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Fe^{+3}-Montmorillonite K10, as Effective, Eco-Friendly, and Reusable Catalyst for the Synthesis of Bis(1*H*-indol-3-yl)methanes under Grinding Condition[1]

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Abstract—Bis(indoyl)methanes have been synthesized via electrophilic reaction of indole and aldehydes in excellent yields under mild reaction conditions in the presence of Fe^{+3}-montmorillonite K10 as catalyst. The catalyst can be recovered and recycled in subsequent reactions without any apparent loss of activity.

Keywords: diindolylmethanes, Fe^{+3}-montmorillonite K10, grind, reusable

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INTRODUCTION

Diindolylmethane (DIM) [or bis(indolyl)methane] is the most active cruciferous substance for promoting beneficial estrogen metabolism in women and men [1]. DIM increases the body's natural metabolism of hormones and promotes good estrogen (2-hydroxy-estrogen) [1]. This indole antioxidant is patented for alleviating symptoms of fibromyalgia [1]. DIM is an effective cancer prevention agent owing to its ability to modulate certain cancer-causing estrogen metabolites [1]. Scientists have demonstrated that DIM induces the apoptosis in human cancer cells [2] and may also normalize abnormal cell growth associated with cervical dysplasia [3]. DIM is proven to have significant physiological activity [4] and may be successfully applied for preventation of breast cancer [5]. Therefore, indole and its derivatives have been a topic of research interest.

Numerous methods of the preparation of bis-indolylmethanes have been reported in the literature employing protic [6] and Lewis acids, such as $LiClO_4$ [7], $InCl_3$ [8], lanthanide triflates [9], NBS [10], I_2 [11], $KHSO_4$ [12], montmorillonite K10 [13], HY-zeolite [14], $[RE(PFO)_3]$ [15], $NaHSO_4$/amberlyst-15 [16], $CuBr_2$ [17], sulfamic acid [18–20], and $ZrCl_4$ [21].

However, several of the reported protocols suffer from significant practical limitations, such as the use of expensive reagents, long reaction time, low yield of the products, and the use of microwave or ultrasonic apparatus, which are not always available in organic chemistry laboratories. Consequently, new procedures free from the above drawbacks are desirable.

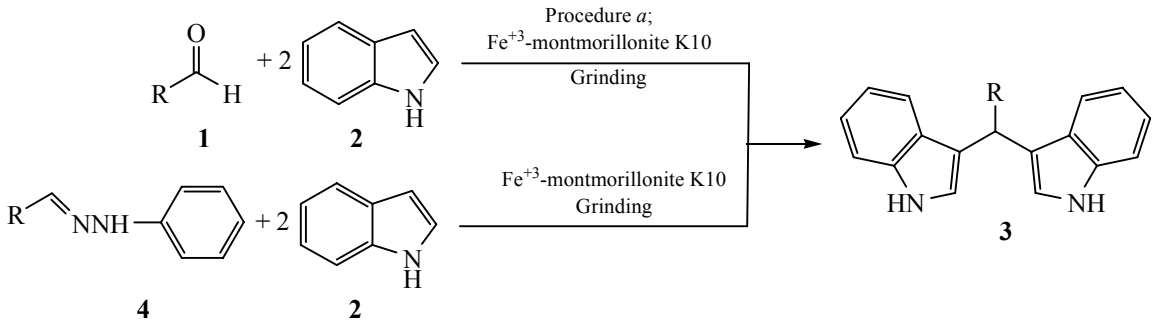
RESULTS AND DISCUSSION

In continuation of our ongoing studies on the synthesis of heterocyclic and pharmaceutical compounds at mild and practical protocols [22–26], we report herein our experimental results obtained in synthesizing diindolylmethanes by the electrophilic reaction of indole and various substituted aldehydes under solvent-free (grinding) conditions (Scheme 1). To the best of our knowledge, data on the synthesis of diindolylmethanes in the presence of Fe^{+3}-montmorillonite K10 under the grinding conditions are lacking from the literature.

In an initial endeavor, 1a, 2 equiv. of indole **2** and Fe^{+3}-montmorillonite K10 (Fe^{+3}–K10) were pulverized with a pestle. After 4 min, 94% of the product was obtained. The reaction was performed in the presence of various aldehydes and the scope and generality of this promoter was determined. To improve the reaction efficiency, hydrazone **4a**, 2 equiv. of indole **2**, and Fe^{+3}–K10 were pulverized with a pestle. The progress

[1] The text was submitted by the authors in English.

Scheme 1. Synthesis of diindolylmethanes in the presence of Fe^{+3}-montmorillonite K10 under grinding conditions.



of a reaction was monitored by thin-layer chromatography (TLC). After 0.5 min of reaction, 98% of the product was obtained. The results are summarized in Table 1.

On the other hand, the synthesis of diindolylmethanes from hydrazone gave shorter reaction time and higher yield than the synthesis from aldehyde. It seems that the conversion of aldehyde to hydrazone assists nucleophilic addition of indoles to aldehyde.

The efficiency of Fe^{+3}-montmorillonite K10 in the synthesis of diindolylmethanes under the grinding conditions (time, yield, and reaction conditions) is given in

Table 1. Grinding-mediated synthesis of diindolylmethanes using Fe^{+3}-montmorillonite K10

Product[a]	Aldehyde	Procedure *a*		Procedure *b*		mp, °C	
		time, min	yield, %[b]	time, min	yield, %[b]	found	calculated
3a	Benzaldehyde	4	94	0.50	98	122–123	125–127 [27a]
3b	4-Nitrobenzaldehyde	2	96	0.33	99	219–221	220–222 [27b]
3c	4-Clorobenzaldehyde	2	95	0.33	97	75–77	77–81 [27b]
3d	4-Hydroxybenzaldehyde	6	92	1.00	94	120–122	120–122 [21]
3e	2- Hydroxybenzaldehyde	8	89	1.50	93	103–105	–
3f	4-Methylbenzaldehyde	6	90	2.00	94	93–94	94–96 [27c]
3g	4-Bromobenzaldehyde	2	94	0.33	96	111–113	110–112 [27d]
3h	4-Fluorobenzaldehyde	2	94	0.33	95	73–74	–
3i	2-Methoxybenzaldehyde	8	87	2.00	92	133–134	134–136 [21]
3j	3- Nitrobenzaldehyde	4	93	0.33	95	266–267	265–266 [27a]
3k	2,4-diClorobenzaldehyde	5	94	0.33	96	100–102	103–105 [21]
3l	Cinnamaldehyde	8	90	2.00	93	94–96	96–98 [21]
3m	*N,N*-diMethylbenzaldehyde	5	91	2.00	94	211–213	210–212 [27d]
3n	Pentanal	2	89	1.00	94	68–70	67–69 [21]
3o	Pyridinecarbaldehyde	5	91	2.50	93	90–91	–
3p	2-Thiophenecarbaldehyde	5	90	1.00	95	185–186	185–188 [27d]

[a] All products were characterized by their physical constant, comparison with authentic samples, and by IR and NMR spectroscopies.
[b] Yields are given for the case of aldehyde.

Table 2. The efficiency of Fe^{+3}-montmorillonite K10 and other catalysts

Catalyst	Condition	Time, min	Yield, %	References
[bmim]BF_4	Room temperature	270	90	[28]
Zeokarb-225	Room temperature	450	95	[29]
Zeolite	Room temperature	120	80	[1]
$HClO_4$–SiO_2	Room temperature	2	94	[30]
$H_3PMo_{12}O_{40}$	Room temperature	19	93	[31]
Schiff Base complex	Reflux	5	92	[32]
Fe^{+3}–K10	Procedure *a*, grinding	4	94	This work
Fe^{+3}–K10	Procedure *b*, grinding	0.5	98	This work

Table 2, as compared with the efficiency of other catalysts. It is clear from Table 2 that our method is simpler, more efficient, and takes less time.

In addition to the simplicity and excellent results, the significant advantage of the process is the simplicity of the product isolation, solvent-free conditions instead of the use of a carcinogenic solvent, and the possibility to recycle Fe^{+3}-montmorillonite K10. After the reaction was complete, the product was easily extracted by $CHCl_3$. The catalyst was washed with $CHCl_3$/acetone and activated at 120°C. The recycled catalyst was examined in the next run. Studying the synthesis of **3a,** as model substrate, showed that the recovered catalyst could be successively recycled in six runs, with the yield preserved.

EXPERIMENTAL

Materials and measurements. The melting points were measured on an Electrothermal 9100 apparatus. IR spectra were determined on a Shimadzu IR-470 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX-500 Avance spectrometer. We used DMSO-d_6 or $CDCl_3$ as solvent and TMS as internal standard. Chemicals were purchased from Merck and Fluka. All solvents used were dried and distilled, according to the standard procedures. All yields refer to isolated products.

General procedure for the preparation of diindolylmethanes. Into a mortar, substituted benzaldehyde **1** (1 mmol) or substituted hydrazone 4 (1 mmol), indole **2** (2 mmol, 0.28 g), and Fe^{+3}-montmorillonite K10 (0.1 g) were added. The mixture was pulverized with a pestle and entered a spontaneous reaction. The progress of a reaction was monitored by thin-layer chromatography (TLC) using EtOAc: petroleum ether (2 : 1) as eluent. The conditions of the reaction are given in Table 2. After the reaction was complete, the product was extracted with $CHCl_3$ (3 × 10 mL) and insoluble catalyst was removed by filtration. The resulting crude material was purified by recrystallization from EtOH to obtain pure products. All synthesized compounds are unknown and were characterized by their physical constants, comparison with authentic samples, IR, ^{1}H NMR, and ^{13}C NMR spectroscopies, and by elemental analysis.

3,3'-[(Phenyl)methylene]bis(1*H*-indole) (3a). mp 122–123°C, IR spectrum (KBr), ν, cm^{-1}: 3396, 3049, 2867, 1602, 1537, 1450, 1338. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ_H, ppm: 5.93 s (1H), 6.73 s (2H), 7.10–7.37 m (12H), 7.57–7.60 m (1H), 7.95 br.s (2H). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ_C, ppm: 33.7, 112.1, 112.9, 116.7, 118.9, 122.2, 125.6, 127.3, 127.8, 129.6, 132.8, 139.0, 146.7. Calculated, %. C 85.68; H 5.63; N 8.69. $C_{23}H_{18}N_2$. Found, %: C 85.65; H 5.74; N 8.66.

3,3'-[(4-Nitrophenyl)methylene]bis(1*H*-indole) (3b). mp 219–221°C, IR spectrum (KBr), ν, cm^{-1}: 3390, 3058, 2856, 1652, 1558, 1506, 1338. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ_H, ppm: 6.01 s (1H), 6.70 d.d (2H, J = 0.8 Hz, J = 2.4 Hz), 7.05 t (2H, J = 8 Hz), 7.22 t (2H, J = 7.2 Hz), 7.36 d (2H, J = 7.6 Hz), 7.41 d (2H, J = 7.6 Hz), 7.52 d (2H, J = 8.4 Hz), 8.04 br.s (2H, NH), 8.12 d (2H, J = 8 Hz). ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ_C, ppm: 32.3, 111.8, 114.6, 117.6, 121.8, 123.8, 124.4, 126.3, 127.0, 132.6, 136.2, 146.2, 148.5. Calculated, %: C 75.19; H 4.66; N 11.44. $C_{23}H_{18}N_2$. $C_{23}H_{17}N_3O_2$ Found, %: C 75.28; H 4.51; N 11.60.

3,3'-[(4-Chlorophenyl)methylene]bis(1*H*-indole) (3c). mp 75–77°C; IR spectrum (KBr), ν, cm^{-1}: 3404, 3049, 2966, 1616, 1560, 1485, 1452. ^1H NMR spectrum (400 MHz, $CDCl_3$), δ_H, ppm: 5.88 s (1H), 6.66 d.d (2H, *J* = 1.2 Hz, *J* = 2.4 Hz), 7.03 t (2H, *J* = 7.2 Hz), 7.20 t (2H, *J* = 8.0 Hz), 7.24–7.37 m (2H), 7.30 d (2H, *J* = 2.0 Hz), 7.38 d (4H, *J* =7.6 Hz), 7.96 br.s (2H). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ_C, ppm: 33.2, 109.4, 115.3, 117.2, 118.4, 119.1, 121.0, 121.9, 124.5, 127.8, 129.1, 135.6, 147.1. Calculated, %: C 77.41; H 4.80; N 7.85. $C_{23}H_{17}ClN_2$. Found, %: C 77.48; H 4.81; N 7.78.

3,3'-[(4-Hydroxyphenyl)methylene]bis(1*H*-indole) (3d). mp 120–122°C; IR spectrum (KBr), ν, cm^{-1}: 3406, 3051, 2935, 1649, 1595, 1452, 1338, 1211. ^1H NMR spectrum (400 MHz, $CDCl_3$), δ_H, ppm: 5.67 s (1H), 6.54–6.79 m (4H), 7.23 d (2H, *J* = 7.5 Hz), 7.56 d (2H, *J* = 7.5 Hz), 8.04–8.23 m (2H), 8.31 t (2H, *J* = 7.8 Hz), 7.37 d (2H, *J* = 7.6 Hz), 7.93 br.s (2H, NH), 9.35 br.s (1H, OH). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ_C, ppm: 31.5, 112.1, 112.7, 115.3, 116.1, 118.8, 124.2, 125.6, 127.8, 128.9, 134.2, 143.6, 147.1. Calculated, %: C 81.63; H 5.36; N 8.28. $C_{23}H_{18}N_2O$. Found, %: C 81.48; H 5.31; N 8.22.

3,3'-[(2-Hydroxyphenyl)methylene]bis(1*H*-indole) (3e). mp 103–105°C. IR spectrum (KBr), ν, cm^{-1}: 3406, 3051, 2935, 1649, 1595, 1452, 1338, 1211. ^1H NMR spectrum (400 MHz, $CDCl_3$), δ_H, ppm: 6.24 s (1H), 6.87 d (2H, *J* = 8.5 Hz), 6.90 d (2H, *J* = 8.5 Hz), 7.52–7.71 m (10H), 7.92 br.s (2H, NH), 9.45 br.s (1H, OH). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ_C, ppm: 36.2, 109.8, 113.2, 115.4, 125.2, 125.7, 127.1, 127.8, 129.3, 131.0, 132.8, 133.1, 137.4, 145.1, 146.9. Calculated, %: C 81.63; H 5.36; N 8.28. $C_{23}H_{18}N_2O$. Found, %: C 81.62; H 5.30; N 8.24.

3,3'-[(4-Methylphenyl)methylene]bis(1*H*-indole) (3f). mp 93–94°C. IR spectrum (KBr), ν, cm^{-1}: 3402, 3046, 2910, 1616, 1506, 1456, 1338, 1218. ^1H NMR spectrum (400 MHz, $CDCl_3$), δ_H, ppm: 2.32 s (3H), 5.65 s (1H), 6.54–6.78 m (12H), 7.67 d (2H, *J* = 8.2 Hz), 7.98 br.s (2H, NH). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ_C, ppm: 24.7, 32.3, 111.3, 111.7, 116.4, 117.2, 121.6, 123.8, 125.7, 129.0, 129.9, 131.2, 135.7, 145.6. Calculated, %: C 85.68; H 5.99; N 8.33. $C_{24}H_{20}N_2$. Found, %: C 85.55; H 5.88; N 8.24.

3,3'-[(4-Bromophenyl)methylene]bis(1*H*-indole) (3g). mp 111–113°C. IR spectrum (KBr), ν, cm^{-1}: 3402, 3040, 2960, 1616, 1540, 1480, 1446, 1338. ^1H NMR spectrum (400 MHz, $CDCl_3$), δ_H, ppm: 5.54 s (1H), 6.46-6.78 m (4H), 7.02–7.45 m (10H), 7.56 br.s (2H, NH). ^{13}C NMR (100 MHz, $CDCl_3$), δ_C, ppm: 35.2, 109.5, 111.2, 119.1, 119.9, 123.2, 125.8, 126.1, 126.8, 129.1, 132.9, 135.4, 145.1. Calculated, %: C 68.84; H 4.27; N 6.98. $C_{23}H_{17}BrN_2$. Found, %: C 68.85; H 4.23; N 6.95.

3,3'-[(4-Fluorophenyl)methylene]bis(1*H*-indole) (3h). mp 73–74°C. IR spectrum (KBr), ν, cm^{-1}: 3440, 3060, 2902, 1600, 1500, 1476, 1454, 1344. ^1H NMR spectrum (400 MHz, $CDCl_3$), δ_H, ppm: 5.61 s (1H), 7.72 d (2H, *J* = 7.8 Hz), 7.90 br.s (2H, NH), 8.15–8.25 m (10H), 8.36 d (2H, *J* = 7.8 Hz). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ_C, ppm: 32.8, 111.2, 112.4, 115.1, 115.9, 123.6, 124.2, 127.8, 128.2, 129.5, 133.4, 137.9, 145.0. Calculated, %: C 68.84; H 4.27; N 6.98. $C_{23}H_{17}BrN_2$. Found, %: C 68.85; H 4.23; N 6.95.

3,3'-[(2-Methoxyphenyl)methylene]bis(1*H*-indole) (3i). mp 134–136°C. IR spectrum (KBr), ν, cm^{-1}: 3410, 3063, 1512, 1432, 1256, 1109. ^1H NMR spectrum (400 MHz, $CDCl_3$), δ_H, ppm: 3.32 s (3H), 6.54 s (1H), 6.87 d (2H, *J* = 7.8 Hz), 7.27–7.56 m (12H), 7.92 br.s (2H, NH). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ_C, ppm: 37.0, 59.6, 110.2, 115.4, 118.0, 121.4, 123.7, 126.9, 127.0, 129.0, 129.9, 133.1, 135.2, 139.8, 143.2, 146.2. Calculated, %: C 81.79; H 5.72; N 7.95. $C_{24}H_{20}N_2O$. Found, %: C 81.85; H 5.76; N 7.99.

3,3'-[(3-Nitrophenyl)methylene]bis(1*H*-indole) (3j). mp 266–267°C. IR spectrum (KBr), ν, cm^{-1}: 3346, 3036, 2948, 1530, 1458, 1355, 1132. ^1H NMR spectrum (400 MHz, $CDCl_3$), δ_H, ppm: 6.25 s (1H), 6.67 t (2H, *J* = 7.6 Hz), 7.17 t (2H, *J* = 7.5 Hz), 7.32–7.56 m (6H), 7.87 d (2H, *J* = 7.7 Hz), 8.02 br.s (2H, NH), 8.13 t (1H, *J* = 1.3 Hz), 8.26 t (1H, *J* = 1.8 Hz). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ_C, ppm: 38.1, 111.8, 117.6, 119.0, 119.5, 121.1, 123.7, 124.7, 125.2, 128.9, 131.5, 135.2, 138.2, 143.1, 147.2, 149.9. Calculated, %: C 81.79; H 5.72; N 7.95. $C_{24}H_{20}N_2O$. Found, %: C 81.85; H 5.76; N 7.99.

3,3'-[(2,4-Dichlorophenyl)methylene]bis(1*H*-indole) (3k). mp 100–102°C. IR spectrum (KBr), ν, cm^{-1}: 3410, 3103, 2965, 1448, 1355, 1189, 1092. ^1H NMR spectrum (400 MHz, $CDCl_3$), δ_H, ppm: 6.35 s (1H), 6.49 t (2H, *J* = 7.8 Hz), 7.19 t (2H, *J* = 7.9 Hz), 7.35–7.66 m (6H), 7.97 d (2H, *J* = 7.8 Hz), 8.02 br.s (2H, NH), 8.13 s (1H). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ_C, ppm: 38.1, 111.8, 117.6, 119.0, 119.5, 121.1, 123.7, 124.7, 125.2, 128.9, 131.5, 135.2, 138.2, 147.2, 149.9. Calculated, %: C 70.60; H 4.12; N 7.16. $C_{23}H_{16}Cl_2N_2$. Found, %: C 70.65; H 4.16; N 7.24.

(*E*)-3,3'-(3-Phenylprop-2-ene-1,1-diyl)bis(1*H*-indole) (3l). mp 94–96°C. IR spectrum (KBr), ν, cm^{-1}: 3450, 3100, 2960, 1590, 1470, 1030. ^1H NMR spectrum (400 MHz, $CDCl_3$), δ_H, ppm: 5.78 s (1H), 6.38 d (1H, *J* = 16.6 Hz), 6.56 d (1H, *J* = 16.6 Hz), 7.17 t (4H, *J* = 7.6 Hz), 7.45–7.68 m (8H), 7.82 t (3H, *J* = 7.9 Hz), 8.07 br.s (2H, NH). Calculated, %: C 70.60; H 4.12; N 7.16. $C_{25}H_{20}N_2$. Found, %: C 70.63; H 4.14; N 7.11.

4-[Di(1*H*-indol-3-yl)methyl]-*N*,*N*-dimethylaniline (3m). mp 211–213°C. IR spectrum (KBr), ν, cm^{-1}: 3348, 3154, 1384, 1255, 1063. ^1H NMR spectrum (400 MHz, $CDCl_3$), δ_H, ppm: 2.53 s (6H), 5.61 s (1H), 7.72 d (2H, *J* = 7.8 Hz), 8.02 br.s (2H, NH), 8.15–8.25 m (10H), 8.36 d (2H, *J* = 7.8 Hz). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ_C, ppm: 32.8, 43.5, 111.2, 112.4, 115.9, 123.6, 124.2, 127.8, 128.2, 129.5, 133.4, 137.9, 143.1, 145.0. Calculated, %: C 82.16; H 6.34; N 11.50. $C_{25}H_{23}N_3$. Found, %: C 82.24; H 6.33; N 11.57.

3,3'-(Pentane-1,1-diyl)bis(1*H*-indole) (3n). mp 68–70°C. IR spectrum (KBr), ν, cm^{-1}: 3465, 3108, 3060, 2980, 1600, 1546, 1250, 1060. ^1H NMR spectrum (400 MHz, $CDCl_3$), δ_H, ppm: 0.87 t (3H, *J* = 6.8 Hz), 1.37–1.63 m (4H) , 2.31 m (2H), 4.64 t (1H, *J* = 6.8 Hz), 6.58 d (2H, *J* = 4.5 Hz), 7.07–7.81 m (6H), 8.09 d (2H, *J* = 8.8 Hz), 7.85 br.s (2H, NH). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ_C, ppm: 19.2, 21.4, 22.3, 24.5, 32.8, 111.2, 123.6, 124.2, 127.8, 129.5, 133.4, 137.9, 145.0. Calculated, %: C 83.40; H 7.33; N 9.26. $C_{21}H_{22}N_2$. Found, %: C 83.38; H 7.21; N 9.31.

3,3'-(Pyridin-4-yl methylene)bis(1*H*-indole) (3o). mp 185–186°C. IR spectrum (KBr), ν, cm^{-1}: 3465, 3006, 2987, 1477, 1365, 1112. ^1H NMR spectrum (400 MHz, $CDCl_3$), δ_H, ppm: 6.24 s (1H), 7.02–7.27 m (10H), 7.84–7.90 m (2H), 7.88 br.s (2H, NH), 8.22–8.30 m (2H). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ_C, ppm: 38.1, 111.8, 119.0, 123.7, 124.7, 128.9, 131.5, 135.2, 138.2,143.4, 147.2, 149.9. Calculated, %: C 76.80; H 4.91; N 8.53. $C_{21}H_{16}N_2S$. Found, %: C 76.76; H 4.89; N 8.55.

3,3'-(Thiophen-2-yl methylene)bis(1*H*-indole) (3p). mp 90–91°C. IR spectrum (KBr), ν, cm^{-1}: 3343, 3175, 1546, 1455, 1256, 1089. ^1H NMR spectrum (400 MHz, $CDCl_3$), δ_H, ppm: 6.24 s (1H), 7.02–7.27 m (10H), 7.84 s (2H), 7.88 br.s (2H, NH), 8.32 s (1H). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ_C, ppm: 38.1, 111.8, 117.6, 119.0, 121.1, 124.7, 128.9, 131.5, 135.2, 138.2, 141.3, 147.2, 149.9. Calculated, %: C 81.71; H 5.30; N 12.99. $C_{22}H_{17}N_3$. Found, %: C 81.77; H 5.27; N 12.98.

CONCLUSIONS

In conclusion, Fe^{+3}-montmorillonite K10, as a mild and efficient catalyst, was studied in the synthesis of diindolylmethanes under grinding conditions. The method applies inexpensive, nontoxic, easy-to-handle, and reusable catalyst, proceeds for a shorter time, gives products in high yield and with a better purity, uses a simple work-up procedure, and is ecologically friendly, which makes it remarkably advantageous over other methods.

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