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SYNTHESIS OF 1,1,2,2,3,3-HEXAMETHYL-4,5-BIS(METHYLENE)CYCLOPENTANE

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Abstract: An efficient synthesis of the title compound **14** is reported, which employs the $ZnCl_2/Et_2O$ catalyzed addition of acetyl chloride (**4**) to 2-methyl-2-butene (**5**) and the $[3^+ + 2]$ cycloaddition of the 1,1,2,3-tetramethylallyl cation to 2,3-dimethyl-2-butene as key steps.

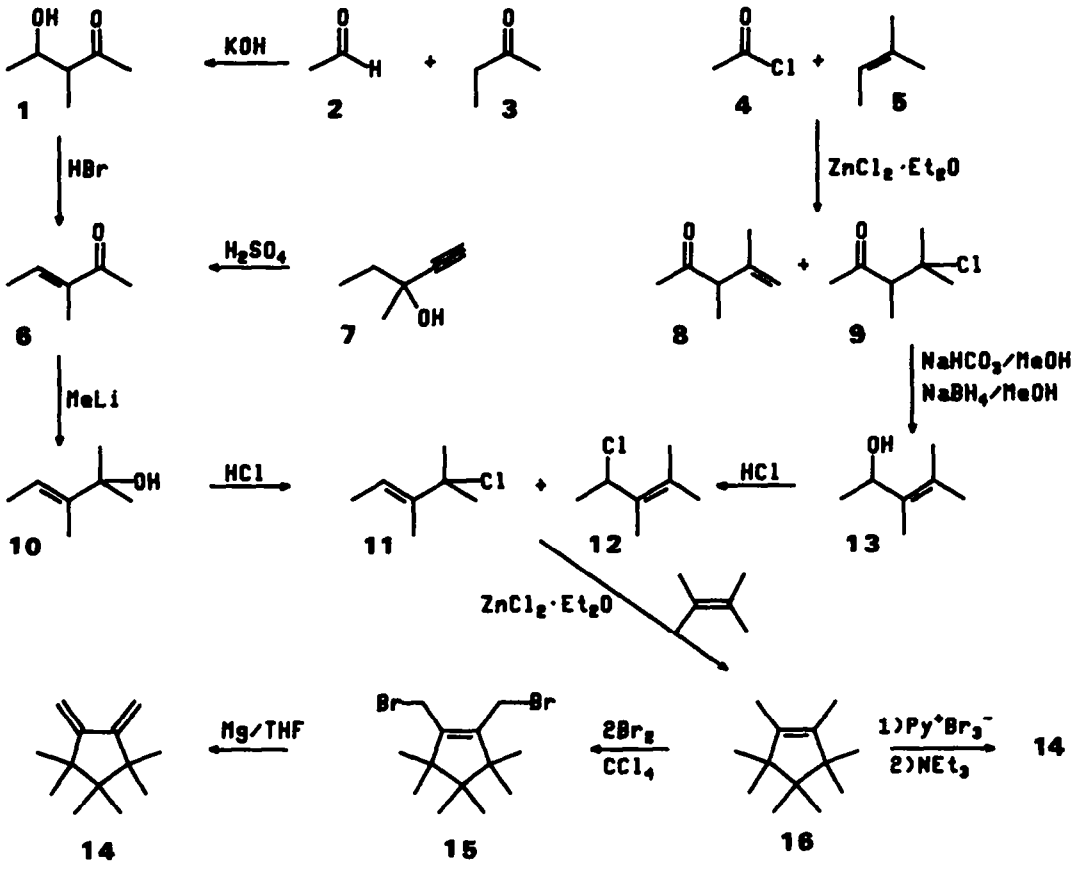
The title compound **14** incorporates a planar 1,3-diene system, the positions 2 and 3 of which are sterically shielded by the adjacent methyl groups. Therefore, the π system of **14** exhibits reduced 1,2-reactivity, and a variety of reactants (dihalocarbenes[1], diphenylketene[2], C,N-diphenylnitrone[3]), which normally undergo only 1,2 additions with 1,3-dienes, were found to give 1,4-addition products with **14**. The diene **14** can, therefore, be used as a new mechanistic probe for the study of cycloaddition reactions. In recent years, various synthetic approaches towards **14** have been accomplished in our laboratory (Scheme 1). In this paper, we discuss the different ways of access and give details on the route, which we presently prefer.

All approaches used proceed *via* octamethylcyclopentene **16**, which is obtained by Lewis acid catalyzed reaction of 2,3-dimethyl-2-butene with the allyl chloride **11** or **12**.[4] As shown in Scheme 1, both allylic alcohols **10** and **13** may serve as precursors for **11** and **12**.

The allyl alcohol **10** has previously been prepared *via* aldol condensation of 2-butanone **3** with acetaldehyde **2**, and reaction of **6** with methylmagnesium iodide.[5] In our hands, the intermediate enone **6** was obtained more purely by Rupe rearrangement[6] of the readily available ynol **7**. We furthermore found that the problems, which were encountered during the workup of **10** prepared from **6** and CH_3MgI,[5] are circumvented when the Grignard reagent is replaced by methyllithium (from CH_3I and Li).

In the alternative route, shown on the right of Scheme 1, 2-methyl-2-butene **5** is acetylated with acetyl chloride **4** in presence of $ZnCl_2/Et_2O$[7] in CH_2Cl_2 to give a 15:85 mixture of **8** and **9** in quantitative yield. With $EtAlCl_2$ catalysis, this reaction was reported to yield 53% of **8** and

Scheme 1



13% of 9.[8] Low yields of 9 were also reported with acetic anhydride as acylating agent: In presence of $EtAlCl_2$ 8 and 9 were obtained in 36 and 35% yield, respectively[8], and only 8 (38%) was formed in the $ZnCl_2$ catalyzed reaction.[9] The crude 9 is successively treated with sodium bicarbonate and sodium borohydride in methanol to afford 13 (contaminated by 3,4-dimethyl-4-penten-2-ol), which is converted into a 1:1.3 mixture of 11 and 12 with gaseous hydrogen chloride in pentane. Treatment of these allylic chlorides with $ZnCl_2/Et_2O/CH_2Cl_2$ in presence of 2,3-dimethyl-2-butene yields 16 *via* $[3^+ + 2]$ cycloaddition of the intermediate tetramethylallyl cation.[9] None of the intermediate products of this four-step synthesis has to be purified, and the yield of 16 is 58% based on 4.

As the dibromide 15 is prepared more easily than the corresponding monobromide,[10] the target molecule 14 is preferentially prepared *via* Br_2 elimination from 15 and not by HBr elimination from 1-bromomethyl-2,3,3,4,4,5,5-heptamethyl-1-cyclopentene. Starting from distilled 16, purification of 15 is not necessary, and 14 is obtained in 62% yield from 16, resulting in an overall yield of 36% based on acetyl chloride 4.

We hope that this convenient access to 14 will stimulate additional work using this diene as a probe in mechanistic studies.

EXPERIMENTAL

^{1}H NMR spectra: JNM-C-60-HL (JEOL) and XL-200 (Varian). ^{13}C NMR spectra: JNM-PS-100 (JEOL) and XL-200 (Varian). TMS as internal standard. Mass spectra (EI): MAT CH 4 (Varian), MAT 311 A (Varian), and 70-250 (VG). IR spectra: IR-435 (Shimadzu) and Beckman Acculab 1.

4-Chloro-3,4-dimethyl-2-pentanone (9). $ZnCl_2$ (36.2 g, 0.266 mol) and diethyl ether (43 mL) were dissolved[7] in 550 mL of dry CH_2Cl_2 and cooled at -75°C. A solution of acetyl chloride (4) (65.1 g, 0.830 mol) and of 2-methyl-2-butene (5) (88.2 g, 1.26 mol) in 50 mL of CH_2Cl_2 was added within 0.5 h, and the mixture was then stored at -20°C for 15 h. The mixture was stirred with 1 L of 10% aqueous NH_4Cl solution at ambient temperature for 30 min and the organic layer was separated, washed with 100 mL of saturated $NaHCO_3$ solution and dried over $MgSO_4$. The solvent was removed at reduced pressure (100 mbar/35°C) to give 122 g of crude 9, which was used for the next step without purification. The NMR resonances (CCl_4) at δ 1.18 (d, J = 7.5 Hz, 3 H), 1.60 (s, 6 H), 2.16 (s, 3 H), 2.93 (q, J = 7.5 Hz, 1 H) are similar to those described for 9 previously[11], and additional signals at δ 2.02 (s), and 4.85 (br. s) with relative intensities 3:2 indicate the presence of approximately 15% of 8.[9]

3,4-Dimethyl-3-penten-2-ol (13). A solution of crude 9 (61 g) in 400 mL of methanol was heated under reflux for 12 h in presence of $NaHCO_3$ (40 g). The mixture was cooled at ambient temperature, $NaBH_4$ (20 g, 0.53 mol) was added in portions (exothermic reaction!) and stirred for 1 h. About 300 mL of methanol was removed by distillation, and 250 mL of water was added to the residue. The solution was extracted with three 200 mL portions of ether, and the combined extracts were dried over $MgSO_4$. The suspension was filtered, and $MgSO_4$ was washed with 100 mL of dry ether. When the ether was evaporated in vacuo (83 mbar, ambient temperature), 40.1 g of crude 13 was obtained (contaminated by 3,4-dimethyl-4-penten-2-ol).
Since compound 13 has not been characterized previously, an analytical sample of 13 was prepared by the above procedure starting from distilled 9. 3,4-Dimethyl-3-penten-2-ol (13): bp. 80°C (bath)/30 mbar. IR (neat): 3328, 2960, 2905, 1446, 1369, 1079, 1024, 900 cm^{-1}. - ^{1}H NMR ($CDCl_3$): δ 1.21 (d, J = 6.5 Hz, 3 H), 1.37 (br. s, OH), 1.66 (br. s, 6 H), 1.70 (br. s, 3 H), 4.87 (br. q, J = 6.5 Hz, 1 H). - ^{13}C NMR ($CDCl_3$): δ 11.34 (q), 19.55 (q), 21.01 (q), 21.07 (q), 66.94 (d), 126.04 (s), 130.67 (s). - Mass spectrum (70 eV): m/z = 114 (m$^+$, 30%), 99 (100), 81 (54), 55 (49), 43 (89), 41 (46). Anal. Calcd for $C_8H_{14}O$ (114.2): C, 73.63; H, 12.36. Found: C, 73.88; H, 12.02%.

4-Chloro-3,4-dimethyl-2-pentene (11) **and 4-Chloro-2,3-dimethyl-2-pentene** (12). Hydrogen chloride was bubbled through a cooled solution (0°C) of crude 13 (40.1 g) in 250 mL of pentane for 1 h. The organic layer was decanted and dried over $MgSO_4$ for 1 h. After filtration, the solvent was evaporated at reduced pressure (250 mbar/20°C) to give 37.9 g of a 1:1.3 mixture (^{1}H-NMR) of 11 and 12, which was used for the next step without purification.

Octamethylcyclopentene (16). The published procedure[4] was modified: $ZnCl_2$ (31.6 g, 0.232 mol) was dissolved in 53 mL of ether and 190 mL of dry CH_2Cl_2 at 0°C, and the clear solution was cooled in a dry ice/methanol bath. A solution of the crude 11/12 mixture (19.0 g, = 0.143 mol) and of 2,3-dimethyl-2-butene (16.7 g, 0.198 mol) in 50 mL of dry CH_2Cl_2 was added dropwise within 25 min while the reaction mixture was kept at -65 to -70°C. The cooling bath was removed, and after 2 h 110 mL of aqueous hydrochloric acid (1:1) was added. The mixture was stirred for 20 min, the organic layer was separated, washed with 50 mL of concentrated ammonia and dried with $MgSO_4$. The solvents were evaporated in vacuo and the residue was distilled to give 16 (21.5 g, 58% based on 4) with bp. 61-63°C/10 mbar. IR (neat): 2980, 2940, 2865, 1480, 1470, 1460, 1450, 1440, 1375, 1365, 1080 cm^{-1}. - ^{1}H NMR (CCl_4): δ 0.79 (s, 6 H), 0.88 (s, 12 H), 1.50 (s, 6 H). - ^{13}C NMR: see ref. 4. - Mass spectrum (70 eV): m/z = 180 (M$^+$, 11%), 165 (100), 123 (75), 109 (72).

1,1,2,2,3,3-Hexamethyl-4,5-bis(methylene)cyclopentane (14). Compound 15 obtained from 18 g (0.1 mol) of 16 by the procedure given in ref. 10, was dissolved in 320 mL of dry THF, magnesium turnings (5.16 g, 0.212 mol) and a few crystals of iodine were added, and heated at reflux for 2 h. Water (400 mL) was added, and 14 was extracted with pentane. The organic layer was dried over $CaCl_2$, the solvent was evaporated and the residue was distilled to give 11.1 g (62% based on 16) of 14. Bp. 50-55°C/1-2 mbar. - IR (neat): 3080, 2990, 2960, 2875, 1765, 1630, 1610, 1460, 1450, 1395, 1375, 1145, 880 cm^{-1}. - ^{1}H NMR (CCl_4): δ 0.78 (s, 6 H), 1.05 (s, 12 H), 4.75 (s, 2 H), 5.30 (s, 2 H). - ^{13}C NMR ($CDCl_3$): δ 21.11 (q), 27.67 (q, double int.), 45.65 (s), 46.23 (s, double int.), 102.71 (t), 158.74 (s). - Mass spectrum (96 eV): m/z = 178 (M$^+$, 18%), 163 (100), 135 (29), 121 (48), 107 (46). - Anal. Calcd for $C_{13}H_{22}$ (178.3): C, 87.56; H, 12.44. Found: C, 87.88; H, 12.64%.

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