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Microwave-assisted solvent-free synthesis and antibacterial evaluation of 1-azabicyclo[3.1.0]hexane-3-enes

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Abstract

This work described a simple and efficient method for the synthesis of 1-azabicyclo[3.1.0]hexane-3-ene derivatives. arylidenmalononitriles and hydroxylamine hydrochloride in the presence of NaOH, under microwave irradiation and solvent-free conditions producing the titled compounds in good to excellent yields. Using of simple chemicals, short reaction times, and solvent-free conditions, high yields of products, high atomic economy , and eco-friendly are the important advantages of this method. The antibacterial effect of 4-amino-2,6-bis(2,4-dichlorophenyl)-1-azabicyclo[3.1.0]hex-3-ene-3,5-dicarbonitrile was evaluated by minimum inhibitory concentration and disk diffusion method against the standard strains of *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Minimum inhibitory concentrations of **2h** were 40 and 30 mg/mL for *P. aeruginosa* and *S. aureus* respectively and the maximum inhibitory zones were 4 and 5 mm on average, respectively.

Keywords: Azabicyclo; microwave irradiation; antibactery; solvent-free; Staphylococcus.

Introduction

Nitrogen-bridged heterocyclic compounds are of biological and pharmacological interest. They are found in natural products, alkaloids and especially in aza-bicyclic compounds. Because of their exclusive properties, most of them are candidate for drug discovery. The prominent biological activities of aza-bicyclic compounds are included in antibacterial and antimicrobial activities, and inhibitors for the microsomal prostaglandin E2, and anti-depressant and anti-malarial, and anti-hypoglycemic and anti-hypertensive. Aza-bicyclo[3.1.0]hexane derivatives have been reported to be used as an efficient plant male gametocide, hepatitis C protease inhibitors and so on [1-3].

In the past decades, many methods have been reported for the synthesis of nitrogen-bridged[4-11] and nitrogen contaningheterocyclic compounds [12-32].The most important reported synthetic methods are included: (I) intramolecular nucleophilic substitution due to the leaving group capacity of the oxygen substituent of 3-methoxypiperidine [33], (II) a three-component reaction between alkyl aryl(hetaryl)ketoximes, acetylene, and

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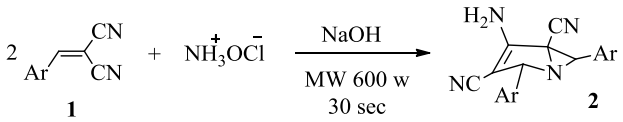
aliphatic ketones in the super basic systems KOH/DMSO and LiOH/CsF/DMSO [34], (III) reaction between ammonium acetate, cyclohexanone and arylaldehydes [35], (IV) reaction between *trans*-ketoaziridine and 1-phenyl-3-arylpyrazole-4-carbaldehydes[36], (V) iodine-mediated domino reaction from easily prepared *N*-allyl enamines [1], (VI) electrolysis of arylidenemalononitriles and malononitrile in alcohols[37], three-component reaction between arylaldehydes, malononitrile and, hydroxylamine hydrochloride in water [38]. Most of the reported methods for the synthesis of aza-bicyclo[3.1.0]hexanes suffer from long reactions times, low reactions yields, using organic solvents and relatively rare starting materials.

Microbial diseases present a significant clinical interest, because some species of bacteria are more virulent than the others and show alteration in sensibility to the conventional antimicrobial drugs, mainly species of the genera *Staphylococcus, Pseudomonas, Enterococcus,* and *Pneumococcus* [39]. The extensive use of the penicillin since the Second World War, promoted the appearance of the first strains of penicillin-resistant bacteria [40].

Antimicrobial resistance is a complex problem that is spreading globally and it is threading all people in all countries. *Pseudomonas aeruginosa* is an opportunistic pathogen causing severe, acute and chronic hospital-associated (nosocomial) infections in burn and immunodeficiency patients [41]. *Staphylococcus aureus* can cause some skin diseases and it is also known as a nosocomial agent. In recent years some strains have shown resistance to as many as 20 compounds [42]. Hence, lots of extensive researches have been launched for achieving new antimicrobial medicines. Despite progress in development of antibacterial agents, there are still special needs to find new antibacterial agents due to development of multidrug resistant bacteria [43].

As a part of our efforts on the development of simple methods to prepare biologically active organic compounds [44-49], and due to the unique chemistry of aza-bicyclic compounds and their biological activity, we report herein a facile route to produce 1-azabicyclo[3.1.0]hexane-3-enes under solvent-free and microwave irradiation conditions (Scheme 1 and Table 1).



Scheme 1. A pseudo three-component reaction to the synthesis of 1-azabicyclo[3.1.0]hexane-3-ene 2 derivatives

Experimental

General information

All chemicals and culture media were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. Arylidenmalononitriles **1** were synthesized by Knoevenagel condensation between arylaldehyde and malononitrile over magnesium phosphates [44], the progress of the reaction was monitored by TLC.

Melting points were measured on an Electro-thermal 9100 apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra ($CDCl_3$ and DMSO-d_6) were recorded on a BRUKER DRX-300 AVANCE spectrometer at 300.1 and 75.4 MHz respectively. Elemental analyses for C, H and N were performed using a CHN-O-Rapid analyzer and the instrument model was Eager 300 for EA11112. The experiments were performed using a microwave oven (ETHOS 1600, Milestone) with a maximum power of 900 Watts specially designed for organic synthesis.

General procedure for the synthesis of 4-amino-2,6-diphenyl-1-azabicyclo[3.1.0]hex-3-ene-3,5-dicarbonitrile 2a

The reaction was carried out by first mixing benzylidenemalononitrile **1** (1 mmol, 0.154 g), hydroxylamine hydrochloride (1 mmol, 0.069 g), and NaOH (1 mmol, 0.040 g), then heating them under microwave irradiation at 600 watts for 30 seconds in solvent free condition. Reaction monitoring by TLC clearly indicated formation of the corresponding 1-azabicyclo[3.1.0]hexane-3-ene **2a**. Upon completion, the reaction mixture was cooled to room temperature and the product was separated by dissolving the reaction mixture in boiling ethanol, and then the product **2a** was obtained as light yellow crystals; yield = 0.236 g (83 %). The structures of the isolated products **2a-h** were deduced from their ^{1}H and ^{13}C NMR spectral data and their melting points values. The melting points values, and spectral data of compounds **2a-h**, were also in good agreement with those of authentic samples [38].

Evaluation of antibacterial effects

The antibacterial effect of 4-amino-2,6-bis(2,4-dichlorolphenyl)-1-azabicyclo[3.1.0]hex-3-ene-3,5-dicarbonitrile **2h** was evaluated by minimum inhibitory concentration (MIC) and disk diffusion methods on the gram positive and gram negative bacteria.

The microorganisms which were used in the experiment were standard strains of *staphylococcus aureus* ATCC25923 (The gram-positive bacterium) and *pseudomonas aeruginosa* ATCC27853 (The gram-negative bacterium).

Minimum Inhibitory concentration (MIC) of **2h** was determined by broth tube dilution technique [32]. The strains were inoculated in 10 ml of MHB (Muller Hinton Broth) and incubated at 37 °C for 24 h. Cultures then adjusted to a concentration of 10^8 CFU/mL by making a suspension in 0.9% saline solution matching to the 0.5 McFarland turbidity standards, in order to inoculate the same dose of bacteria in repeating the experiment. The absorbance of the cultured media was also determined at 600 nm, using the spectrophotometer apparatus. To do the MIC, 10 tubes containing 1ml of MHB and 1 mL of 0.5 MacFarland bacterial suspensions were used. The concentration of **2h** in each tube was determined as follow; 2, 5, 10, 15, 20, 25, 30, 35, 40, 45 mg/ mL. The cultures were incubated at 37 °C for 24 h.

The antibacterial effect of **2h** was also evaluated with Kirby-Bauer disk diffusion method [51]. Using a sterile swap, aliquots from the 0.5 McFarland bacterial suspensions were spread on dishes with MHA (Muller Hinton Agar). Sterile blank paper disks were then placed on MHA surface and 40 and 30 mg/mL of **2h** were added per disk of *Pseudomonas aeruginosa* and *Staphylococcus aureus* respectively.

The disks soaked with sterile distilled water and ethanol, were used as negative control. Then the halos of bacterial growth inhibition were measured.

The characterization data of the compounds **2a-h** are given below.

4-Amino-2,6-bis (phenyl)-1-aza-bicyclo[3.1.0]hex-3-ene-3,5-dicarbonitrile, (2a, $C_{19}H_{14}N_4$)

Light yellow crystals; yield: 79 %; isolated products: 0.23 gr; IR (KBr): 3379 (s), 3346 (m), 3281 (w), 3218 (s), 2259 (w), 2206 (s), 1671 (s), 1619 (s), 1428 (w), 774 (m), 695 (s) and 531 cm^{-1} (m); ^{1}H NMR (299.9 MHz, $CDCl_3$, 25°C, TMS): δ=3.37 (s, 1H; CH), 4.96 (s, 1H), 5.03 (br. s, 2H; NH_2), 7.42 ppm (m, 10H; 10CH); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25°C, TMS): δ=41.96 (CH), 56.82 (C), (CH), 73.51(C), 78.33 (C), 113.14 and 15.01 (2CN), 126.71, 127.43, 128.68, 128.76, 128.99, 129.24 and 129.49 (10 CH), 132.04 and 139.85 (2C), 154.26 ppm (C-NH_2); Anal.Calcd for ($C_{19}H_{14}N_4$), (298.34), C, 76.49; H, 4.73; N, 18.78: Found: C, 76.47 ; H, 4.70; N, 18.75 %.

4-Amino-2,6-bis(4-methylphenyl)-1-aza-bicyclo[3.1.0]hex-3-ene-3,5-dicarbonitrile (2b, $C_{21}H_{16}N_4$)

Yellow crystals; yield: 80 %; isolated products: 0.26 gr; IR (KBr): 3443 (s), 3334 (s), 2922 (m), 2193 (s), 1652 (s), 1606 (s), 1510 (w), 1418 (m), 1156 (s), 810 (m), 603 (m) and 499 cm^{-1} (w); ^{1}H NMR (299.9 MHz, $CDCl_3$, 25°C, TMS): δ=2.27 and 2.28 (2s, 6H; 2 CH_3), 3.21 (s, 1H; CH), 4.77 (s, 1H; CH), 6.15 (br. s, 2H; NH_2), 7.08 (d, ^3J(H,H)=8.09 Hz, 2H; 2CH), 7.12 (d, ^3J(H,H)=8.1 Hz, 2H; 2CH), 7.19 (d, ^3J(H,H)=7.8 Hz, 2H; 2CH), 7.21 (d, ^3J(H,H)=8.1 Hz, 2H; 2CH); ^{13}C NMR (75.4 MHz, $CDCl_3$, 25°C, TMS): δ=21.19, 21.25 ($2CH_3$), 49.28 (CH), 54.12 (C), 71.52 (CH), 72.84 (C), 114.85 and 116.92 (2CN), 126.75, 127.35, 129.23 and 129.49 (8CH), 137.65, 138.20, 138.85 and 139.06 (4C), 155.28 ppm (C-NH_2); Anal.Calcd for ($C_{21}H_{16}N_4$), (324.38), C, 77.28; H, 5.56; N, 17.17: Found: C, 77.30; H, 5.55; N, 17.13 %.

4-Amino-2,6-bis (4-methoxyphenyl)-1-aza-bicyclo[3.1.0]hex-3-ene-3,5-dicarbonitrile (2c, $C_{19}H_{18}N_4O_2$)

Light yellow crystals; yield: 92 %; isolated products: 0.31 gr; IR (KBr): 3378 (s), 3012 (m), 2231 (s),1659 (s), 1621 (s), 1578 (s), 1122 (m), 750 (s), 564 (m) and 413 cm^{-1} (w); ^{1}H NMR (250.1 MHz, $CDCl_3$, 25°C, TMS): δ=3.30 (S, 1H; CH), 3.80 and 3.83 (2S, 6H; $2OCH_3$), 4.88 (s, 1H; CH), 5.03 (br. S, 2H; NH_2), 6.89 (d, ^3J(H,H)=8.7, 2H; 2CH), 6.95 (d, ^3J(H,H)=8.7, 2H; 2CH), 7.30 (d, ^3J(H,H)=8.5, 2H; 2CH), 7.33 ppm (d, ^3J(H,H)=8.2, 2H; 2CH); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25°C, TMS): δ=55.32 ($2OCH_3$), 55.54 (C), 56.90 (CH), 73.21 (CH), 76.47 (C), 114.16 (2CH), 114.30 (CN), 114.33 (2CH), 114.66 (CN), 128.10 and, 128.68 (4CH), 129.83 and 132.50 (2C), 150.16 and 152.42 (2C), 153.99 ppm (C-NH_2); Anal.Calcd for ($C_{19}H_{18}N_4O_2$), (334.37), C, 70.38; H, 5.06; N, 15.63; Found: C, 70.45; H, 5.11; N, 15.74 %.

4-Amino-2,6-bis(4-cholorophenyl)-1-aza-bicyclo[3.1.0]hex-3-ene-3,5-dicarbonitrile (2d, $C_{19}H_{12}N_4Cl_2$)

White crystals; yield: 78 %; isolated products:.0.29 gr; IR (KBr): 3428 (s), 3333 (m), 2202 (s), 1653 (s), 1606 (m), 1487 (m), 1390 (m), 1069 (s), 1013 (m) and 814 cm^{-1} (m); ^{1}H NMR (299.9 MHz, $CDCl_3$, 25°C, TMS): δ=3.26 (s, 1H; CH), 4.81 (s, 1H; CH), 6.38 (br. s, 2H; NH_2),7.29 ppm (m, 8H; 8CH); ^{13}C NMR (75.4 MHz, $CDCl_3$, 25°C, TMS): δ=49.23 (CH), 55.37 (C), 72.51 (CH),

74.73 (C), 113.77 and 115.82 (2CN), 122.36, 123.34 (2C), 128.50 and 129.11 (4CH), 131.55 (C), 131.72 and 131.93 (4CH), 139.52 and 155.40 ppm (2C). Anal.Calcd for ($C_{19}H_{12}N_4Cl_2$), (367.23), C, 62.14; H, 3.29; Cl, 19.31; N, 15.26: Found: C, 62.10; H, 3.27; Cl, 19.29; N, 15.24 %.

4-Amino-2,6-bis(4-bromophenyl)-1-aza-bicyclo[3.1.0]hex-3-ene-3,5-dicarbonitrile (2e, $C_{19}H_{12}N_4Br_2$)

White crystals; yield: 90%; isolated products: 0.41 gr; IR (KBr): 3427 (s), 3332 (s), 2244(s), 2199 (m), 1651 (s), 1604 (m), 1484 (m), 1387 (m), 1012 (m), 814 (s), and 492 cm^{-1} (m); ^1H NMR (299.9 MHz, $CDCl_3$, 25°C, TMS): δ=3.34 (s, 1H; CH), 4.91 (s, 1H; CH), 5.10 (br. s, 2H; NH_2), 7.28 (d, ^3J(H,H)=8.7 Hz, 2H, 2CH), 7.30 (d, ^3J(H,H)=8.7 Hz; 2H), 7.54 (d, ^3J(H,H)=8.4 Hz, 2H), 7.58 ppm (d, *J* = 8.4 Hz, 2H; 2CH).^{13}C NMR (75.4 MHz, $CDCl_3$, 25°C, TMS): δ=49.28 (CH), 54.12 (C), 71.52 (CH), 72.84 (C), 114.85 and 116.92 (2CN), 121.79 and 122.62 (2C), 129.45, 130.04, 131.86 and 132.25 (8CH), 133.19 (C), 141.46 (C), 155.88 ppm (C-NH_2). Anal.Calcd for $C_{19}H_{12}Br_2N_4$ (456.13), C, 50.03; H, 2.65; Br, 35.04; N, 12.28): Found: C, 50.10; H, 2.68; Br, 35.08; N, 12.33%.

4-Amino-2,6-bis(4-Nitrophenyl)-1-aza-bicyclo[3.1.0]hex-3-ene-3,5-dicarbonitrile (2f, $C_{19}H_{12}N_6O_4$)

Dark crystals; yield: 75 %; isolated products: 0.29 gr; IR (KBr): 3433 (s), 3352 (m), 2226 (s), 2132 (m), 1649 (s), 1611 (m), 1458 (m), 1361 (m), 1019 (m), 752 (s), and 412 cm^{-1} (m); ^1H NMR (299.9 MHz, $CDCl_3$, 25°C, TMS): δ=3.49 (s, CH; CH). 5.03 (s, CH; CH), 6.50 (br. s, 2H; NH_2), 7.59 (d, *j*= 8.7 Hz, 2H), 7.61 (d,^3J(H,H)= 8.7, 2H), 8.13 (d, ^3J(H,H)=8.6 Hz, 2H, 2CH), 8.18 ppm (d, ^3J(H,H)=8.7 Hz, 2H, 2CH); ^{13}C NMR (75.4 MHz, $CDCl_3$, 25°C, TMS): δ=40.03 (CH), 40.86 (C), 54.39 (CH), 77.70 (C), 113.24 and 115.18 (2CN), 123.71, 124.11 127.56, 128.59 (8CH), 139.35 and 147.23 (2C), 147.80 and 148.26 (2C-NO_2), 155.46 ppm (C-NH_2); Anal.Calcd for ($C_{19}H_{12}N_6O_4$), (388.34), C, 58.76; H, 3.11; N, 21.64; Found: C, 58.70; H, 3.09; N, 21.63 %.

4-Amino-2,6-bis(2-cholorophenyl)-1-aza-bicyclo[3.1.0]hex-3-ene-3,5-dicarbonitrile (2g, $C_{19}H_{12}N_4Cl_2$)

Lemon-colored crystals; yield: 89 %; isolated products: 0.33 gr; IR (KBr): 3292 (s), 3189 (s), 2287 (s), 2180 (m), 1665 (s), 1649 (s), 1433 (m), 654 (m), 545 (m) and 490 cm^{-1} (m); ^1H NMR (299.9 MHz, $CDCl_3$, 25°C, TMS): δ=3.55 (s, 1H; CH), 5.29 (s, 1H; CH), 6.53 (br. s, 2H; NH_2), 7.19 (m, 3H; 3CH),7.31 (d.t, ^3J(H,H)=7.8 and 2.1 Hz, 2H; 2CH), 7.34 (d.t, ^3J(H,H)=7.8 and 2.1 Hz, 2H; 2CH), 7.44 ppm (d.d, ^3J(H,H)=6.9 and 2.7 Hz, 1H; CH); ^{13}C NMR (75.4 MHz, $CDCl_3$, 25°C, TMS): δ=48.55 (C), 54.28 (CH), 69.91 (CH), 72.71 (C), 113.61 and 113.69 (2CN), 115.79 (C), 127.17, 127.41, 128,72, 128,90, 129.08, 129.15, 130.24 and 130.58 (8 CH), 133.44 and 134.10 (2C-Cl), 137.35 (C), 156.19 ppm (C-NH_2); Anal.Calcd for ($C_{19}H_{12}N_4Cl_2$), (367.23), C, 62.14; H, 3.29; Cl, 19.31; N, 15.26: Found: C, 62.17; H, 3.31; Cl, 19.29, N, 15.28 %.

4-Amino-2,6-bis(2,4 dicholorophenyl)-1-aza-bicyclo[3.1.0]hex-3-ene-3,5-dicarbonitrile (2h, $C_{19}H_{10}N_4Cl_4$)

Opalescent crystals; yield: 93 %; isolated products: 0.40 gr; IR (KBr): 3458 (s), 3328 (s), 3219 (m), 2200 (s), 1655 (s), 1599 (m), 1470 (m), 1378 (m), 1099 (m), 819 (m), 630 (m), and 445 cm^{-1} (w); ^1H NMR (299.9 MHz,

$CDCl_3$, 25°C, TMS): δ=3.49 (s, 1H; CH), 5.22 (s, 1 H; CH), 6.69 (br. s, 2H; NH_2), 7.15 (d, ^3J(H,H)=8.4 Hz, 1H; CH), 7.25 (m, 2H; 3CH), 7.35 ppm (m, 3H; 3CH); ^{13}C NMR (75.4 MHz, $CDCl_3$, 25°C, TMS): δ=48.52 (C), 53.58 (CH), 69.38 (CH), 72.06 (C), 113.39 and 115.56 (2CN), 127.60, 127.70 (2CH), 129.02 (C), 129.10, 129.65, 129.73 and 129.99 (4CH), 134.20, 134.76, 134.94, 135.63 and 135.94 (5C), 156.12 ppm (C-NH_2); Anal.Calcd for ($C_{19}H_{10}N_4C_{l4}$), (436.12), C, 52.33; H, 2.31; Cl, 32.52; N, 12.85: Found: C, 52.24; H, 4.29; Cl, 32.49, N, 12.81 %.

Table 1. Microwave–assisted synthesis of 1-azabicyclop[3.1.0]hexenes 2 in solvent-free conditions

Product 2	Ar	Yield[a]/ %	m.p /°C
2a	Ph	83	167-169
2b	4-MePh	86	173-176
2c	4-MeOPh	95	184-186
2d	4-ClPh	90	203-208
2e	4-BrPh	85	196-199
2f	4-NO_2Ph	78	177-180
2g	2-ClPh	86	157-159
2h	2,4-Cl_2Ph	89	190-192

[a]Isolated yields

Table 2. Synthesis of **2a** at various microwave powers and times

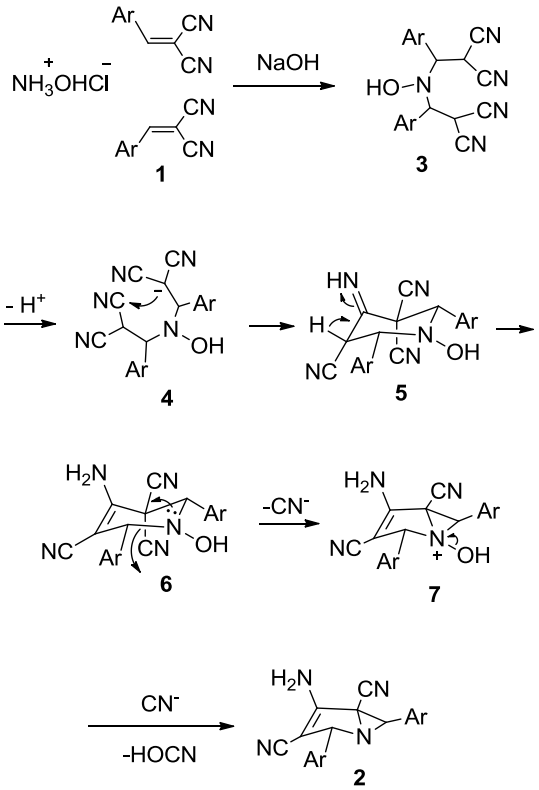
Entry	Microwave power/ watts	Time/ seconds	Yeild[a]/ %
1	100	30	5
2	180	30	8
3	300	30	18
4	450	30	30
5	600	30	83
6	900	30	57
7	600	45	64
8	600	60	52
9	900	15	65
10	900	45	43

[a]Isolated yields

Results and discussion

Microwave irradiation plays a significant role in many chemical syntheses and also in the presented method. The method was promoted rapidly by microwave irradiation for the synthesis of 1-azabicyclo[0,1,3]hexane-3-ene **2**. It provides the required activate energy for this reaction conveniently. To optimize this reaction, the **2a** preparation was selected as a model, and then the effects of microwave power to the reaction yields were tested. The results were indicated in Table 2. As can be seen from Table 2, at low and high microwave powers, the reaction yields were low. It may be because of low reaction rate and being incomplete at low temperatures, and also formation of the other byproducts at high powers. According to the Tables 2 the highest yield was obtained under microwave irradiation 600 watts for 30 seconds.

A proposed mechanistic pathway for the reaction is provided in Scheme 2, it is reasonable to assume that the first step may involve Michael addition of one molecule of hydroxylamine hydrochloride to two molecules of 2-benzylidenemalononitrile **1** to form the intermediate **3**, deprotonation. then cyclization of intermediate **3** gives 1-hydroxy-4-iminopiperidine **5** which undergoes a [1,3] H-shift producing enamine **6**. The nitrile elimination and intramolecular cyclization of **6** [10] along with elimination of OH moiety produce 4-amino-2,6-diaryl-1-azabicyclo[3.1.0]hex-3-ene-3,5-dicarbonitrile **2** (Scheme 2).



Scheme 2. A possible mechanism for the synthesis of 1-azabicyclo[3.1.0]hexane-3-ene derivatives

In order to evaluate the antibacterial effect of 4-amino-2,6-bis(2,4-dichlorolphenyl)-1-azabicyclo[3.1.0]hex-3-ene-3,5-dicarbonitrile **2h**, we determined the Minimum Inhibitory concentration (MIC) of **2h** and used the disc diffusion method then. Minimum Inhibitory concentrations of **2h** were 40 and 30 mg/mL for *P. aeruginosa* and *S. aureus* respectively. The halos of bacterial growth inhibition were measured then. Maximum inhibitory zones were 4 and 5 mm on average, respectively.

Although the results showed that this new chemical has antimicrobial effect against some bacteria such as Pseudomonas aeruginosa and Staphylococcus aureus, there are still more investigations needed; particularly its effects on the human body used as an antimicrobial medicine.

Conclusion

In conclusion, we have developed a simple and efficient method for the synthesis of -azabicyclo[3.1.0]hexane-3-enes in Solvent-free and microwave irradiation conditions. Use of simple chemicals, high yields of products, short reaction times, and eco-friendly, and high atomic economy are the important advantages of this method. The investigation of the antibacterial effect of 4-amino-2,6-bis(2,4-dichlorolphenyl)-1-azabicyclo[3.1.0]hex-3-ene-3,5-dicarbonitrile **2h**, showed that, it has antimicrobial effect against some bacteria such as *Pseudomonas aeruginosa* and *Staphylococcus aureus*.

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