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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[1]. In this regard, there is a great deal of interest in developing new strategies for the synthesis of spirocycles[2]. 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[3] and as chiral catalysts[4]. In addition, a variety of natural and non-natural products contain a spiro-junction in their structures[5]. Various biologically promising natural as well as non-natural products contain bicyclo[2.2.2]octane (Figure 1)[6] as the core structural unit.

Strategy

Although, numerous methods are available for the synthesis of spirocyclics[7], very few of them deal with the spirocyclic frameworks containing bicycle-[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 C_2-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] cycloadditon protocols as key steps.

Results and Discussion

In continuation of our research to generate spirocycles[8], we started our journey with the preparation of dione **4** starting with a simple and commercially available hydroquinone **1** followed by tetra-propargylation under NaH/propargyl bromide conditions gave the compound **5** (Scheme I)[9].

The tetra propargylated dione **5** was then subjected to two-fold [2+2+2] co-trimerization with 2-butyne-1,4-diol **6** in the presence of Wilkinson's catalyst and a catalytic amount of titanium isopropoxide to deliver the tetraol **7**, which on treatment with PBr_3 in CH_2Cl_2 without isolating the intermediate diol afforded the desired tetra-bromo derivative **8** (Scheme II). Since the isolation of tetra-ol **7** was difficult by column chromatography, we were in search of an alternative route to tetra-bromo derivative **8** and thus avoiding the formation of tetra-ol **7**. For this purpose, the mono alkyne partner required is propargyl halide. Moreover, realization of [2+2+2] sequence without the involvement of the diol intermediate amounts to the "step economy"[10]. In this context, we directly subjected the tetra-propargylated compound **5** with 2-butyne-1,4-dibromide **9** in the presence of Wilkinson's catalyst. However, unfortunately we did not realize the desired product. This observation provided an opportunity to optimize the reaction conditions and search for alternate procedures. In this regard, we examined the catalytic activity of Mo complexes in [2+2+2] cycloaddition reaction[11]. To our surprise treating the tetra propargyl building block **5** with 1,4-dibromobutadiyne in the presence of hexacarbonyl molybdenum complex $Mo(CO)_6$ under microwave (MW) irradiation conditions in CH_3CN at 90°C temperature was found to be suitable for the synthesis of spiro annulated tetrabromo building block **8** in good yield (40%) (Scheme II).

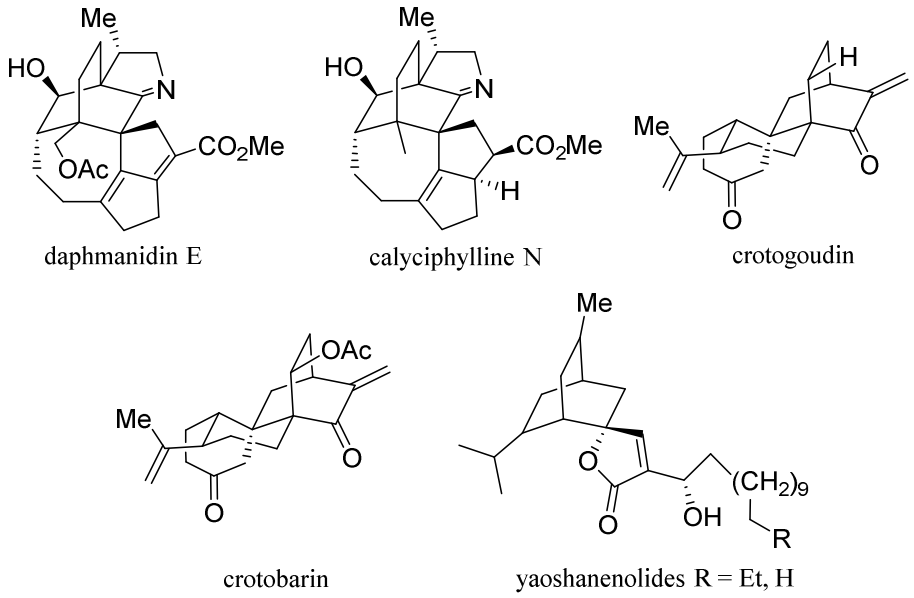
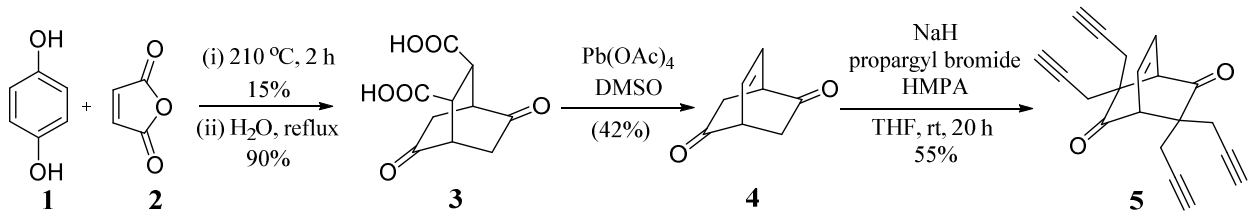


Figure 1 — List of some biologically active compounds containing bicyclo[2.2.2] unit



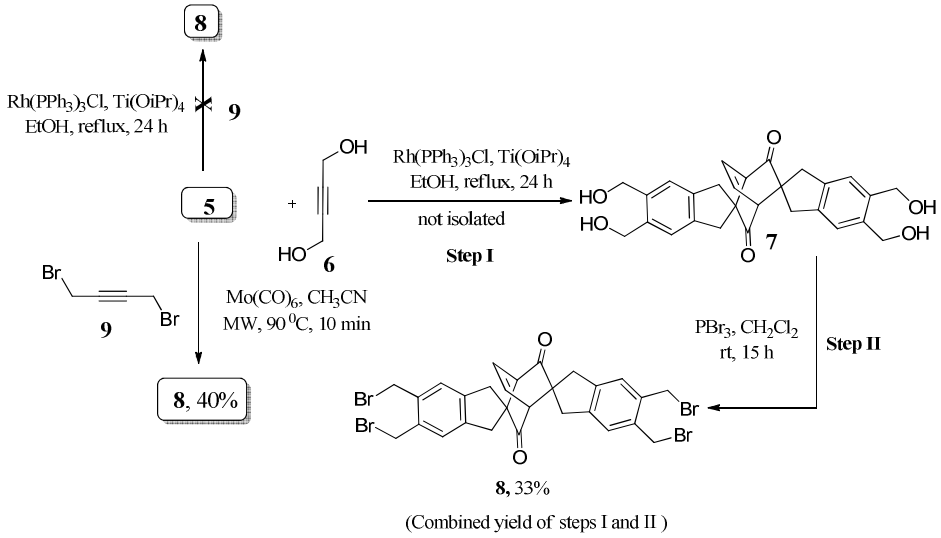
Scheme I — Synthesis of tetra-propargylated building block**5**

Thereafter, the tetrabromide **8** was successfully converted into the sultine derivative **10** using Rongalite[12]. This was followed by the DA[13] sequence with tetracyanoethylene which delivered the DA adduct **11** in 67% yield (Scheme III).

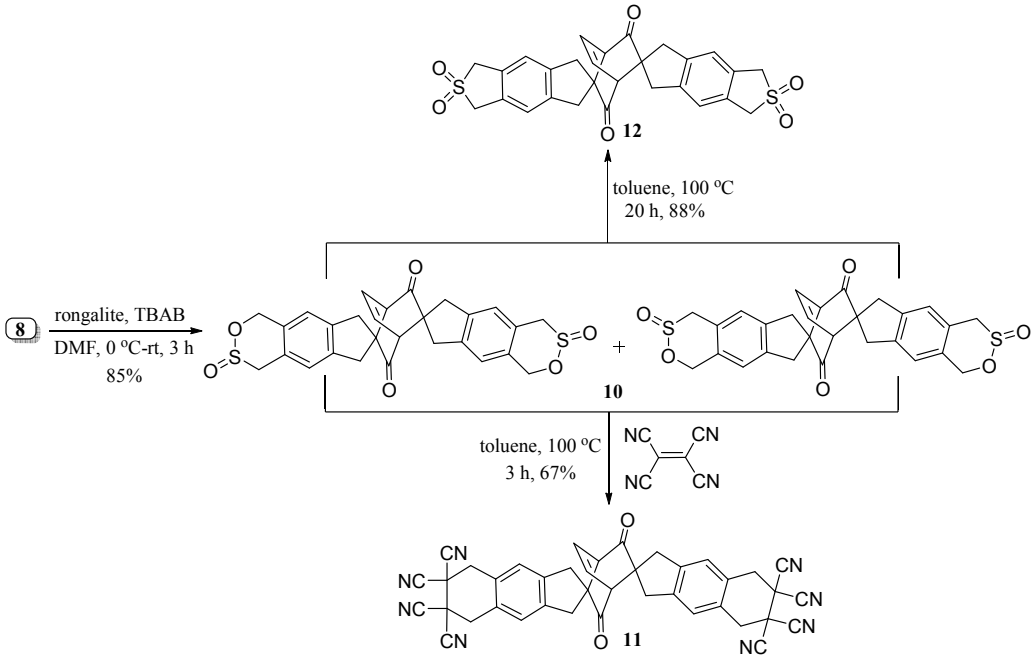
In addition, sulfones are useful building blocks which are considered as 'drug-like' molecules and they are also valuable synthons for the construction of C–C bonds[14]. In view of these applications and also to expand the scope of our methodology, the sultine derivative **10** was rearranged to bis-sulfone 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 (*J*) are given in Hertz (Hz) and chemical shifts are denoted in parts per million (δ, 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 $CHCl_3$. Proton nuclear magnetic resonance (^{1}H NMR, 400 MHz and 500 MHz) spectra and carbon nuclear magnetic resonance (^{13}C NMR, 100 MHz and 125 MHz) spectra were recorded on a Bruker spectrometer. The high-resolution mass measurements were carried out by



Scheme II — Synthesis of tetra-bromo building block **8**



Scheme III — Synthesis of bis-armed spirocycles **11** and **12** containing bicyclo[2.2.2]octane system

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_4Cl (5 mL) solution. Aqueous layer was then extracted with EtOAc and dried over anhyd. Na_2SO_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. R_f = 0.75 (silica gel, 10% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 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); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.98, 26.35, 45.98, 58.10, 73.14, 73.15, 77.65, 78.27, 131.63, 206.63; IR (neat): 1735, 2165 3019, cm^{-1}; HRMS (ESI, Q-Tof): Calcd for $C_{20}H_{17}O_2$ $[M+H]^+$ *m/z* 289.1229. Found: 289.1226.

Synthesis of compound 8 (Method A)

To a solution of tetra-yne **5** (100 mg) and propargyl halide **9** (3 equiv.) in dry CH_3CN, $Mo(CO)_6$ (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. 245-47°C. R_f = 0.55 (silica gel, 10% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.74 (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); ^{13}C NMR (100 MHz, $CDCl_3$): δ 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 $C_{28}H_{24}{}^{79}Br_4NaO_2$ $[M+Na]^+$ *m/z* 734.8363. Found: 734.8367.

Synthesis of compound 7

The solution of compound **5** with 2-butyne-1,4-diol **6** (5equiv) in dry ethanol (~5 mL per mmol) was degassed with nitrogen for 15 min. Wilkinson's catalyst (5 mol%) and $Ti(O^iPr)_4$ (50 mol%) was then added and the reaction mixture was refluxed for 24 h. At the conclusion of the reaction (TLC monitoring), the solvent was removed under reduced pressure and the crude product **7** 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_2Cl_2 (~8 mL per mmol) at 0°C, was added a solution of PBr_3 (6 equiv) in CH_2Cl_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_2Cl_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. R_f = 0.42 (silica gel, 50% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 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); ^{13}C NMR (125 MHz, $CDCl_3$): δ 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, 2932, 3023 cm^{-1}; HRMS (ESI, Q-Tof): Calcd for $C_{28}H_{24}KO_6S_2$ $[M+K]^+$ *m/z* 559.0578. Found: 559.0572.

Synthesis of compound 11

The solution of compound **10** and the tetracyanoethylene (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. R_f = 0.45 (silica gel, 50% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.72-2.82 (m, 4H), 3.25 (d, J = 15.96 Hz, 2H),

3.37-3.44 (m, 4H), 3.79 (brs, 8H) 6.62 (d, J = 3.60 Hz, 2H), 7.03 (d, J = 8.64 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 36.00, 38.63, 42.11, 45.67, 53.72, 58.63, 110.64, 124.43, 125.06, 125.49, 132.25, 141.83, 142.15, 210.72; IR (neat): 1640, 2260, 1726, 2940, 3012 cm^{-1}; HRMS (ESI, Q-Tof): Calcd for $C_{40}H_{24}N_8NaO_2$ $[M+Na]^+$ *m/z* 671.1914. Found: 671.1908.

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). Time 20 h. m.p. 270-75°C. R_f = 0.45 (silica gel, 50% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.73 (t, J = 17.88 Hz, 4H), 3.26 (d, J = 16.12 Hz, 2H), 3.37-3.41 (m, 4H), 4.28-4.36 (m, 8H), 6.62 (d, J = 3.68 Hz, 2H), 7.11 (d, J = 8.64 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 42.31, 45.89, 53.66, 57.04, 58.69, 122.23, 122.65, 130.34, 132.22, 140.84, 141.18, 211.08; IR (neat): 1266, 1604, 1723, 2855, 2929, 3010 cm^{-1}; HRMS (ESI, Q-Tof): Calcd for $C_{28}H_{24}NaO_6S_2$ $[M+Na]^+$ *m/z* 543.0842. Found: 543.0838.

Conclusion

In summary, we have demonstrated 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 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.

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