International Journal of ChemTech Research
CODEN(USA): IJCRGG ISSN : 0974-4290
Vol.4, No.4, pp 1654-1657, Oct-Dec 2012

Cyclization of PAMAM G0 and G1 dendrimer using DMAD and 2-benzylidenemalononitrile

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Abstract: The reaction of PAMAM (G0 or G1) with DMAD and 2-benzylidenemalononitrile was carried out and the cyclized products were obtained in high yields, without using special procedure for purification.
Keywords*:* PAMAM, DMAD, 2-Benzylidenemalononitrile, G0, G1.

Introduction and Experimental

PAMAM dendrimers have received lots of attention because of the high density of terminal amine groups that provides a large number of reactive sites for many potential applications. For example, Crooks *et al*. demonstrated that PAMAM dendrimers could be attached to an activated mercaptoundecanoic acid to form self-assembled monolayer by covalent amide linkages. These surface confined dendrimer monolayers were used as chemical sensors and catalytic interfaces[1] .
They are especially attractive for binding metal ions in aqueous solution due to their controlled size[2] . PAMAM dendrimers are carrier molecules for MRI contrast agents and can be applied in the targeted delivery of drugs as well as transfection vectors in gene therapy[3-4] . Intramolecular photo cycloaddition cinnamoyl shell-modified PAMAM dendrimers has been reported[5] . In continuation of our work on dendrimers [6-7] in this paper cyclization of PAMAM G0 and G1 dendrimer using DMAD and 2-benzylidenemalononitrile would be presented.

General

All reactions were performed under an atmosphere pressure. All reagents and solvents, unless otherwise specified, were obtained from Merck Chemical Company. PAMAM dendrimers (G0 and G1) were synthesized according to the established procedure[8] . Melting points were determined using a Bamstead Electrotermal 9200 instrument. IR spectra were recorded on a Shimadzu FT-IR 8400 spectrophotometer with samples prepared as KBr discs. ^{1}H and ^{13}C NMR spectra were recorded at 25 ◦C with Bruker BRX 250 AVANCE using tetramethylsilane as an internal standard. High resolution Mass Spectra were recorded on a Shimadzu GT-17A spectrometer.

The reaction of PAMAM (G0) with DMAD for the synthesis of 1

G0 of PAMAM (1.0 g, 1.0 equiv.) and DMAD (0.577 g, 2.0 equiv.) were dissolved in methanol (20 mL) and heated under reflux for 3 hours. The solvent was evaporated off in vacuum to yield a tar residue which was solidified on standing. It was

then recrystallized from ethanol. The crystalline compound was washed with ethyl acetate (2x 3 mL). This was dissolved in chloroform (10 mL) and filtered. The solvent was evaporated off to leave the pure product of **1** as a pale yellow powder. (1.15 g, 80%), m.p. : 166-167 °C, *m/z* (EI) 736 (M^+); FT-IR: 1620 cm^{-1} (C=C), 1658 cm^{-1} (C=O amide), 1697 cm^{-1} (C=O ester) , 3078 cm^{-1} (C=C-H) , 3201 cm^{-1} (NH amide), 3325 cm^{-1} (NH amide), ^{1}H NMR ($CDCl_3$) : 3.43 (m, 16H, CH_2) , 3.53 (m, 20H, CH_2); 3.70 (s, 6H, OCH_3) , 5.60 (s, 2H, C=CH), 7.87(s, 4H, NH) , 8.29 (s, 4H, NH) , ^{13}C NMR ($CDCl_3$): 30.0 (CH_2), 39.4 (CH_2), 40.6 (CH_2) , 51.1 (CH_3), 86.8 (CO-*C*=C), 149.4 (C=*C*-NH), 162.0 (NHCO) ,171.3 (COO).

The reaction of PAMAM (G1) with DMAD for the synthesis of 2

G1 of PAMAM (1.0 g, 1.0 equiv.) and DMAD (4.0 equiv.) were reacted as those described for **1** to get the product **2** as a pale yellow compound (1.07 g, 82%) m.p.:149-153 °C , FT-IR: 1620 cm^{-1} (C=C), 1658 cm^{-1} (C=O amide), 1697 cm^{-1} (C=O ester) , 3078 cm^{-1} (C=C-H) , 3201 cm^{-1} (NH amide), 3325 cm^{-1} (NH amide); ^{1}H NMR ($CDCl_3$) : 3.44 (m, 48H, CH_2) , 3.53 (m, 52H, CH_2), 3.74 (s, 12H, OCH_3) , 5.60 (s, 4H, C= CH), 7.87(s, 8H, NH) , 8.30 (s, 12H, NH) , ^{13}C NMR ($CDCl_3$): 39.4 (CH_2), 40.6 (CH_2) , 51.1 (CH_3), 86.8 (CO-*C*=C), 149.4 (C=*C*-NH), 162.0 (NHCO) ,171.3 (COO).

The reaction of PAMAM (G0) with 2-Benzylidenemalononitrile for the synthesis of 3

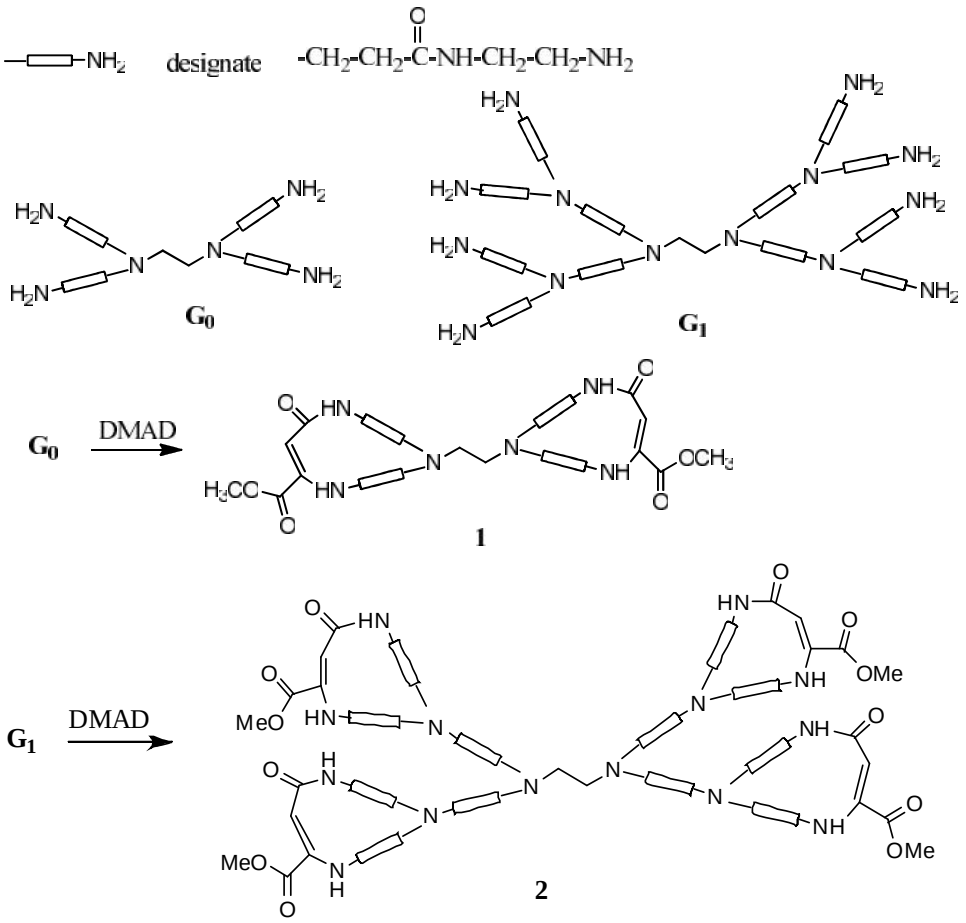
G0 of PAMAM (1.0 g, 1.0 equiv.) and 2-Benzylidenemalononitrile (0.66 g, 2.0 equiv.) were dissolved in methanol (20 mL) and heated under reflux for 3 hours. The solvent was evaporated off in vacuum to yield a tar residue which was solidified on standing. It was then recrystallized from ethanol to give the product **3** as a pale brown crystals (1.1 g, 70%) m.p.: 269-272 °C, *m/z* (EI) 824 (M^+), FT-IR : 2198 cm^{-1} (CN), 700, and 733 cm^{-1} (Ar) , 1566 cm^{-1} (C=C, Ar), 1643 cm^{-1} (C=O amide) , 3201 and 3340 cm^{-1} (NH_2); ^{1}H NMR (DMSO): , 3.30 (m, 4H , *NH*CH_2), 3.32 (m , 28 H, CH_2) , 3.48 (m , 8H, CH_2) , 4.11 (s , 2H , Ar-CH) , 7.31 (m , 10 H, Ar) , 8.01 (broad, 8H, NHCO and NH_2); ^{13}C NMR (DMSO) : 46.6 (CH_2), 52.7 (CH_2), 71.8 (PhCH), 80.5 (CN-*C*=C), 117.2 (CN), 128.2, 128.9, 130.3, 135.6, 152.7, 154.3 (CNC=*C*NH_2), 160.0 (CO).

The reaction of PAMAM (G1) with 2-Benzylidenemalononitrile for the synthesis of 4

G1 of PAMAM (1.0 g, 1.0 equiv.) and 2-Benzylidenemalononitrile (0.45 g, 4.0 equiv.) were reacted as those described for **3** to get the product **4**, pale brown oil , (1.05 g, 73%) m.p.: 256-259 °C ; FT-IR : 2198.7 (CN) , 1473.5 and 1566.1 cm^{-1} , 3201.6 cm^{-1} , 3340.5 cm^{-1} (NH) , 1643.2 cm^{-1} (C=O amid); ^{1}H NMR (DMSO): 3.30 (8H, *NH*CH_2), 3.35(m , 52 H, CH_2) , 3.48 (m , 48H, CH_2) , 4.01 (s , 4H, Ar-CH) , 7.31(m , 20 H, Ar) , 8.02(broad, 20H, NHCO and NH_2) ,; ^{13}C NMR (DMSO) : 46.6 (CH_2), 52.7 (CH_2), 71.8 (Ar-CH), 80.5 (CN-*C*=C), 117.2 (CN), 128.2, 128.9, 130.3, 135.6, 152.7, 154.3 (CNC=*C*NH_2), 160.0 (CO).

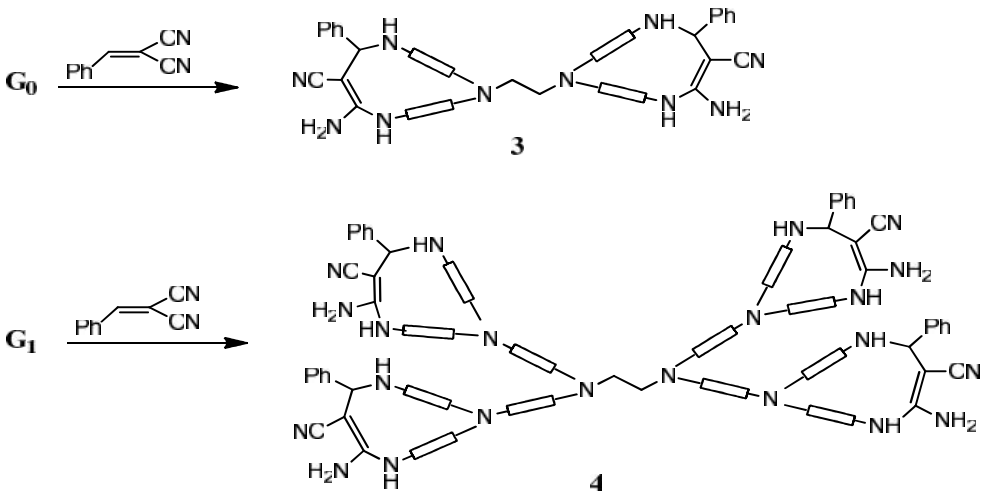
Results and Discussion

PAMAM (G0 or G1) and DMAD (2.0 and 4.0 equivalents, respectively) were heated under reflux for 3 hours and the cyclized products were obtained in high yields without using special procedure for purification such as flash column chromatography. Compound **1** has been satisfactorily characterized by mass spectrometry. Comparison of the FTIR and ^{1}H NMR spectra of the products **1** and **2** with those of G0 and G1, respectively confirmed the occurrence of double-bond addition (Scheme 1). It shows the absorption at 1620 cm^{-1} and at 1658 cm^{-1} for C=C and C=O (amide) stretching, correspondingly. Also absorptions at 3078 and 1697 cm^{-1} are characteristic for vinylic C-H and ester C=O stretching, respectively. This can be further evidenced by ^{1}H NMR spectrum from the strong signal of vinyl proton at 5.6 ppm. The ^{13}C NMR spectra of **1** and **2** were recorded to obtain more information about the DMAD addition reactions. The signals at 86.8 and 149.4 ppm for C=C and that of 171.3 ppm (COO) indicates that the addition occurs at the main reaction (Scheme 1).



Scheme 1: The reaction of G0 and G1 with DMAD

In the other cyclization reaction PAMAM (G0 and G1) was reacted with 2-benzylidenemalononitrile, in 2 and 4 equivalents, respectively (Scheme 2). Both compounds **3** and **4** derivative of G0 and G1 exhibited a signal in the ^{13}C NMR spectrum at 117.2 ppm for the nitrile carbon, and showed absorption at 2198 cm^{-1} (CN) in the infrared spectrum. There are also two bands, characteristic of primary amines which could be observed in the region of 3201 and 3340 cm^{-1}. Compound **3** was satisfactorily characterized by mass spectrometry.



Scheme 2: The reaction of G0 and G1 with 2-Benzylidenemalononitrile

In conclusion, a general and convenient method for the cyclization of PAMAM (G0 or G1) with DMAD and 2-benzylidenemalononitrile has been developed and the cyclized products were obtained in high yields, without using special procedure for purification. The main advantages of these reactions are mild reaction conditions and high yields. The new compounds could be of interest in carrier molecules for MRI contrast agents and in the targeted delivery of drugs as well as transfection vectors in gene therapy[3-4] .

Acknowledgment

We are grateful to the Research Council of Payame Noor University, I. R. of Iran, for the financial support of this work.

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