Two directional approach to spirocycles containing bicyclo[2.2.2]octane system via a [2+2+2] co-trimerization and Diels-Alder reaction

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A simple and atom economic/step economic route for the synthesis of bis-armed spirocycles including bis-armed spirosulfone derivative containing bicyclo[2.2.2]octane ring system by utilizing a MW assisted Mo(CO)₆ catalyzed two-directional [2+2+2] co-trimerization and the [4+2] cycloaddition reaction as key steps, is reported.

Keywords: Bicyclo[2.2.2]octane, spirocycles, [2+2+2] co-trimerization, DA reaction, sulfone

Creation of molecular diversity and complexity from simple precursors is the major objective of the diversity-oriented synthesis. In this regard, there is a great deal of interest in developing new strategies for the synthesis of spirocycles. In several instances the presence of a quaternary centre may contribute towards the biological activity. Recently, spirocycles have received much attention due to their applications as chiral ligands and as chiral catalysts. In addition, a variety of natural and non-natural products contain a spiro-junction in their structures. Various biologically promising natural as well as non-natural products contain bicyclo[2.2.2]octane (Figure 1) as the core structural unit.

Strategy
Although, numerous methods are available for the synthesis of spirocyclics, very few of them deal with the spirocyclic frameworks containing bicyclo[2.2.2]octane system. Natural products containing bicyclo[2.2.2] unit and the documented difficulties in their synthesis inspired us to develop new methods. In this regard, we were interested to generate intricate C₂-symmetric bis-armed spirocycles containing bicyclo[2.2.2]octane unit in their structures via Mo(CO)₆ catalyzed two-directional [2+2+2] co-trimerization and [4+2] cycloaddition protocols as key steps.

Results and Discussion
In continuation of our research to generate spirocycles, we started our journey with the preparation of dione starting with a simple and commercially available hydroquinone followed by tetrapropargylation under NaH/propargyl bromide conditions gave the compound. The tetra propargylated dione was then subjected to two-fold [2+2+2] co-trimerization with 2-butyne-1,4-diol in the presence of Wilkinson’s catalyst and a catalytic amount of titanium isopropoxide to deliver the tetraol, which on treatment with PBr₃ in CH₂Cl₂ without isolating the intermediate diol afforded the desired tetra-bromo derivative and thus avoiding the formation of tetra-ol. For this purpose, the mono alkyn partner required is propargyl halide. Moreover, realization of [2+2+2] sequence without the involvement of the diol intermediate amounts to the “step economy”.

In this context, we directly subjected the tetra propargylated compound with 1,4-dibromobutadiyne in the presence of hexacarbonyl molybdenum complex Mo(CO)₆ under microwave (MW) irradiation conditions in CH₃CN at 90°C temperature was found to be suitable for the synthesis of spiro annulated tetrabromo building block in good yield (40%) (Scheme II).
Thereafter, the tetrabromide 8 was successfully converted into the sultine derivative 10 using Rongalite\textsuperscript{12}. This was followed by the DA\textsuperscript{13} sequence with tetracyanoethylene which delivered the DA adduct 11 in 67\% yield (Scheme III).

In addition, sulfones are useful building blocks which are considered as ‘drug-like’ molecules and they are also valuable synths for the construction of C-C bonds\textsuperscript{14}. In view of these applications and also to expand the scope of our methodology, the sultine derivative 10 was rearranged to bis-sulfone derivative 12 under toluene reflux conditions in good yield (Scheme III).

**Experimental Section**

All commercially available reagents were used without further purification. Reactions involving air sensitive catalysts or reagents were performed in degassed solvents. Moisture sensitive materials were transferred using syringe-septum techniques and the reactions were maintained under nitrogen atmosphere. Analytical thin layer chromatography (TLC) was performed on (7.5 × 2.5 cm) glass plates coated with Acme’s silica gel GF 254 (containing 13\% calcium sulfate as a binder) by using a suitable mixture of EtOAc and petroleum ether for the development. Column chromatography was performed by using Acme’s silica gel (100-200 mesh) with an appropriate mixture of EtOAc and petroleum ether. The coupling constants (\textit{\textit{J}}) are given in Hertz (Hz) and chemical shifts are denoted in parts per million (\textit{\textit{\delta}}, ppm) downfield from internal standard, tetramethylsilane (TMS). The abbreviations, s, d, t, q, m, dd and td, refer to singlet, doublet, triplet, quartet, multiplet, doublet of doublets, and triplet of doublets respectively. Infrared (IR) spectra were recorded on Nicolet Impact-400 FT-IR spectrometer in CHCl\textsubscript{3}. Proton nuclear magnetic resonance (\textsuperscript{1}H NMR, 400 MHz and 500 MHz) spectra and carbon nuclear magnetic resonance (\textsuperscript{13}C NMR, 100 MHz and 125 MHz) spectra were recorded on a Bruker spectrometer. The high-resolution mass measurements were carried out by
using electrospray ionization (ESI, Q-ToF) spectrometer. Melting points were recorded on a Veego melting point apparatus. Compound 4 was prepared according to the literature procedure\(^9\).

**Synthesis of compound 5**

To a suspension of sodium hydride (8 equiv) in dry THF (~5 mL per mmol), was added the compound 4 and the reaction mixture was stirred at RT for 10 min. Later, propargyl bromide (6 equiv) was added and the stirring was continued for 20 h at the same temperature. At the conclusion of the reaction (TLC monitoring), the reaction mixture was quenched with saturated aq. NH\(_4\)Cl (5 mL) solution. Aqueous layer was then extracted with EtOAc and dried over anhyd. Na\(_2\)SO\(_4\). The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography using appropriate mixtures of EtOAc-petroleum ether to afford the desired compound 5. White solid. Yield 55% (349 mg
from 300 mg). Time 20 h. m.p.130-33°C. Rf = 0.75 (silica gel, 10% EtOAc-petroleum ether); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 2.14-2.17 (m, 4H), 2.33 (dd, \(J_1 = 1.25\) Hz, \(J_2 = 16.07\) Hz, 2H), 2.40 (dd, \(J_1 = 1.10\) Hz, \(J_2 = 16.22\) Hz, 2H), 2.48 (dd, \(J_1 = 1.29\) Hz, \(J_2 = 16.70\) Hz, 2H), 2.81 (dd, \(J_1 = 1.65\) Hz, \(J_2 = 16.96\) Hz, 2H), 3.62 (t, \(J = 3.62\) Hz, 2H), 6.51 (t, \(J = 3.75\) Hz, 2H); \(^1\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 24.98, 26.35, 45.98, 58.10, 73.14, 73.15, 77.65, 78.27, 131.63, 206.63; IR (neat): 1216, 1598, 1729, 2857, 2952, 3020 cm\(^{-1}\); HRMS (ESI, Q-Tof): Calcd for C\(_{20}\)H\(_{17}\)O\(_2\) [M+H]\(^+\) \(m/z\) 289.1226. White solid. Yield 85% (37 mg from 100 mg). Time 3 h. m.p. 233-35°C. Rf = 0.42 (silica gel, 50% EtOAc-petroleum ether); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 2.70 (t, \(J = 16.20\) Hz, 4H), 3.22 (dd, \(J_1 = 7.00\) Hz, \(J_2 = 15.80\) Hz, 2H), 3.29-3.35 (m, 4H), 3.48 (dd, \(J_1 = 7.44\) Hz, \(J_2 = 15.24\) Hz, 2H), 4.30-4.32 (m, 2H), 4.85 (dd, \(J_1 = 6.98\) Hz, \(J_2 = 14.27\) Hz, 2H), 5.20 (d, \(J = 13.36\) Hz, 2H), 6.52 (brs, 2H), 6.97-7.06 (m, 4H); \(^1\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 42.28, 45.88, 53.58, 53.72, 57.41, 57.86, 58.70, 58.76, 63.84, 64.04, 121.96, 122.10, 122.40, 122.53, 125.38, 125.70, 125.87, 126.14, 126.23, 132.12, 132.21, 133.13, 133.45, 139.91, 140.17, 140.60, 140.96, 211.26, 211.41; IR (neat): 1217, 1647, 1720, 2330, 3023 cm\(^{-1}\); HRMS (ESI, Q-Tof): Calcd for C\(_{20}\)H\(_{24}\)BrNaO\(_2\) [M+Na]\(^+\) \(m/z\) 559.0578. Found: 559.0572.

**Synthesis of compound 8 (Method A)**

To a solution of tetra-ynyl 5 (100 mg) and propargyl halide 9 (3 equiv.) in dry CH\(_2\)CN, Mo(CO)\(_6\) (5 mol%) was added and the reaction mixture was irradiated under MW conditions for 10 min. After the completion of reaction (TLC monitoring), the solvent was concentrated at reduced pressure and the crude product was purified by silica gel column chromatography. White solid. Yield 40% (100 mg from 100 mg). Time 24 h. m.p. 286-87°C. Rf = 0.45 (silica gel, 50% EtOAc-petroleum ether); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 2.72-2.82 (m, 4H), 3.25-3.35 (m, 4H), 3.48 (dd, \(J_1 = 15.96\) Hz, 2H), 4.30-4.32 (m, 4H), 6.52 (brs, 2H), IR (neat): 1216, 1598, 1729, 2857, 2952, 3020 cm\(^{-1}\); HRMS (ESI, Q-Tof): Calcd for C\(_{20}\)H\(_{23}\)BrNaO\(_2\) [M+H]\(^+\) \(m/z\) 734.8363. Found: 734.8367.

**Synthesis of compound 7**

The solution of compound 5 with 2-butylene-1,4-diol 6 (5 equiv.) in dry ethanol (∼5 mL per mmol) was degassed with nitrogen for 15 min. Wilkinson’s catalyst (5 mol%) and Ti(O\(_\text{Pr}\))\(_4\) (50 mol%) was then added and the reaction was refluxed for 24 h. At the conclusion of the reaction (TLC monitoring), the solvent was removed under reduced pressure and the crude product was directly subjected to the next step without further purification.

**Synthesis of compound 8 (Method B)**

To a solution of the tetra-ol 7 in CH\(_2\)Cl\(_2\) (∼8 mL per mmol) at 0°C, was added a solution of PBr\(_3\) (6 equiv) in CH\(_2\)Cl\(_2\) (∼3 mL per mmol) by using a dropping funnel. The reaction mixture was stirred at RT for 15 h. At the conclusion of the reaction (TLC monitoring), the reaction mixture was poured into ice-cooled water and the organic layer was extracted with CH\(_2\)Cl\(_2\). The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography by using appropriate mixtures of EtOAc-petroleum ether to deliver the desired product 8.

**Synthesis of compound 10**

To a solution of tetra-bromide 8 and TBAB (2 equiv) in DMF (10 mL), was added rongalite (10 equiv) at 0°C. The reaction mixture was then stirred at 0°C for 3 h and at RT for another 3 h. At the conclusion of the reaction (TLC monitoring), the aqueous layer was extracted with EtOAc and washed with water (4×50 mL) to remove the excess amount of DMF. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (50-60% EtOAc-petroleum ether) to deliver the desired sultine derivative 10. White solid. Yield 85% (37 mg from 60 mg). Time 3 h. m.p. 233-35°C. Rf = 0.42 (silica gel, 50% EtOAc-petroleum ether); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 2.70 (t, \(J = 16.72\) Hz, 4H), 3.23 (d, \(J = 16.15\) Hz, 2H), 3.37 (d, \(J = 16.55\) Hz, 2H), 3.43 (t, \(J = 3.80\) Hz, 2H), 4.65 (d, \(J = 2.67\) Hz, 8H), 6.58 (t, \(J = 3.85\) Hz, 2H), 7.17 (d, \(J = 8.88\) Hz, 4H); \(^1\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 30.36, 30.39, 42.25, 45.93, 53.61, 58.73, 127.07, 127.53, 132.26, 135.94, 141.43, 141.77, 211.29; IR (neat): 1216, 1598, 1729, 2857, 2952, 3020 cm\(^{-1}\); HRMS (ESI, Q-Tof): Calcd for C\(_{29}\)H\(_{42}\)BrNaO\(_2\) [M+H]\(^+\) \(m/z\) 559.0578. Found: 559.0572.

**Synthesis of compound 11**

The solution of compound 10 and the tetracyanaoethylene (3 equiv) in toluene (20 mL) was refluxed for 24 h. At the conclusion of the reaction (TLC monitoring), the solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (40-50% EtOAc-petroleum ether) to deliver the desired DA product 11. White solid. Yield 67% (4 mg from 5 mg). Time 24 h. m.p. 286-87°C. Rf = 0.45 (silica gel, 50% EtOAc-petroleum ether); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 2.72-2.82 (m, 4H), 3.25 (d, \(J = 15.96\) Hz, 2H),
The solution of compound 10 in toluene (20 mL) was refluxed for 20 h. At the conclusion of the reaction (TLC monitoring), the solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (50% EtOAc-petroleum ether) to provide the desired product 12. White solid. Yield 88% (7 mg from 8 mg). Time 20 h. m.p. 270-75°C. 

Reference:

Supplementary Information
Supplementary information is available in the website http://nopr.niscair.res.in/handle/123456789/60.

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References

Synthesis of compound 12
The solution of compound 10 in toluene (20 mL) was refluxed for 20 h. At the conclusion of the reaction (TLC monitoring), the solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (50% EtOAc-petroleum ether) to provide the desired product 12. White solid. Yield 88% (7 mg from 8 mg).

Conclusion
In summary, we have demonstrated a simple and atom economic/step economic route for the synthesis of bis-armed spirocycles including bis-armed spirofuran derivative containing bicyclo [2.2.2] octane system by utilizing a MW assisted Mo catalyzed two-directional [2+2+2] co-trimerization and the [4+2] cycloaddition reaction as key steps. The strategy demonstrated here for Mo catalyzed [2+2+2] co-trimerization may be useful for the synthesis of diverse and intricate compounds.

Supplementary Information
Supplementary information is available in the website http://nopr.niscair.res.in/handle/123456789/60.