SHORT PAPER

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The synthesis and X-ray crystal structure of 6-bromo-2,4,4-trimethyl-cyclohex-2-enone

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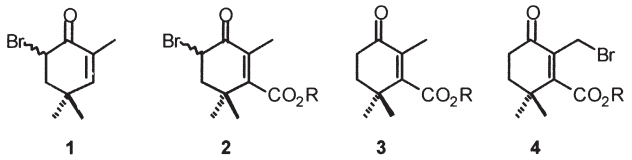
Regiospecific bromination of 2,4,4-trimethyl-cyclohex-2-enone was achieved and the X-ray crystal structure of 6-bromo-2,4,4-trimethyl-cyclohex-2-enone is presented.

Keywords: bromination, 2,4,4-trimethyl-cyclohex-2-enone, X-ray crystal structure

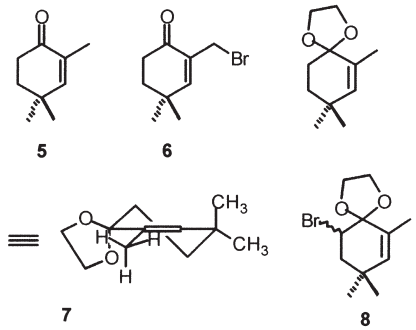
In the course of investigating various strategies towards the total synthesis of tetranortriterpenes (*e.g.* methyl angolensate and mexicanolide[1]) our group required various mono brominated 2,4,4-trimethyl-cyclohex-2-enones as starting materials, in particular, 6-bromo-2,4,4-trimethyl-cyclohex-2-enone (**1**).



1 **2** **3** **4**

Although, the synthesis of **1** has not previously been reported, a similar α-brominated derivative (**2**) resulted when cyclohexenone (**3**) was reacted with *N*-bromosuccinimide (NBS) in the presence of light,[2] along with the allylic bromide **4** as the major product irrespective of the conditions used.[2]

Initially, 2,4,4-trimethyl-cyclohex-2-enone **5** (commercially available) was reacted with NBS to compare regio isomer ratios, with those from substrate **3**. Surprisingly, however, 2-bromomethyl-4,4-dimethyl-cyclohex-2-enone (**6**) was the only detectable (GC/MS) product (52% isolated) (69% based on starting material recovery). The absence of the desired product (**1**) suggests enolisation of the conjugated ketone **5**, required for electrophilic bromination (α-bromination), is sluggish, perhaps related to the disruption of the α,β-keto conjugation. Removing conjugation would eliminate both double bond polarisation relatively promoting allylic bromination. However, when ketal **7** was subjected to the same conditions, followed by deprotection, 6-bromo-2,4,4-trimethyl-cyclohex-2-enone (**1**) was obtained in 65% yield as the sole product. Bromination (Br_2) of cyclohexanone ketals has been reported to give α-brominated cyclohexanones, after deprotection,[3] although examples containing the two active sites (α and allylic) have not been investigated. Additionally, this process has not been reported to occur with NBS, although, bromine is most likely the active reagent in this case. Mechanistically, it is believed[4] that traces of acid catalyse ketal ring opening affording an enol, which reacts with bromine followed by ring closure to give the α-brominated ketal (*e.g.* **8**). In view of the above, obtaining **1** as the sole product is thought to be a combination of the spiro-1,3-dioxolane group blocking the methyl group (**7**) and the sensitive nature of this group to enolisation in the presence of acid.



5 **6** **7** **8**

The crystal structure of **1** (Fig. 1) reveals a slightly puckered ring conformation. Atoms C1–C4, C7, Br1 and O1 all lie on a crystallographic mirror plane. Atoms, C5 and C6 (and their associated H-atoms) were disordered about the mirror plane and restrained to 50% occupancy. There are two possible models that fit the observed disorder, but the one shown (with C5 and C6 on opposite sides of the mirror plane) is the only one that is chemically sensible. The alternative envelope conformation was rejected on the basis of an unrealistically short C5–C6 bond length. The structure may be considered to comprise disorderd enantiomeric pairs (C6 being the chirotopic atom). The greatest strain is apparent at the *gem* dimethyl substituted atom C4 (C8–C4–C5 95.6(4)° and C8'–C4–C5 124.9(5)°). The bromo occupies an equatorial position with respect to the six-membered ring.

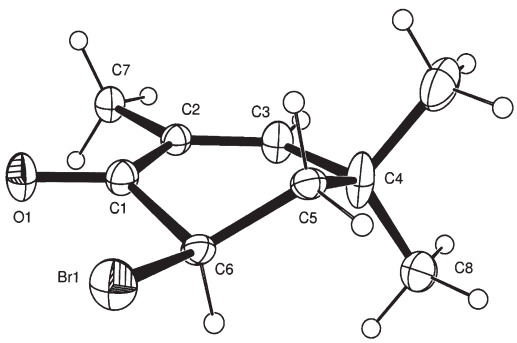


Fig.1 ORTEP drawing of compound 1 (30% probability ellipsoids).

In conclusion 2,4,4-trimethyl-cyclohex-2-enone can be regiospecifically brominated affording 6-bromo-2,4,4-trimethyl-cyclohex-2-enone or 2-bromomethyl-4,4-dimethyl-cyclohex-2-enone depending on whether the ketone function is masked or unmasked, respectively. Crystallography has shown that the compound crystallises as a racemate, with bond lengths and angles as expected for a compound of this type. Further derivatisation of **1** and **6** will be reported in due course.

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Experimental

Physical methods: ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ACF200 in deuteriochloroform ($CDCl_3$) and spectra referenced to chloroform (7.24 ppm). Accurate and low resolution mass spectral data were obtained on a KRATOS MS 25 RFA. Microanalyses were performed in-house by the University of Queensland Microanalytical Service. GC/MS data were recorded on a Hewlett-Packard 5890A chromatograph fitted with a (DBS EC-5 Alltech column 30m × 0.25 mm), coupled to a 5970 series mass spectrometer. Anhydrous solvents were prepared according to Perin and Armarego, 'Purification of laboratory solvents', 3rd edn. Melting points were determined on a Fischer Johns Melting Point apparatus and are uncorrected.

2-Bromomethyl-4,4-dimethyl-cyclohex-2-enone ***6****:* 2,4,4-Trimethylcyclohex-2-enone (0.5 g, 3.62 mmol) and *N*-bromosuccinimide (0.676 g, 3.80 mmol) were dissolved in anhydrous carbon tetrachloride (12 ml) under argon and refluxed with illumination (100W tungsten lamp). The reaction was deemed complete on flotation of succinimide (~50 min). The reaction mixture was filtered through cotton wool and the precipitate washed with light petroleum (2 × 10 ml). The solvent was removed *in vacuo* without external heating. The residue was then subjected to Kugelrohr distillation affording recovered starting material (0.12 g) (35°/0.01 mmHg) and the titled compound (0.41 g, 52%) (70°/0.01 mmHg). . ^{1}H NMR δ 1.13 (s, 6H); 1.75–1.86 (m, 2H); 2.42–2.50 (m, 2H); 4.00 (d, 2H, *J* 0.74); 6.76 (t, 1H, *J* 0.74). ^{13}C NMR δ 27.5, 27.7, 33.3, 34.4, 35.8, 133.5, 158.7, 196.7. Mass spectrum *m*/*z* (EI) 218/216 ($M^{+\bullet}$, 10/10%), 201 (2), 190 (3), 175 (2), 161 (2), 148 (33), 137 (100), 127 (8), 109 (12), 95 (16), 81 (20), 77 (11). Anal. Calcd for $C_9H_{13}{}^{81}BrO$: $M^{+\bullet}$ 216.0094. Found: 216.0157.

2,4,4-Trimethyl-1,1-spiro-(1,3-doxolane)-cyclohex-2-ene 7: 2,4,4-Trimethylcyclohex-2-enone (1 g, 7.24 mmol) was dissolved in anhydrous benzene (50 ml) under argon and to this was added dried toluenesulfonic acid (20 mg) and anhydrous ethylene glycol (0.8 ml, 14.5 mmol). The mixture was refluxed with a Dean-Stark apparatus (side arm contained 4Å molecular sieves) for 19h under argon. On cooling solid sodium carbonate (500 mg) was added and the mixture stirred for 10 min followed saturated sodium carbonate solution (20 ml). The organic layer was partitioned and the aqueous washed with diethyl ether (20 ml). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo* affording the title compound. The residue was used without further purification. ^{1}H NMR δ 0.96 (s, 6H); 1.50–1.58 (m, 2H); 1.61 (d, 3H, *J* 1.2); 1.70-1.80 (m, 2H); 3.96 (s, 4H); 5.36 (bs, 1H). ^{13}C NMR δ 16.6, 28.7, 30.9, 32.0, 34.8, 65.2, 107.3, 131.6, 139.7. Mass spectrum *m*/*z* (EI) 182 ($M^{+\bullet}$, 3%), 167 (5), 154 (34), 137 (9), 126 (100), 111 (7), 99 (51), 95 (17), 86 (11). *Anal*. Calcd for $C_{11}H_{18}O_2$: $M^{+\bullet}$ 182.1287. Found: 182.1309.

6-Bromo-2,4,4-trimethyl-cyclohex-2-enone 1: Ketal **7** (450 mg, 2.47 mmol) and *N*-bromosuccinimide (571 mg, 3.21 mmol) were dissolved in anhydrous carbon tetrachloride (7 ml) under nitrogen and irradiated with a 100W tungsten lamp (lamp placed directly in front of flask) for 20 mins. The solvent was evaporated and the flask placed in the fridge open to the moist atmosphere for two weeks. The crystalline material was collected on tissue paper washed with distilled water and a small portion of cold light petroleum (350 mg, 65%), m.p. 72–74°C. ^{1}H NMR δ 1.17 (s, 3H); 1.19 (s, 3H); 1.79 (s, 3H); 2.32–2.44 (m, 2H); 4.83 (dd, 2H, *J* 10.67, 7.72); 6.42 (bs, 1H). ^{13}C NMR δ 16.5, 26.2, 30.2, 35.6, 47.8, 50.3, 131.0, 154.6, 191.9. Mass spectrum *m*/*z* (EI) 218/216 ($M^{+\bullet}$, 11/11%), 162/160 (7/8), 137 (43), 110 (100), 95 (19), 82 (15), 67 (34). *Anal*. Calcd for $C_9H_{13}{}^{81}BrO$: C, 49.79; H, 6.04; $M^{+\bullet}$ 216.0121. Found: C, 49.91; H, 6.11; 216.0153.

Crystallography: Cell constants were determined for all complexes by least-squares fits to the setting parameters of 25 independent reflections measured on an Enraf-Nonius CAD4 four-circle diffractometer employing graphite-monochromated Mo Kα radiation (0.71073 Å) and operating in the ω–2θ scan mode. The crystal was cooled to 150 K with an Oxford Cryostream cooler. Data reduction and empirical absorption correction (ψ-scans) were performed with the WinGX package.[5] The structure was solved by Patterson methods with SHELXS-86[6] and refined by full-matrix least-squares analysis with SHELXL-97.[7] All non-H atoms were refined with anisotropic thermal parameters and H-atoms were included at estimated positions and refined according to a riding model. A drawing of the molecule (Fig. 1) was produced with ORTEP showing the atomic nomenclature.[8] Crystallographic data (in CIF format) have been deposited with the Cambridge Crystallographic Data Centre.

Crystal data: $C_9H_{13}BrO$, M = 217.10, orthorhombic, a = 7.539(1), b = 8.717(2), c = 14.256(3) Å, U = 936.9(3) Å^3, D_c = 1.539 g cm^{-3}, T = 150 K, space group *Pmcn* (variant of *Pnma*, No. 62), Z = 4, μ(Mo-Kα) = 43.31 cm^{-1}, 1263 reflections measured, 892 unique (R_{int} = 0.0931), R_1 = 0.0521 (obs. data), wR_2 = 0.1244 (all data).

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