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A Facile Synthesis of Indole Derivatives Catalyzed by $CeCl_3.7H_2O$ Under Microwave Irradiation

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ABSTRACT

Bis(2-methylindolyl)methane and bis(indolyl)methane derivatives were synthesized in presence of catalytic amount of $CeCl_3.7H_2O$ in CH_3CN under microwave irradiation in good to excellent yields.

Keywords: *$CeCl_3.7H_2O$; Solvent; Microwave; Bis(2-methylindolyl)alkanes; Bis(indolyl)alkanes.*

1. INTRODUCTION

Indole and their derivatives have many applications in medicine. They have pharmacological and biological active properties. Bis(indolyl)alkanes are most active cruciferous substances for promoting beneficial estrogen metabolism and used as antibiotics [1]. Development of bis(indolyl)alkane synthesis has been of considerable interest in organic synthesis because of their wide occurrence in various natural products particularly from marine sources possessing pharmaceutical activity and tranquilising ability [2]. Bis(indolyl)alkanes contain two indole or substituted indole units in a molecule. Synthetically these compounds are obtained from the condensation of indoles or substituted indoles with aldehydes or ketones in the presence of acid catalysts.

Several reagents have been reported to catalyse the reaction which include $Incl_3$ [3], $In(OTf)_3$ [4], InF_3 [5], $Dy(OTf)_3$ [6], $Ln(OTf)_3$ [7], $LiClO_4$ [8], Zeokarb-225 [9], molecular iodine [10], montmorillonite K10 [11], $NbCl_5$ [12], silica chloride [13], $ZrOCl_2{\cdot}8H_2O$/silica gel [14], $ZrOCl_2$ in CH_3CN [15], SiO_2-$POCl_2$ [16],silica sulfuric acid [17], fluoroboric acid adsorbed on silica gel [18], P_2O_5/SiO_2 [19], hexamethylene tetramine bromine [20], ionic liquids in conjugation with $In(OTf)_3$ or $FeCl_3.6H_2O$ [21], TiO_2 [22], $FeCl_3$ [23], $TiCl_4$ [24], protic solvents [25], and [Cu(3,4-tmtppa)] $(MeSO_4)_4$ [26]. Further, triphenyl phosphoniumper chlorate [27], molybdato phosphoric acid [28] and trichloro-1,3,5-triazine [29] have been used to catalyse the reaction. Recently, sodium bisulphate [30], tetrabutyl ammonium tribromide [31], PEG-supported sulphonic acid [32], glycerin-$CeCl_3.7H_2O$ [33], fuller's earth [34], SBA-15-supported poly(4-styrenesulfonyl (perfluorobutylsulfonyl)imide) [35] and iron (III) (salen)Cl [36] have also been employed to accomplish this transformation. But many of these methods have the following drawbacks such as use of expensive reagents, longer reaction times, cumbersome workup methods and low yields of products, complicated manipulations along with the involvement of environmentally toxic media, using an excess of solvent and often toxic or hazardous chemicals are employed, in addition to that molecular iodine can catalyse this transformation more efficiently but requires washing of aqueous sodiumthiosulphate in order to decompose iodine, corrosive reagents, large amounts of solid supports which would eventually result in the production of large amounts of toxic waste, and solid acid-catalysts such as zeolite need very high temperature for reactivation.

Microwaves are well known to promote the synthesis of a variety of organic compounds where chemical reactions are accelerated because of selective absorption of microwaves by polar molecules [37]. By conventional heating method, the products are obtained in lower yields and required longer reaction times as compared with microwave irradiation. In continuation of our work on microwave assisted syntheses [38], in this paper cerium chloride heptahydrate ($CeCl_3.7H_2O$) [39], an inexpensive and easily available catalyst has been employed for condensation of indole/2-methylindole with various aldehydes in acetonitrile solvent under microwave irradiation. The described method utilizes less catalyst and solvent and also avoids cumbersome workup procedure.

2. EXPERIMENTAL

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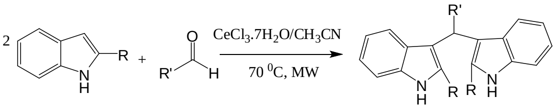
2.1 Materials and methods

The reagents were purchased from Sd-fine, Loba, AVRA, and SRL, India. Aldehydes were purified by distillation and all other reagents were used as-received from commercial sources without further purification. The IR spectra were recorded in the range of 450-4000 cm^{-1} on a Perkin-Elmer FTIR spectrometer using KBr pellet. The ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 400 spectrometer in the indicated solvent. High-resolution mass spectra (HRMS), electron spray ionization (ESI) mode, were obtained on Micro hybrid quadrupole time of flight (Q-Tof)-mass spectrometer.

2.2 General procedure for synthesis of bis(2-methylindolyl)methane derivatives



Where R is H or CH$_3$;R' is alkyl, aryl, substituted aryl, heteroaryl

Scheme 1. Synthesis of bis(2-methylundolyl) methane/bis(indolyl)methane derivatives.

A mixture of 2-methylindole (2 mmol), aldehyde (1 mmol), CeCl$_3$.7H$_2$O (0.5 mmol) and CH$_3$CN (1 ml) was taken in a 10 ml thick-walled glass reaction tube equipped with a magnetic stirrer (Scheme 1). The glass reaction tube was then placed inside a CEM Discover microwave reactor, operated at 70 ^{o}C, power 200 W for 6 min. After the reaction time (monitored by TLC), the reaction mixture was dissolved in dichloromethane, washed with water and the solvent was removed. The crude was purified by recrystallization from ethyl acetate/petroleum ether (1/2) to obtain bis(2-methylindolyl)methanes in 55-96% yields. The products were identified by their IR, HRMS, ^{1}H and ^{13}C NMR spectra.

2.3 General procedure for synthesis of bis (indolyl)methane derivatives.

A mixture of indole (2 mmol), aldehyde (1 mmol), CeCl$_3$.7H$_2$O (0.5 mmol) and CH$_3$CN (1 ml) was taken in a 10 ml thick-walled glass reaction tube equipped with a magnetic stirrer (Scheme 1). The glass reaction tube was then placed inside a CEM Discover microwave reactor, operated at 70 ^{o}C, power 200 W for 6 min. After the reaction time (monitored by TLC), the reaction mixture was dissolved in dichloromethane, washed with water and the solvent was removed. The crude was purified by recrystallization from ethyl acetate/petroleum ether (1/2) to obtain bis(indolyl)methanes in 74-94% yields. The products were identified by their IR, HRMS, ^{1}H and ^{13}C NMR spectra.

2.4 Spectral data for selected compounds

3,3'-Bis(2-methylindolyl)-3-nitrophenyl methane (1c)

IR (KBr): ν 3401, 3380, 3052, 2915, 2851, 1625, 1520, 1456, 1340, 1234, 737, 600 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d$_6$) δ ppm: 2.05 (6H, s, 2×-CH$_3$ on indole), 6.0 (1H, s, Ar-CH), 6.60-7.40 (12H, m, Ar-H), 10.60 (2H, br s, NH); ^{13}C NMR (500 MHz, DMSO-d$_6$) δ ppm: 12.3, 38.6, 111.0, 110.4, 118.6, 120.2, 121.4, 123.3, 128.3, 129.9, 133.0, 135.5, 135.9, 148.2; HRMS (ESI) *m/z*: calcd for $C_{25}H_{21}N_3O_2$ [M$^+$+K] 434.1271, found 434.1280.

2-Chlorophenyl-3,3'-bis(2-methylindolyl) methane (1d)

IR (KBr): ν 3445, 3392, 3054, 2916, 2853, 1743, 1616, 1458, 1341, 1299, 1024, 750, 602 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d$_6$) δ ppm: 2.05 (6H, s, 2×-CH$_3$ on indole), 6.0 (1H, s, Ar-CH), 6.60-8.10 (12H, m, Ar-H), 10.60 (2H, br s, NH); ^{13}C NMR (500 MHz, DMSO-d$_6$) δ ppm: 12.1, 37.2, 110.8, 111.0, 118.2, 118.6, 120.1, 127.1, 128.4, 128.7, 129.7, 131.2, 132.6, 133.9, 135.4, 142.0; HRMS (ESI) *m/z*: calcd for $C_{25}H_{21}N_2Cl$ [M$^+$+K] 423.1030, found 423.1042.

3,3'-Bis(2-methylindolyl)-4-methoxyphenyl methane (1e)

IR (KBr): ν 3403, 3055, 2917, 2843, 1607, 1511, 1459, 1342, 1237, 1025, 740, 602 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d$_6$) δ ppm: 2.05 (6H, s, 2×-CH$_3$ on indole), 3.75 (3H, s, -OCH$_3$), 5.9 (1H, s, Ar-CH), 6.60-7.20 (12H, m, Ar-H), 10.60 (2H, br s, NH); ^{13}C NMR (500 MHz, DMSO-d$_6$) δ ppm: 12.3, 38.2, 55.3, 110.7, 113.0, 113.7, 118.3, 118.9, 119.9, 128.7, 130.0, 132.3, 135.5, 136.6, 157.8; HRMS (ESI) *m/z*: calcd for $C_{26}H_{24}N_2O$ [M$^+$+K] 419.1526, found 419.1520.

3,4-Dihydroxyphenyl-3,3'-bis(2-methylindolyl) methane (1g)

IR (KBr): ν 3403, 3055, 2917, 2854, 1607, 1511, 1459, 1279, 1015, 740, 613 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d$_6$) δ ppm: 2.05 (6H, s, 2×-CH$_3$ on indole), 5.70 (1H, s, Ar-CH), 6.40-7.20 (11H, m, Ar-H), 8.60 (2H, d, -OH), 10.60 (2H, br s, NH); ^{13}C NMR (500 MHz, DMSO-d$_6$) δ ppm: 12.3, 38.3, 110.6, 113.3, 115.5, 116.7, 118.2, 119.0, 119.8, 128.8, 132.2, 135.4, 135.6, 143.5, 145.1; HRMS (ESI) *m/z*: calcd for $C_{25}H_{22}N_2O_2$ [M$^+$+Na] 405.1579, found 405.1570.

2-Furyl-3,3'-bis(2-methylindolyl)methane (1h)

IR (KBr): ν 3403, 3055, 2928, 2854, 1607, 1459, 1215, 1015, 740, 602 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm: 2.14 (6H, s, 2×-CH$_3$ on indole), 5.82 (1H, s, Ar-CH), 6.35-7.60 (11H, m, Ar-H), 10.60 (2H, br s, NH); ^{13}C NMR (400 MHz, DMSO-d$_6$) δ ppm: 11.5, 32.5, 106.8, 110.3, 110.7, 118.0, 119.6, 127.7, 131.7, 134.9, 141.2, 156.9; HRMS

(ESI) *m/z*: calcd for $C_{23}H_{20}N_2O$ [M^++K] 379.1213, found 379.1218.

3,3'-Bis(2-methylindolyl)isobutane (1i)

IR (KBr): ν 3410, 3389, 3051, 2944, 2924, 2860, 1613, 1465, 1243, 1021, 746, 598 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ ppm: 0.9 (6H, d, -$CH(CH_3)_2$), 2.3 (6H, s, 2×-CH_3 on indole), 3.9 (1H, d, Ar-CHCH), 6.80-7.60 (8H, m, Ar-H), 10.60 (2H, br s, NH); ^{13}C NMR (500 MHz, DMSO-d_6) δ ppm: 12.9, 22.8, 30.1, 42.9, 110.7, 113.9, 118.3, 119.4,119.7, 128.1, 131.8, 135.5; HRMS (ESI) *m/z*: calcd for $C_{22}H_{24}N_2$ [M^++K] 355.1577, found 355.1585.

3,3'-Bis(2-methylindolyl)propane (1j)

IR (KBr): ν 3390, 3051, 2956, 2925, 2861, 1614, 1455, 1244, 1011, 737, 599 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ ppm: 0.9 (3H, t, -CH_2-CH_3), 2.25 (6H, s, 2×-CH_3 on indole), 4.2 (1H, t, Ar-CH-CH_2), 6.70-7.40 (8H, m, Ar-H), 10.60 (2H, br s, NH); ^{13}C NMR (500 MHz, DMSO-d_6) δ ppm: 12.8, 27.8, 36.6, 110.7, 110.9, 118.3, 119.6, 120.3, 128.3, 129.1, 131.5, 135.5, 136.5; HRMS (ESI) *m/z*: calcd for $C_{21}H_{22}N_2$ [M^++Na] 325.1681, found 325.1674.

3. RESULTS AND DISCUSSION

As a model reaction, electrophilic substitution reaction between 2-methylindole and benzaldehyde has been studied under microwave irradiation. The reaction has been carried out at three different temperatures in presence of $CeCl_3.7H_2O$ and with different amounts of catalyst to optimize the reaction conditions in order to obtain 3,3'-bis(2-methylindolyl)phenylmethane in high yield (Table 1). The reaction between 2-methylindole and benzaldehyde with 0.25 mmol and 0.50 mmol of $CeCl_3.7H_2O$ by grinding method in the absence of microwaves at room temperature yielded 47 and 55% of the product respectively (entries 2 & 6, Table 1). When the reaction was performed in the absence of solvent at 80 °C after microwave irradiation for 7 min, a yield of 38% (entry 4, Table 1) was observed due to poor interaction between the reactants and catalyst. It is found that 0.5 mmol of $CeCl_3.7H_2O$ catalyses the reaction between 2

Table 1. Optimization of reaction conditions for synthesis of 3,3'-bis(2-methylindolyl) phenylmethane.

Entry	Catalyst	Solvent	Temperature (˚C)	Time (min)	Yield (%)
1	No Catalyst	CH_3CN	70	05	43
2	$CeCl_3.7H_2O$ (0.25 mmol)	No solvent	RT	05	47[a]
3	$CeCl_3.7H_2O$ (0.25 mmol)	CH_3CN	70	06	80
4	$CeCl_3.7H_2O$ (0.25 mmol)	No solvent	80	07	38
5	$CeCl_3.7H_2O$ (0.25 mmol)	CH_3CN	80	05	80
6	$CeCl_3.7H_2O$ (0.5 mmol)	No solvent	RT	05	55[a]
7	$CeCl_3.7H_2O$ (0.5 mmol)	CH_3CN	80	02	68
8	$CeCl_3.7H_2O$ (0.5 mmol)	CH_3CN	70	06	96

Reaction conditions: Molar ratio (2-methylindole: benzaldehyde)= 2:1; a in the absence of microwaves; power: 200W

Table 2. Synthesis of 3,3'-bis(2-methylindolyl)phenylmethane in different solvents.

Entry	Solvent (Boiling point, ˚C)	Dielectric constant	Dielectric loss	Tan δ	Yield (%)
1	C_2H_5OH (78)	24.3	22.866	0.941	87
2	CH_3CN (82)	37.5	2.325	0.062	96
3	n-C_3H_7OH (97)	20.1	15.216	0.757	90
4	H_2O (100)	80.4	9.889	0.123	90

Reaction conditions: Molar ratio (2-methylindole: benzaldehyde)= 2:1; catalyst: CeCl3.7H2O (0.5 mmol); temperature: 70 ˚C; time: 06 min; power: 200W

Table 3. Synthesis of bis(2-methylindolyl)methane derivatives.

Entry	Aldehyde	Product	Yield (%)
1	Benzaldehyde	1a	96[25]
2	4-Hydroxybenzaldehyde	1b	73[13]
3	3-Nitrobenzaldehyde	1c	84[34]
4	2-Chlorobenzaldehyde	1d	81[24]
5	4-Methoxybenzaldehyde	1e	94[34]
6	4-Methylbenzaldehyde	1f	82[25]
7	3,4-Dihydroxybenzaldehyde	1g	81
8	Furan-2-carbaldehyde	1h	93
9	2-Methylpropanal	1i	55
10	Propanal	1j	78

Reaction conditions: Molar ratio (2-methylindole: aldehyde)= 2:1; temperature: 70 ˚C;time: 6 min; catalyst: CeCl3.7H2O (0.5 mmol); solvent: acetonitrile (1 ml)

Table 4. Synthesis of bis(indolyl)methane derivatives.

Entry	Aldehyde	Product	Yield (%)
1	Benzaldehyde	2a	82[25]
2	4-Hydroxybenzaldehyde	2b	77[19]
3	3-Nitrobenzaldehyde	2c	74[19]
4	2-Chlorobenzaldehyde	2d	82/9 min[25]
5	4-Methoxybenzaldehyde	2e	94[25]
6	4-Methylbenzaldehyde	2f	80[25]
7	Furan-2-carbaldehyde	2g	85[25]
8	2-Methylpropanal	2h	75[35]
9	Propanal	2i	84[35]

Reaction conditions: Molar ratio (indole: aldehyde)= 2:1; temperature: 70 ˚C; time: 8 min; catalyst: CeCl .7 H O (0.5 mmol); solvent: acetonitrile (1 ml)

methylindole and benzaldehyde in 1 ml of acetonitrile at 70 ^{o}C (power 200 W) after.microwave irradiation for 6 min to yield 96% of 3,3'-bis(2-methylindolyl)phenylmethane Table 2 shows synthesis of 3,3'-bis(2-methylindolyl) phenylmethane in different solvents with their boiling points, dielectric constants, dielectric loss values and tan δ [40]. The reaction between 2-methylindole and benzaldehyde in presence of $CeCl_3.7H_2O$ was studied at 70 ^{o}C (power 200 W) for 6 min under microwave irradiation in ethanol, acetonitrile, 1-propanol and water (Table 2). It was found that maximum yield was obtained in acetonitrile, a polar aprotic solvent. However, similar yields were obtained in other polar protic solvents, i.e., ethanol, propanol and water. It was also observed that acetonitrile, a polar aprotic solvent, with lower dielectric loss gave the highest product yield under microwave irradiation conditions. Therefore, further reactions were studied in acetonitrile solvent.

To study scope and generality of the reaction, the optimized conditions were extended to the reaction of aryl, heteroaryl and aliphatic aldehydes with 2-methylindole or indole under 200 W microwave power at 70 ^{o}C.The results of electrophilic substitution reaction of 2-methylindole with various aldehydes catalysed by $CeCl_3.7H_2O$ under microwave irradiation after 6 min were shown in Table 3. The bis(2-methylindolyl)methane derivatives were obtained in 55-96 % yield in acetonitrile solvent. It can be seen that the yields in the electrophilic substitution reactions of aliphatic aldehydes were lower compared to those with aromatic aldehydes. This may be attributed to the lower boiling points of aliphatic aldehydes.

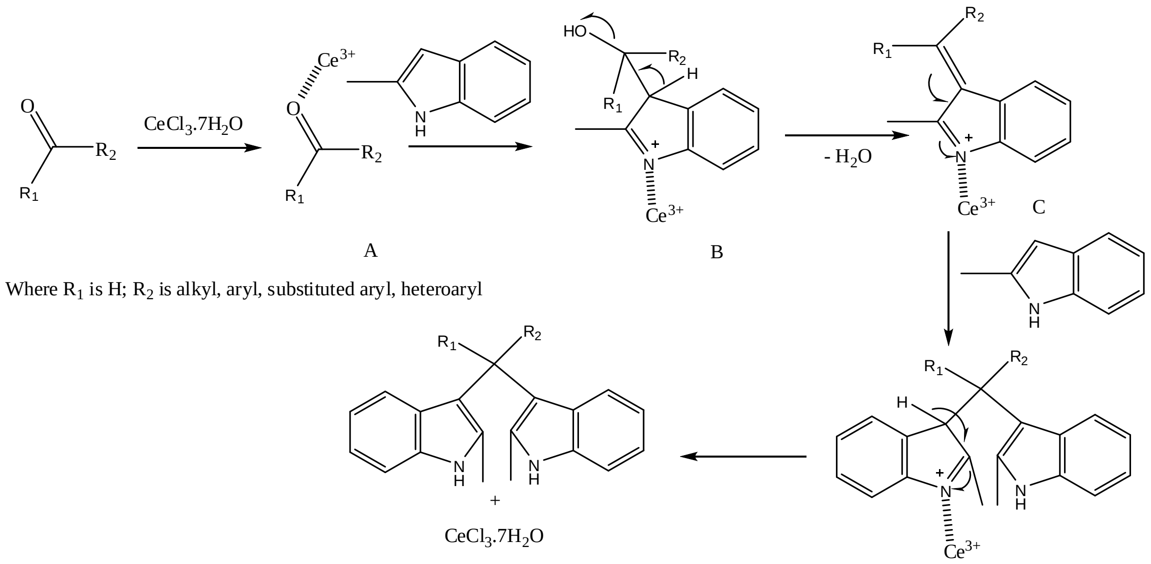
The results of electrophilic substitution reaction of indole with various aldehydes catalyzed by $CeCl_3.7H_2O$ under microwave irradiation after 6-12 min were summarized in Table 4. The bis(indolyl)methane derivatives were obtained in 74-94% yield in acetonitrile solvent. The electrophilic substitution reactions between indole with 2-chlorobenzaldehyde and 3,4-dihydroxybenzaldehyde required 9 and 12 min to obtain corresponding products in 82 and 79% yields respectively.

Mechanism

$CeCl_3.7H_2O$ catalyzes the reaction between 2-methylindole and aldehyde as a mild Lewis acid $CeCl_3.7H_2O$ has (*i*) Ce^{3+} site, which is of Lewis-acid type and (*ii*) O^{2-} site, which is of Lewis-base type. The activation of carbonyls through hydrogen bonding by Lewis acids is known. A possible mechanism for this reaction using $CeCl_3.7H_2O$ is shown in the reaction Scheme 2. The Lewis acid moiety (Ce^{3+}) activates the carbonyl groups to give intermediate **A** and is followed by 2-methylindole attack to **A** to give **B** and loss of H_2O from **B** to afford **C** which is activated by $CeCl_3.7H_2O$. The other 2-methylindole is then added to **C**in the following step to give the final product, bis(2-methylindolyl)methane derivative.

4. CONCLUSIONS

In summary, the electrophilic substitution reaction of indole with aldehydes was successfully carried out in the presence of catalytic amount of $CeCl_3.7H_2O$ in acetonitrile solvent under



Where R_1 is H; R_2 is alkyl, aryl, substituted aryl, heteroaryl

Scheme 2. Possible mechanism for the reaction between 2-methylindole and aldehyde catalyzed by $CeCl_3.7H_2O$

microwave irradiation. This method is simple, convenient and environmentally friendly. This method offers several significant advantages, such as high conversions, easy handling, cleaner reaction profile, shorter reaction times and also $CeCl_3.7H_2O$ is a readily available cheap and safe catalyst which makes it a useful and attractive process for the rapid synthesis of indole derivatives. The reaction conditions were mild and the products were obtained in good to excellent yields.

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