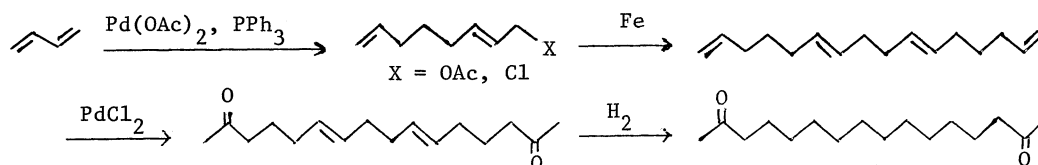


SYNTHESIS OF 2,15-HEXADECANEDIONE, A PRECURSOR OF MUSCONE, FROM BUTADIENE

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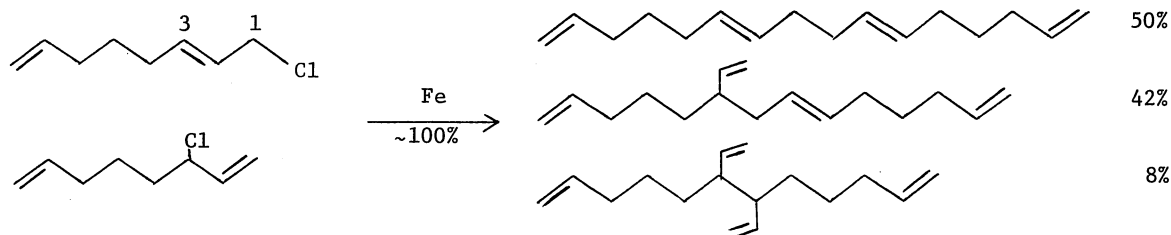
1-Acetoxy-2,7-octadiene obtained by the palladium catalyzed dimerization of butadiene in acetic acid was converted to 1-chloro-2,7-octadiene. Coupling of this allylic chloride with iron powder in DMF afforded 1,6,10,15-hexadecatetraene as a main product. Selective oxidation of the terminal double bonds to methyl ketones catalyzed by palladium chloride and cuprous chloride, followed by hydrogenation gave 2,15-hexadecanedione.

Palladium compounds are useful reagents for organic synthesis mainly in two ways; 1. oxidation of olefins to carbonyl compounds with Pd(II) salts,¹ and 2. dimerization of butadiene with palladium phosphine complexes.² This paper describes a novel synthesis of 2,15-hexadecanedione using these two reactions of palladium in key steps. Muscone (3-methylcyclopentadecanone) is a naturally occurring fragrant compound with musk odor and its synthesis has been a challenging problem of organic synthesis. One method is intramolecular aldol condensation of 2,15-hexadecanedione to form 15-membered ketone.³ However, few synthetic methods for this diketone have been reported.⁴⁻⁷ We found that the diketone can be synthesized by the following sequences starting from butadiene. This process, using easily available materials, is shorter and more practical than the known methods.



Dimerization of butadiene in acetic acid in the presence of palladium acetate and triphenylphosphine as a catalyst affords a mixture of 1-acetoxy-2,7-octadiene and 3-acetoxy-1,7-octadiene.² The mixture was converted in a high yield to a mixture of 1-chloro-2,7-octadiene and 3-chloro-1,7-octadiene (3:1, bp 64-66°C/19 mm) by hydrolysis, followed by treatment with thionyl chloride.

Coupling of allylic halides is a useful reaction for the synthesis of natural products and usually nickel carbonyl is used as a coupling agent.⁸ We found that the simplest procedure is the use of iron powder as a coupling agent.⁹ To the above mixture of the chlorides (50 g) in DMF (130 ml), iron powder (42 g, washed with dilute hydrochloric acid and dried) was added. The mixture was stirred at 150°C for 5 hr. Gas chromatographic analysis showed that the chlorides were converted into a mixture of tetraenes in nearly quantitative conversion. The crude mixture was distilled at 80-100°C/2.5 mm. A gas chromatogram showed the presence of three isomers, namely 1-1, 1-3 and 3-3, coupled products in a ratio of 50:42:8. Even when the pure 1-chloro-2,7-octadiene was subjected to the coupling, the mixture



of the same composition was obtained. The lower boiling 3-3 and 1-3 coupled products were separated from the desired 1-1 product by fractional distillation. Repeated distillation gave pure 1,6,10,15-hexadecatetraene (bp 125°C/5 mm).

The next step is the selective oxidation of the terminal olefinic bonds to methyl ketones catalyzed by palladium chloride. Usually the rate of oxidation of terminal olefins by palladium chloride is higher than that of internal ones. Step-wise oxidation can be monitored by TLC. In a typical example, palladium chloride (1 mmol, 0.173 g) and cuprous chloride (10 mmol, 1.0 g) were suspended in a mixture of water (0.7 ml) and DMF (10 ml). The mixture was shaken under oxygen atmosphere at room temperature until absorption of oxygen ceased. Then the tetraene (5 mmol, 1.09 g) was added and the solution was shaken for 5 hr under oxygen atmosphere. Dilute hydrochloric acid was added and the product was extracted with dichloromethane. The solvent was removed and the residue was subjected to silica gel column chromatography. The starting tetraene and hexadeca-6,10,15-triene-2-one (bp 126°C/1 mm) were eluted at first with dichloromethane. Then hexadeca-6,10-diene-2,15-dione (0.71 g, mp 47-48°C, m/e 250(M^+); Anal. found: C, 76.38; H, 10.57. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47) was isolated. The recovered tetraene and monoketone were subjected to the oxidation again with palladium chloride (0.5 mmol, 0.086 g) and cuprous chloride (5 mmol, 0.5 g) in water (0.7 ml) and DMF (10 ml) for 5 hr. The monoketone (0.23 g) and diketone (0.36 g) were isolated again. The combined yield of the diketone was 1.07 g (85%). When the oxidation was carried out for longer period of time until the tetraene disappeared completely, the diketone was partially oxidized further to the triketone (mp 75.0-75.5°C). The hydrogenation of the diketone catalyzed by palladium on carbon gave 2,15-hexadecanedione in 91% (mp 84-84.5°C, lit.³ mp 84-86°C, mass: m/e 254(M^+)). The hydrogenation of the triketone gave 2,6(or 7),15-hexadecanetrione (mp 94.0-94.5°C).

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