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Wacker oxidation with 2,5-diallyl PCUD derivatives

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Herein is reported a simple synthetic approach to functionalized polycyclic cage compounds related to Cookson's dione derivative by utilizing Claisen rearrangement, Diels−Alder reaction (DA), [2+2] photocycloaddition, Luche reduction, dehydration, and Wacker oxidation as key steps. Access to such hybrid molecules containing heterocycles and caged systems provides new opportunities in medicinal chemistry and access to high energy density materials (HEDMs). 2,5-Diallyl cage compounds containing diallyl moiety have been successfully functionalized into methyl ketones by Wacker oxidation.

Keywords: Claisen rearrangement, Dehydration, Luche reduction, PCUD, Wacker oxidation

In recent years, synthetic chemists developed several strategies for assembling functionalized polycyclic cage compounds. Due to high symmetry, unusual ring strain, rigid and compact molecular architecture, polycyclic cage compounds generate a wide range of applications in several areas such as medicinal chemistry[1], high-energy materials[2], supramolecular chemistry as well as ligand design[3], polymers[4], thermostable oils[5] (Fig. 1). So, chemists have been interested in expanding the utility of cage compounds during the past two decades by creating new chemical space.

There are several cage molecules reported that contain heteroatoms such as nitrogen and oxygen which show improved properties like they function as high energy density materials (HEDMs) with enhanced performance as compared to other conventional materials[6]. As a result of their widespread use in civil, defense, and aerospace engineering, high-energy materials such as oxidizers, energetic fuels, propellants, and explosives are being discovered[7].

In this regard, various nitro groups are incorporated within the cage framework and such compounds improve the detonation performance, density, and thermal stability[8]. To expand the cage compound library and to prepare hybrid molecules containing heterocycles and caged systems, Kotha and co-workers synthesized various nitrogen-containing cage molecules with triazole derivatives (**7** and **8**), Oxazole containing compound **9** is accessible starting with commercially available starting materials such as 2,3-dimethoxyhydroquinone, 1,4-dimethoxybenzene, and dicyclopentadiene using DA reaction, and [2+2] photocycloaddition as key steps[9] (Fig. 2). These oxazole derivatives are also useful in bioorganic chemistry, agrochemicals, and pharmaceuticals. Nitro group containing cage compound **10** which shows very high density[10].

Hence, we are also interested in synthesizing functionalized cage compounds by utilizing simple strategies like Claisen rearrangement, Luche reduction, dehydration, and very less explored Wacker oxidation where aldehydes or methylketone are produced from terminal olefins by Markovnikov or anti-Markovnikov addition of H_2O using palladium-based catalysts, copper salt as the redox co-

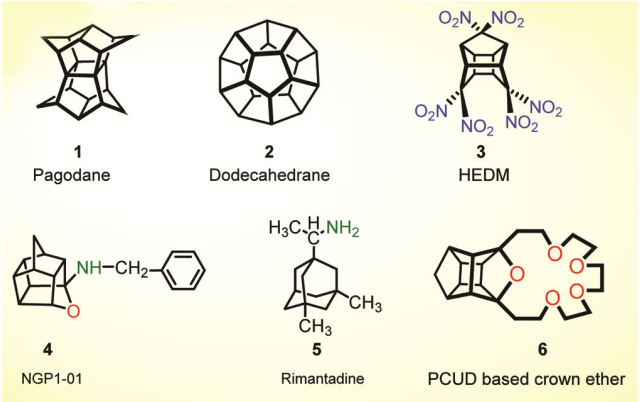


Fig. 1 — Examples of cage compounds

catalyst and oxygen as the re-oxidant[11] in cage compounds chemistry. Several methyl ketones are known to be biologically important and have natural origins. They are found in mammals, fungi, bacteria, insects, and plants as the essential oil of lime leaves, cloves, and cinnamon oil. The methyl ketones like nonan-2-one, undecan-2-one, and tridecan-2-one were found in the essence of coconut oil[12].

Results and Discussion

Towards the synthesis of polycyclic derivatives, our journey begins with the synthesis of known 2,5-diallylcage dione **17**. In this regard, commercially available hydroquinone **11** was subjected to O-allylation using allyl bromide in acetone at reflux conditions to give O-allylated product **12** with 85% yield. Then, compound **12** was heated at a high temperature (170-180°C) that resulted into Claisen rearrangement[13] to produce a mixture of isomers of diallyl diols (2,5-diallylhydroquinone **13** and 2,3 diallyl hydroquinone **14**) in 67% yield in a 1:1 ratio. Further, oxidation of hydroquinone derivatives **13** with manganese dioxide (MnO_2) gave the corresponding diallyl quinone **15** which were later subjected to a [4+2] cycloaddition with cyclopentadiene in methanol at 0°C-RT produced the cycloadduct **16** in 87% yield. Subsequently, a [2+2] photocycloaddition delivered the required cage dione **17** in 78% (Scheme 1)[14].

Later, we treated 2,5-diallyl cage compound **17** with 8 equivalents of Luche reagent[15] to obtain the *cis* dihydroxy compound **18** in good yield, which on treatment with catalytic amount of *p*-TSA produced the cyclic ether **19** (25% yield). Here the reduced yield may be due to some unidentified and unusual rearrangement occurring in the acidic medium at this stage. The cyclic ether **19** derived from 2,5-diallyl compound was then subjected to Wacker oxidation using $CuCl_2$ and $PdCl_2$ catalyst in DMF and water (4:1) ratio in open air gave mono keto derivative **20** instead of diketo derivative **20a** (Scheme 2).

Although, we have tried different conditions for diketone compound **20a** (Table 1) but surprisingly, here we observed the isomerization of one of the double bonds which is confirmed by ^{13}C NMR and ^{13}C DEPT study of compound **20** as the characteristic peak for terminal allyl group at 116 ppm was missing.

Also, we were keen to find out the outcome of the oxidation of compound **17** under Wacker oxidation conditions. So, compound **17** was treated with 10 mol% $PdCl_2$ catalyst and $CuCl_2$ co-catalyst in DMF: H_2O (4:1) solvent, and found that an interesting diketone compound **21** (Scheme 3) was formed and the structure of compound **21** was confirmed by ^{13}C NMR .

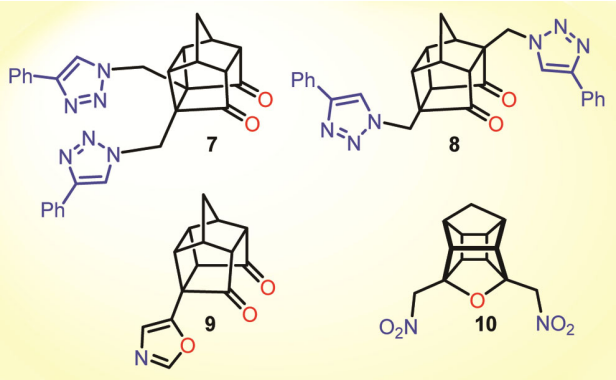
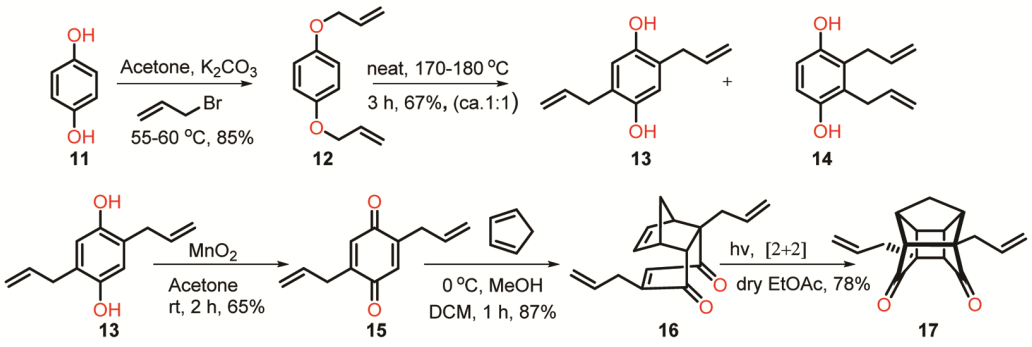


Fig. 2 — Various functionalized cage diones containing nitrogen-rich moiety

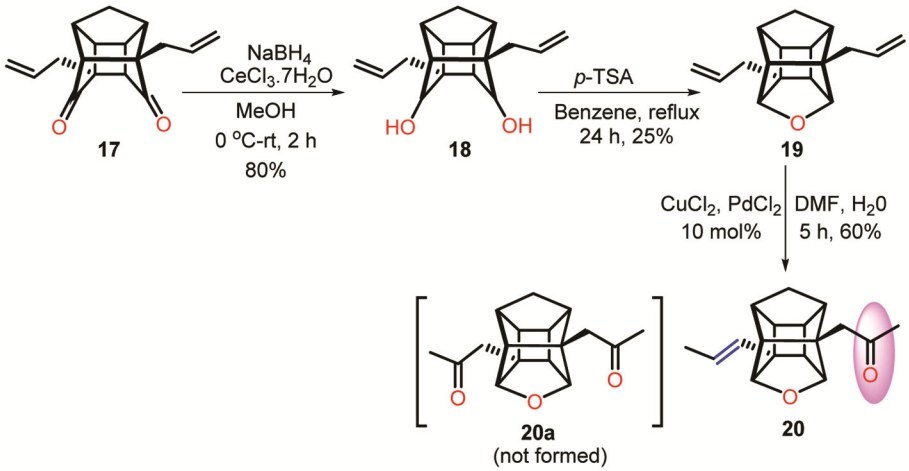
Experimental Section

Materials and Physical measurements

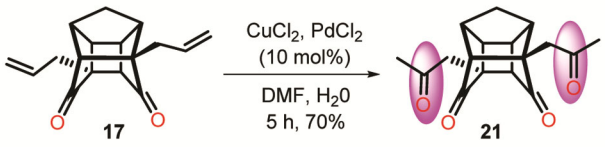
All chemicals were purchased from Sigma Aldrich and Spectrochem Company and used without further purification. Chromatography was used to monitor the progress of all reactions (TLC analysis) using suitable solvent systems (EtOAc/Pet ether) and UV light for observation and immersion in $KMnO_4$ solution for



Scheme 1 — Synthesis of 2,5-cage dione **17**



Scheme 2 — Synthesis of functionalized cage derivatives **18**, **19**, and **20**



Scheme 3 — Synthesis of the tetraketo compound **21**

Table 1 — Different conditions attempted for the synthesis of compounds **20** and **20a**

Entry	Catalyst Concentration (mol %)	Time (h)	Solvent (4:1)	Yield (%) **20**	**20a**
1	10	5	DMF:H_2O	60	–
2	10	24	DMF:H_2O	56	–
3	20	5	DMF:H_2O	58	–
4	20	24	DMF:H_2O	55	–

observation. By syringe-septum, moist-sensitive (dry/anhydrous) reactions were performed on oven-dried glassware in a nitrogen/argon atmosphere. Column chromatography was done with 100-200 mesh silica gel in all cases with appropriate solvent systems. On the Nicolet Impact-400 FTIR spectrometer, all IR samples were recorded with $CHCl_3$ as solvents. Nuclear magnetic resonance (NMR) spectra (^{1}H and ^{13}C NMR) have been recorded on 400 and 500 MHz spectrometers (Bruker) with $CDCl_3$ solvent and chemical shifts (δ, ppm) are reported relative to internal standard such as TMS. The standard abbreviations s, d, t, q and m, refer to singlet, doublet, triplet, quartet, and multiplet, respectively. Coupling constants (*J*) are reported in Hertz. Mass spectra (HRMS) have been recorded under positive ion electrospray ionization (ESI, Q-TOF) mode. The single-crystal X-ray diffraction analysis was carried out with graphite monochromated Mo Kα radiation and the structure was resolved by shelxl97 and refined by full-matrix least-squares against F 2 using shelxl97 software.

(1s,3Ar,5S,6S)-1,3-Diallyloctahydro-2*H*-3,5,1-(epiethane[1,1,2]tril)cyclobuta[cd]- pentalene-2,7-dione, 17

The DA adduct **16** (1 g, 0.32 mmol) was dissolved in dry EtOAc (300 mL) and irradiated in a Pyrex immersion well by using a 125 W UV Hg lamp (homemade) for 2 h under a nitrogen atmosphere at RT. At the conclusion of the reaction (TLC monitoring), the solvent was evaporated under reduced pressure and the crude residue was purified by silica gel column chromatography to give cage dione **17**. Yield 795 mg (80%). Appearance: Colourless liquid. R_f = 0.5 (5% Ethylacetate-petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.77 (d, *J* = 11.1 Hz, 1H), 2.01 (d, *J* =11.1 Hz, 1H), 2.12-2.45 (m, 6H), 2.61 (d, *J*= 4.4 Hz, 1H), 2.76 (d, *J*= 3.6 Hz, 1H), 2.84-3.01 (m, 2H), 4.97-5.05 (m, 4H), 5.64-5.75 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 213.4, 212.3, 133.5, 132.8, 118.5, 118.2, 61.4, 60.0, 51.3, 47.7, 43.9, 41.8, 39.5, 35.4, 35.1, 33.5.

(1S,2S,3aR,5S,6S,7S)-1,3-Diallyloctahydro-1*H*-3,5,1-(epiethane[1,1,2]triyl)cyclobuta[cd]- pentalene-2,7-diol, 18

Compound **17** (500 g, 2.083 mmol) dissolved in 30 mL methanol, then $CeCl_3.7H_2O$ (1.5 g, 4.164 mmol) was added and allowed to cool to 0°C in an ice-water bath. Sodium borohydride (160 mg, 4.164 mmol) was added slowly in portions for 15 min and allowed to be stirred for 3 h. Gradually the yellow reaction mixture changed to milky white. After the reaction (TLC

monitoring), the reaction mixture was quenched with ice water and organic compound extracted with EtOAc. The filtrate was evaporated under reduced pressure and crude purified by column chromatography to get compound **18**. Yield 400 mg (75%). Appearance: White colour. m.p.112-115°C. R_f = 0.5 (20% EtOAc-petroleum ether); IR (Neat): 3314, 2955, 1740, 1635, 1202, 1168, 1003, 917, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.81-5.70 (m, 2H), 5.13-5.07 (m, 4H), 3.76 (s, 2H), 2.63 (s, 2H), 2.50-2.41 (m, 4H), 2.26 (d, *J* = 17.83 Hz, 4H), 1.64 (d, *J* = 10.86 Hz, 1H), 1.13 (d, *J* = 10.11 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.2, 135.2, 117.1, 116.9, 74.5, 52.5, 51.0, 45.5, 42.9, 42.5, 41.7, 39.9, 39.0, 35.2, 33.1; HRMS (ESI, Q-ToF): *m/z* Calcd for $C_{17}H_{23}O_2$ $[M+H]^+$: 259.1694. Found: 259.1693.

(1S,2aS,4aR,6S,6aS,8S)-2a1,8-Diallyloctahydro-1*H*-1,3,4,6-(epiethane[1,1,2,2]tetrayl)penta- leno[1,6-bc]furan, 19

To a solution of compound **18** (400 mg) in dry benzene (30 mL) was added TSOH (50 mg) and heated to reflux for 48 h. At the conclusion of the reaction (TLC monitoring), the reaction mixture was cooled to RT and the solvent was removed. Then reaction mixture was subjected to silica gel column chromatography to furnish **19**. Yield 90 mg (25%). Appearance: oily liquid. R_f = 0.7 (1% EtOAc-petroleum ether); IR (Neat): 2950, 1745, 1635, 1200, 1168, 1053, 1003, 910, 765 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.88-5.74 (m, 1H), 5.58 (d, *J* = 15.21 Hz, 1H), 5.49-5.44 (m, 1H), 5.06-5.02 (m, 3H), 4.52-4.50 (m, 1H), 4.40 (d, *J* = 4.61 Hz, 1H), 2.55-2.45 (m, 2H), 2.38-2.36 (m, 3H), 2.25-2.24 (m, 2H), 2.27 (d, *J* = 6.80 Hz, 2H), 1.93 (d, *J* = 11.07 Hz, 1H), 1.68 i(d, *J* = 6.22 Hz, 3H), 1.50 (d, *J* = 10.50 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ. 135.2, 134.4, 122.4, 116.4, 90.8, 88.6, 66.2, 60.4, 54.9, 48.3, 46.3, 44.3, 43.3, 42.9, 37.6, 37.4, 18.1; HRMS (ESI, Q-ToF): *m/z* Calcd for $C_{17}H_{21}O$ $[M+H]^+$: 241.1591. Found: 241.1587.

1-((2aS,2a1S,3S,4aS,6aS)-3-((E)-Prop-1-en-1-yl)hexahydro-1*H*-1,3,4,6-(epiethane[1,1,2,2]- tetrayl) pentaleno[1,6-bc]furan-6a(2a*H*)-yl)propan-2-one, 20

The compound **19** (60 mg, 0.247 mmol) was dissolved in DMF and water (4:1), then $CuCl_2$ (10 mol%) and $PdCl_2$ (10 mol%) were added to the reaction mixture and allowed to stir at RT for 5 h. At the conclusion of the reaction (TLC monitoring), water was added to the reaction mixture and extracted with ethyl acetate. The solvent was evaporated and residue was purified by a silica-gel column chromatography to give compound **20**. Yield 37 mg (60%). Appearance: colourless liquid. R_f = 0.3 (10% EtOAc-petroleum ether); IR (Neat): 2950, 1740, 1635, 1202, 1168, 1153, 1005, 917, 767 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.57 (d, *J* = 16.49 Hz, 1H), 5.50-5.43 (m, 1H), 4.48 (t, *J* = 4.03 Hz, 2H), 2.76 (d, *J* = 18.01 Hz, 1H), 2.66 (d, *J* = 18.09 Hz, 1H), 2.60-2.56 (m, 1H), 2.54(d, *J* = 4.47 Hz, 1H), 2.50-2.49 (m, 1H), 2.42-2.38 (m, 2H), 2.29 (d, *J* = 5.41 Hz, 1H), 2.11 (s, 3H), 1.92 (d, *J* = 10.31 Hz, 1H), 1.68 (d, *J* = 5.93 Hz, 3H), 1.49 (d, *J* = 10.64 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.5, 134.2, 122.5, 90.4, 89.3, 66.1, 60.3, 52.0, 48.5, 47.0, 46.8, 45.8, 43.7, 42.7, 38.0, 30.6, 18.1; HRMS (ESI, Q-ToF): *m/z* Calcd for $C_{17}H_{21}O_2$ $[M+H]^+$: 257.1536. Found: 257.1536.

(1S,3aR,5S,6S)-1,3-Bis(2-oxopropyl)octahydro-2*H*-3,5,1-(epiethane[1,1,2]triyl)cyclobuta[cd]- pentalene-2,7-dione, 21

The compound **17** (100 mg, 0.416 mmol) was dissolved in DMF and water (4:1), then $CuCl_2$ (10 mol%) and $PdCl_2$ (10 mol%) was added to the reaction mixture and allowed to stir at RT for 5 h. At the conclusion of reaction (TLC monitoring), water was added to the reaction mixture and extracted with ethyl acetate. Solvent was evaporated and residue was purified by a silica-gel column chromatography to give compound **21**. Yield 79 mg (70%). Appearance: Colourless solid. m.p.120-125°C. R_f = 0.3 (20% EtOAc-petroleum ether); IR (Neat): 2950, 1740, 1755, 1210, 1165, 1153, 1002, 917, 768 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.0 (s, 1H), 2.99-2.92 (m, 2H), 2.89-2.73 (m, 3H), 2.65-2.61 (d, *J* = 18.01 Hz, 1H), 2.54-2.34 (m, 2H), 2.11 (s, 6H), 2.02 (m, 2H), 1.90-1.83 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ. 212.2, 204.7, 60.6, 55.2, 51.7, 47.8, 47.3, 44.1, 43.8, 40.7, 40.1, 39.1, 35.9, 30.9, 30.2; HRMS (ESI, Q-ToF): *m/z* Calcd for $C_{17}H_{19}O_4$ $[M+H]^+$: 287.1205. Found: 287.1201.

Conclusion

In summary, we have developed a new and simple synthetic route to new cage derivatives **18**, **19**, **20** and **21** containing diverse functional groups. These functionalized PCUD derivatives can serve as important synthons for synthesizing biologically active compounds and for further synthetic manipulations.

Supplementary Information

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

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