A FACILE AND EFFICIENT METHOD FOR THE SYNTHESIS OF BIS(INDOLYL)METHANES CATALYZED BY SELECTFLUOR™ UNDER CONVENTIONAL HEATING AND MICROWAVE IRRADIATION

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Abstract: Electrophilic substitution reaction of indoles with different aldehydes was carried out using selectfluor™ as a catalyst which was resulted in the formation of bis (indolyl) methanes in good to excellent yields (72-96%). The desired products were obtained by both conventional heating and microwave irradiation under solvent-free conditions.
Keywords: Indoles, aldehydes, bis(indolyl)methanes, selectfluor™, conventional heating and microwave irradiation.

Introduction

Indole and its myriad derivatives have captured the attention of synthetic organic chemists and the investigation of these derivatives continues because of their significant contributions as therapeutic agents(1-2). During the past few years a large number of natural products containing bis(indolyl)methanes(3), bis(indolyl)ethanes(4) have been isolated from marine sources and some of these exhibited interesting biological properties. Therefore, such molecules have been very interesting targets for synthetic organic chemists. Several methods have been reported for the synthesis of bis(indolyl)methanes such as the reaction of indole with aromatic or aliphatic aldehydes and ketones resulting in the formation of azafulvenium salts, which further undergo addition of second molecule of indole to afford bis(indolyl)methanes(5).

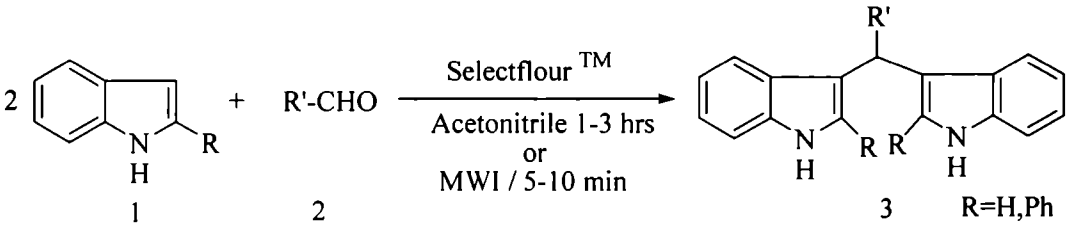
In addition protic acids as well as Lewis acids are known to promote these reactions(6-8). Several catalysts such as lanthanide triflates(9a), sulfamic acid(9b), $In(OTf)_3$(9c), I_2(9d), $CeCl_3.7H_2O.NaI$-SiO_2(9e), HY-Zeolite(9f), amberlyte(9g) and ionic liquids(9h) are also found to catalyze these reactions. However, these catalysts still need activation before use. New promoters with low toxicity, moisture and air tolerance, and low cost continue to merit exploration.

Recently, selectfluor™ [chloromethyl-4-fluoro-1, 4-diazoniabicyclo [*2.2.2*] octane bis(tetrafluoroborate)] has been introduced commercially as a user-friendly electrophilic fluorinating agent. It is readily available at low cost and used as an excellent deprotection

reagent for the *p*-methoxybenzylidene (PMP), tetrahydropyranyl (THP) and dithiane groups due to its Lewis acidity (10). It also fluorinates a variety of electron-rich carbon centers with high yields(11). However, there are no reports on the use of selectfour™ as a catalyst for the one-pot synthesis of bis(indolyl)methanes. Herein, we report the use of selectfour™ as an efficient catalyst for the preparation bis(indolyl)methanes by electrophilic substitution of indole with aldehydes in solution as well as microwave irradiation.

Results and Discussion

Initially, we studied the reaction of indole (entry 1, 1a) with 4-(methylthio) benzaldehyde **2a** in the presence of selectfluor™ (5 mol %) in acetonitrile at ambient temperature, the 90% conversion of bis(indolyl)methanes **3a** was observed in 3 hrs (scheme-1).



Scheme-1

Encouraged by these results, we examined various aldehydes and indoles (R=H, Ph) under optimized conditions (Table 1). The above reaction was carried out in different solvents like tetrahydrofuran, toluene, methylene chloride and methanol which yielded 62%, 70%, 68% and 72 % respectively. Among the different solvents investigated acetonitrile was found to be the best in terms of yield (92%) and quality. Furthermore, the use of 5 mol% of selectfluor™ is enough to promote the reaction. There are no improvements in reaction rates and yields by increasing the amount of catalyst from 5 mol% to 10 mol%.

Moreover, application of microwave irradiation has opened a new prospective in synthetic organic chemistry, not only in terms of high yields and selectivity, but also ease of the reaction conditions and rate of acceleration(12). Hence, microwaves have been applied to accelerate reaction rate for a wide variety of chemical transformations and also to improve the yields in most cases. Along this line it was observed that, when a mixture of 2-phenyl indole **1** and 4-(methylthio)benzaldehyde **2e** was irradiated in a microwave (600 W) in the presence of selectfluor™ (5 mol %), the reaction went to completion within 6 min with an excellent yield (96 %). The same reaction was extended to indole and 2-phenyl indole **1** with different aromatic aldehydes **2a-m** in the presence of selectfluor™ (5 mol %) under microwave irradiation conditions to afford corresponding bis(indolyl) methanes **3a-m**. All the reactions were completed in a short time (5-10 min) with excellent yields and these results are summarized in Table 1.

To summarize, the reactions between substituted indoles and various aromatic aldehydes in the presence of selectfluor™ as catalyst were carried out under microwave irradiation as well as conventional reflux conditions. The reaction rates and the product yields under

both the conditions were compared and it was found that the reaction rates and yields were dramatically enhanced by microwave irradiation. All the products were characterized by MR, IR, ^{1}H NMR, ^{13}C NMR and mass spectral data and were also compared with authentic samples.

Table 1. Selectfluor ^{TM} catalyzed one pot synthesis of bis (indolyl) methanes.

Entry	Indole 1(R)	Aldehydes 2 (R')	Product 3	Method A		Method B	
				Time (hr)	Yield[a] (%)	Time (min)	Yield[a] (%)
1	H	4-SCH_3-C_6H_4	3a	3	92	5	96
2	H	C_6H_5	3b	2	85	6	94
3	H	4-OCH_3-C_6H_4	3c	3	72	5	92
4	H	2-NO_2-C_6H_4	3d	3.5	80	10	88
5	Ph	4-SCH_3-C_6H_4	3e	4.5	88	6	96
6	Ph	4-F-C_6H_4	3f	4	90	5	93
7	Ph	C_6H_5	3g	4.5	85	8	92
8	Ph	3-Cl-C_6H_4	3h	5	75	5	94
9	Ph	4-OH-C_6H_4	3i	4	78	9	92
10	Ph	4-Cl-C_6H_4	3j	3.5	82	5	95
11	Ph	2,4-Cl_2-C_6H_3	3k	3	80	7	88
12	Ph	2-Cl-C_6H_4	3l	5	85	6	85
13	Ph	4-OCH_3-C_6H_4	3m	4.5	86	9	94

[a] Isolated yields.

Conclusions

In summary, the paper describes a facile synthesis of bis (indolyl) methanes using selectfluor^{TM} under conventional as well as microwave irradiation. The microwave

irradiation method offers several advantages including high yields of products very short reaction times , inexpensive catalyst and ease isolation of products , which makes the reaction process convenient more economic and environmental benign.

Experimental

Microwave irradiation was carried out in (SANYO EM-350S model). The infrared spectra were recorded on a Nicolet impact – 410 FTIR spectrometer using KBr pellet technique. The NMR spectra were recorded on a Varian 300 MHz spectrometer with TMS as an inernal standard and chemical shifts are reported in ppm, where as electron impact mass spectra (EIMS) were recorded on a MI Ver.14 on UIC 002002 EI-70 eV spectrometer and elemental analysis carried out in Heraeus CHN rapid analyzer. Finally melting points were determined by the open capillary method and are uncorrected.

General Procedure:

Conventional method (method A): A mixture of indole (2 mol), aldehyde (1 mol) and selectflour^{TM} (5 mol %) was refluxed in acetonitrile (15ml) for an appropriate time as mentioned in the table 1. The progress of the reaction was monitored by TLC and at the completion, the solvent was removed in vacuo to yield the crude product, the obtained solid was washed with water and it was further purified by flash column chromatography on silica gel eluting with EtOAc/ Hexanes: 2/8 to obtain the desired product in the pure form.

Microwave irradiation method (method B): To a mixture of aldehyde (1 mol) and β-naphthol (2 mol), selectflour^{TM} (5mol %) was added and the mixture was inserted in a microwave oven (SANYO EM-350S model). The reaction mixture was heated at 600W for the appropriate time as mentioned in the table1. The progress of the reaction was monitored by TLC and at the completion, the catalyst was removed by adding water and filtered the crude product. This was further purified by flash column chromatography on silica gel eluting with EtOAc/ Hexanes: 2/8, to obtain the desired product in the pure form.

Spectral data of the following compounds:

3a. mp 108-110°C; IR (KBr, cm^{-1}): 3410, 1630, 1382, 730, 680; ^1H NMR (300 MHz, $CDCl_3$): δ 2.41 (s, 3H, SCH_3), 5.92 (s, 1H, CH), 6.66 (s, 2H, CH 2-indole), 7.05-7.40 (m, 12H, ArH), 8.10 (broad, 2H, NH indole); EIMS *m/z* (M^+): 368; Anal.Calcd. $C_{24}H_{20}N_2S$: C 78.23, H 5.47, N 7.60; Found: C 78.25, H 5.45, N 7.64.

3b. m.p. 149-150°C; IR (KBr, cm^{-1}): 3520, 1780, 1480, 830. 750; ^1H NMR (300 MHz, $CDCl_3$): δ 6.13 (s, 1H, CH), 6.50 (s, 2H, CH 2-indole), 6.90-7.61 (m, 13H, ArH), 8.55 (broad, 2H, NH indole); EIMS m/z (M^+): 322; Anal.Calcd. $C_{23}H_{18}N_2$: C 85.68, H 5.63, N 8.69; Found: C 85.66, H 5.65, N 8.66.

3c. m.p. 102-104 °C; IR (KBr, cm^{-1}): 3360, 1605, 1345, 715; ^1H NMR (300 MHz, $CDCl_3$): δ 3.82 (s, 3H, OCH_3), 6.12 (s, 1H, CH), 6.23 (s, 2H, CH 2-indole), 7.15-7.60 (m, 12H, ArH), 9.20 (broad, 2H indole); EIMS: m/z (M^+): 352; Anal.Calcd. $C_{24}H_{20}N_2O$: C 81.79, H 5.72, N 7.95; Found: C 81.82, H 5.70, N 7.92.

3d. m.p. 215-217 °C; IR (KBr, cm^{-1}): 3315, 1612, 1582, 1230, 712; ^1H NMR (300 MHz, DMSO-d_6): δ 6.22 (s, 1H, CH), 6.43 (s, 2H, CH 2-indole), 6.88-7.53 (m, 12H, ArH), 8.10 (broad, 2H, indole); EIMS: m/z (M^+): 367; Anal.Calcd. $C_{23}H_{17}N_3O_2$: C 75.19, H 4.66, N

11.44; Found: C 75.21, H 4.63, N 11.42.

3e. m.p. 205-207 °C; IR (KBr, cm^{-1}): 3412, 1629, 1350, 735, 446, 1424; ^1H NMR (300 MHz, $CDCl_3$): δ 2.39 (s, 3H, SCH_3), 6.06 (s, 1H, CH), 6.81-7.34 (m, 22H, ArH), 8.06 (broad, 2H, indole); ^{13}C NMR (300 MHz, $CDCl_3$): δ 39.3, 110.9, 114.4, 114.8, 118.9, 121.1, 121.2, 127.11, 128.0, 128.27, 130.4, 130.5, 133.0, 135.5, 136.2, 141.0, 158.6, 163.4; EIMS m/z (M^+):520; Anal.Calcd. $C_{36}H_{28}N_2S$: C 83.04, H 5.42, N 5.38; Found: C 83.00, H 5.44, N 5.40.

3f. mp 190-192°C; IR (KBr, cm^{-1}): 3342, 3313, 2939, 1715, 1543, 1520, 1415; ^1H NMR (300 MHz, $CDCl_3$): δ 2.46 (s, 3H,SCH_3), 6.05(s,1H,CH), 6.20-7.33(m, 22H, ArH), 8.03 (Broad, 2H, NH indole); ^{13}C NMR (300 MHz, $CDCl_3$): 44.7, 82.4, 82.8, 83.3, 116.3, 119.9, 124.0, 125.2, 126.7, 131.5, 132.3, 133.3, 133.6, 133.7, 134.9, 138.4, 140.2, 140.9, 141.6, 147.8; EIMS m/z (M^+): 492; Anal.Calcd. $C_{35}H_{25}FN_2$: C 85.34, H 5.12, N 5.69; Found: C 85.36, H 5.15, N 5.67.

3g. mp 253-255 °C; IR (KBr, cm^{-1}): 3569, 3422, 3056, 3019, 2366, 2342, 1598, 1486, 1456, 1446, 1306, 1156; ^{1}HNMR (300 MHz, $CDCl_3$): δ 6.08 (s, 1H, CH), 6.73-7.49 (m, 23H, ArH), 11.42 (Broad, 2H, NH indole); ^{13}C NMR (300 MHz, $CDCl_3$): δ 40.4, 111.8, 119.0, 121.3, 126.4, 127.6, 128.5, 128.7, 129.2, 133.2, 135.8, 136.8, 145.9; EIMS m/z (M^+): 474; Anal.Calcd. $C_{35}H_{26}N_2$: C 88.58, H 5.52, N 5.90; Found: C 88.60, H 5.50, N 5.92

3h. mp 194-196 °C; IR (KBr, cm^{-1}): 3409, 3054, 2923, 1582, 1430, 1331,742. ^1H NMR (300 MHz, $CDCl_3$): δ 5.98 (s, 1H, CH), 6.70-7.41(m, 22H, ArH), 11.42 (broad, 2H, NH indole).^{13}C NMR (300 MHz, $CDCl_3$): δ 39.6, 112.4, 114.1, 119.6, 121.3, 121.9, 127.0, 128.3, 128.4, 128.7, 129.0, 129.1, 129.2, 131.1, 133.4, 133.9, 136.5, 137.1, 143.0. EIMS: m/z (M^+): 509; Anal.Calcd $C_{35}H_{25}ClN_2$: C 82.58, H 4.95, N 5.50; Found: C 82.60, H 4.92, N 5.52.

3i. mp 226-228 °C; IR (KBr, cm^{-1}): 3405, 3321, 3011, 1588, 1465, 1201, 1023. . ^1H NMR (300 MHz, DMSO-d_6): δ 5.94 (s, 1H, CH), 6.64-7.32 (m, 22H, ArH), 8.33 (broad, 1H, NH indole), 9.50 (broad, 2H, Ar-OH). ^{13}C NMR (300 MHz, $CDCl_3$): 39.1, 110.7, 115.1, 115.6, 115.9, 118.7, 120.9, 121.6, 126.9, 128.0, 128.2, 128.7, 129.9, 133.1, 135.2, 136.1, 154.9; EIMS: m/z (M^+): 490; Anal.Calcd $C_{35}H_{26}N_2O$: C 85.69, H 5.34, N 5.71; Found: C 85.66, H 5.36, N 5.73.

3j. mp 212-214 °C; IR (KBr, cm^{-1}): 3320, 1655, 1450, 1317 730. . ^1H NMR (300 MHz, $CDCl_3$): δ 5.31(s, 1H, CH), 6.04-7.99 (m, 22H, ArH), 9.90(broad, 2H, NH indole). ^{13}C NMR(300Mz,$CDCl_3$):
39.9,111.5,114.8,119.4,121.6,121.7,127.6,128.5,128.8,131.0,131.6,133.5,136.2,136.7,144.5; EIMS: m/z (M^+): 508; Anal.Calcd $C_{35}H_{25}ClN_2$ C 82.58, H 4.95, N 5.50; Found: C 82.62, H 4.92, N 5.53.

3k. mp 269-271 °C; IR (KBr, cm^{-1}): 3388, 3122, 2965, 1534, 1244, 1098, 854. . ^1H NMR (300 MHz, DMSO-d_6): δ 6.2(s, 1H, CH), 6.75-7.50 (m, 21H, ArH), 9.47(broad, 2H, NH indole). ^{13}CNMR (300Mz, , DMSO- d_6): 38.1,110.9,113.1, 119.1,120.2,121.1,126.4,127.1,127.9,128.2,128.6,129.1,132.2,132.4,132.9,134.8,136.0,141.3; EIMS: m/z (M^+): 542; Anal.Calcd: $C_{35}H_{24}Cl_2N_2$ C 77.35, H 4.45, N 5.15; Found: C 77.32, H 4.48, N 5.17.

3l. mp 232-234 °C; IR (KBr, cm^{-1}): 3124, 2934, 1755, 1478, 1190, 1056. ^1H NMR (300 MHz, $CDCl_3$): δ 6.12(s, 1H, CH), 6.70-7.55 (m, 22H, ArH), 11.36 (broad, 2H, NH indole); ^{13}C NMR (300 MHz, $CDCl_3$): 39.9, 111.1, 120.2, 121.0, 122.1, 127.1,

128.0, 128.5, 128.7, 129.0, 129.2, 130.2, 133.2, 136.2, 144.9; EIMS: m/z (M^+): 508; Anal.Calcd: $C_{35}H_{25}ClN_2$ C 82.58, H 4.95, N 5.50; Found: C 82.61, H 4.89, N 5.54.
3m. mp 201-203 °C; IR (KBr, cm^{-1}): 3278, 3045, 1632, 1322, 1265, 1067. ^1H NMR (300 MHz, DMSO-d_6): δ 3.97 (s, 3H, OCH_3), 6.05 (s, 1H, CH), 6.77-7.32 (m, 22H, ArH), 8.05 (broad, 2H, NH indole). EIMS: m/z (M^+): 504; Anal.Calcd: $C_{36}H_{28}N_2O$: C 85.69, H 5.59, N 5.55; Found: C 85.72, H 5.57, N 5.57.

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