Allylation of caged diketones *via* fragmentation methodology

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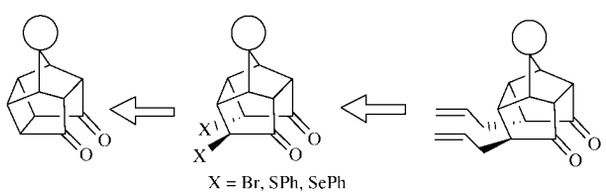
Fragmentation methodology was utilized to allylate some polycyclic diketones where ionic reactions are inappropriate. These allylated derivatives serve as useful precursors for the synthesis of higher polyquinanes.

Strained polycyclic molecules exhibit remarkable structural parameters which deviate from normal values. Therefore, syntheses and reactions of strained molecules contribute significantly to our understanding of chemical bonding and reactivity. With the accessibility of several modern synthetic methods at our disposal, polycyclic molecules are now readily available in large quantities. Consequently, they have emerged as useful synthons for complex synthetic targets.[1,2]

In connection with polyquinane syntheses, Cookson's cage dione **1**[3] was identified as a useful building block for further synthetic exploration.[4] For example, derivatives of **1** were used in the synthesis of natural products (*e.g.* coriolin)[4] and non-natural products such as dodecahedrane,[5] pentaprismane,[6] and garudane.[7] Military applications of caged molecules led to the development of high energy density fuels and explosives.[8] Various allylated derivatives of **2**[9] through the intermediate **3** may provide access to unknown polycyclic frames (Scheme 1).



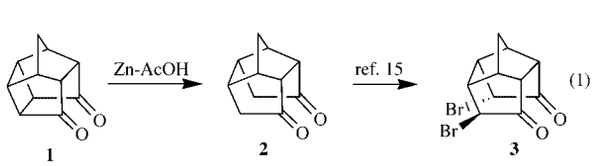
Scheme 1

Since the allyl group is useful for subsequent synthetic transformations this proposition is worthy of systematic investigation. In this paper, we disclose our results to allylate various derivatives of **2** *via* the fragmentation methodology.

Our initial efforts indicated that ionic conditions are incompatible to allylate **2** due to unwanted transannular cyclizations and aldol-type reactions. Allylation of **2** using the Claisen rearrangement as the key step[10a] gave a very low yield of mono-allylated derivative **6**, and even under forcing reaction conditions no diallylated product **5** was observed.[10b]

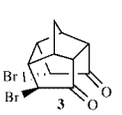
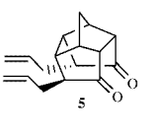
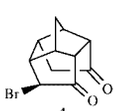
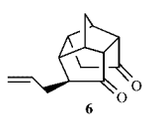
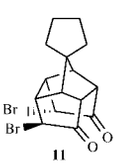
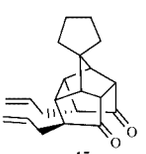
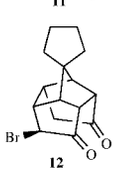
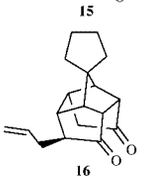
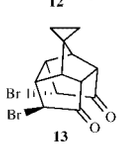
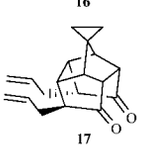
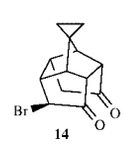
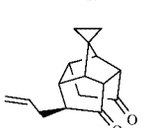
Initial observations of Migata,[11] and Preyire,[12] Keck and others[13] have shown that free radical allylation with allylstannanes is a synthetically useful method to functionalize organic molecules where traditional methods fail. Moreover, radical reactions[14] tolerate several functional groups and there is no need to use the protective group strategies.

To test the idea of allylation of polycyclic diketones, dibromo compound **3** was prepared from the readily available pentacyclic dione **1** by a two step sequence [eqn. (1)].[15] Allyltributyltin was prepared from tributyltin chloride, allyl chloride and magnesium under ultrasonic conditions.[16] The reaction of the dibromide **3** with allyltributyltin in the presence of radical initiator (AIBN) in toluene at 80 °C gave diallyldione **5** in 76% isolated yield (Table 1). At the conclusion of the reaction (TLC), the reaction mixture was concentrated and the crude product obtained was charged on a silica gel column. Elution with 3% ethyl acetate–petroleum ether gave diallyldione **5** (mp 84–85 °C). The molecular ion (M^+: 256) of **5** indicated that two allyl groups had been introduced in the tetracyclic system **2**. From the symmetry considerations the two allyl groups can possess *exo*,*exo* or *endo*,*endo* orientation. The stereochemistry assigned for **5** is *exo*,*exo* because of favorable steric interactions.

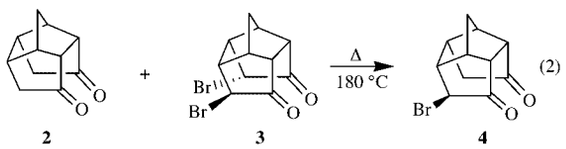


Having established the conditions for allylation of dibromo derivative **3**, we next turned our attention to apply this method-

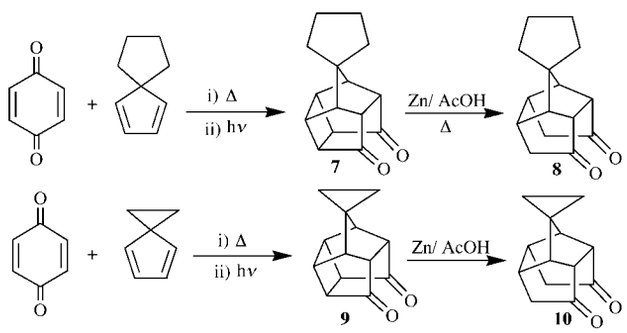
Table 1

	Starting bromide	Allylated product	Yield (%)	Mp/°C
1	 **3**	 **5**	76	84–85
2	 **4**	 **6**	75	78–80
3	 **11**	 **15**	70	108–109
4	 **12**	 **16**	84	129–130
5	 **13**	 **17**	75	85–87
6	 **14**	 **18**	64	120–122

ology to some other derivatives. In this regard we prepared monobromo derivative **4** [eqn. (2)].[17]



Thus, the dione **2** and dibromide **3**[15] were heated as a solid mixture at 180 °C to give monobromo derivative **4** (58%) along with some starting materials **2** and **3**. Along similar lines bromo compounds **11**–**14** were prepared by adoption of known procedures *via* intermediates **8**[18] and **10** (Scheme 2). Allylation of



Scheme 2

these bromo compounds to generate mono **16**, **18** and diallylated **15**, **17** caged derivatives are shown in Table 1.

In conclusion, we have shown for the first time the applicability of the fragmentation methodology to allylate related compounds of Cookson's dione without the need for protective group strategies. In view of the diverse applications of dione **1** in organic synthesis the methodology developed here may find useful applications in the synthesis of new strained molecules.

Experimental

General details

Tetrahydrofuran (THF) was distilled from sodium–benzophenone immediately prior to use. Melting points are uncorrected. Pet ether refers to the fraction of petroleum ether with a boiling point 60–80 °C. Infrared spectra were recorded on a Nicolet 400 FT IR spectrometer in KBr–$CHCl_3$ with absorptions in cm^{-1}. ^1H NMR spectra were determined on a Bruker 300 MHz spectrometer as $CDCl_3$ solutions. *J* Values are in hertz. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Mass spectra were recorded on a GCD 1800A Hewlett-Packard GC-MS spectrometer. Microanalyses were carried out on a Carlo-Erba Struentazione MOD 1106 instrument.

Zinc–AcOH reduction of spiro-dione 9

A mixture of spiro-dione **9** (400 mg, 2 mmol) and activated zinc (1.5 g, 23.1 mmol) in glacial acetic acid (10 ml) was stirred for 4 h. The reaction mixture was concentrated and diluted with water (10 ml) and extracted with dichloromethane (2 × 25 ml). The organic layer was washed with saturated sodium bicarbonate solution, brine and dried over $MgSO_4$. The organic layer was concentrated at reduced pressure to give tetracyclic spiro-cage dione **10** (308 mg, 76%); mp 103–105 °C (Found: C, 76.89; H, 6.79. $C_{13}H_{14}O_2$ requires C, 77.20; H, 6.98%); ν_{max} ($CHCl_3$)/cm^{-1} 1742; δ_H (300 MHz, $CDCl_3$): 2.85–2.92 (m, 4H), 2.29 (s, 2H), 2.21–2.26 (m, 2H), 2.16 (s, 2H), 0.63–0.77 (m, 4H); δ_C (75.5 MHz, $CDCl_3$): 217.7, 59.2, 53.6, 40.1, 39.3, 31.4, 5.5, 4.4; *m*/*z* 202 (M^+).

General procedure for dibromination of caged diones[15b]

To a solution of caged dione **2** (174 mg, 1 mmol) in acetic acid (5 ml), pyridinium tribromide (640 mg, 2 mmol) was added and the reaction mixture was heated at 50 °C. Once the colour of the reaction mixture turned yellow, the heating was continued for 2–3 h. Then the reaction mixture was cooled to room temperature and diluted with ice cold water and a white precipitate was obtained and filtered and washed with water. Recrystallisation of the crude product from toluene gave white crystals of dibromide **3** (185 mg, 56%); mp 211–213 °C (lit.,[15] 217–218 °C). A similar procedure was followed for the preparation of compounds **11** and **13**.

Preparation of compound 11. To a solution of dione **8** (460 mg, 2 mmol) in acetic acid (10 ml), pyridinium bromide perbromide (1.28 g, 4 mmol) was added and the reaction mixture was heated at 50 °C for 2 h. After work up the crude product was crystallized in toluene to give pure compound **11** (500 mg, 64%); mp 210–212 °C (Found: C, 46.20; H, 4.10. $C_{15}H_{16}O_2Br_2$ requires C, 46.42; H, 4.16%); ν_{max} (CCl_4)/cm^{-1} 1768; δ_H (300 MHz, $CDCl_3$): 4.28 (s, 2H), 3.04–3.08 (m, 4H), 2.98–2.99 (m, 2H), 1.57–1.77 (m, 8H); *m*/*z* 388 (M^+).

Preparation of compound 13. The dione **10** (100 mg, 0.5 mmol) was treated with pyridinium bromide perbromide (320 mg, 1 mmol) according to the general procedure to give compound **13** (86 mg, 48%); mp >200 °C decomposed (Found: C, 43.30; H, 3.24. $C_{13}H_{12}O_2Br_2$ requires C, 43.36; H, 3.36%); ν_{max} (KBr)/cm^{-1} 1755; δ_H (300 MHz, $CDCl_3$): 4.30 (s, 2H), 3.11–3.15 (m, 4H), 2.73–2.74 (m, 2H), 0.73–0.86 (m, 4H); δ_C (75.5 MHz, $CDCl_3$): 208.9, 58.1, 51.9, 51.0, 47.1, 30.9, 5.8, 4.6; *m*/*z* 360 (M^+).

General procedure for monobromination of caged diones[16]

Tetracyclic dione **2** (528 mg, 3 mmol) and dibromo derivative **3** (830 mg, 2.5 mmol) were ground well and the solid mixture was heated at 180 °C over a period of 10 minutes. Then the reaction mixture was cooled to room temperature and charged on a silica gel column. Elution of the column with 10% ethyl acetate–pet ether gave dibromide **3** (78 mg, 7%) and continued elution of the column with 12% ethyl acetate–pet ether gave monobromo compound **4** (400 mg, 52%); mp 119–120 °C (lit.,[16] 123–124 °C). Further elution of the column with 15% ethyl acetate–pet ether gave compound **2** (156 mg, 29%).

Preparation of compound 12. Using the above mentioned general procedure the compound **12** was prepared. Tetracyclic dione **8** (260 mg, 1.13 mmol) and dibromide **11** (388 mg, 1 mmol) were mixed and heated at 150 °C for 10 min. The resulting mixture was purified on a silica gel column by eluting with 10% ethyl acetate–pet ether mixture to give **11** (50 mg, 11%). Continued elution with the same solvent system gave compound **12** (145 mg, 41%); mp 204–208 °C (Found: C, 58.10; H, 5.40. $C_{15}H_{17}O_2Br$ requires C, 58.27; H, 5.54%); ν_{max} (KBr)/cm^{-1} 1755; δ_H (300 MHz, $CDCl_3$): 4.31 (s, 1H), 2.91–2.98 (m, 4H), 2.85–2.86 (m, 1H), 2.53–2.54 (m, 1H), 2.21–2.26 (m, 2H), 1.54–1.79 (m, 8H); *m*/*z* 309 (M^+).

Further elution of the column with 12% ethyl acetate–pet ether mixture gave **8** (120 mg, 46%).

Preparation of compound 14. Using the above mentioned general procedure, the dibromide **13** (90 mg, 0.25 mmol) and dione **10** (75 mg, 0.37 mmol) were mixed well and heated at 180 °C for 4 min. The resulting mixture was purified under similar conditions mentioned above, to give dibromide **13** (31 mg, 23%) and compound **14** (21 mg, 20%); mp 138–140 °C (Found: C, 55.32; H, 4.52. $C_{13}H_{13}O_2Br$ requires C, 55.54; H, 4.66%); ν_{max} (KBr)/cm^{-1} 1755.8; δ_H (300 MHz, $CDCl_3$): 4.33 (s, 1H), 3.00–3.08 (m, 4H), 2.60 (s, 1H), 2.23–2.35 (m, 3H), 0.67–0.82 (m, 4H); *m*/*z* 281 (M + 1).

Continued elution of the column with the same solvent system gave the dione **10** (14 mg, 18%).

General procedure for allylation of caged diones

To a solution of dibromo compound **3** (4 g, 12 mmol) in dry degassed toluene (20 ml), allyltributyltin[15] (15 ml, 48 mmol) and AIBN (720 mg, 4.4 mmol) were added and the reaction mixture was heated at 80 °C for 2 h. Then, the reaction was cooled and the solvent was evaporated under reduced pressure to give a crude product which was washed with pet ether to remove tin impurities and the product obtained was purified on a silica gel column (eluted with 2% ethyl acetate–pet ether) to furnish the allylated derivative **5** (2.34 g, 76%); mp 84–85 °C (Found: C, 79.62; H, 7.84. $C_{17}H_{20}O_2$ requires C, 79.65; H, 7.86%); ν_{max} (KBr)/cm^{-1} 1757; δ_H (300 MHz, $CDCl_3$): 5.68–5.81 (m, 2H), 5.02–5.08 (m, 4H), 2.90 (t, J = 1.6, 2H), 2.75 (d, J = 1.6, 2H), 2.37–2.46 (m, 4H), 2.28 (dd, J = 4.9, 10.0, 2H), 1.86–2.05 (m, 4H); δ_C (75.5 MHz, $CDCl_3$): 219.0, 135.0, 117.0, 58.8, 49.2, 45.4, 43.4, 35.8, 34.6; *m*/*z* 256 (M^+).

Preparation of compound 15. Following the above procedure, dibromide **11** (100 mg, 0.3 mmol), AIBN (25 mg, 0.15 mmol) and allyltributyltin (0.372 ml, 1.2 mmol) were dissolved in dry degassed toluene (7 ml) and heated at 80 °C for 2 h and the crude reaction mixture was purified by eluting with 2% ethyl acetate–pet ether mixture on a silica gel column to give compound **15** (65 mg, 70%); mp 108–109 °C (Found: C, 79.95; H, 8.17. $C_{21}H_{26}O_2$ requires C, 81.25; H, 8.44%); ν_{max} (KBr)/cm^{-1} 1742; δ_H (300 MHz, $CDCl_3$): 5.67–5.81 (m, 2H), 5.00–5.07 (m, 4H), 2.86 (d, J = 1.4, 2H), 2.28–2.55 (m, 8H), 1.90–2.01 (m, 2H), 1.51–1.72 (m, 8H); δ_C (75.5 MHz, $CDCl_3$): 218.9, 135.6, 117.0, 59.2, 57.3, 53.9, 49.3, 43.5, 35.9, 32.6, 30.1, 25.8; *m*/*z* 310 (M^+).

Preparation of compound 17. Dibromide **13** (130 mg, 0.36 mmol), AIBN (25 mg, 0.15 mmol) and allyltributyltin (0.45 ml, 1.44 mmol) were dissolved in dry degassed toluene (5 ml) and heated at 80 °C for 2 h. Then the resulting crude product was purified on a silica gel column by eluting with 2% ethyl acetate–pet ether mixture to give compound **17** (76 mg, 75%); mp 85–87 °C (Found: C, 80.58; H, 7.83. $C_{19}H_{22}O_2$ requires C, 80.82; H, 7.85%); ν_{max} (KBr)/cm^{-1} 1755; δ_H (300 MHz, $CDCl_3$): 5.68–5.81 (m, 2H), 5.00–5.07 (m, 4H), 2.93 (m, 2H), 2.64 (d, J = 1.6, 2H), 2.24–2.43 (m, 6H), 1.88–2.00 (m, 2H), 0.64–0.76 (m, 4H); δ_C (75.5 MHz, $CDCl_3$): 218.9, 135.6, 117.1, 59.6, 51.4, 49.2, 44.2, 35.8, 31.5, 5.7, 4.5; *m*/*z* 282 (M^+).

Using the general procedure described above for allylated derivatives, mono allylated compounds were prepared from the corresponding monobromo derivatives.

Preparation of compound 6. The mono bromide **4** (1.25 g, 5 mmol), AIBN (150 mg, 0.91 mmol) and allyltributyltin (3.1 ml, 10 mmol) were dissolved in dry degassed toluene (10 ml) and heated at 80 °C for 2 h. The resulting crude product was charged on a silica gel column and on elution with 2% ethyl acetate–pet ether gave monoallylated compound **6** (820 mg, 75%); mp 78–80 °C (Found: C, 77.08; H, 7.61. $C_{14}H_{16}O_2$ requires C, 77.75; H, 7.46%); ν_{max} (KBr)/cm^{-1} 1749; δ_H (300 MHz, $CDCl_3$): 5.67–5.80 (m, 1H), 5.00–5.07 (m, 2H), 2.66–2.87 (m, 5H), 2.22–2.48 (m, 5H), 1.98–2.05 (m, 1H), 1.90 (dd, J = 11.0, 13.6, 2H); δ_C (75.5 MHz, $CDCl_3$): 218.9, 217.8, 135.6, 117.0, 59.0, 58.4, 48.9, 47.9, 45.4, 43.0, 40.7, 39.1, 35.8, 34.6; *m*/*z* 216 (M^+).

Preparation of compound 16. By adoption of the general procedure, the mono bromide **12** (103 mg, 0.33 mmol) was treated with AIBN (25 mg, 0.15 mmol), allyltributyltin (0.20 ml, 0.66 mmol) in dry degassed toluene (5 ml) and heated at 80 °C for 2 h. The resulting crude product was purified on a silica gel column by eluting with 2% ethyl acetate–pet ether mixture to give the monoallylated compound **16** (75 mg, 84%); mp 129–130 °C (Found: C, 79.33; H, 7.91. $C_{18}H_{22}O_2$ requires C, 79.96; H, 8.20%); ν_{max} (KBr)/cm^{-1} 1755.8; δ_H (300 MHz, $CDCl_3$): 5.67–5.80 (m, 1H), 5.00–5.07 (m, 2H), 2.80–2.85 (m, 3H), 2.14–2.56 (m, 7H), 2.20–2.35 (m, 3H), 1.91–2.00 (m, 1H), 1.51–1.77 (m, 8H); δ_C (75.5 MHz, $CDCl_3$): 218.8, 217.8, 135.7, 117.0, 59.3, 58.7, 57.3, 56.2, 53.8, 48.8, 43.0, 40.7, 39.0, 35.9, 32.5, 30.1, 25.8; *m*/*z* 270 (M^+).

Preparation of compound 18. Using the general procedure mentioned above the monobromo compound **14** (40 mg, 0.14 mmol) was treated with AIBN (15 mg, 0.09 mmol), allyltributyltin (0.086 ml, 0.28 mmol) in dry degassed toluene (5 ml) and heated at 80 °C for 2 h. The resulting mixture was purified on a silica gel column by eluting with 2% ethyl acetate–pet ether mixture to give compound **18** (22 mg, 64%); mp 120–122 °C (Found: C, 79.34; H, 7.38. $C_{16}H_{18}O_2$ requires C, 79.31; H, 7.49%); ν_{max} (CCl_4)/cm^{-1} 1755; δ_H (300 MHz, $CDCl_3$): 5.67–5.80 (m, 1H), 5.00–5.06 (m, 2H), 2.86–2.93 (m, 3H), 2.59–2.68 (m, 1H), 2.16–2.45 (m, 6H), 1.88–1.98 (m, 1H), 0.62–0.77 (m, 4H); δ_C (75.5 MHz, $CDCl_3$): 218.7, 217.7, 135.7, 117.1, 59.8, 59.2, 53.7, 51.4, 48.8, 43.8, 40.7, 39.8, 35.8, 31.5, 5.6, 4.7; *m*/*z* 242 (M^+).

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Notes and references

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