)methyl]benzonitrile (3c): Pale brown colored solid. mp: 209-210 °C; IR (KBr): 740, 1091, 1336, 1417, 1456, 1497, 1602, 2224, 2924, 3430; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.93 (s, 1H, Ar-CH), 6.66 (s, 2H), 7.00-7.04 (m, 2H), 7.20 (m, 2H), 7.31-7.38 (m, 4H), 7.44 (d, 2H, *J* =

ISSN: 2249 –4820
Chemistry & Biology Interface, 2012, 2, 3, 199-205

8.3 Hz), 7.55 (d, 2H, *J* = 8.4 Hz), 7.99 (brs, 2H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 108.56, 111.48, 116.74, 118.30, 118.84, 118.97, 120.98, 123.71, 126.32, 129.22, 132.00, 136.50, 150.79; MS (ES): m/z = 346 (M^-H); ESI-HRMS: *m/z* $[M-H]^+$ for $C_{24}H_{16}N_3$ calculated: 346.1344, found: 346.1331.

3-[(4-chlorophenyl)(1H-indol-3-yl)methyl]-1*H*-indole (3d**).** Brown colored solid. mp: 98-101°C; IR (KBr): 742, 1012, 1089, 1454, 1487, 3052, 3414; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.86 (s, 1H, Ar-CH), 6.64 (d, 2H, *J* = 1.6 Hz), 6.98-7.00 (m, 2H), 7.2 (t, 2H, *J* = 8.4 Hz), 7.20-7.25 (m, 4H), 7.34 (d, 2H, *J* = 8.8 Hz), 7.95 (brs, 2H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 111.42, 117.49, 118.18, 118.94, 120.87, 123.53, 126.40, 127.89, 130.01, 130.18, 136.52, 143.91; MS (ES): m/z = 358.2 (M^-); HRMS (ESI): for $C_{25}H_{21}N_2O_2$ calculated: 381.1603, found 381.1607.

3,3'-((4-methoxyphenyl)methylene)bis(1*H*-indole) (3e): Brown colored solid. mp: 194-195 °C; IR (KBr): 740, 1093, 1347, 1244., 1508, 3055, 3395; 1H NMR (400 MHz, CDCl3): δ = 3.7(s, 3H,) 5.77 (s, 1H), 6.58 (d, 2H, J = 1.6 Hz), 6.73-6.77 (m, 2H,), 7.10-7.19 (m, 4H), 7.27-7.33 (m, 4H,), 7.98 (brs, 2H, NH); 13C NMR (75 MHz, CDCl3): δ = 39.4, 55.2, 111.0, 113.6, 119.2, 120.0, 120.1, 121.9, 123.5, 127.1, 129.6, 136.2, 136.7, 157.9; MS (ES): m/z = 351 (M-).

3,3'-(benzo[d][1,3]dioxol-5-ylmethylene)bis(1*H*-indole) (3f**):** Brownish yellow colored solid. mp: 99-100 °C; IR (KBr): 741, 1037, 1093, 1242, 1336, 1485, 3055, 3410; 1H NMR (400 MHz, CDCl3): δ = 5.7(s, 1H,) 5.8 (s, 2H), 6.59-6.66 (m, 2H), 6.74-6.77 (m, 2H), 6.91-6.95 (m, 2H), 7.07-7.18 (m, 2H,),7.26-7.33(m,4H) 7.83 (brs, 2H, NH); 13C NMR (75 MHz, CDCl3): δ = 40.0, 100.8, 108.0, 109.3, 111.1, 119.3, 119.8, 119.9, 121.6, 122.0, 123.5, 127.0, 136.7, 138.2, 145.8, 147.5; MS (ES): m/z = 365(M-).

3-[(Furan-2-yl)(1H-indol-3-yl)methyl]-1*H*-indole (3g**).** Off-white colored solid. mp: 113-115 °C; IR (KBr): 742, 783, 1008, 1454, 3053, 3412; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.88 (s, 1H, Ar-CH), 6.08 (d, 1H, *J* = 2.8 Hz), 6.35-6.36 (m,1H), 6.86-6.90 (m, 2H), 7.00-7.04 (m, 4H), 7.32 (d, 2H, *J* = 8.0 Hz), 7.39 (d, 2H, *J* = 8.0 Hz), 7.51 (d, 1H, *J* = 2.0 Hz), 10.82 (brs, 2H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 33.55, 105.73, 110.11, 111.38, 115.65, 118.16, 118.94, 120.77, 123.17, 126.30, 136.32, 141.18, 157.50; MS (ES): m/z = 311.2 (M^-).

3-[1-(1H-indol-3-yl)butyl]-1*H*-indole (3h**).** Light brown colored thick liquid. IR (KBr): 736, 1012, 1095, 1454, 1614, 2850, 2926, 3408; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.91 (t, 3H, *J* = 7.2 Hz), 1.30 (m, 2H), 2.20 (m, 2H), 4.39 (t, 1H, *J* = 7.6 Hz), 6.86-6.82 (m, 2H), 6.99-6.85 (m, 2H), 7.10 (d, 2H, *J* = 2.0 Hz), 7.29 (d, 2H, *J* = 7.6 Hz), 7.50 (d, 2H, *J* = 8.0 Hz), 10.70 (brs, 2H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.21, 21.40, 33.64, 38.11, 111.01, 118.89, 119.59, 120.44, 121.34, 121.61, 121.61, 127.11, 136.48; MS (ES): m/z = 287.20 (M^-); HRMS (ESI): for $C_{20}H_{19}N_2$ calculated: 278.1548, found: 278.1553.

3-(1-(1H-indol-3-yl)octyl)-1*H*-indole (3i**).** Light brown colored thick liquid. IR (KBr): 582, 740, 1010, 1093, 1336, 1417, 1456, 1618, 2852, 2926, 3415; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.82 (t, 3H, *J* = 6.4 Hz), 1.31 (m, 10H), 2.16 (d, 2H, *J* = 6.4 Hz), 4.36 (t, 1H, *J* = 7.6 Hz), 6.86-6.82 (m, 2H), 6.99-6.96 (m, 2H), 7.19 (d, 2H, *J* = 2.0 Hz), 7.27 (d, 2H, *J* = 8.0 Hz), 7.47 (d, 2H, *J* = 8.0 Hz), 10.70 (brs, 2H, NH); ^{13}C NMR (75

ISSN: 2249 –4820

Chemistry & Biology Interface, 2012, 2, 3, 199-205

MHz, $CDCl_3$): δ 14.10, 22.66, 28.33, 29.29, 29.75, 31.91, 33.98, 35.87, 111.02, 118.90, 119.59, 120.47, 121.35, 121.61, 127.11, 136.50; MS (ES): m/z 343.4 (M^-).

Acknowledgements

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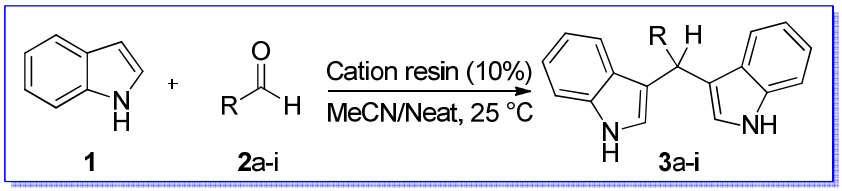
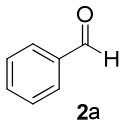
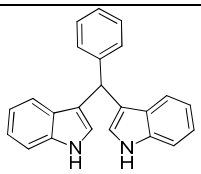
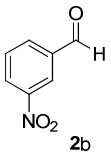
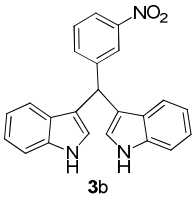
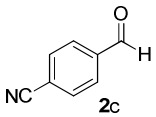
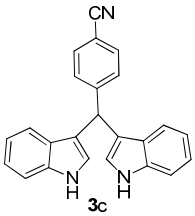
Schemes and Tables



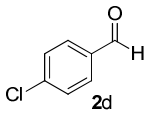
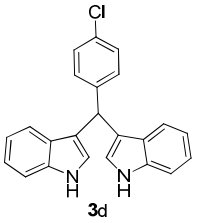
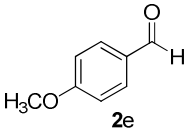
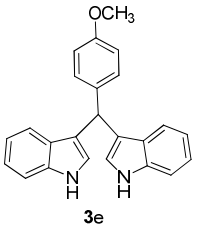
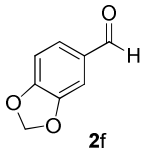
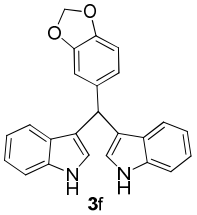
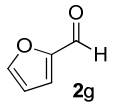
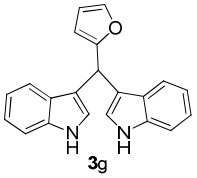
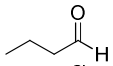
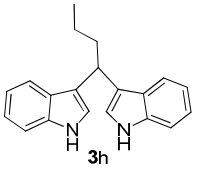
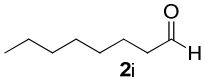
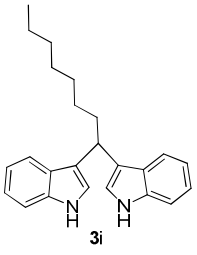
Scheme 1. Synthesis of bis-indolylmethanes using cation exchange resin

Table 1. Reaction of various aldehydes (**2**a-i) with indole (**1**) using cation exchange resin under solvent and solvent-free conditions at 25 °C

entry	aldehyde **2**	bis-indolylmethane **3**	reaction time and yield (%)	
			solvent	solvent-free
1	 **2a**	 **3a**	8h; 90	15min; 90
2	 **2b**	 **3b**	5h; 94	10 min; 92
3	 **2c**	 **3c**	5h; 90	10 min; 92

ISSN: 2249 –4820

Chemistry & Biology Interface, 2012, 2, 3, 199-205

4	 2d	 3d	5h; 93	15 min; 92
5	 2e	 3e	8h; 90	20 min; 90
6	 2f	 3f	8h; 93	20 min; 90
7	 2g	 3g	8h; 90	20 min; 90
8	 2h	 3h	5h; 94	15 min; 93
9	 2i	 3i	5h; 93	15 min; 90

ISSN: 2249 –4820

Chemistry & Biology Interface, 2012, 2, 3, 199-205

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