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Novel Synthetic Method for Muscone

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Abstract: Muscone is a precious fragrant compound scarce in nature. Many attempts to synthesize this unique natural product have been carried out. In this work, a novel synthetic method for the preparation of muscone from 3-methyl-15-hydroxypentade-canoate is provided. Benzimidazolium salt was used as tetrahydrofolate coenzyme model at formic acid oxidation level and Grignard reagent as nucleophile to which a one-carbon unit was transferred. The biomimetic synthesis of muscone was successfully accomplished using the addition-hydrolysis reaction of benzimidazolium salt with the Grignard reagent.

Keywords: Benzimidazolium salt, biomimetic synthesis, Grignard reagent, muscone, 3-methyl-15-hydroxypentadecanoate

Musk is a precious natural perfume and rare medicinal material. Muscone (3methylcyclo-pentadecanone) is the main odorous compound of the musk pod obtained from the male musk deer *Moschus moschiferus*, and its structure was determined in 1926.^[1] For more than half a century, many people have been working on the synthesis of muscone to find cheap artificial synthetic routes, and a lot of patents have been published. The synthesis of muscone has been a popular problem in organic synthesis.^[2]

The tetrahydrofolate coenzymes are involved in the biochemical transfer of a one-carbon fragment at different oxidation levels. When the one-carbon unit is at the formic and oxidation level, the imidazoline with a fivemembered ring structure is the active site (Scheme 1).^[3] If we use benzimidazolium salt as tetrahydrofolate coenzyme model to react with the nucleophilic

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Scheme 1.

reagent, such as a Grignard reagent, the one-carbon unit at the formic acid oxidation level will be transferred to the nucleophilic reagent and the biomimetic synthesis to initiate the one-carbon unit transfer reaction of tetrahydrofolate coenzyme will be accomplished.

We provide a convenient synthetic method for muscone by the intramolecular addition-hydrolysis reaction of Grignard reagent with quaternary C=N bond of benzimidazolium salt **2**, which served as the methyl-substituted one-carbon unit model of tetrahydrofolate coenzyme. The route of the new synthetic method is shown in Scheme 2.

It has been reported that compounds with quaternary C=N double group react with Grignard reagents.^[4] However, the method for preparing muscone from Grignard reagents and benzimidazolium salt has not been reported in literature. Because benzimidazole can be prepared from 3-methyl-15-hydroxy- pentadecanoate, the method provides an



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important route for preparing muscone from hydroxy ester and Grignard reagents.

In our experiments, the addition reaction of the Grignard reagent with benzimidazolium salt was carried out. Benzimidazolidine obtained from the addition reaction could be hydrolyzed directly to give muscone in acidic solution after the addition reaction was finished, a convenient and simple synthetic method for muscone.

Benzimidazolium salt **2** can be synthesized via bromination of benzimidazolium salt **1** with hydrobromic acid. Benzimidazolium salt **1** can be synthesized from iodomethane and benzimidazole obtained from 1,2-benzenediamine and 3-methyl-15-hydroxypentadecanoate under microwave irradiation.^[5] Grignard reagent was prepared from magnesium and benzimidazolium salt **2** in ethyl ether.^[6] These starting materials are readily available. Muscone was synthesized in two steps from benzimidazolium salt and magnesium.

The yield of muscone was 42%, as described in the experimental section, which is low. It is believed that the reason the yield was lower is the formation of some side products, such as the intermolecular product, hydrolysis product, and decomposition product. Further investigation of this reaction is being conducted in our laboratory.

The mechanism for the reaction of benzimidazolium salt with nucleophile has been proposed in our earlier article.^[7] The preparative reaction described in this article can be reasonably explained by an intramolecular addition reaction of Grignard reagent with the polarized C==N bond of benzimidazo-lium salt and the formation of benzimidazolidine, which can be hydrolyzed in acidic solution to give muscone (Scheme 3).



Scheme 3.

EXPERIMENTAL

Melting points were taken on a XT-4 micromelting apparatus (Beijing) and are uncorrected. TLC analysis was carried out on glass plates coated with silica gel-G, and spots were visualized using an ultraviolet (UV) lamp. Elemental analyses were performed with a Vario EL-III instrument (Germany) infrared (IR) spectra in cm⁻¹ and were recorded on a Brucker EQUIOX-55 spectrometer (Germany). ¹Proton magnetic resonance spectra (H NMR) spectra were recorded at 400 MHz on a Varian INOVA-400 spectrometer (USA), and chemical shifts were reported relative to internal Me₄Si.

General Procedure for the Preparation of Benzimidazolium Salt 2

Benzimidazolium salt **2** can be synthesized via bromination of benzimidazolium salt **1** with hydrobromic acid. Benzimidazolium salt **1** can be synthesized from iodomethane and benzimidazole obtained from 1,2-benzenediamine and 3-methyl-15-hydroxypentadecanoate under microwave irradiation.^[5] 3-Methyl-15-hydroxypentadecanoate was prepared from ethyl crotonate and 12-iodododecanol under sonication according to the literature.^[8] A solution of sodium (0.02 mol) in ethanol was treated with 0.02 mol of benzimidazole, 0.06 mol of iodomethane, and 25 mL of benzene, and then the mixture was refluxed for 18 h. The solvent was removed and the residue was recrystallized from water to give the bisbenzimidazolium salt.

General Procedure for Muscone

A 250-mL, three-necked, round-bottomed flask, fitted with a tantalum wire Hershberg stirrer and a condenser, was arranged for use with a nitrogen atmosphere. Benzimidazolium salt (2.8 g, 5 mmol), magnesium (0.4 g, 15 mmol), and 20 mL of anhydrous ether were placed in the flask. The flask was warmed in a water bath and a small crystal of iodine was added. After the reaction initiated, 2.8 g (5 mmol) of benzimidazolium salt and 150 mL of anhydrous ether were added to the reaction mixture again. The mixture was stirred at refluxing temperature for 28 h and then a 10% solution of hydrochloric acid was added slowly; the resulting mixture was heated at 45-50°C for 1 h with stirring. Ether was removed and the residue was extracted with chloroform $(3 \times 30 \text{ mL})$. The combined organic extracts were washed with 5% sodium bicarbonate and dried over anhydrous magnesium sulfate. After evaporation of the solvent, the crude product was purified by silicagel column chromatography (hexane/EtoAc 20:1) to give 0.5 g of muscone (3) as colorless oil. Yield: 42%, v_{max} (KBr): 1715 (C=O), 2920, 2850, 719. Anal. C₁₆H₃₀O calcd.: C, 80.67; H, 12.60. Found: C, 80.16; H, 12.85. ¹H NMR (CDC₁₃/TMS), δ (ppm): 0.92 (d, J = 6 Hz., 3H, CH₃), 1.10–2.00 (m, 23H, CH₂, CH), 2.10–2.52 (m, 4H, CH₂). MS m/z: 238 (M⁺).

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