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Host/guest inclusion system of surfactants with β-cyclodextrin as a viable catalyst for one-pot synthesis of *mono*- and *bis* (indolyl)methylmalononitriles in H_2O

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Abstract: In this study, encapsulation processes of cetyltrimethylammonium bromide (CTAB) or sodium dodecyl sulfate (SDS) monomers into the cavity of β-cyclodextrin (β-CD) were applied to synthesize *mono*- and *bis* (indolyl)methylmalononitrile derivatives by a one-pot three-component reaction of an aldehyde, malononitrile, and indole in an aqueous solution. These two inclusion complexes proved to be superior to CTAB or SDS individually, as cationic or anionic surfactants, respectively, for accessing high yields of pure products within shorter reaction times. In addition, simple isolation of products and mild reaction conditions are the other advantages of this green procedure.

Key words: Conductance, β-cyclodextrin, encapsulation, inclusion complexes, surfactants

1. Introduction

The insolubility of most organic substances in water and the distribution or deactivation of many active substrates, reagents, and catalysts by water molecules are the two significant limitations of organic reactions in aqueous media.[1] To overcome these constraints, there are some strategies that facilitate the use of water as a solvent for a wide variety of organic reactions. In this regard, the use of organic co-solvents,[2–4] water-stable Lewis acids,[5–9] surfactants,[10–12] or Brønsted/Lewis acid-surfactant-combined catalysts[13–16] is the most important recently reported strategy. Host/guest inclusion catalysts (ICs) have also been of considerable interest for preparing organic compounds in water. Such ICs can be defined as supramolecules consisting of two or more distinct species, which are capable of self-assembling through noncovalent interactions without any loss in their chemical identity.[17] The stability of host/guest complexes is achieved through intermolecular interactions, such as hydrogen bonds, established between the interacting species. The minimum condition required for the formation of an inclusion compound is the geometric compatibility between the host and guest molecules following the principles of molecular recognition.[18] Therefore, the size and conformation of the guest must be appropriate enough to be included in the host cavity. β-Cyclodextrin β-CD lies in the class of encapsulation supramolecular host compounds, which is important in the development of host/guest systems. β-CD is a cyclic oligosaccharide formed by α-D-glucose units linked through glycosidic α-1,4 bonds.[19] Topologically, β-CD is usually characterized as a doughnut or a wreath-shaped truncated cone, combining the hydrophilic and hydrophobic region. β-CD forms ICs with smaller molecules that fit into its 6-6.4 Å cavity. The hydrophobic cavity of β-CD allows this molecule to encapsulate a variety of nonpolar molecules of a suitable size.[20,21]

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Surfactants also have distinctly separate hydrophilic and hydrophobic parts and commonly show self-assembly, resulting in different structures such as micelles as well as vesicles.[22] Current investigations in surfactant science are driven by the requirements that design surfactants possess enhanced physicochemical properties, specific applications in modern technologies, and new utilization in complex systems.[23−25] Hence, investigations of the host/guest relationship of β-CD and surfactants in complex systems are important because they make it possible to design new surfactants and corresponding supramolecules for specific applications. These complexes are of interest for scientific research, and they exist in aqueous solutions in comparison with classical catharses. Since indole derivatives have been widely found in biologically active compounds, various research groups have turned their attention to access this class of heterocyclic compounds.[26] In continuation of our previous work on the development of new synthetic methodologies,[27] herein we report a convenient, practical, green, and efficient reaction for the synthesis of (indolyl)methylmalononitrile derivatives via a one-pot three-component reaction of an aldehyde, a malononitrile, and an indole in H_2O using inclusion compounds of β-CD and CTAB or SDS. The main goal of this study was to investigate the formation of ICs of CTAB and SDS with β-CD in aqueous media and then to compare their inclusion efficiency with respect to the surfactants individually.

2. Results and discussion

In our initial study, the conductivity of CTAB and SDS in an experimental solution was measured to get information about the transport property of ICs as well as the stoichiometry of the complexes. CTAB and SDS are charged structures and have considerable conductivity in aqueous solutions. By adding β-CD to the solution of CTAB or SDS, the conductivity of the solution was decreased, which is due to the inclusion of the hydrophobic part of CTAB or SDS molecules one by one into the nonpolar cavity of β-CD. A decrease in the solution conductivity by adding β-CD was attributed to the formation of ICs between CTAB or SDS and β-CD molecules. After a certain concentration of β-CD, no change was observed in the conductivity, indicating that the stoichiometry of the inclusion complex of β-CD with CTAB or SDS in this concentration range was almost a 1:1 molar ratio. This points out that CTAB or SDS is in a complex situation. The conductivity values of each IC are tabulated in Table 1.

The FT-IR spectra of β-CD, β-CD/SDS, and SDS as well as β-CD, β-CD/CTAB, and CTAB were recorded. The peak at 3371 cm^{-1} was attributed to the stretching mode of OH in β-CD. After complexion of β-CD with CTAB or SDS, the peak at 3371 shifted to $\sim$3360 cm^{-1}. This was probably caused by the effect of the ion-dipolar interaction of β-CD with CTAB or SDS when the hydrophobic part of CTAB or SDS was inside the cavity of β-CD.

The catalytic activity of these two IC systems was investigated for the synthesis of 3-substituted indole derivatives via three-component reactions of aldehyde, malononitrile, and indole. In order to optimize the reaction conditions and to achieve the highest yield, the model reaction of benzaldehyde, malononitrile, and indole was initially carried out under different conditions in the aqueous solution of β-CD/CTAB or β-CD/SDS. The results are summarized in Table 2. The reaction was first performed in H_2O in the absence of CTBA and SDS at room temperature. According to the data obtained, no reaction occurred (Table 2, Entry 1). Similar reactions were then attempted in the presence of CTAB or SDS, as cationic and anionic surfactants, in the pre-cmc and post-cmc regions. However, it was noticed that no reaction would occur when the concentration of CTAB was less than the cmc_1 (Table 2, Entry, 2), while the formation of the product was more facile and proceeded with a high yield in the presence of CTBA or SDS at their cmc_1 concentrations (Table 2, Entries 3, 10). At this stage, the higher reaction loading of the surfactant had no significant influence on the reaction

Table 1. Conductance values of CTAB and SDS with the corresponding concentration of β-CD in an aqueous medium at 20.0 ± 0.2 °C.

	β-CD (mM)	Cond. (mS cm^{-1})
CTAB[a)]	0	0.238 ± 0.002
	0.2	0.233 ± 0.003
	0.5	0.195 ± 0.002
	0.8	0.175 ± 0.001
	1	0.170 ± 0.002
	2	0.171 ± 0.001
	3	0.170 ± 0.002
SDS[b)]	0	0.687± 0.001
	2	0.657 ± 0.002
	5	0.558 ± 0.003
	7	0.398 ± 0.002
	8	0.245± 0.002
	9	0.255± 0.001
	10	0.250± 0.002

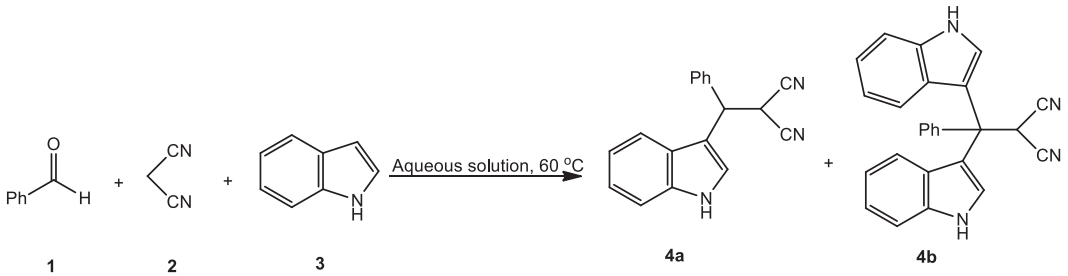
[a)] Concentration of CTAB is 1 mM (cmc_1).
[b)] Concentration of SDS is 8.2 mM (cmc_1).

time and yield. When the reaction was performed in an aqueous solution of β-CD/CTAB (1 mM:2 mM) or β-CD/SDS (1 mM:1.5 mM) micelles mixed system, the formation of the product was more facile and proceeded in a shorter time (Table 2, Entries 8, 13). To find the optimum reaction temperature, the model reaction was carried out in a solution of β-CD/CTAB (1 mM:2 mM) mixed system at 25, 60, and 80 °C, which resulted in the isolation of the product yields of 55%, 90%, and 70%, respectively. In order to evaluate the efficiency of ICs, the reuse of β-CD/CTAB or β-CD/SDS mixed system in the model reaction was investigated. The inclusion complexes of β-CD/CTAB or β-CD/SDS could be easily recovered by filtration, and the new substrates were added for the next cycle. The recycled experimental solution of β-CD/CTAB or β-CD/SDS was efficient enough to turn the condensation reaction of the aldehyde, malononitrile, and indole into the corresponding (indolylmethyl)malononitrile even after three consecutive times with an activity loss of about 15%–20%.

According to the obtained results, the catalytic effect of the inclusion complexes of β-CD/CTAB or β-CD/SDS in this three-component reaction can be explained as follows. Aldehydes, malononitrile, and indole, which are expected to produce (indolylmethyl)malononitrile derivatives, are hydrophobic molecules in water. In the inclusion compounds of β-CD/CTAB or β-CD/SDS, the hydrophobic moieties escape from the wider and narrower edges of β-CD, which encircle the micelle hydrophobic core of CTAB or SDS inside the β-CD cave where the reactions take place more easily.

Mono- and *bis* (indolyl)methylmalononitrile derivatives were synthesized under the optimized conditions. As it was observed, the process could tolerate both electron-donating and electron-withdrawing substituents in the substrates. In all cases, reactions proceed efficiently in H_2O under mild conditions to afford the corresponding products in high yields. The results are summarized in Table 3. All the products were characterized by mp, and IR, ^{1}H NMR, and ^{13}C NMR spectra.

Table 2. Optimization traits for the one-pot synthesis of indolylmethylmalononitrile and *bis* (indolyl) methylmalononitrile in aqueous solution [a].



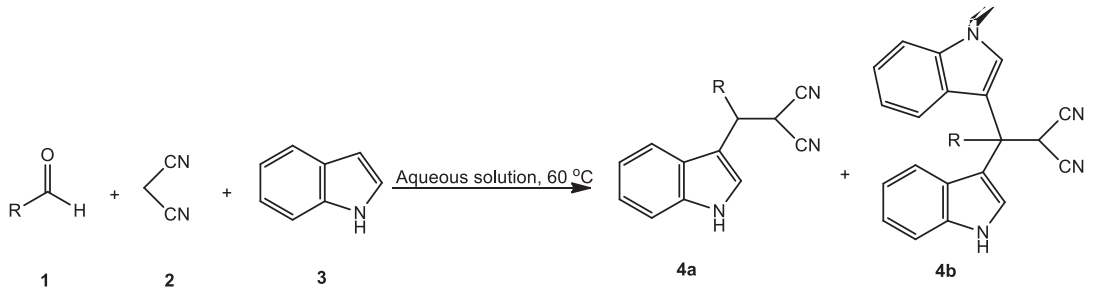
Entry	Aqueous solution (conc.)	Time (h)	Yield (%) [b]	
			4a	**4b**
1	-----	7	0	0
2	CTAB (0.5 mM)	7	0	0
3	CTAB (1 mM) cmc_1	7	85	5
4	CTAB (2 mM) cmc_2	7	85	5
5	β-CD (1 mM)	7	20	0
6	CTAB/β-CD 1:1 (1 mM:1 mM)	7	30	5
7	CTAB/β-CD 1:1 (2 mM:2 mM)	7	30	5
8	CTAB/β-CD 1:2 (1 mM:2 mM)	7	25	0
9	CTAB/β-CD 2:1 (2 mM:1 mM)	2	90	5
10	SDS (8.2 mM) cmc_1	12	20	75
11	SDS/β-CD 1:1 (8.2 mM:8.2 mM)	12	20	35
12	SDS/β-CD 1.25:1 (10.3 mM:8.2 mM)	12	20	35
13	SDS/β-CD 1.5:1 (12.3 mM:8.2 mM)	3.5	5	87
14	SDS/β-CD 1:1.5 (8.2 mM:12.3 mM)	12	10	30

[a] Reaction conditions: aldehyde (1 mmol), malononitrile (1 mmol), indole (1–2 mmol). [b] Isolated yield.

This one-pot three-component reaction involves Knoevenagel condensation and Michael addition occurring in a sequence. These processes take place in β-CD/CTAB or β-CD/SDS inclusion complexes, which have highly effective catalytic behavior in terms of their host/guest interactions. The formation of the products can be rationalized by the initial Knoevenagel reaction between aromatic aldehydes and malononitrile. Afterwards, Michael addition reaction between Knoevenagel adduct and indole gives the desired (indolyl)methylmalononitrile derivatives. Dehydrogenation of (indolyl)methylmalononitrile in a solution with β-CD/SDS resulted in (indolyl)methylenemalononitriles. *Bis* (indolyl)methylmalononitriles was obtained by the second conjugate addition of indole with (indolyl)methylenemalononitriles.

To study the wide capability of the β-CD/CTAB catalytic system, we further investigated the reaction of malononitrile with benzaldehyde to yield the corresponding 2-benzylidenemalononitrile via Knoevenagel condensation reaction. The reaction was carried out in aqueous solution of β-CD, CTAB, β-CD/CTAB, SDS, and β-CD/SDS. It was shown that CTAB and SDS, as cationic and anionic surfactants respectively, accelerate this reaction, but the inclusion complexes of β-CD/CTAB or β-CD/SDS were not more effective in this reaction. The results are summarized in Table 4.

Table 3. Synthesis of indolylmethylmalononitrile and *bis* (indolyl)methylmalononitriles derivatives in the presence of inclusion complexes.

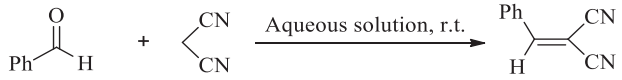


1 2 3 4a 4b

Entry	R	CTAB/β-CD 2:1 (2 mM:1 mM) **4a**		Ref.	SDS/β-CD 1.5:1 (12 mM:8.2 mM) **4b**		Ref.
		Time (min)	Yield (%) [a)]		Time (min)	Yield (%) [a)]	
1	C_6H_5	110	90	[27]	210	87	[32]
2	4-ClC_6H_4	80	87	[27]	150	85	[32]
3	4-$MeOC_6H_4$	120	80	[28]	210	80	[26]
4	4-MeC_6H_4	100	90	[28]	200	90	[26]
5	4-HOC_6H_4	120	80	[29]	210	80	[32]
6	4-$iprC_6H_4$	100	85	[29]	200	85	[26]
7	4-$O_2NC_6H_4$	45	95	[30]	140	95	[26]
8	4-FC_6H_4	80	90	[31]	140	90	[32]

[a)] Isolated yield

Table 4. Optimization traits for the synthesis of 2-benzylidenemalononitrilein in an aqueous solution [a)].



Entry	Aqueous solution	Time (min)	Yield (%) [b)]
1	-	240	85
2	CTAB (1 mM) cmc_1	10	87
3	β-CD (0.5 mM)	10	50
4	CTAB/β-CD 1:1 (1 mM:1 mM)	10	30
5	CTAB/β-CD 2:1 (2 mM:1 mM)	10	90
6	SDS (8.2 mM)	5	90
7	SDS/β-CD 1:1 (8.2 mM:8.2 mM)	5	20
8	SDS/β-CD 1.5:1 (12.3 mM:8.2 mM)	5	95

[a)] Reaction conditions: benzaldehyde (1 mmol), malononitrile (1 mmol),
[b)] Isolated yield

3. Experimental

All the organic materials were purchased commercially from Sigma-Aldrich and Merck and used without further purification. The inclusion compounds were characterized by FT-IR and their conductivity in experimental solutions. The conductance measurements were carried out in a Systronic-308 conductivity meter using a dip-type immersion conductivity cell, CD-10, having a cell constant of approximately (0.1 $\pm$ 0.001) cm^{-1}. The measurements were completed in a water bath maintained within a temperature range of 20.0 $\pm$ 0.2 °C. The synthesized products were characterized by mp, and IR, ^{1}H NMR, and ^{13}C NMR spectra. The melting points were determined by Büchi melting point B-540 B.V.CHI apparatus in open capillaries. The points were uncorrected. The FT-IR spectroscopy of the samples as KBr pellets was carried out on a Bruker Eqinox 55 FT-IR spectrometer in the 400–4000 cm^{-1} region. ^{1}H and ^{13}C NMR spectra were recorded at 25 °C and on a 400 MHz or 500 MHz (Bruker Avance) instrument using TMS as the internal standard. The chemical shifts were given in parts per million (ppm). All the reactions and the purity of the products were monitored using thin-layer chromatography (TLC) on aluminum-backed plates coated with Merck Kieselgel 60 F_{254} silica gel and by watching the spots under ultraviolet light.

3.1. General procedure for the synthesis of the indolylmethylmalononitrile derivatives

Aldehyde (1 mmol), malononitrile (1 mmol, 0.07 g), and indole (1 mmol, 0.12 g) were added to a magnetically stirred soln. of β-CD/CTAB (1 mM:2 mM) in H_2O (5 mL). The mixture was then stirred at 60 °C for a given time. The progress of the reaction was followed by TLC. After completion of the reaction, the precipitated products were filtrated off and washed with hot H_2O. The crude products were purified by recrystallization in EtOH. The results are summarized in Table 3.

3.2. General procedure for the synthesis of the *bis* (indolyl)methylmalononitrile derivatives

Aldehyde (1 mmol), malononitrile (1 mmol, 0.07 g), and indole (2 mmol, 0.24 g) were added to a magnetically stirred soln. of β-CD/SDS (1 mM:1.2 mM) in H_2O (5 mL). The mixture was then stirred at 60 °C for a given time. The progress of the reaction was followed by TLC. After completion of the reaction, the precipitated products were filtrated off and washed with hot H_2O. The crude products were purified by recrystallization in EtOH. The results are summarized in Table 3.

3.3. Selected data

3.3.1. 2-((Indolyl)(phenyl)methyl)malononitrile (Table 3, 4a, Entry 1)

White crystals, mp 75–77 °C. IR: 3346 (NH stretching), 3031(=CH stretching), 2898 (CH stretching), 2258 (C≡ N), 1620, 1458 (C=C). ^{1}H NMR (400 MHz, $CDCl_3$): 4.46 (d, J = 6.3 Hz, 1 H, CH), 4.95 (d, J = 6.4 Hz, 1 H, CH), 7.10–7.26 (m, 2 H, ArH), 7.35–7.55 (m, 6 H, ArH), 7.70–7.75 (m, 2 H, ArH), 8.89 (s, 1 H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 28.6, 42.4, 111.6, 112.3, 113.8, 114.1, 118.5, 118.8, 121.6, 122.7, 125.8, 127.7, 128.0, 128.6, 136.1, 139.2.

3.3.2. 2-((Indolyl)(4-chlorophenyl)methyl)malononitrile (Table 3, 4a, Entry 2)

White crystals, mp 74–75 °C. IR: 3380 (NH stretching), 3047 (=CH stretching), 2890 (CH stretching), 2260 (C≡ N), 1600, 1480 (C=C). ^{1}H NMR (400 MHz, DMSO-d_6): 4.95 (d, J = 8.1 Hz, 1 H, CH), 5.22 (d, J = 8.1 Hz, 1 H, CH), 7.15 (t, J = 6.9 Hz, 1 H, ArH), 7.40–7.60 (m, 8 H, ArH), 9.25 (s, 1 H, NH). ^{13}C NMR (100

MHz, DMSO-d_6): 27.7, 41.5, 110.8, 112.1, 113.4, 115.5, 118.9, 121.7, 122.6, 125.0 125.8, 128.2, 130.1, 135.4, 136.0, 143.3.

3.3.3. 2-((Indolyl)(p-tolyl)methyl)malononitrile (Table 3, 4a, Entry 4)

Pale yellow crystals, mp 117–119 °C. IR: 3350 (NH stretching), 3035 (=CH stretching), 2883 (CH stretching), 2225 (C≡ N), 1588, 1459 (C=C). ^{1}H NMR (400 MHz, DMSO-d_6): 2.27 (s, 3 H, CH_3), 5.17 (d, J = 9.2 Hz, 1 H, CH), 5.82 (d, J = 9.2 Hz, 1 H, CH), 6.90–7.05 (m, 2 H, ArH), 7.20 (d, J = 8.0 Hz, 2 H, ArH), 7.41 (d, J = 8.0 Hz, 2 H, ArH), 7.55–7.70 (m, 3 H, ArH), 10.80 (s, 1 H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 20.5, 28.7, 42.1, 111.6, 112.4, 113.8, 118.5, 121.6, 122.6, 125.8, 127.9, 129.1, 130.1, 130.6, 136.2, 139.5, 143.1.

3.3.4. 2-((Indolyl)(4-hydroxyphenyl)methyl)malononitrile (Table 3, 4a, Entry 5)

Yellow crystals, mp 172–174 °C. IR: 3386, (OH and NH stretching), 3055 (=CH stretching), 2910 (CH stretching), 2226 (C≡ N), 15610, 1445 (C=C). ^{1}H NMR (400 MHz, DMSO-d_6): 3.40 (s, 1H, OH), 5.10 (d, J = 9.2 Hz, 1 H, CH), 5.70 (d, J = 9.1 Hz, 1 H, CH), 6.68 (d, J = 8.4 Hz, 2 H, ArH), 6.90–715 (m, 3 H, ArH), 7.30 (d, J = 8.4 Hz, 2 H, ArH), 7.52–7.85 (m, 2 H, ArH), 10.17 (s, 1 H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 23.3, 40.5, 112.7, 114.1, 115.0, 115.2, 116.5, 118.2, 118.6, 118.7, 120.8, 121.5, 122.7, 129.1, 133.8, 140.4.

3.3.5. 2-((Indolyl)(4-nitrophenyl)methyl)malononitrile (Table 3, 4a, Entry 7)

Yellow crystals, mp 200–201 °C. IR: 3378 (NH stretching), 3054 (=CH stretching), 2890 (CH stretching), 2248 (C≡ N), 1607, 1471 (C=C). ^{1}H NMR (400 MHz, DMSO-d_6): 5.51 (d, J = 9.2 Hz, 1 H, CH), 5.99 (d, J = 9.2 Hz, 1 H, CH), 6.95–7.15 (m, 2 H, ArH), 7.40–7.60 (m, 3 H, ArH), 7.80 (d, J= 8.8 Hz, 2 H, ArH), 8.10 (d, J = 8.8 Hz, 2 H, ArH), 10.33 (s, 1 H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 28.1, 41.7, 111.2, 111.7, 113.4, 113.6, 118.3, 119.1, 121.1, 123.8, 123.9, 125.6, 129.4, 136.0, 142.6, 145.0.

3.3.6. 2-((Indolyl)(4-fluorophenyl)methyl)malononitrile (Table 3, 4a, Entry 8)

White crystals, mp 113–114 °C. IR: 3360 (NH stretching), 3034 (=CH stretching), 2883 (CH stretching), 2267 (C≡ N), 1605, 1466 (C=C). ^{1}H NMR (400 MHz, DMSO-d_6): 5.27 (d, J = 9.2 Hz, 1 H, CH), 5.84 (d, J = 9.2 Hz, 1 H, CH), 7.00–7.20 (m, 4 H, ArH), 7.40–7.60 (m, 5 H, ArH), 10.25 (s, 1 H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 28.7, 41.5, 111.6, 112.1, 113.7, 113.9, 114.7, 115.5, 118.9, 121.7, 122.6, 125.8, 130.1, 135.4, 136.0 143.3.

3.3.7. 2-(Di(1H-indol-3-yl)(phenyl)methyl)malononitrile (Table 3, 4b, Entry 1)

Red crystals, mp 89–91 °C. IR: 3398 (NH stretching), 3030 (=CH stretching), 2950 (CH stretching), 2190 (C≡ N), 1610, 1470 (C=C). ^{1}H NMR (500 MHz, $CDCl_3$): 5.85 (s, 1 H, CH), 6.95 (s, 2 H, CH), 7.05–7.15 (m, 4 H, ArH), 7.30–7.50 (m, 7 H, ArH), 7.55–7.65 (m, 2 H, ArH), 9.58 (s, 2 H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): 30.6, 45.7, 111.4, 112.6, 119.5, 120.3, 121.5, 122.3, 124.0, 126.5, 127.5, 128.6, 129.1, 135.9, 137.1, 148.4.

3.3.8. 2-((4-Chlorophenyl)di(1H-indol-3-yl)methyl)malononitrile (Table 3, 4b, Entry 2)

Light red crystals, mp 90–91 °C. IR: 3401 (NH stretching), 3052 (=CH stretching), 2923 (CH stretching), 2245 (C≡ N), 1616, 1465 (C=C). ^{1}H NMR (500 MHz, $CDCl_3$): 5.89 (s, 1 H, CH), 6.96 (s, 2 H, CH), 705–7.30 (m, 8 H, ArH), 7.50 (d, J = 8.1 Hz, 2 H, ArH), 7.75 (d, J = 8.0 Hz, 2 H, ArH), 9.60 (s, 2 H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): 37.6, 48.5, 109.8, 110.7, 115.8, 118.4, 120.0, 121.4, 122.6, 125.5, 128.3, 130.0, 131.8, 138.0, 147.0, 149.1.

3.3.9. 2-(Di(1H-indol-3-yl)(p-tolyl)methyl)malononitrile (Table 3, 4b, Entry 4)

Red crystals, mp 174–176 °C. IR: 3380 (NH stretching), 3030 (=CH stretching), 2923 (CH stretching), 2267 (C≡ N), 1610, 1475 (C=C). ^{1}H NMR (500 MHz, $CDCl_3$): 2.54 (s, 3 H, CH_3), 5.32 (s, 1 H, CH), 6.80 (s, 2 H, CH), 7.15–7.30 (m, 8 H, ArH), 7.40 (d, J = 7.3 Hz, 2 H, ArH), 7.49 (d, J = 7.5 Hz, 2 H, ArH), 8.93 (s, 2 H, NH); ^{13}C NMR (125 MHz, $CDCl_3$): 21.4, 37.8, 55.7, 112.6, 113.4, 119.6, 120.1, 120.9, 122.3, 124.0, 126.5, 127.5, 128.6, 129.1, 137.1, 144.4.

3.3.10. 2-((4-Hydroxyphenyl)di(1H-indol-3-yl)methelyl)malononitrile (Table 3, 4b, Entry 5)

Red crystals, mp 126–128 °C. IR: 3407 (OH and NH stretching), 3055 (=CH stretching), 2922 (CH stretching), 2220 (C≡ N), 1611, 1455 (C=C). ^{1}H NMR (500 MHz, $CDCl_3$): 5.30 (s, 1 H, OH), 5.65 (s, 1 H, CH), 6.90 (s, 2 H, CH), 7.00 (d, J= 8.2 Hz, 2 H, ArH), 7.20–7.35 (m, 4 H, ArH), 7.50 (d, J = 8.1 Hz, 2 H, ArH), 7.55–7.70 (m, 4 H, ArH), 9.90 (s, 2 H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): 32.0, 49.0, 111.0, 111.6, 119.5, 122.1, 123.0, 125.8, 128.2, 129.0, 129.5, 132.6, 136.5, 138.0, 143.2, 147.5.

3.3.11. 2-(Di(1H-indol-3-yl)(4-nitrophenyl)methelyl)malononitrile (Table 3, 4b, Entry 7)

Yellow crystals, mp 160–162 °C. IR: 3412 (NH stretching), 3052 (=CH stretching), 2923 (CH stretching), 2257 (C≡ N), 1610, 1456 (C=C). ^{1}H NMR (500 MHz, $CDCl_3$): 5.93 (s, 1 H, CH), 6.94 (s, 2 H, CH), 7.10–7.34 (m, 8 H, ArH), 7.56 (d, J = 8.3 Hz, 2 H, ArH), 7.86 (d, J = 8.2 Hz, 2 H, ArH), 9.30 (s, 2 H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): 36.0, 48.9, 111.0, 112.0, 113.2, 119.7, 120.1, 122.0, 123.7, 124.0, 128.0, 130.5, 133.4, 138.5, 148.0, 149.7.

3.3.12. 2-((4-Fluorophenyl)di(1H-indol-3-yl)methyl)malononitrile (Table 3, 4b, Entry 8)

Red crystals, mp 132–135 °C. IR: 3403 (NH stretching), 3072 (=CH stretching), 2928 (CH stretching), 2215 (C≡ N), 1601, 1476 (C=C). ^{1}H NMR (500 MHz, $CDCl_3$): 5.75 (s, 1 H, CH), 6.97 (s, 2 H, CH), 7.15–7.30 (m, 8 H, ArH), 7.45–7.70 (m, 4 H, ArH), 9.80 (s, 2 H, NH) ^{13}C NMR (125 MHz, $CDCl_3$): 39.9, 48.0, 110.0, 111.2, 116.0, 119.0, 120.6, 121.2, 123.7, 126.2, 128.4, 130.0, 136.7, 138.0, 147.5, 150.1.

4. Conclusion

In this paper, we have reported a remarkable and expedient technique for the rapid synthesis of *mono*- and *bis* (indolyl)methylmalononitriles by one-pot three-component condensation of aldehyde, malononitrile, and indole. ICs of β-CD/CTAB or β-CD/SDS proved to accelerate this reaction. The proposed method can be used to prepare a wide variety of (indolyl)methylmalononitrile derivatives, some of which would need toxic conditions and a long reaction time to be made via other established methods.

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