Indian Journal of Chemistry
Vol. 62, November 2023, pp. 1147-1150
DOI: 10.56042/ijc.v62i11.1580

Synthesis of N-cinnamoyl dipeptide esters and investigation of their self-assembly leading to nanorods formation

Saurabh Shete*[a], Manoj Gavali[b], M M V Ramana[b], Mandar Maduskar[b], Nanabhau Karanjule[a] & Dilip Kumar Yadav[a]

[a] Department of Chemistry, K J Somaiya College of Science and Commerce, Vidyanagar, Vidyavihar, Mumbai 400 077, India
[b] Department of Chemistry, University of Mumbai, Mumbai 400 098, India

E-mail: saurabh@somaiya.edu

Received 19 May 2023; accepted (revised) 18 October 2023

Synthesis of novel N-cinnamoyl dipeptide esters have been carried out under solution phase conditions. The synthesized compounds have been characterized by IR, NMR and mass spectrometry. These compounds readily self-assemble to form nanorods. Their morphology have been studied using SEM and TEM.

Keywords: Peptides, Dipeptides, Self-Assembly, Nanostructures, Nanorods

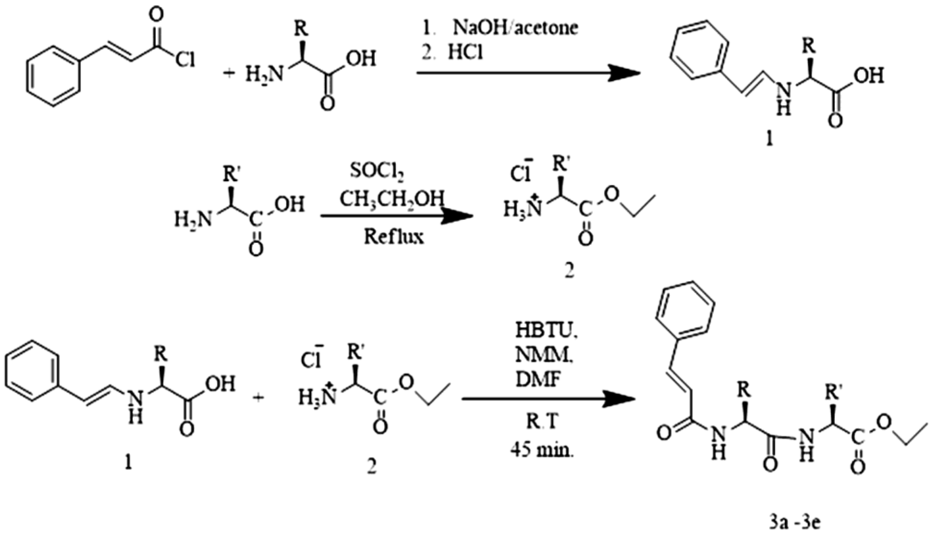
Self-Assembly is the process in which individual components form highly ordered structure under appropriate conditions[1]. The arrangement is held together by weak, non-covalent interactions which include ionic bonds, hydrogen bonds, hydrophobic and Vander Waals interaction. Although the forces involved are weak, their collective strength gives a very stable and robust structure. Peptide nanotubes have been used as templates to design metal porphyrins[2]. Monodisperse peptide nanotubes have also been prepared with the help of polycarbonate membranes[3]. Health *et al*. reported a technique for chemically self-assembling Single Walled Carbon Nano Tubes (SWNTs) to form ropes at room temperature with minimal lithography[4]. Single walled carbon nanotubes can also act as chemical sensors[5] for detecting NO_2 or NH_3.Histidine rich peptides have also been used as templates for making gold nanowires[4]. Peptides showing surfactant like behaviour have also been reported[6]. These peptides consist of a polar head and a non-polar tail consisting of a string of hydrophobic amino acids. Zhang *et al*. have reported the self-assembly of an oligopeptide to form a macroscopic membrane[6]. The advantage of using short peptides for designing nanostructures is that peptides are readily synthesized in good yield and in shorter time. Their properties can be modified with different functional groups, and they are biocompatible.

There are several examples of molecular self-assembly such as folding of polypeptides into protein[7], fabrication of self-assembled monolayers (SAMs) of organic molecules on metal surface, development of semi crystalline thin films of uniform thickness using block copolymer[8], use of hexa-perihexabenzocoronene liquid crystals along with perylene dye for development of photovoltaic technology[9].

Short peptides are simple to synthesize and can be useful as bio models for studying self-assembly[10]. In our present work, we attempted to synthesize five N-Cinnamoyl dipeptide esters. N-Cinnamoyl amino acids have been studied for their anti-bacterial activity[11]. It was used as the starting material for the synthesis of dipeptide esters. Cinnamoyl group can play a key role in π-π stacking interactions to assist molecular self-assembly. The general scheme for the synthesis of N-Cinnamoyl dipeptide ester is as mentioned in Scheme 1.

Experimental Details

The chemicals and solvents were purchased from SRL, Sigma Aldrich and Alfa Aesar and were used without further purification. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on Bruker AVANCE spectrometer. TMS is used as internal standard and DMSO-d_6 as solvent for obtaining NMR spectra. Perkin-Elmer Frontier IR spectrometers was used for IR spectra. Morphological studies were done using 150 KeV Zeiss Ultra Field Emission SEM.



Scheme 1 — General Synthetic Methodology employed for N-Cinnamoyl dipeptide esters

General procedure for the synthesis of N-cinnamoyl dipeptide ester, 3

Synthesis of N-cinnamoyl amino acid, 1

Amino acid (0.010 mol) was dissolved in 3.6 ml of water containing sodium hydroxide (0.010 mol, 0.40 g). 3.6 mL of acetone was added to it. The solution was cooled in an ice bath. Cinnamoyl chloride (0.011mol, 1.8 g) and a solution of Sodium hydroxide (0.011 mol, 0.44 g in 1.8 mL of water) were added alternately to the precooled amino acid solution ensuring that the solution remains alkaline. The resulting solution was continued to stir for an additional one hour. The solution was acidified to pH4 with conc. hydrochloric acid under ice cold conditions. The resulting solid was filtered and washed with cold water and recrystallized from aqueous ethanol to give N-Cinnamoyl amino acid.

Synthesis of Amino acid ester hydrochloride[12], 2

Amino acid (0.010 mol) is added to 45 mL of ethyl alcohol. The resulting suspension is cooled in an ice bath. Thionyl chloride (0.015 mol, 1.78 g) is added to it dropwise. The solution is then refluxed for four hours and refrigerated overnight. Excess alcohol is removed under vacuum to get white crystals of amino acid ester hydrochloride **(2)**. The product is recrystallized from alcohol-ether mixture.

Synthesis of N-cinnamoyl dipeptide ester, 3

A mixture of N-Cinnamoyl-Amino acid (0.010 mol) and HBTU (0.011mol) were stirred in 15 mL of Dimethylformamide at room temperature for 5 minutes. To this N-Methyl Morpholine (0.030 mol, 3.29 mL) and amino acid ester hydrochloride (0.011 mol) were added and the resulting solution was stirred for 45 minutes. The solution was poured in cold water (50 mL). The resulting solid was filtered, recrystallized from ethyl alcohol-water and dried in vacuum to give N-Cinnamoyl-dipeptide ester **(3)**. The yield and melting point of the product obtained is as mentioned in Table 1.

Table 1 — N-Cinnamoyl dipeptide esters synthesized

Compd	R	R’	Yield (%)	m.p. (°C)
3a	-H	-H	68	142
3b	$-CH_3$	-H	73	159
3c	$-CH_2Ph$	-H	64	176
3d	-H	$-CH_2Ph$	65	145
3e	$-CH_3$	$-CH_2Ph$	61	167

3a: m.p 142°C. IR (KBr): 3260 (N-H Stretching), 3081 (Aromatic =C-H), 1740 (C=O ester), 1657 (C=O amide), 1615 (C=O Cinnamamide), 1551 (C=C), 1205 cm^{-1} (C-O stretching); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.17 (t, 3H, *J*= 6Hz, CH_3ester), 3.82-3.88 (m, 4H, two CH_2, Gly), 4.07 (q, 2H, *J*=6Hz, CH_2 ester), 6.72 (d, 1H, *J*=18 Hz, α-CH Cinnamoyl group), 7.36-7.58 (m, 6H, aromatic and β-CH, Cinnamoyl group), 8.35 (t, 1H, NH Gly), 8.41 (t, 1H, NH, Gly); ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.48 (CH_3 ester), 41.12 (CH_2 Gly), 42.38 (CH_2 Gly), 60.91 (CH_2 ester), 122.30 (α-CH Cinnamoyl group), 128.00, 129.40, 129.99, 135.25 (CH, aromatic), 139.54 (β -CH Cinnamoyl group), 165.80 (C=O Cinnamamide), 169.94 (C=O Ester), 170.18 (C=O amide).

3b: m.p 159°C. IR (KBr): 3272 (N-H Stretching), 3059 (Aromatic =C-H), 1759 (C=O ester), 1667 (C=O Amide), 1644 (C=O Cinnamamide), 1604 and 1529

(C=C), 1203 cm^{-1} (C-O stretching); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.170 (t, 3H, *J*=6Hz, CH_3, ester), 1.270 (d, 2H, *J* = 6 Hz, β-CH_3, Ala), 3.820-3.840 (m, 2H, CH_2, Gly), 4.070 (q, 2H, *J* = 6 Hz, CH_2, ester), 4.420 - 4.520 (m, 1H, α-CH, Ala), 6.750 (d, 1H, *J*=15 Hz, α-CH, Cinnamoyl group), 7.350 - 7.560 (m, 6H, aromatic and β-CH, Cinnamoyl group), 8.320 (d,1H,NH, Ala), 8.370 (t,1H,NH, Gly); ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.47 (CH_3, ester), 18.82 (β-CH_3, Ala), 41.14 (CH_2, Gly), 48.48 (α-CH, Ala), 60.84 (CH_2, ester), 122.52 (α-CH, Cinnamoyl group), 127.95, 129.39, 129.92, 135.35aromatic), 139.38 (β-CH, Cinnamoyl group), 166.03 (C=O, Cinnamamide), 170.13 (C=O, ester), 173.28 (C=O, amide).

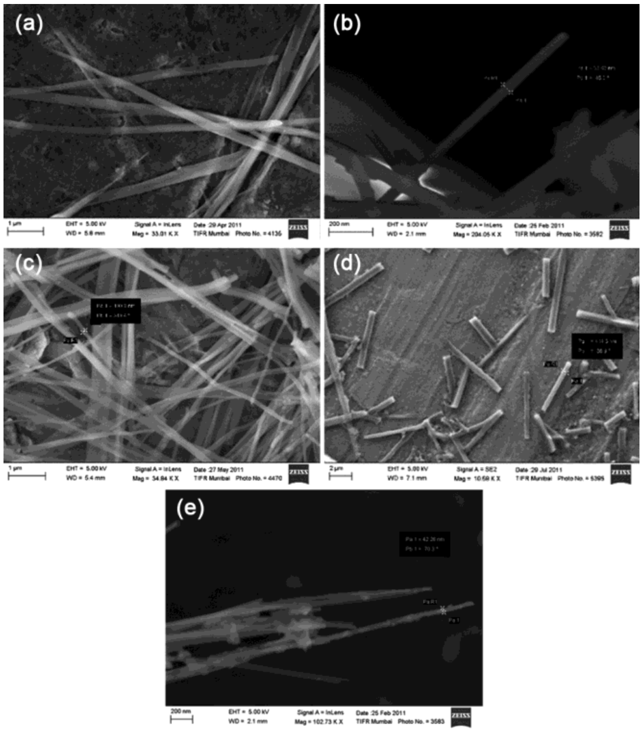


Figure 1 — SEM Images of N-Cinnamoyl-Gly-Gly-OEt (3a), N-Cinnamoyl-Ala-Gly-OEt (3b), N-Cinnamoyl-Phe-Gly-OEt (3c), N-Cinnamoyl-Gly-Phe-OEt (3d) and N-Cinnamoyl-Ala-Gly-OEt (3e)

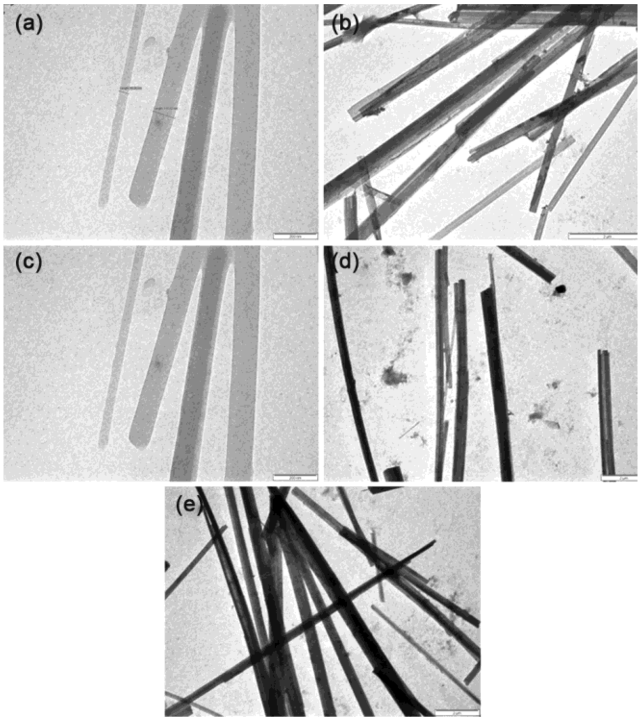


Figure 2 — TEM Images of N-Cinnamoyl-Gly-Gly-OEt (3a), N-Cinnamoyl-Ala-Gly-OEt (3b), N-Cinnamoyl-Phe-Gly-OEt (3c), N-Cinnamoyl-Gly-Phe-OEt (3d) and N-Cinnamoyl-Ala-Gly-OEt (3e)

Results and Discussion

Five novel N-cinnamoyl dipeptide esters were successfully synthesized in good yields. Their morphology was studied using SEM and TEM (Fig. 1 and Fig. 2 respectively). They were found to exhibit nanorods with diameter ranging from 100 nm to about 1.5 µm and length in several micrometres. Thus, the molecular self-assembly in peptides is aided by π-π stacking interactions due to the presence of aromatic ring and π bond present in the cinnamoyl group.

Conclusion

N-Cinnamoyl dipeptide esters will be promising candidates in the form of bio models for prion diseases such as Alzheimer's disease. The ease of synthesis and self-assembly of N-cinnamoyl dipeptide esters will be useful for its potential applications in material science, medicine and biotechnology.

Acknowledgements

The authors are thankful to Department of Chemistry, University of Mumbai for instrumentation access. The authors are grateful to TIFR, Mumbai and SAIF, IIT Bombay for SEM and TEM studies respectively.

Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776.

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