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A Qatar Foundation Academic Journal

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Research article

Synthesis, antimicrobial, antioxidant and insect antifeedant activities of some aryl bicyclo[2.2.1]heptene-2-yl-methanones

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ABSTRACT

Background: The aim of this study was to synthesize aryl heptene[2.2.1]methanone derivatives, including 2-naphthyl-based heptene[2.2.1]methanones, by an aqueous phase fly-ash catalyzed [4+2] cycloaddition Diels-Alder reaction of cyclopentadiene and aryl chalcones: to evaluate their antimicrobial, antioxidant and insect antifeedant activities.

Methods: Green solvent ethanol-assisted aqueous phase fly-ash catalyzed [4+2] cycloaddition Diels-Alder reaction, was adopted for the synthesis of aryl heptene[2.2.1]methanone derivatives. These methanones were characterized by IR, NMR and mass spectroscopical data. The antimicrobial and antioxidant activities of the synthesized methanones were evaluated using *E. coli, S. aureus, P. aeruginosa, K. pneumonia, P. vulgaris* and *E. faecalis* bacteria, fungal species, DPPH radical scavenging and 4^{th} instar larvae *Achoea Janata L* castor leaf disc, bio-assay methods.

Results: Yields of the synthesized aryl heptene[2.2.1]methanone derivatives were over 60%. All compounds resulted in a 20–24 mm zone of inhibition for at least one bacterial strain. Methanones 13, 14, 16, 18 and 19 resulted in maximal antifungal activities against *C. albicans, Penicillium sp.* and *A. niger* fungal species. Compound 17 shows significant anti- oxidant activity against DPPH radical scavenging activity. Ketone 13 resulted in maximal insect antifeedant activities of methanones (compounds 11–19).

Conclusion: A series of methanone derivatives have been synthesized by aqueous-phase fly-ash-catalyzed Diels-Alder [4+2] cycloaddition of cyclopentadiene and aryl *E*-chalcones. The parent, halogen and dimethylamino substituted compounds shown significant antibacterial activity against *P. vulgaris, E. coli, S. aureus, P. aeruginosa, K. pneumonia* and *E. faecalis* bacterial strains. Methanone that possesses dimethylamino, halogens, methoxy and nitro substituents shows significant antifungal activities against *C.albicans, Penicillium sp.* and *A. niger* fungal strains. Antioxidant activities were measured; the compounds containing hydroxy and methoxy substituents showed antioxidant activity. Compound 13 shows insect antifeedant activity against the 4^{th} instar larvae *Achoea Janata L.*

Keywords: Diels-Alder reaction, bicyclo[2.2.1]heptene-2-yl-methanones, antimicrobial activities, antioxidant activity, insect antifeedant activity

http://dx.doi.org/10.5339/connect.2014.18

Submitted: 21 April 2014
Accepted: 12 June 2014

QSCIENCE.com
An Initiative of Qatar Foundation

Cite this article as: Thirunarayanan G. Synthesis, antimicrobial, antioxidant and insect antifeedant activities of some aryl bicyclo[2.2.1]heptene-2-yl-methanones, *QScience Connect* 2014:18 http://dx.doi.org/10.5339/connect.2014.18

INTRODUCTION

The reactivity, selectivity, endo-, exo-mechanistic aspects and solvent effects of this Diels-Alder[4+2] reaction have been reported.[1–5] The aqueous phase Diels-Alder reaction is important for the synthesis of organic substrates, especially bicyclo compounds with stereo selectivity and specificity, and the procedure can be carried out safely with good yields, without the generation of hazardous waste.[6–8] Rideout and Breslow[9] have studied the aqueous phase reaction of cyclopentadiene and vinyl methyl ketones in water, and the reaction rate is more than 700 times faster than in organic solvents. Many catalysts, including Lewis acids,[3] Bronsted acids,[3,10] asymmetric catalysts with helical polymers,[11] Cu^{2+} ion-mediated nanotubes[12], DNA and micellar-based catalysts[7,13–16] have been employed for this [4+2] cycloaddition Diels-Alder reaction of cyclopentadiene(diene) and *E*-chalcones (dienophiles). Fly-ash, a byproduct of industrial combustion, contains many chemical compounds[17–21] such as, SiO_2, Fe_2O_3, Al_2O_3, CaO, MgO, organic mud and insoluble residues. This waste fly-ash can be used as catalyst for organic synthesis. The fly-ash particles are in the silt-sized range of 2–50 microns[22]. Glass, mullite-quartz and magnetic spinel are the three major mineralogical matrices identified in fly-ash. The elements Si, Al, Fe, Ca, C, Mg, K, Na, S, Ti, P and Mn are the constituents of fly-ash. The solubility of fly-ash has been extensively investigated and it is largely dependent on factors specific to the extraction procedure. Long-term leaching studies predict that fly-ash will lose substantial amounts of soluble salts over time, but simulation models predict that the loss of trace elements from fly-ash deposits through leaching will be very slow. Small amounts of radioisotopes also are found in fly-ash but do not appear to be hazardous. The synthesis of 2-naphthyl based-heptane[2.2.1]methanones by aqueous phase fly-ash catalyzed Diels-Alder reaction of cyclopentadiene and 2-naphthyl chalcones has not been reported.

Hence, the author has synthesized some 2-naphthyl-based heptene[2.2.1]methanones derivatives, including 2-naphthyl-based heptene[2.2.1]methanones by an aqueous phase fly-ash catalyzed [4+2] cycloaddition Diels-Alder reaction of cyclopentadiene and aryl chalcones. The yields of the synthesized aryl heptene[2.2.1]methanone derivatives were more than 60%. Also the author has evaluated their pharmacological activities, including antimicrobial, antioxidant activities and insect antifeedant activities using the appropriate microbial strains with Bauer-Kirby,[23] DPPH radical scavenging[24] and castor leaf disc bio-assay methods.[25]

METHODS

General

All chemicals were procured from Sigma-Aldrich and E. Merck. Fly-ash was collected from the Thermal Power Plant-II, Neyveli Lignite Corporation (NLC), Neyveli, Tamil Nadu, India. Melting points of substituted aryl bicyclo[2.2.1]heptene-2-yl-methanones were determined in open glass capillaries on a Mettler FP51 melting point apparatus and are uncorrected. Infrared spectra (KBr, 4000–400 cm^{-1}) were recorded on Thermo scientific Nicolet iS5, US-made Fourier transform spectrophotometer. The NMR spectra of selective compounds were recorded on a Bruker AV 400 spectrometer operating at 400 MHz for ^1H NMR spectra and 100 MHz for ^{13}C NMR spectra in $CDCl_3$ solvent using TMS as internal standard. Electron impact and chemical ionization mode FAB^+ mass spectra were recorded with a Shimadzu spectrometer.

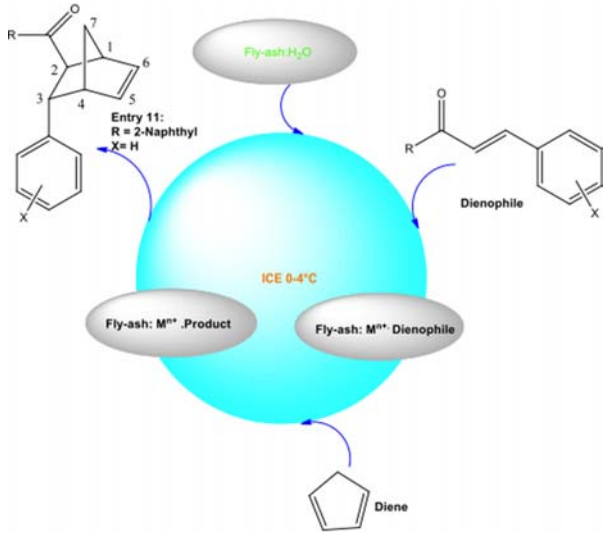
Synthesis of 2-naphthyl chalcones

The substituted styryl 2-naphthyl ketones were synthesized as described in reference.[26]

General procedure for synthesis of 2-naphthyl bicyclo[2.2.1]heptene-2-yl-methanones

Appropriate equimolar quantities of 2-naphthyl chalcones (2 mmol) in 15 mL of ethanol, cyclopentadiene (2 mmol) and 4 g of fly-ash in 20 mL of water were stirred for 6 h at 0–4°C overnight (Scheme 1). Progress of the reaction was monitored by thin-layer chromatography. Dichloromethane (10 mL) was added and the extract was separated by filtration. The filtrate was washed with water, brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated to give a solid product. The crude product was further purified by recrystallization with ethanol.

(Naphthalen-2-yl)(3-phenylbicyclo[2.2.1]hept-5-en-2-yl)methanone (compound 11): IR (KBr, cm^{-1}): ν = 3057, 2987, 1662, 1548, 1467, 1082, 838; ^1H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ = 2.66 (dd, 1H, H_1, J = 8.4 and 5.2 Hz), 3.19 (t, 1H, H_2, J = 19 Hz), 3.62 (t, 1H, H_3, J = 19 Hz), 2.02 (dd, 1H, H_4, J = 11.6



Scheme 1. **The reaction cycle for the synthesis of aryl bicyclo[2.2.1]heptene-2-yl-methanones by aqueous phase fly-ash catalyzed Diels-Alder reaction of aryl chalcones and cyclopentadiene.**

and 9.2 Hz), 5.50 (d, 1H, H_5, $J = 16$ Hz), 5.93 (d, 1H, H_6, $J = 16$ Hz), 2.15 (dd, 1H, H_7, $J = 10.0$ and 4.4 Hz), 1.58 (dd, 1H, $H_{7'}$, $J = 11.6$ and 5.2 Hz), 6.61-8.43(m, 12H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C, TMS): $\delta = 190.53$ (CO), 40.33 (C_1), 54.47 (C_2), 46.03 (C_3), 50.29 (C_4), 135.47 (C_5, C_6), 45.86 (C_7), 130.02 ($C_{1'}$), 133.12 ($C_{2'}$), 127.43 ($C_{3'}$), 128.34 ($C_{4'}$), 133.58 ($C_{5'}$, $C_{10'}$), 127.82 ($C_{6'}$), 128.68 ($C_{7'}$), 126.88 ($C_{8'}$), 130.85 ($C_{9'}$), 141.34 ($C_{1''}$), 127.24 ($C_{2''}$, $C_{6''}$), 128.48 ($C_{3''}$, $C_{5''}$), 125.98 ($C_{4''}$).

(3-(4-Chlorophenyl)bicyclo[2.2.1]hept-5-en-2-yl)(naphthalen-2-yl)methanone (compound 12): IR (KBr, cm^{-1}): $\nu = 3028$, 2932, 2852, 1653, 1636, 1558, 1541, 1507, 1178, 1089, 814; ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): $\delta = 2.49$ (dd, 1H, H_1, $J = 6.2$ and 7.7 Hz), 3.88 (t, 1H, H_2, $J = 22$ Hz), 3.50 (t, 1H, H_3, $J = 26$ Hz), 2.55 (dd, 1H, H_4, $J = 8.6$ and 6.6 Hz), 5.01 (d, 1H, H_5, $J = 17$ Hz), 5.10 (d, 1H, H_6, $J = 17$ Hz), 2.13 (dd, 1H, H_7, $J = 10.8$ and 7.6 Hz), 1.48 (dd, 1H, $H_{7'}$, $J = 8.3$ and 7.5 Hz), 6.63-8.41(m, 11H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C, TMS): $\delta = 190.15$ (CO), 41.16 (C_1), 54.08 (C_2), 46.07 (C_3), 51.29 (C_4), 135.17 (C_5, C_6), 46.83 (C_7), 130.12 ($C_{1'}$), 133.26 ($C_{2'}$), 127.70 ($C_{3'}$), 128.20 ($C_{4'}$), 133.79 ($C_{5'}$, $C_{10'}$), 127.35 ($C_{6'}$), 128.58 ($C_{7'}$), 126.82 ($C_{8'}$), 130.28 ($C_{9'}$), 144.85 ($C_{1''}$), 128.65 ($C_{2''}$, $C_{6''}$), 128.48 ($C_{3''}$, $C_{5''}$), 132.48 ($C_{4''}$).

(3-(2,4-Dichlorophenyl)bicyclo[2.2.1]hept-5-en-2-yl)(naphthalen-2-yl)methanone (compound 13): IR (KBr, cm^{-1}): $\nu = 3049$, 2912, 1662, 1627, 1603, 1566, 1411, 1179, 1050, 983, 809; ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): $\delta = 2.82$ (dd, 1H, H_1, $J = 7.2$ and 3.6 Hz), 3.76 (t, 1H, H_2, $J = 32$ Hz), 3.58 (t, 1H, H_3, $J = 32$ Hz), 2.850 (dd, 1H, H_4, $J = 4.8$ and 1.6 Hz), 5.39 (d, 1H, H_5, $J = 16$ Hz), 5.96 (d, 1H, H_6, $J = 16$ Hz), 2.16 (dd, 1H, H_7, $J = 10.8$ and 4.4 Hz), 1.60 (dd, 1H, $H_{7'}$, $J = 10.8$ and 5.2 Hz), 7.11-8.38(m, 10H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C, TMS): $\delta = 189.38$ (CO), 34.88 (C_1), 54.93 (C_2), 37.42 (C_3), 44.54 (C_4), 135.73 (C_5, C_6), 45.96 (C_7), 131.05 ($C_{1'}$), 132.98 ($C_{2'}$), 127.35 ($C_{3'}$), 128.55 ($C_{4'}$), 133.65 ($C_{5'}$, $C_{10'}$), 127.38 ($C_{6'}$), 128.64 ($C_{7'}$), 126.78 ($C_{8'}$), 130.36 ($C_{9'}$), 142.96 ($C_{1''}$), 131.65 ($C_{2''}$), 127.48 ($C_{3''}$), 132.48 ($C_{4''}$), 127.48 ($C_{5''}$), 128.24 ($C_{6''}$).

(3-(4-Diethylaminophenyl)bicyclo[2.2.1]hept-5-en-2-yl)(naphthalen-2-yl)methanone (compound 14). IR (KBr, cm^{-1}): $\nu = 3447$, 3067, 2923, 2853, 1660, 1526, 1464, 1348, 1173, 860; ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): $\delta = 2.88$ (dd, 1H, H_1, $J = 8.2$ and 9.4 Hz), 3.22 (t, 1H, H_2, $J = 29$ Hz), 3.65 (t, 1H, H_3, $J = 28$ Hz), 2.72 (dd, 1H, H_4, $J = 7.6$ and 5.6 Hz), 5.49 (d, 1H, H_5, $J = 18$ Hz), 5.96 (d, 1H, H_6, $J = 18$ Hz), 2.14 (dd, 1H, H_7, $J = 7.5$ and 4.5 Hz), 1.54 (dd, 1H, $H_{7'}$, $J = 10.6$ and 6.6 Hz), 3.54 (q, 2H, CH_2, $J = 14$ Hz), 1.27 (t, 3H, CH_3, $J = 17$ Hz), 6.61-8.29(m, 11H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C, TMS): $\delta = 190.53$ (CO), 40.34 (C_1), 54.81 (C_2), 46.22 (C_3), 50.37 (C_4), 135.64 (C_5, C_6), 45.41 (C_7), 129.85 ($C_{1'}$), 131.38 ($C_{2'}$), 127.26 ($C_{3'}$), 128.09 ($C_{4'}$), 133.47 ($C_{5'}$, $C_{10'}$), 128.08 ($C_{6'}$), 128.58 ($C_{7'}$), 126.89 ($C_{8'}$), 130.28 ($C_{9'}$), 136.96 ($C_{1''}$), 127.38 ($C_{2''}$, $C_{6''}$), 115.28 ($C_{3''}$, $C_{5''}$), 148.48 ($C_{4''}$), 41.18 (CH_2), 15.73 (CH_3).

(3-(4-Dimethylaminophenyl)bicyclo[2.2.1]hept-5-en-2-yl)(naphthalen-2-yl)methanone (compound 15). IR (KBr, cm^{-1}): $\nu = 3445$, 2923, 2852, 1664, 1592, 1576, 1361, 1046, 812; ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): $\delta = 2.78$ (dd, 1H, H_1, $J = 7.2$ and 12.4 Hz), 2.61 (t, 1H, H_2, $J = 29$ Hz), 3.48 (t, 1H, H_3, $J = 29$ Hz), 2.73 (dd, 1H, H_4, $J = 10.8$ and 4.8Hz), 5.49 (d, 1H, H_5, $J = 18$ Hz), 5.96 (d, 1H, H_6, $J = 18$ Hz), 2.67 (dd, 1H, H_7, $J = 13.8$ and 8.2 Hz), 1.40 (dd, 1H, $H_{7'}$, $J = 12.8$ and 3.2 Hz), 2.85 (s, 6H, $2CH_3$); 6.95-8.33(m, 11H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C, TMS): $\delta = 190.55$ (CO), 41.20 (C_1), 54.81 (C_2), 45.19 (C_3), 50.37 (C_4),

135.27 (C_5, C_6), 46.22 (C_7), 130.25 ($C_{1'}$), 131.46 ($C_{2'}$), 128.16 ($C_{3'}$), 127.17 ($C_{4'}$), 133.26 ($C_{5'}$, $C_{10'}$), 128.32 ($C_{6'}$), 128.18 ($C_{7'}$), 125.69 ($C_{8'}$), 130.08 ($C_{9'}$), 136.26 ($C_{1''}$), 127.78 ($C_{2''}$, $C_{6''}$), 115.84 ($C_{3''}$, $C_{5''}$), 148.80 ($C_{4''}$), 40.18 (CH_3).

(3-(4-Fluorophenyl)bicyclo[2.2.1]hept-5-en-2-yl)(naphthalen-2-yl)methanone (Compound 16). IR (KBr, cm^{-1}): ν = 3057, 2953, 1662, 1628, 1507, 1413, 1229, 1178, 1050, 835; ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ = 2.84 (dd, 1H, H_1, J = 9.2 and 6.7 Hz), 3.76 (t, 1H, H_2, J = 14 Hz), 3.68 (t, 1H, H_3, J = 34 Hz), 2.83 (dd, 1H, H_4, J = 7.5 and 8.3 Hz), 5.57 (d, 1H, H_5, J = 19 Hz), 5.68 (d, 1H, H_6, J = 19 Hz), 2.56 (dd, 1H, H_7, J = 7.2 and 9.5 Hz), 1.63 (dd, 1H, $H_{7'}$, J = 10.6 and 9.6 Hz), 7.08-8.12(m, 11H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C, TMS): δ = 191.37 (CO), 42.81 (C_1), 54.03 (C_2), 46.27 (C_3), 50.90 (C_4), 135.37 (C_5, C_6), 47.17 (C_7), 131.05 ($C_{1'}$), 132.16 ($C_{2'}$), 128.91 ($C_{3'}$), 127.96 ($C_{4'}$), 133.39 ($C_{5'}$, $C_{10'}$), 128.89 ($C_{6'}$), 128.28 ($C_{7'}$), 125.36 ($C_{8'}$), 130.11 ($C_{9'}$), 142.34 ($C_{1''}$), 120.23 ($C_{2''}$, $C_{6''}$), 116.76 ($C_{3''}$, $C_{5''}$), 161.40 ($C_{4''}$).

(3-(4-Hydroxyphenyl)bicyclo[2.2.1]hept-5-en-2-yl)(naphthalen-2-yl)methanone (Compound 17). IR (KBr, cm^{-1}): ν = 3447, 2923, 2849, 1637, 1402, 1019, 871; ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ = 2.85 (dd, 1H, H_1, J = 9.4 and 8.6 Hz), 3.66 (t, 1H, H_2, J = 32 Hz), 3.99 (t, 1H, H_3, J = 33 Hz), 2.70 (dd, 1H, H_4, J = 8.2 and 9.6 Hz), 5.47 (d, 1H, H_5, J = 16 Hz), 5.77 (d, 1H, H_6, J = 16 Hz), 2.72 (dd, 1H, H_7, J = 10.6 and 6.6Hz), 1.75 (dd, 1H, $H_{7'}$, J = 5.6 and 9.7 Hz), 6.97-8.24(m, 11H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C, TMS): δ = 189.21 (CO), 42.72 (C_1), 54.22 (C_2), 46.21 (C_3), 51.32 (C_4), 135.62 (C_5, C_6), 46.74 (C_7), 131.19 ($C_{1'}$), 132.23 ($C_{2'}$), 128.52 ($C_{3'}$), 127.57 ($C_{4'}$), 133.79 ($C_{5'}$, $C_{10'}$), 128.31 ($C_{6'}$), 128.39 ($C_{7'}$), 125.59 ($C_{8'}$), 130.25 ($C_{9'}$), 139.04 ($C_{1''}$), 129.30 ($C_{2''}$, $C_{6''}$), 118.27 ($C_{3''}$, $C_{5''}$), 158.29 ($C_{4''}$).

(3-(4-Methoxyphenyl)bicyclo[2.2.1]hept-5-en-2-yl)(naphthalen-2-yl)methanone (Compound 18). IR (KBr, cm^{-1}): ν = 3420, 3055, 2931, 2849, 1655, 1595, 1582, 1466, 1319, 1257, 1035, 833; ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ = 2.81 (dd, 1H, H_1, J = 17.6 and 4.4 Hz), 3.82 (t, 1H, H_2, J = 28 Hz), 3.18 (t, 1H, H_3, J = 27 Hz), 2.71 (dd, 1H, H_4, J = 18 and 2.4 Hz), 5.58 (d, 1H, H_5, J = 18 Hz), 5.62 (d, 1H, H_6, J = 18 Hz), 2.55 (dd, 1H, H_7, J = 17.2 and 5.2 Hz), 1.56 (dd, 1H, $H_{7'}$, J = 22.4 and 4.0 Hz), 3.69 (s, 3H, CH_3), 7.263-8.56(m, 11H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C, TMS): δ = 190.05 (CO), 42.72 (C_1), 54.77 (C_2), 46.17 (C_3), 51.32 (C_4), 135.58 (C_5, C_6), 45.86 (C_7), 131.97 ($C_{1'}$), 132.48 ($C_{2'}$), 128.32 ($C_{3'}$), 127.65 ($C_{4'}$), 133.61 ($C_{5'}$, $C_{10'}$), 128.39 ($C_{6'}$), 128.47 ($C_{7'}$), 125.79 ($C_{8'}$), 130.61 ($C_{9'}$), 139.49 ($C_{1''}$), 127.92 ($C_{2''}$, $C_{6''}$), 115.98 ($C_{3''}$, $C_{5''}$), 158.82 ($C_{4''}$), 62.78 (CH_3).

(3-(4-Nitrophenyl)bicyclo[2.2.1]hept-5-en-2-yl)(naphthalen-2-yl)methanone (Compound 19). IR (KBr, cm^{-1}): ν = 3459, 3067, 1606, 1625, 1588, 1526, 1462, 1348, 1173, 993, 822; ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): δ = 3.03 (dd, 1H, H_1, J = 6.8 and 6.0 Hz), 3.75 (t, 1H, H_2, J = 37 Hz), 3.58 (t, 1H, H_3, J = 37 Hz), 2.75 (dd, 1H, H_4, J = 18.2 and 4.8 Hz), 5.965 (d, 1H, H_5, J = 19 Hz), 5.39 (d, 1H, H_6, J = 19 Hz), 2.20 (dd, 1H, H_7, J = 4.8 and 12.8 Hz), 1.44 (dd, 1H, $H_{7'}$, J = 10.8 and 7.2 Hz), 7.29-8.30(m, 11H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C, TMS): δ = 189.39 (CO), 43.72 (C_1), 52.48 (C_2), 44.54 (C_3), 50.36 (C_4), 135.72 (C_5, C_6), 46.57 (C_7), 132.01 ($C_{1'}$), 132.98 ($C_{2'}$), 128.85 ($C_{3'}$), 127.82 ($C_{4'}$), 133.83 ($C_{5'}$, $C_{10'}$), 128.90 ($C_{6'}$), 128.92 ($C_{7'}$), 125.85 ($C_{8'}$), 130.82 ($C_{9'}$), 153.29 ($C_{1''}$), 128.15 ($C_{2''}$, $C_{6''}$), 125.35 ($C_{3''}$, $C_{5''}$), 146.82 ($C_{4''}$).

Antimicrobial activity

The antimicrobial activities of the prepared bicyclo[2.2.1]heptene-2-yl-methanones (compounds 11–19) were evaluated by measuring the zone of inhibition of the compounds against the indicated bacterial and fungal strains. Two Gram-positive pathogenic strains (*Staphylococcus aureus*, *Enterococcus faecalis*) and four Gram-negative strains (*Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Proteus vulgaris*) were chosen. The disc diffusion technique followed the Bauer-Kirby[22,23] method, at a concentration of 250 μg/mL with ampicillin and streptomycin used as the standard drugs. For the study of antifungal activities of all methanones with *Candida albicans* the disc diffusion technique was followed, while the two other strains (*Penicillium* sp. and *Aspergillus niger)*, the dilution method[23] was used. The drug dilution was 50 μg/mL. Griseofulvin was used as the standard drug.

Measurement of antibacterial sensitivity

The antibacterial sensitivity assay was performed using the Bauer-Kirby[22,23] disc diffusion technique. In each Petri plate 0.5 mL of the bacterial test sample was spread uniformly over solidified Mueller-Hinton agar using a sterile glass spreader. Then, 5 mm discs made from Whatman No.1 filter paper, were saturated with the potential inhibitor solution and placed on the medium using sterile forceps. Plates were incubated for 24 h at 37°C upside down to prevent the collection of water droplets.

After 24 h, the plates were examined and the diameter values of the zone of inhibition were measured. Triplicate results were recorded.

Measurement of antifungal sensitivity

Antifungal sensitivity was determined by using the Bauer-Kirby[22,23] disc diffusion technique. The PDA medium was prepared and sterilized as above and added to the Petri plate containing 1 mL of the fungal species. The plate was rotated clockwise and counter clockwise for uniform spreading. The discs were impregnated with the test solution, prepared by dissolving 15 mg of the methanone in 1 mL of DMSO solvent. The medium was allowed to solidify and incubate for 24 h. Plates were examined and the diameter of the zone of inhibition was measured. Triplicate results were recorded.

Antioxidant activity

The antioxidant activities of the synthesized methanones (compounds 11–19) were evaluated by the DPPH radical scavenging technique[22]. Acetate (0.1 mol/L) was prepared by dissolving 1.64 g of sodium acetate in 15 mL of water and 150 μL of acetic acid. The final volume was adjusted to 20 mL by adding water. DPPH solution (0.2 mmol) was prepared by dissolving 3.9 g of DPPH in 50 mL of ethanol, and α-tocopherol solution was prepared by adding 1 mg to 10 mL of ethanol. A series of test tubes was arranged with 1.0 mL of buffer solution mixed with 0.5 mL of DPPH solution. A series of concentrations of synthesized methanones with α-tocopherol (1 μg in 1 mL of ethanol) was added to each tube and mixed. After 30 min at room temperature, the absorbance of each solution was measured by UV spectrophotometry at 517 nm. A mixture of buffer solution and ethanol was used as the reference for the spectrophotometer. A graph was plotted with the weight of the compound *versus* absorption and IC_{50} values were determined. The antioxidant activity was expressed in terms of IC_{50} (μg/mL, concentration required to inhibit DPPH radical formation by 50%). Alpha-Tocopherol was used as a positive control. The radical scavenging activity was calculated as

$$\text{DPPH radical scavenging activity (\% of inhibition)} = \frac{\text{Control absorbance} - \text{Sample absorbance}}{\text{Control absorbance}} \times 100$$

Measurement of Insect antifeedant activity

Generally, organic compounds that have carbonyl, unsaturation and halogen substitutions, possess insect antifeedant activity. Therefore, the author examined the insect antifeedant activity of these bicyclo[2.2.1]heptene-2-yl methanone derivatives (compounds 11–19) and found them to be active as insect antifeedants. Performed with a 4^{th} instar larva *Achoea janata L* against castor *semilooper*, these were reared, as described, on the leaves of castor, *Ricinus communis*, in the laboratory at the temperature range of 26°C ± 1°C and a relative humidity of 75–85%. The leaf – disc bioassay method was used against the 4^{th} instar larvae to measure the antifeedant activity. The 4^{th} instar larvae were selected for testing because the larvae at this stage feed voraciously.

Castor leaf discs of a diameter of 1.85 cm were punched and intact with the petioles. The synthesized aryl bicyclo [2.2.1]heptane-2-yl methanones (entries 11–19) were dissolved in acetone at a concentration of 200 ppm dipped for 5 minutes. The leaf discs were air-dried and placed in a 1 litre beaker containing little water in order to facilitate translocation of water. The leaf discs remain fresh throughout the duration of the rest, 4^{th} instar larvae of the test insect, which had been preserved on the leaf discs of all bicyclo[2.2.1]hepane-2-yl methanones, were allowed to feed on them for 24 h. The area of the leaf disc consumed was measured using Dethler's method[25].

RESULTS AND DISCUSSION

The synthesis of aryl bicyclo[2.2.1]heptene-2-yl-methanone derivatives by aqueous phase fly-ash catalyzed Diels-Alder reaction with cyclopentadiene as the diene and *E*-chalcones as dienophiles was undertaken. We obtained aryl bicyclo[2.2.1]heptene-2-yl-methanones by aqueous phase Diels-Alder reaction of *E*-enones and cyclopentadiene, under solvent-free cooling conditions. During the reaction the chemical species present in the fly-ash catalyzed the [4+2] cycloaddition reaction. The proposed general reaction cycle is shown in Scheme 1. In this reaction the yield obtained was greater than 60%.

Table 1. The physical constants, analytical and mass fragments of the aryl bicyclo[2.2.1]heptene-2-yl-methanone derivatives.

Compd.	R	R′	M.F.	MW	Mp (°C)	Yield (%)	Micro analysis (%)			Mass (*m/z*)
							C	H	N	
1	C_6H_5	H	$C_{20}H_{18}O$	274	–	64	–	–	–	[a]274 [M^+]
2	2-Pyridine	H	$C_{19}H_{17}NO$	275	–	60	–	–	–	[b]275 [M^+]
3	2-Pyridine	4-Cl	$C_{19}H_{16}ClNO$	309	–	60	–	–	–	[b]309 [M^+], 311 [M^{2+}]
4	2-Pyridine	4-OCH_3	$C_{20}H_{17}NO_2$	305	–	65	–	–	–	[b]305 [M^+]
5	2-Pyridine	4-CH_3	$C_{20}H_{17}NO$	289	–	64	–	–	–	[b]289 [M^+]
6	2-Pyridine	4-NO_2	$C_{19}H_{16}N_2O_3$	320	–	60	–	–	–	[b]320 [M^+]
7	2-Imidazole	H	$C_{17}H_{16}N_2O$	264	–	63	–	–	–	[c]264 [M^+]
8	2-Imidazole	2-Br	$C_{17}H_{15}BrN_2O$	343	–	60	–	–	–	[c]343 [M^+], 345 [M^{2+}]
9	2-Imidazole	4-Cl	$C_{17}H_{15}ClN_2O$	299	–	61	–	–	–	[c]299 [M^+], 301 [M^{2+}]
10	2-Imidazole	4-OCH_3	$C_{18}H_{18}N_2O_2$	294	–	64	–	–	–	[c]294 [M^+]
11	2-Naphthyl	H	$C_{20}H_{18}O$	324	116–117	65	88.82 (88.85)	5.18 (6.21)	–	324 [M^+], 197, 155, 121, 93, 77, 68, 52, 42, 29, 27
12	2-Naphthyl	4-Cl	$C_{20}H_{19}ClO$	358	142–143	63	79.96 (80.33)	5.29 (5.34)	–	358 [M^+], 360 [M^{2+}], 323, 247, 231, 203, 155, 127, 111, 77, 35, 29
13	2-Naphthyl	2,4-Cl_2	$C_{20}H_{18}Cl_2O$	393	138–139	60	73.33 (73.29)	4.59 (4.61)	–	393[M^+], 395[M^{2+}], 397[M^{4+}], 357, 323, 247, 155, 127, 121, 111, 93, 70, 29
14	2-Naphthyl	4-$N(CH_3)_2$	$C_{26}H_{25}NO$	367	128–129	63	85.02 (84.98)	6.82 (6.86)	3.84 (3.81)	367 [M^+], 352, 337, 323, 247, 240, 212, 155, 127, 120, 93, 77, 15
15	2-naphthyl	4-$N(C_2H_5)_2$	$C_{28}H_{29}NO$	395	116–117	62	85.28 (85.22)	7.32 (7.39)	3.57 (3.54)	395 [M^+], 380, 366, 352, 323, 247, 240, 155, 148, 127, 91, 77, 29, 15
16	2-Naphthyl	4-F	$C_{20}H_{19}FO$	342	130–132	62	84.23 (84.19)	5.62 (5.65)	–	342 [M^+], 344 [M^{2+}], 323, 247, 187, 155, 127, 95, 93, 77, 29, 19
17	2-Naphthyl	4-OH	$C_{20}H_{20}O_2$	340	152–153	64	84.72 (84.68)	5.88 (5.92)	–	340 [M^+], 323, 247, 213, 185, 169, 155, 127, 93, 77, 29, 17
18	2-Naphthyl	4-OCH_3	$C_{25}H_{22}O_2$	354	120–121	65	84.70 (84.72)	6.18 (6.26)	–	354 [M^+], 339, 323, 247, 199, 155, 107, 93, 91, 77, 31, 15
19	2-Naphthyl	4-NO_2	$C_{24}H_{19}NO_3$	369	132–134	60	78.07 (78.03)	5.2 (5.18)	7.35 (7.39)	369 [M^+], 323, 247, 242, 214, 155, 127, 122, 93, 88, 77, 46, 27, 15

[a] Ref.[16]; [b] Ref. [4]; [c] Ref. [7].

Table 2. The effect of reuse of the catalyst on the yield of the aqueous phase Diels-Alder reaction of styryl 2-naphthyl ketone and cyclopentadiene (compound 11).

Run	1	2	3	4	5
Yield (%)	65	60	53	40	40

The determined physical constants and mass fragments are presented in Table 1. The reusability of the catalyst in this cycloaddition reaction was studied with 2 mmol of 2-naphthyl chalcone and 2 mmol of cyclopentadiene and is presented in Table 2 (compound 11). The first run gave 65% yield; the second and third runs gave 60 and 53% yields, and the fourth and fifth runs gave 40%. The chalcone-containing electron-donating substituents (OCH_3) gave a higher yield than electron-withdrawing (halogen and nitro) substituents. The effect of the catalyst on this reaction was studied by varying the catalyst quantity from 0.5 to 5 g. As the catalyst quantity increased from 0.5 to 4 g the percentage of product increased from 60–65%. Further increases in catalyst amount beyond 4 g did not increase the percentage of product. The effect of catalyst content is shown in Figure 1. The optimum quantity of catalyst was found to be 4 g for 0.52 g of naphthyl chalcone substrate. The ratio of 2-naphthyl chalcone, cyclopentadiene substituents and the fly-ash catalyst ratio is 1:1:3. The effect of solvents on this reaction was studied with the same quantity of reactants, including with methanol, dichloromethane, dioxane and tetrahydrofuran and are presented in Table 3. The highest yield was obtained in ethanol, with fly-ash in water medium. The infrared and NMR data of selected compounds are summarized in the experimental section, the NMR spectra (Figs. S1–S10) and mass (Figs. S11–S15) are given in supplementary data.

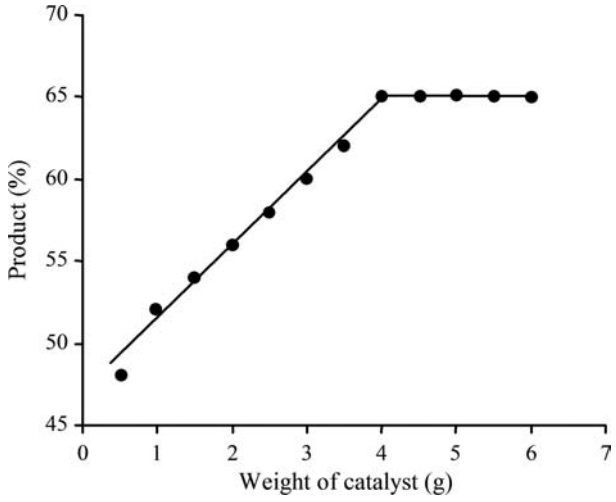


Figure 1. The effect of catalyst loading.

Antibacterial sensitivity assay

The vinyl ketones, aza-vinyl ketones and bicyclo methanones possess antimicrobial activities.[26] In the present study, disc-diffusion technique was followed using the Bauer-Kirby[22] method, at a concentration of 250 μg/mL, with ampicillin and streptomycin used as the standard drugs. The measured antibacterial activities of all methanones are presented in Table 4. Compound 13, showed the maximum zone of inhibition against *Escherichia coli*, at 20–24 mm, compared to other methanones, such as 12, 15, 16, 18 and 19. These latter compounds are moderately active, with 13–19 mm zones of inhibition. Ketone 17 was active with an 8–12 mm of zone of inhibition.

Table 3. The effect of solvents on the aqueous phase Diels-Alder reaction of styryl 2-naphthyl ketone and cyclopentadiene (compound 11).

Solvent	Ethanol	Methanol	Dichloromethane	Dioxane	Tetrahydrofuran
Yield	65	63	62	60	62

Table 4. Antibacterial[a], antifungal[b] and antioxidant[c] activities of (2-naphthyl)-3-(substituted phenylbicyclo[2.2.1]hept-5-en-2-yl)methanones.

	Antibacterial activity						Antifungal activity			
							Disc diffusion technique (250 μg/mL)	Drug dilution method (250 μg/mL)		
Compd.	*E. coli*	*S. aures*	*P. aeruginosa*	*K. pneumoniae*	*P. vulgaris*	*E. faecalis*	*C. albicans*	*Penicillium* sp.	*A. niger*	Antioxidant activity (DPPH radical scavenging)
11	−	−	+	±	++	++	±	+	+	28.78 ± 1.18
12	+	++	+	++	+	±	+	±	+	23.81 ± 1.94
13	++	++	++	++	+	++	++	+	++	19.58 ± 1.09
14	−	±	−	−	+	+	−	++	+	22.95 ± 1.54
15	+	+	++	+	++	+	+	−	±	21.45 ± 1.64
16	+	++	+	++	−	++	+	−	++	17.95 ± 1.24
17	±	−	+	−	±	+	−	+	−	37.01 ± 1.65
18	+	+	±	−	++	±	++	++	+	35.34 ± 1.72
19	+	−	+	++	++	−	+	++	+	11.04 ± 1.82

[a] Disc size: 6.35 mm; duration: 24–45 h; standard: ampicillin (30–33 mm) and streptomycin (20–25 mm); control: methanol; −: no activity; ±: active (8–12 mm); +: moderately active (13–19 mm); ++: active (20–24 mm).
[b] Standard: griseofulvin and gentamycin; duration: 72 h; control: methanol; medium: Potato dextrose agar; ++: no fungal colony; +: one fungal colony; ±: two-three fungal colonies; −: Multiple fungal colonies.
[c] Standard: α-Tocopherol (39.14 ± 1.57).

The parent compounds 11 and 14 were inactive. The ketones 12, 13 and 16 were found to be effective against *S. aureus* strain, with 20–24 mm of zones of inhibition. Compounds 15 and 18 are moderately active with 13–19 mm of zones of inhibition. The methanone 14 was moderately active with an 8–12 mm zone of inhibition. Compounds 1, 17 and 19 were inactive against *S. aureus*. The methanone derivatives 13 and 15 were shown to be more active against *Pseudomonas*, with greater than a 20 mm zone of inhibition, while the other derivatives showed zones of inhibition between 12–19 mm. Compound 14 was inactive against the *Pseudomonas aeruginosa* strain. Ketones 12, 13, 16 and 19 were more effective against the *Klebsiella pneumoniae* strain with 20–24 mm zones of inhibition, while ketone 15 showed moderate activity with a 13–19 mm zone of inhibition. The parent compound 11 was active with an 8–12 mm zone of inhibition. Ketones 14, 17 and 18 were inactive against the *K. pneumoniae* species. The methanones 11, 15, 18 and 19 were active when they were screened with *Phaseolus vulgaris*, with 20–24 mm zones of inhibition and compounds 12–14 were moderately active with 13–19 mm zones of inhibition. Ketone 16 was ineffective against the *P. vulgaris* strain. The ketones 11, 13 and 16 showed greater activity against *Enterococcus faecalis*, with 20–24 mm zones of inhibition. Compounds 14, 15 and 17 were moderately active with 13–19 mm zones of inhibition. The methanones 12 and 18 were active with 8–12 mm zones of inhibition. Ketone 19 was inactive when it was screened against *E. faecalis*.

Antifungal sensitivity assay

The observed antifungal activities of all prepared methanones (compounds 11–19) are presented in Table 4. The study of antifungal activities of all methanones against *Candida albicans* showed that compounds 13 and 18 are most effective, with 20 mm zones of inhibition at 250 μg/mL per disc. Methanones 12, 15, 16 and 19 are moderately active with 13–19 mm zones of inhibition and compound 11 was active with an 8–12 mm zone of inhibition. The compound containing a 4-diethylamino substituent was inactive against *C. albicans*. Compounds 14, 18 and 19 are more effective against *Penicillium* species relative to compounds 11, 13 and 17. The methanones 15 and 16 were inactive against the *Penicillium* sp. fungal strain. The zone of inhibition of ketones 13 and 16 was most effective against *Aspergillus niger* relative to compounds 11, 12, 14, 18 and 19. The 4-hydroxy substituted ketone 17 showed little to no effectiveness with any fungal strain. The presence of a chloro, dimethyl, diethyl, fluoro, methoxy and nitro substituents appear to be responsible for the antimicrobial activities of methanones.

Antioxidant activity

The hydroxylated and methoxylated organic compounds possess antioxidant activity.[17–19,27–30] In the present study, the antioxidant activities of the 2-naphthyl-based methanones were measured using the DPPH radical scavenging method. The observed antioxidant activities of methanones are presented in Table 4. From Table 4, the hydroxy- and methoxy-substituted methanones (compounds 17 and 18) showed significant antioxidant activity. The other ketones, including the parent compound, showed less antioxidant activity.

Table 5. The insect antifeedant activities of the 2-naphthyl bicyclo[2.2.1]hepatene-2-yl-methanones.

Compound	R′	4–6 pm	6–8 pm	8–10 pm	10–12 pm	12–6 am	6–8 am	8 am–12 Nn	12 Nn–2 pm	2–4 pm	Total leaf disc consumed in 24 hrs
11	H	1	1	1	0.5	0.5	1	1	1	1	8
12	4-Cl	0.5	0.25	0.25	0.5	0.5	0.5	1	1	0.5	5
13	2,4-Cl_2	0.25	0.25	0.25	0.25	0.5	0.5	0.5	1	0.5	4
14	4-$N(C_2H_5)_2$	1	2	2	1	0	0	1	1	1	9
15	4-$N(CH_3)_2$	1	0.5	1	1	1	1	0.5	0.5	0.5	7
16	4-F	0.5	1	0.5	0.25	0.25	1	0.5	1	0.5	5.5
17	4-OH	1	0.5	1	1	1	0.5	1	0.5	0.5	7
18	4-OCH_3	1	1	0.5	1	0.5	0.5	0.5	0.5	0.5	6
19	4-NO_2	1	0.5	1	0.5	0.5	1	1	1	1	8

Number of leaf discs consumed by the insect (Values are mean + SE of five).

Table 6. Antifeedant activity of compound 13 (3-(2,4-dichlorophenyl)bicyclo[2.2.1]hept-5-en-2-yl) (naphthalen-2-yl)methanone showed an appreciable antifeedant activity at 3 different concentrations.

ppm	4–6 pm	6–8 pm	8–10 pm	10–12 pm	12 am–6 am	6–8 am	8 am–12 Nn	12 Nn–2 pm	2–4 pm	Total leaf disc consumed 24 h
50	0.25	0.25	0.25	0	0	0	0	0	0	0.75
100	0.25	0.5	0.25	0	0	0	0	0	0	1
150	0.25	0	0.25	0	0	0	0	0	0	0.5

Number of leaf discs consumed by the insect (Values are mean + SE of five).

Insect antifeedant activity

The halo-substituted enones possess insect antifeedant activity.[19,20,27,31,32] In the present investigation, the observed antifeedant activity of bicyclo[2.2.1]heptene-2-yl methanones is presented in Table 5, which reveals that compound 13 (3-(2,4-dichlorophenyl)bicyclo[2.2.1]hept-5-en-2-yl) (naphthalen-3-yl)methanone was found to act as a satisfactory antifeedant. This test was performed with insects that only ate two-leaf discs soaked in the solution of this compound. Compound 12 showed enough antifeedant activity, but less than 13. Furthermore, compound 13 was subjected to the measurement of antifeedant activity at different 50, 100, 150 ppm concentrations. Our observations reveal that as the concentrations decreased, the activity also decreased. Results in Table 6 show that 13 (3-(2, 4-dichlorophenyl)bicyclo[2.2.1]hept-5-en-2-yl)(naphthalen-3-yl)methanone shows appreciable antifeedant activity at a 150 ppm concentration.

CONCLUSION

A series of aryl bicyclo[2.2.1]heptene-2-yl-methanone derivatives have been synthesized by aqueous-phase fly-ash-catalyzed Diels-Alder [4+2] cycloaddition of cyclopentadiene and aryl *E*-chalcones. The yields of the methanones were greater than 60%. The antimicrobial activities of the methanones (compounds 11–19) have been evaluated using Bauer-Kirby methods.

The parent compound shows significant antibacterial activity against *P. vulgaris* and *E. faecalis* bacterial strains, with 20–24 mm zones of inhibition. Methanone derivatives, containing chloro substituents, showed greater activity with 20–24 mm zones of inhibition against *E. coli, S. aureus, P. aeruginosa* and *E. faecalis* bacterial strains. The dimethylamino-substituted compounds were more active against *P. aeruginosa* and *P. vulgaris* bacterial strains, with 20–24 mm zones of inhibition. Methanone with 4-F substituents were active with 20–24 mm zones of inhibition against *S. aureus, K. pneumoniae* and *E. faecalis* bacterial strains. Methoxy substituted compounds showed excellent activity with 20–24 mm of zones of inhibition against the *P. vulgaris* strain. Nitro-substituted ketone showed a 20–24 mm zone of inhibition against the *K. pneumoniae* and *P. vulgaris* strains. Chloro-substituted methanones were more active against *Penicillium* sp. and *A. niger* fungal species. The 4-F substituted ketone showed antifungal activity only against the *A. niger* fungal strain. The methoxy substituted ketones showed maximum antifungal activity against *C. albicans* and *Penicillium* sp. fungal strains. The ketone with nitro-substituent was most active against the *Penicillium* sp. fungal strain. The diethyl, dimethyl, fluoro, methoxy and nitro substituents of the methanones have good antimicrobial activities.

The antioxidant activities of the methanones (compounds 11–19) were measured by a DPPH radical scavenging method; the compounds containing hydroxy and methoxy substituents showed antioxidant activity. Compound 13 shows good insect antifeedant activity against the 4th instar larvae *Achoea Janata L* with castor leaf disc bio-assay method.

COMPETING INTEREST

The authors have declared that no competing interests exist.

Acknowledgements

The author (Dr. GT) gratefully acknowledges the University Grants Commission, New Delhi, India, for financial support Grant No. F.30-23/2011(SA-II), through the UGC-PDF Research Award.

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