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NOVEL AROMATIC SYSTEM-III: 2,3-DIMETHYL BENZOCYCLOHEPTEN-5-ONE

B. Srinivasulu*

Department of Chemistry, Nizam College, Osmania University, Hyderabad-500001, Telangana, India.

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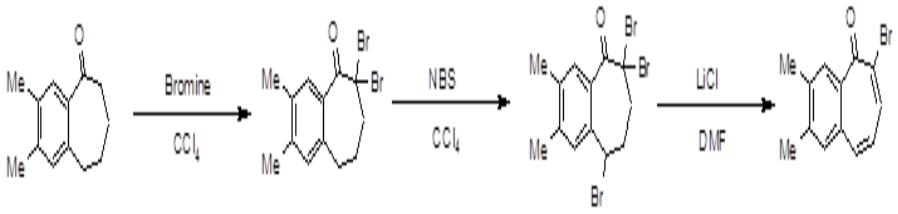
***Corresponding Author**
B. Srinivasulu
Department of Chemistry, Nizam College, Osmania University, Hyderabad-500001, Telangana, India.

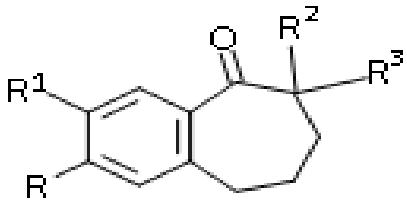


ABSTRACT

The use of lithium chloride in boiling dimethylforamide has been shown to give high yields of 2,3-dimethyl benzocyclohepten-5-one (**4**) from 2,3-dimethyl-6,6-dibromo-6,7,8,9-tetrahydrobenzocyclohepten-5-one **(3)**. Similar elimination occurs from 2,3-dimethyl-6,9-dibromo-6,7,8,9-tetrahydrobenzo- cyclohepten-5-one **(5)** to give (**4**).

KEYWORDS: Lithium chloride, dimethylformamide, NBS, cyclohepten-5-one.

Previously we have reported the synthesis of the structural analogues of substituted-6,7,8,9-tetrahydrobenzocyclohepten-5-ones.[1,2] Some of the bromo derivatives (la-d) showed some activity in murine p388 tests during routine anti-tumor screening,[3] thus a program of structural modification of 2,3-dimethyl benzocyclohepten-5-one **(2)**[4] was undertaken in the present investigation to study the structure activity relationship.



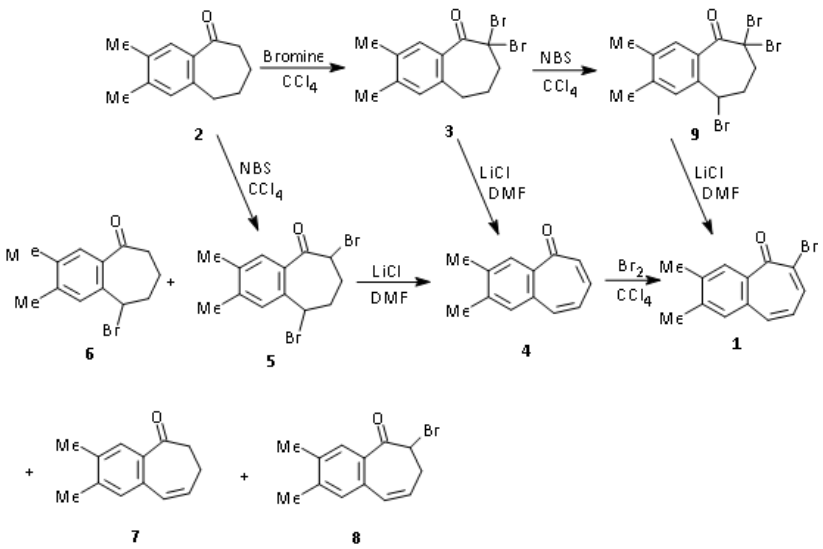
1a, R = OMe; R^1 = OAc; R^2 = R^3 =Br
b, R = OMe; R^1 = OAc; R^2 = H; R^3 = Br

c, R = R^1 = OAc; R^2 = R^3 = Br

d, R = R^1 = OAc; R^2 = R^3 = Br

2,3-Dimethyl-6,7,8,9-tetrahydrobenzocyclohepten-5-one **(2)** was brominated with bromine in carbon tetrachloride to give 2,3-dimethyl-6,6-dibromo-6,7,8,9-tetrahydrobenzocyclohepten-5-one **(3)**. The dibromo ketone **(3)** was converted into the corresponding 2,3-dimethyl benzocyclohepten-5-one **(4)** by boiling with a solution of lithium chloride in DMF for 1 h. The dibromo ketone (**3**), obtained by treatment of (**2**) with bromine in carbon tetrachloride was clearly shown by its ^{1}H NMR spectrum to be the 6,6-dibromo derivative (broad triplets at δ 2.90-3.30 due to the 7- and 9- methylene groups).

It has been reported[5] that bromination of tetrahydro benzocycloheptenone with *N*-bromosuccinimide (NBS) (2 equiv.) gave the 9,9-dibromo derivative. We have repeated the same reaction using NBS (2 equiv.) as a brominating agent on our ketone (**2**) to see whether the second bromine atom tend to enter into C-9 or C-6 position. This confirmatory work was necessary since there are reports[6] of NBS reactions which tended to introduce a second bromine atom into benzocycloalkanones at a position α to the carbonyl group rather than in the benzylic position and geminal with the first bromine atom.



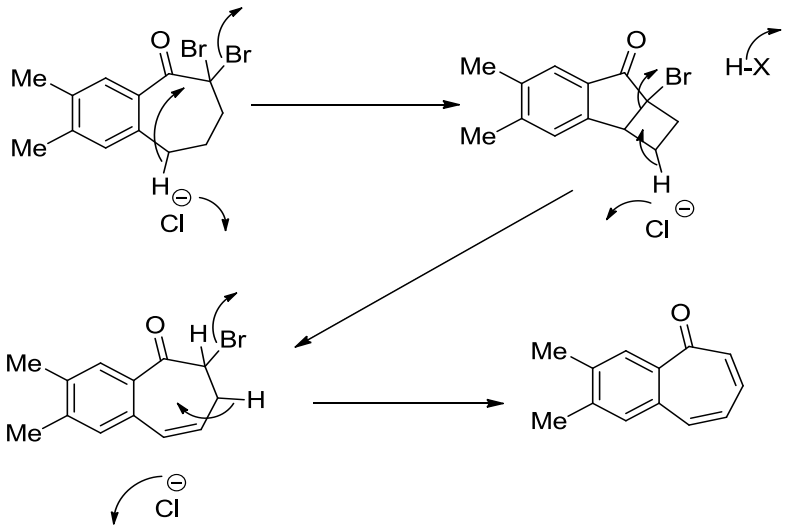
Scheme 1

When dimethylketone (**2**) was treated with NBS (2 equiv.) substitution was observed at C-9 and C-6 yielding the dibromoketone (**5**) as revealed by the ^{1}H NMR spectrum (1H multiplets at δ 4.85 and 5.40 attributed to the 6- and 9-protons respectively). Dehydrobromination of the

6,9-dibromoderivative **(5)** with lithium chloride in boiling DMF gave the expected benzotropone **(4)**. An attempt to obtain a monobromo derivative by reaction of (**2**) and NBS (1 equiv.) gave a mixture of products, including the 6,9-dibromo derivative **(5)**, 2,3-dimethyl-9-bromo-6,7,8,9-tetrahydro benzocyclohepten-5-one **(6)**, 6,7-dihydrobenzocyclo-heptenone **(7)** and 2,3-dimethyl-6-bromo-6,7-dihydro benzocyclohepten-5-one **(8)** (Scheme 1). All these compounds were characterized with the help of chemical and spectral evidences.

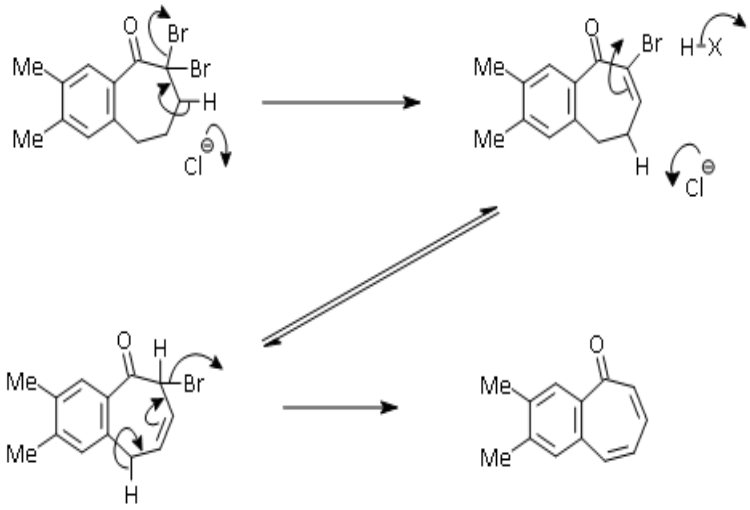
Treatment of 6,6-dibromoketone **(3)** with NBS gave a tribromoketone which was characterized as 6,6,9-tribromotetrahydro benzocycloheptenone **(9)**. Upon dehydro bromination of (**9**) with lithium chloride in drmethylformamide gave a mono bromo-benzocycloheptenone **(10)**. The structure of **10** was established by its ^{1}H NMR and mass spectral data and elemental analysis. The same bromo derivative **(10)** was obtained by bromination of (**4**) with bromine in CCl_4 at room temperature.

Encouraged by these results, we have made a few variations in dehydrobromination conditions; for example, collidine could be used to convert dibromoketone (**5**) into benzocyclo heptenone **(4)** although the reaction was not as clean as that of lithium chloride. Lithium carbonate could be substituted for lithium chloride with little change in yield.



Mechanism- I

A number of mechanisms for the dehydrobromination have been suggested.[6] It has been reported[7] that the efficiency of halide ion as a base in DMF solution is due to the low solvation. The mechanism may involve the elimination of two molecules of hydrogen bromide **(Mechanism-I & II)** from the correspondingα,α-dibromoketone.



Mechanism-II

EXPERIMENTAL

Melting points were determined in open glass capillaries on a Polmon melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Gemini (200 MHz) spectrometer (chemical shifts are recorded in δ ppm); internal standard was TMS. IR spectra were recorded in $CHCl_3$ on a Perkin-Elmer spectrophotometer. Mass spectra were taken on a VG micro mass 7070 H mass spectrometer and elemental analysis was carried out with a Cairo Erbra Model 1106 Elemental Analyser.

2,3-Dimethyl-6,6-dibromo-6,7,8,9-tetrahydrobenzocyclohepten-5-one (3)

Bromine (2.0 g, 12 mmole) in carbon tetrachloride (15 mL) was added dropwise to a stirred solution of **2** (1.0 g, 10 mmol) in carbon tetrachloride (50 mL), the solution was then boiled for 1 hr and the solvent was removed under reduced pressure. The residue (1.9 g, 83%) was almost pure dibromoketone **(3)**. M.P. 142.6°C. IR($CHC1_3$): υ 1770, 1687 cm^{-1}; ^{1}H NMR ($CDC1_3$): δ 1.90-2.15 (m, 2H, 8-H), 2.90-3.30 (m, 4H, 7 & 9-H), 2.30 (s, 6H, 2 Me), 7.10 (s, 1H, 1-H) and 7.55 (s, 1H, 4-H); MS : m/z= 346 (M^+. 100%), 318, 272, 241, 238, 191, 173, 163, 145, 133, 115, 105, 93, 85, 82. Anal. Calcd for $C_{13}H_{14}Br_2O$: C, 45.11; H, 4.08%. Found: C, 45. 18; H, 4.00%.

Preparation of 2,3-dimethyl-6,6,9-tribromo-6,7,8,9-tetrahydrobenzo-cyclohepten-5-one (9)

a) A solution of the 6,9-dibromoketone **5** (1.5 g, 1 mmole) and phenyl trimethylammonium tribromide (1.69 g) in dry THF (25 mL) was left at room temperature for 24 h. Workup gave the unchanged dibromoketone **(5)**.

b) A mixture of 6,6-dibromoketone 6 (1.5 g, 3 mmole), NBS (0.5 g), benzoyl peroxide (20 mg) in dry carbon tetrachloride gave after boning (4.5 h) the tribromoketone 9 in 93.3% yield, m.p. 82.6°C.

IR ($CHC1_3$): υ 1704 cm^{-1}; ^1H NMR ($CDC1_3$): δ 2.80-3.20 (m, 4H, 7 & 8-H), 2.38 (s, 6H, 2 Me), 5.40-5.70 (m, 1H, 9-H), 7.10 (s, 1H, 1-H) and 7.50 (s, 1H, 4-H); MS: m/z = 425 (M^+), 397, 350, 317, 272, 191, 163, 117 (100%), 105, 91, 82. Anal. Calcd for $C_{13}H_{13}Br_3O$: C, 36.74; H, 3.08%. Found: C, 36.77; H, 3.00%.

General procedure for dehydrobrominations

Preparation of 2,3-dimethylbenzocyclohepten-5-one (4)

A mixture of 6,6-dibromoketone 3 (0.5 g, 1.176 mmole) anhy. lithium chloride (0.15 g, 3 mmole) and dry DMF (30 mL) was boiled and stirred under nitrogen for 3 h. The mixture was cooled and DMF removed under reduced pressure. Water was added, and the mixture was thoroughly extracted with ether. The combined extracts were dried (Na_2SO_4), evaporation of the solvent gave a solid 2,3-dimethylbenzocyclohepten-5-one (4) (75%), which crystallized from ethanol as off-white crystals. m.p. 102.4°C.

IR ($CHC1_3$): υ 1667, 1600, 1208 cm^{-1}; ^1H NMR ($CDC1_3$): δ 6.60-7.90 (m, 4H, seven-membered ring-H), 2.37 (s, 6H, 2 Me), 7.60 (s, 1H, 1-H) and 8.40 (s, 1H, 4-H); MS: m/z= 184 (M^+), 156 (100%), 131, 114, 83, 73. Anal. Calcd for $C_{13}H_{12}O$: C, 84.74; H, 6.56%. Found: C, 84.68; H, 6.66%.

Monobromination of 2,3-dimethyl-6,7,8,9-tetrahydrobenzo-cycIohepten-5-one with N-bromosuccinimide (NBS)

A mixture of dimethylbenzocyclohepten-5-one (2) (2.0 g, 10.63 mmole) NBS (1 equiv.) and benzoylperoxide (50 mg) in dry carbontetrachloride (50mL) was boiled (6h) over a 500 w lamp. Filtration, and evaporation of the CCL_4 gave a thick brown oil. TLC showed four spots. PLC [3 runs of the oil (1.0 g)] gave four bands.

(i) 2,3-Dimethyl-6,9-dibromo-6,7,8,9-tetrahydrobenzocyclohepten-5-one **(5)**: Yield 48%. m.p. 63°C.

IR ($CHC1_3$): υ 1770, 1687 cm^{-1} ; ^1H NMR ($CDC1_3$): δ 1.95-2.15 (m, 2H, 8-H), 2.85-3.00 (m, 2H, 7-H), 4.85-5.10 (m, IH, 6-H), 5.40-5.65 (m, IH, 9-H), 2.30 (s, 6H, 2 Me), 7.11 (s, IH, 1-

H) and 7.50 (s, IH, 4-H). Anal. Calcd for $C_{13}H_{14}Br_2O$: C, 45.11 ; H, 4.08%. Found: C, 45.13; H, 4.02%.

(ii) 2,3-Dimethyl-9-dibromo-6,7,8,9-tetrahydrobenzocyclohepten-5-one **(6)** : Yield 18%. m.p. 105°C.

IR ($CHC1_3$): υ 1770, 1685 cm^{-1}; ^1H NMR ($CDC1_3$): δ 2.00-3.00 (m, 6,7 & 8-H), 5.40-5.60 (m, IH, CHBr Ar), 2.27 (s, 6H, 2 Me), 7.10 (s, IH, 1-H) and 7.50 (s, IH, 4-H). MS : m/z 267 (M^+ 100%), 187, 159, 148, 133, 119, 117, 92. Anal. Calcd for $C_{13}H_{15}BrO$: C, 58.44 ; H, 5.66%. Found: C, 58.51 ; H, 5.68%.

(iii) *2,3-Dimethyl-6-bromo-6,7-dihydrobenzocyclohepten-5-one* **(7)**: Yield 19%. m.p.77°C.

IR ($CHC1_3$): υ 1660, 1670 cm^{-1}; ^1H NMR ($CDC1_3$): δ 2.40-3.00 (m, 2H, methylene-H), 4.86-5.01 (m, IH, CHBr), 6.50 and 4.80 (dd, 2H, 8 & 9-H), 2.38 (s, 6H, 2 Me), 7.00 (s, IH, 1-H) and 7.30 (s, IH, 4-H). MS : m/z 265 (M^+.), 237, 185, 156 (100%), 141, 117, 91, 92, 77. Anal. Calcd for $C_{13}H_{13}BrO$: C, 58.88; H, 4.94%. Found: C, 59.01; H, 5.00%.

(iv) 2,3-Dimethyl-6,7-dihydrobenzocyclohepten-5-one **(8)**: Yield 12%. m.p. 118.5°C.

IR ($CHC1_3$): υ 1660, 1672 cm^{-1}; ^1H NMR ($CDC1_3$): δ 1.60-3.20 (m, 4H, methylene-H), 2.38 (s, 6H, 2 Me), 6.50 and 6.45 (dd, 2H, 8 & 9-H), 7.10 (s, IH, 1-H) and 7.60 (s, 1H, 4-H). MS : m/z 186 (M^+), 157, 131 (100%), 117, 91. Anal. Calcd for $C_{13}H_{14}O$: C, 83.82 ; H, 7.58%. Found: C, 84.02; H, 7.56%.

2,3-Dimethyl-6-bromobenzocyclohepten-5-one (10)

a) From the reaction of tribromoketone 9 (1 mmole) and lithium chloride (0.2 g) in DMF (50 mL) the 6-bromoketone **(10)** (80%) was obtained as pale yellow prisms, m.p. 83.4°C.

IR ($CHC1_3$): υ 1630, 1619, 1596 cm^{-1}; ^1H NMR ($CDC1_3$): 6 6.40-6.80 (t, 1H, 8-H), 7.30-7.70 (d, 1H, J = 11.3 Hz, 9-H), 7.80-8.20 (d, 1H, J = 9.3 Hz, 7-H), 2.38 (s, 6H, 2 Me), 7.60 (s, 1H, 1-H) and 8.40 (s, 1H, 4-H). MS: m/z 263 (M^+), 239, 235, 207, 194, 188, 179, 162 (100%), 141, 131, 114, 97, 81. Anal. Calcd for $C_{13}H_{11}BrO$: C, 59.33; H, 4.21%. Found: C, 59.12; H, 4.28%.

b) A solution of 2,3-dimethylbenzocyclohepten-5-one (4) (0.5 g) in DMF (5 mL) was treated drop wise at room temperature with bromine (0. 5 g) in DMF (5 mL). After 0.5 h the solution was heated to complete the reaction and then DMF was removed and the residue was separated by column chromatography to afford 2,3-dimethyl-6-bromo benzocyclohepten-5-

one (60mg). The unchanged 2,3-dimethylbenzocyclohepten-5-one (4) (150mg) was recovered.

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