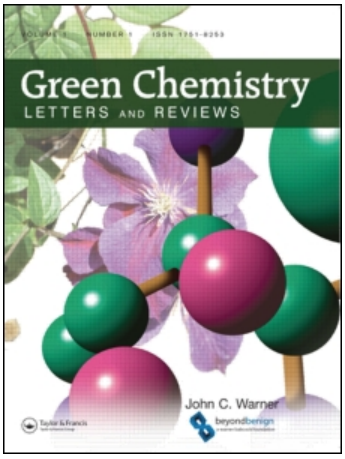

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RESEARCH ARTICLE

MK-10 clay catalyzed, one pot, three component and efficient synthesis of novel 4-(2′,5′-disubstituted-1′H-indol-3′-yl)-2,6-bis(2″,5″-disubstituted-1″H-indol-3″-yl) pyridine-3,5-dicarbonitrile under conventional and microwave irradiation

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A series of title compounds were synthesized via a one pot, multicomponent reaction of 2,5-disubstituted indole 3-carboxaldehydes, 3-cyanoacetyl indoles, and ammonium acetate under microwave irradiation and conventional method in a short time to afford the corresponding products in high yields. It is an ideal, efficient, and environmental benign reaction. The structures of products thus obtained are confirmed by their melting point, IR, ^{1}HNMR, and mass spectral data.

Keywords: indole; pyridine; microwave irradiation; solid support; conventional method; environmental benign

Introduction

It has been reported in the literature that the structure of cytotoxic natural products can be compared to synthetic 3-substituted indole derivatives acting as antiangiogenic inhibitors of the KDR kinase (*1*). Synthesis of 3,5-bis(2-indolyl)pyridine and 3-[(2-indolyl)-5-phenyl]pyridine derivatives as CDK inhibitors and cytotoxic agents by Jacquemard et al. (*2,3*). Also naturally occurring and synthetic compounds containing pyridine scaffold possess interesting pharmacological properties (*4*). Hence, in an ongoing program devoted to the design of DNA-binding anticancer agents, we have developed non-fused tris-aromatic compounds containing pyridine as the central ring (*5,6*).

To the best of our knowledge, there have been few reports about the synthesis of bis-indolyl and tri-indolyl derivatives incorporated with pyridine moieties (*7,8*).

Organic synthesis involving greener process has been investigated worldwide due to stringent environment and economic regulations (*9–11*). Microwave-assisted reactions, which required short reaction times are becoming more popular for organic chemists (*12–14*), due to eco-friendly nature, along with the fact that reactions can be run in open vessels (thus avoiding risk of high pressure) and synthesis can be performed on a preparative scale (*15,16*).

In continuation of our ongoing interest in green chemistry, we have developed a mild and expedient synthesis for tris-indolyl incorporated with pyridine nucleus using montmorillonite K-10 (MK-10) clay as the catalyst. The method is highly efficient and free from aforesaid drawbacks. A brief account of our work and its main findings as well as the advantages of this method over the existing synthetic routes are discussed in this communication. MK-10 clay (*17*) is known to behave as both a protic and a Bronsted acid (Hammett acidity function, H_0: -5.5 to 5.9) and has a large specific surface area (500–760 m^2/g). We therefore, used this clay in acetic acid and ethylene glycol (as an energy transfer agent and homogenizer to increase the reaction temperature) for the reaction of 2,5-disubstituted indole 3-carboxaldehydes, 2,5-disubstituted 3-cyanoacetyl indole and ammonium acetate under microwave irradiation [neat, solid supported (MK-10 clay)] and conventional conditions (Scheme 1). The synthesis affords 4-(2′5′-disubstituted-1′H-indol-3′-yl)-2,6-bis(2″,5″-disubstituted-1″H-indol-3″-yl)pyridine-3,5-dicarbonitrile.

Results and discussion

In the present investigation, the reaction (Scheme 1) was carried out with microwave irradiation by taking 2,5-disubstituted indole 3-carboxaldehydes, 2,5-disubstituted 3-cyanoacetyl indoles and ammonium acetate

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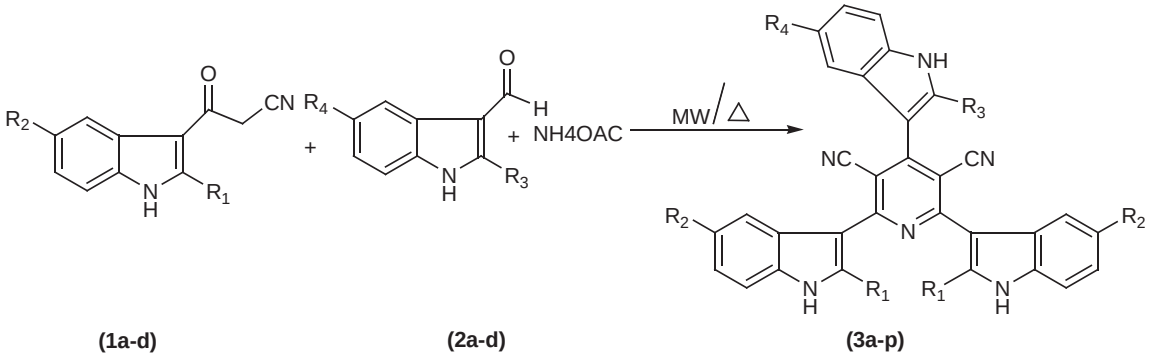

Scheme 1. R_1 = Ph, Me, or H; R_2 = Cl, Me, or H; R_3 = Ph, Me, or H; R_4 = Cl, Me or H.

in the presence of a MK-10 clay in 1:2 ml acetic acid and ethylene glycol for 8–10 minutes. The products were obtained in good yields but the use of MK-10 clay as the mineral support therefore eliminates the necessity of an external base/strong acid for the synthesis of title product which was formed in reasonable purity. When the reaction was carried out using conventional heating the products were obtained in moderate yield in 12–14 hours (Table 1).

The reaction has also been performed under neat conditions (without solvent support or catalyst). However, no reaction occurred under neat conditions but the reaction could be made successful by adding 1:2 ml acetic acid and ethylene glycol. The role of acetic acid and ethylene glycol is to function as an energy transfer medium and homogenizer to increase the reaction temperature. However, products are formed in comparatively lower yields in this case compared to the solid supported. The optimum conditions were found to be the microwave synthesis in acetic acid and ethylene glycol in MK-10 clay.

Conventional synthesis suffers from disadvantages such as long reaction periods and low yields (Table 2). Hence, we have developed a new, economical, safe, environmentally benign, one-pot synthesis of novel 4-(2′5′-disubstituted-1′H-indol-3′-yl)-2, 6-bis (2″,5″-disubstituted-1″H-indol-3″-yl) pyridine-3, 5-dicarbonitrile under microwave irradiation. The method of

Table 1. Comparative study of the synthesis of **(3a–d).**

Entry	Method	Conventional (reflux) microwave power (%)	Reaction time (min)	Isolated yield (%)	
				MW	Δ
3a	Δ (Acetic acid & ethylene glycol)	Reflux	840	–	46
	MW (Neat)	50	10	Nil	–
	MW (Acetic acid & ethylene glycol)	50	10	83	–
	MW (Acetic acid & ethylene glycol + MK-10)	50	10	88	–
3b	Δ (Acetic acid & ethylene glycol)	Reflux	840	–	49
	MW (Neat)	50	10	Nil	–
	MW (Acetic acid & ethylene glycol)	50	10	75	–
	MW (Acetic acid & ethylene glycol + MK-10)	50	10	82	–
3c	Δ (Acetic acid & ethylene glycol)	Reflux	720	–	47
	MW (Neat)	50	08	Nil	–
	MW (Acetic acid & ethylene glycol)	50	08	70	–
	MW (Acetic acid & ethylene glycol + MK-10)	50	10	75	–
3d	Δ (Acetic acid & ethylene glycol)	Reflux	720	–	48
	MW (Neat)	50	08	Nil	–
	MW (Acetic acid & ethylene glycol)	50	08	72	–
	MW (Acetic acid & ethylene glycol + MK-10)	50	08	76	–

Table 2. Comparative data of conventional (A) and MW (B) methods for the synthesis of compounds (**3a–p**).

					Conventional method		Microwave method			
Entry	R_1	R_2	R_3	R_4	Time (min)	Yield (%)	Time (min)	Power (%)	Yield (%)	MP (°C)
3a	Ph	Cl	Ph	Cl	840	46	10	50	88	210–12
3b	Ph	Cl	Ph	Me	840	49	10	50	82	203–04
3c	Ph	Cl	Me	H	720	47	10	50	75	242–41
3d	Ph	Cl	H	H	720	48	08	50	76	255–56
3e	Ph	Me	Ph	Cl	840	51	10	50	78	206–07
3f	Ph	Me	Ph	Me	840	53	10	50	80	195–97
3g	Ph	Me	Me	H	840	52	10	50	82	248–50
3h	Ph	Me	H	H	720	49	08	50	75	211–12
3i	Me	H	Ph	Cl	720	50	10	50	77	261–62
3j	Me	H	Ph	Me	840	52	10	50	80	200–01
3k	Me	H	Me	H	840	55	10	50	90	190–91
3l	Me	H	H	H	840	50	08	50	83	208–09
3m	H	H	Ph	Cl	840	48	10	50	80	203–04
3n	H	H	Ph	Me	840	51	10	50	78	185–88
3o	H	H	Me	H	720	50	08	50	77	198–99
3p	H	H	H	H	720	48	08	50	75	253–55

synthesis (8–10 minutes) using acetic acid and ethylene glycol along with solid support gives excellent yields (75–90%).

Experimental

Melting points were determined in open capillary tubes and are uncorrected. IR Spectra were recorded in KBr on a Perkin–Elmer FTIR Spectrophotometer (cm^{-1}) and ^1H NMR Spectra were recorded on BRUKER AVENE II 400 MHz NMR Spectrometer (Chemical shift in δ ppm downfield from TMS as an internal reference). The mass spectra were recorded on LC-MSD-Trap-SL instrument and Microwave reactions carried out in ONIDA 20STP21 800W (Sl.no. MO 20SG05101262) multimode domestic microwave oven.

General procedure for the synthesis of 4-(2′,5′-disubstituted-1′H-indol-3′-yl)-2,6-bis(2″,5″-disubstituted-1″H-indol-3″-yl)pyridine-3,5-dicarbonitrile

Conventional method

A mixture of 2,5-disubstituted indole 3-carboxaldeyhde (1 mmol), 2,5-disubstituted 3-cyanoacetyl indole (2 mmol), ammonium acetate (5 mmol), acetic acid (1 ml), and ethylene glycol (2 ml) were heated at 150°C (oil bath) for the given time. The reaction mixture was allowed to cool at room temperature and poured into crushed ice. The solid thus obtained was dried and recrystallized from DMF and Ethanol affording the title compounds (**3a–p**) with 46–55% yield (Table 2).

Microwave-assisted synthesis

Neat reaction

A mixture of 2,5-disubstituted indole 3-carboxaldeyhde (1 mmol), 2,5-disubstituted 3-cyanoacetyl indole (2 mmol), and ammonium acetate (5 mmol) were introduced in an open borosil glass vessel (to decrease internal pressure). This was subjected to microwave irradiation for 8–10 minutes with 50% microwave power (Table 1), and no product was found with neat.

Neat with acetic acid and ethylene glycol

A mixture of 2,5-disubstituted indole 3-carboxaldeyhde (1 mmol), 2,5-disubstituted 3-cyanoacetyl indole (2 mmol), ammonium acetate (5 mmol), acetic acid (1 ml), and glycol (2 ml) (as an energy transfer medium) were introduced in an open borosil glass vessel (to decrease internal pressure). This was subjected to microwave irradiation for 8–10 minutes with 50% microwave power (Table 1) to give an oily product, which solidified on standing was washed with ice cold water to give crude product. The product was recrystallized from DMF or Ethyl alcohol to afford the title compound with good yield (Table 2).

Neat with AcOH and Glycol.+Solid support

A mixture of 2,5-disubstituted indole 3-carboxaldeyhde (1 mmol), 2,5-disubstituted 3-cyanoacetyl indole (2 mmol), ammonium acetate (5 mmol), acetic acid (1 ml), and glycol (2 ml) (as an energy transfer medium) on 2 grams of MK-10 clay were introduced

in an open borosil glass vessel (to decrease internal pressure). This was subjected to microwave irradiation for 8–10 minutes with different microwave power (Table 1). The product was washed with ice cold water to give crude product and recrystallized from DMF or ethyl alcohol to afford the title compound which was found to be in good purity (TLC) with very good yield (Table 1).

The IR spectrum of **3a** has shown characteristic peaks at 3379 (N-H), 3281 (N-H), 3101 (C-H), 2983 (C-H), 2336 (C≡N), 1634 (C=N), 1579 (C=C), 789(C-Cl) cm^{-1} corresponding to the tris-indolyl pyridine. This confirms the reaction of (**1a–d**), (**2a–d**) and ammonium acetate to give products (**3a–p**). ^{1}H NMR Spectrum of **3a** has displayed a downfield signal at δ10.1 (s, 2H) integrating for protons of indole at 2 and 6 positions. Less deshielded peak of NH at δ 9.6 (s, 1H) integrating for the remaining indole NH. A multiplet observed between δ 6.9 and 7.8 (m, 24H, ArH) integrating for 24 aromatic protons. ^{13}C NMR Spectrum of **3a** has displayed a downfield signal at δ168 integrating for C-2 and C-6 carbon atoms of pyridine and δ151 integrating for C-4 carbon of pyridine. Peaks at δ140, 134, 131, 129, 128, 127, 122, 120, 116, 114, 112, and 100 for indole and phenyl carbons. Peaks at δ118 integrated for cyano carbon and at δ106 corresponding to the C-3 and C-5 carbons of pyridine.

Mass spectrum of **3a** has displayed very weak molecular ion peak at 804 (M+.) (2%), 806 (M+2) (2%), 808 (M+4) (0.7%), 810 (M+6) (0.3%), peak at m/z 578 (M+1) (62%), m/z 580 (M+2) (37%), 582 (M+4) (6%), and peaks at 326 (M+1) (100%), 328 (M+2) (33%), 314 (M+1) (36%), 316 (M+2) (12%), 226 (M+1) (48%), 228 (M+2) (16%) corresponding to the isotopic contributions of chlorine atoms in the molecule. This fragmentation pattern supported the formation of the title compound.

2,4,6-tris(5-chloro-2-phenyl-1H-indol-3-yl)pyridine-3,5-dicarbonitrile (3a)
m.p. 210–12°C; IR (KBr): ν_{max}/cm^{-1} = 3379, 3281, 3101, 2983, 2336, 1634, 1579, 789.
^{1}H NMR (DMSO-d^6): δ = 10.1 (br. s, 2H, NH), 9.6 (br. s, 1H, NH), 6.8–7.6 (m, 24H, ArH).
^{13}C NMR (DMSO-d^6): δ = 168, 151, 140, 134, 131, 129, 128, 127, 122, 120, 118, 116, 114, 112, 106, 100.
MS: m/z (%) = 804 (M+.) (2%), 806 (M+2) (2%), 808 (M+4) (0.7%), 810 (M+6) (0.3%), 578 (M+1) (62%), 580 (M+2) (37%), 582 (M+4) (6%), 326 (M+1) (100%), 328 (M+2) (33%), 314 (M+1) (36%), 316 (M+2) (12%), 226 (M+1) (48%), 228 (M+2) (16%).
Analysis calculated for $C_{49}H_{27}Cl_3N_6$: C, 73.01; H, 3.38; N, 10.43 found: C, 73.06; H, 3.42; N, 10.47.

2,6-bis(5-chloro-2-phenyl-1H-indol-3-yl)-4-(5-methyl-2-phenyl-1H-indol-3-yl)pyridine-3,5-dicarbonitrile (3b)
m.p. 203–04°C; IR (KBr): ν_{max}/cm^{-1} = 3343, 3201, 3129, 2921, 2331, 1618, 1569, 791.
^{1}H NMR (DMSO-d^6): δ = 10.4 (br. s, 2H, NH), 9.5 (br. s, 1H, NH), 6.7–7.5 (m, 24H, ArH), 2.2 (s, 3H, CH_3).
Analysis calculated for $C_{50}H_{30}Cl_2N_6$: C, 76.43; H, 3.85; N, 10.70 found: C, 76.47; H, 3.90; N, 10.74.

4-(2-methyl-1H-indol-3-yl)-2,6-bis(5-methyl-2-phenyl-1H-indol-3-yl)pyridine-3,5-dicarbonitrile (3g)
m.p. 248–50°C; IR (KBr): ν_{max}/cm^{-1} = 3298, 3210, 3070, 2925, 2366, 1635, 1578, 748.
^{1}H NMR (DMSO-d^6): δ = 10.7 (br. s, 2H, NH), 10.1 (br. s, 1H, NH), 6.7–7.6 (m, 20H, ArH), 2.4 (s, 3H, CH_3), 2.1 (s, 6H, CH_3).
Analysis calculated for $C_{46}H_{32}N_6$: C, 82.61; H, 4.82; N, 12.57 found: C, 82.63; H, 4.85; N, 12.63.

4-(1H-indol-3-yl)-2,6-bis(5-methyl-2-phenyl-1H-indol-3-yl)pyridine-3,5-dicarbonitrile (3h)
m.p. 211–12°C; IR (KBr): ν_{max}/cm^{-1} = 3286, 3221, 3085, 2925, 2361, 1617, 1582, 749.
^{1}H NMR (DMSO-d^6): δ = 10.6 (br. s, 2H, NH), 9.8 (br. s, 1H, NH), 6.8–7.6 (m, 21H, ArH), 2.0 (s, 6H, CH_3).
Analysis calculated for $C_{45}H_{30}N_6$: C, 82.55; H, 4.62; N, 12.84 found: C, 82.58; H, 4.65; N, 12.88.

4-(5-chloro-2-phenyl-1H-indol-3-yl)-2,6-bis(2-methyl-1H-indol-3-yl)pyridine-3,5-dicarbonitrile (3i)
m.p. 261–62°C; IR (KBr): ν_{max}/cm^{-1} = 3234, 3223, 3067, 2920, 2349, 1634, 1581, 747.
^{1}H NMR (DMSO-d^6): δ = 9.8 (br. s, 2H, NH), 9.2 (br. s, 1H, NH), 6.8–7.8 (m, 16H, ArH), 2.4 (s, 6H, CH_3).
Analysis calculated for $C_{39}H_{25}ClN_6$: C, 76.40; H, 4.11; N, 13.71 found: C, 76.43; H, 4.15; N, 13.75.

2,6-bis(2-methyl-1H-indol-3-yl)-4-(5-methyl-2-phenyl-1H-indol-3-yl)pyridine-3,5-dicarbonitrile (3j)
m.p. 200–01°C; IR (KBr): ν_{max}/cm^{-1} = 3305, 3234, 3065, 2920, 2363, 1605, 1580, 748.
^{1}H NMR (DMSO-d^6): δ = 9.8 (br. s, 2H, NH), 9.0 (br. s, 1H, NH), 6.8–7.7 (m, 16H, ArH), 2.6 (s, 3H, CH_3), 2.2 (s, 6H, CH_3).
Analysis calculated for $C_{40}H_{28}N_6$: C, 81.06; H, 4.76; N, 14.18 found: C, 81.09; H, 4.80; N, 14.20.

2,6-di(1H-indol-3-yl)-4-(2-methyl-1H-indol-3-yl) pyridine-3,5-dicarbonitrile (3o)
m.p. 198–99°C; IR (KBr): ν_{max}/cm^{-1} = 3290, 3205, 3015, 2921, 2350, 1634, 1581, 747.

^{1}H NMR (DMSO-d^6): δ = 10.9 (br. s, 2H, NH), 10.2 (br. s, 1H, NH), 6.8–7.6 (m, 14H, ArH), 2.2 (s, 3H, CH_3).
MS: m/z (%) = 488 (M+.) (100%), 372 (43%), 230 (15%), 116 (10%).
Analysis calculated for $C_{32}H_{20}N_6$ C, 78.67; H, 4.13; N, 17.20 found: C, 78.70; H, 4.15; N, 17.24.

2,4,6-tri(1H-indol-3-yl)pyridine-3,5-dicarbonitrile (3p)
m.p. 253–55°C; IR (KBr): ν_{max}/cm^{-1} = 3298, 3219, 3029, 2920, 2357, 1635, 1580, 749.
^{1}H NMR (DMSO-d^6): δ = 10.4 (br. s, 2H, NH), 9.7 (br. s, 1H, NH), 6.8–7.5 (m, 15H, ArH).
MS: m/z (%) = 474 (M+.) (100%), 358 (55%), 216 (25%), 116 (14%).
Analysis calculated for $C_{31}H_{18}N_6$: C, 78.47; H, 3.82; N, 17.71 found: C, 78.50; H, 3.85; N, 17.74.

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