報 文

A Facile Synthesis of 2,15-Hexadecanedione
using Alkyl Sulfone

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2,15-Hexadecanedione (5), a key intermediate for the synthesis of *dl*-muscone, was prepared from alkyl sulfone. The Claisen condensation of 1,6-bis(*p*-toluenesulfonyl) hexane (1) and ethyl 4,4-(ethylenedioxy) valerate afforded 2,2,15,15-bis(ethylenedioxy)-6,11-bis(*p*-toluenesulfonyl)-5,12-hexadecanedione (2) in quantitative yield. The reductive elimination of the sulfonyl groups, the Wolff-Kishner reduction, and hydrolysis of the diacetal gave 2,15-hexadecanedione (5) in good yield.

1 Introduction

The musk has been used as valuable perfumes since old days. Odoriferous constituents of the natural musk have been isolated, determined, and synthesized. On the other hand, the musk-like artificial odoriferous compounds have been prepared and used instead of natural products.

Muscone [(−)-3-methylcyclopentadecanone] is a main constituent of musk pod obtained from the male deer, *Moschus moschiferus*. Many reports were developed for the synthesis of muscone¹⁾. In these methods, 2,15-hexadecanedione was an important intermediate for the synthesis of *dl*-muscone. Seven examples for the synthesis of 2,15-hexadecanedione (5) have been reported as follows: (A) the Kolbe reaction of 8-oxononanoic acid²⁾; (B) the alkylation of ethyl 3-oxobutylate with 1,10-dibromodecane³⁾; (C) the reduction of 5,5''-diacetyl-2,2',5',2''-terthienyl which was prepared by the acylation of 2,2',5',2''-terthienyl⁴⁾; (D) the hydrolysis of 2-methoxycarbonyl-3-methyl-3-cyclopentadecen-1-one which was prepared by the ring enlargement reaction of cyclopentadecanone enamine⁵⁾; (E) the coupling reaction of 1-chloro-2,7-octadiene which was obtained from dimerization of butadiene⁶⁾; (F) the coupling reaction of methyl vinyl ketone with 1,7-octadiene in the presence of TiCl₄, LiAlH₄, Cu(OAc)₂⁷⁾; (G) the coupling reaction of 7,7-ethylenedioxy-1-octyne which was yielded by the photoxidation of 1,2-dimethyl-1-cyclohexene

in several steps⁸⁾. The cyclization of 2,15-hexadecanedione (5) was described by Stoll in 1947, who obtained 15-membered cyclic ketone in 17% yield^{2a)}. Recently, Tsuji *et al.* reported the intramolecular aldol condensation of 2,15-hexadecanedione (5) promoted by dialkylaluminum aryloxide in combination with a tertiary amine to form a mixture of dehydromuscones in 65% yield⁹⁾.

In this paper, we wish to report a new method for the synthesis of 2,15-hexadecanedione (5) which was obtained from 1,6-bis(*p*-toluenesulfonyl)hexane (1) in 69% overall yield. There are some characteristics of this procedure compared with the other known methods. These are: (1) high yield; (2) short process; (3) simple procedure; (4) inexpensive and readily available materials. **Scheme-1** shows the synthetic route of 2,15-hexadecanedione (5).

a: Lithium diisopropylamide (LDA), b: ethyl 4,4-(ethylenedioxy)valerate, c: Al-Hg, 10% aq. THF
d: hydrazine hydrate, KOH, e: 5% HCl.

Scheme-1 Procedure for the preparation of 2,15-hexadecanedione.

2 Experimental

2.1 Analytical apparatus.

Melting points were taken on a Yanagimoto micro melting point apparatus and uncorrected. Infrared spectra were measured on a JASCO IR-S or Shimadzu IR-27 G spectrophotometer. ¹H-NMR spectra were recorded on a Varian EM-390 spectrometer at 90 MHz, using TMS ($\delta=0.00$ ppm) as an internal standard.

2.2 1,6-Bis(*p*-toluenesulfonyl)hexane (1).

1,6-Dibromohexane (10 g, 41 mmol) was added to a stirred solution of sodium *p*-toluenesulfinate tetrahydrate (25 g, 100 mmol) in ethanol (100 ml). The mixture was stirred for 10 h under reflux. The mixture was diluted with water (1000 ml) to form white solid. The solid was filtered, washed with water, and dried to give (1) in 95% yield, mp 142~143°C. IR (nujol) 1310, 1140 cm⁻¹. NMR (CDCl₃) δ 1.2~1.9 (8 H, m), 2.35 (6 H, s), 2.9~3.15 (4 H, m), 7.30, 7.82 ppm (8 H, an A₂B₂ pattern, $J=7.5$ Hz). Found: C, 61.36; H, 6.60%. Calcd for C₂₆H₂₈O₄S₂: C, 60.89; H, 6.64%.

2.3 2,2,15,15-Bis(ethylenedioxy)-6,11-bis(*p*-toluenesulfonyl)-5,12-hexadecanedione (2).

To a cold solution (-78°C) of LDA, which was prepared from *n*-BuLi (15% hexane solution, 8.0 g, 18.8 mmol) and diisopropylamine (2.0 g, 19.8 mmol) in dry THF (15 ml), was added a solution of the sulfone (1) (1.7 g, 4.5 mmol) in dry THF (75 ml). After the mixture was stirred for 1 h, ethyl 4,4-(ethylenedioxy)valerate (1.7 g, 9.9 mmol) in dry THF (15 ml) was added and stirred for 1 h at -78°C. The mixture was stirred for additional 2 h at room temperature, quenched with cold 2% aq. sulfuric acid, and extracted with chloroform. The extract was washed with water, dried (Na₂SO₄), and concentrated to give (2) in 90% yield. The compound (2) was purified by recrystallization from ether to give pure (2) as white crystals, mp 129~131°C. IR (nujol) 1715, 1305, 1140 cm⁻¹. NMR (CDCl₃) δ 1.0~3.1 (28 H, m), 3.93 (8 H, s), 4.05 (2 H, t), 7.40, 7.70 ppm (8 H, an A₂B₂ pattern, $J=7.5$ Hz). Found: C, 60.04; H, 6.75%. Calcd. for C₃₄H₄₆O₁₀S₂: C, 60.16; H, 6.83%.

2.4 2,2,15,15-Bis(ethylenedioxy)-5,12-hexadecanedione (3).

To a solution of the sulfone (2) (0.3 g, 0.44 mmol) in 10% aq. THF (30 ml) was added aluminum amalgam (0.6 g, 22 mmol) with stirring. The mixture was stirred for 5 h at room temperature, and then filtered. The filtrate was diluted with water and extracted with ether. The extract was washed with water, dried (Na₂SO₄), and concentrated to give (3) (90%) as a crystalline compound. The compound (3) was further purified by recrystallization from CCl₄ to give pure (3) as colorless needles, mp 120~121.5°C. IR (nujol) 1710, 1140, 1040 cm⁻¹. NMR (CDCl₃) δ 1.1~1.7 (14 H, br), 1.7~2.0 (4 H, m), 2.25~2.35 (8 H, m), 3.86 ppm (8 H, s).

2.5 2,2,15,15-Bis(ethylenedioxy)hexadecane (4).

The diketone (3) (1.5 g, 4.0 mmol), hydrazine hydrate (2 g, 40 mmol), and powdered KOH (2 g, 35.7 mmol) were added to diethylene glycol (30 ml). The mixture was stirred for 1.5 h at 120°C. At the end of this period, water formed was distilled, and residue was further heated at 195°C for 4 h. The cooled mixture was diluted with 100 ml of water, acidified with 5% HCl, and extracted with ether. The ether layer was washed with water and dried (Na₂SO₄). After removal of the solvent, the diacetal (4) was obtained in 90% yield. The compound (4) was further purified by recrystallization from methanol to give pure (4) as colorless needles, mp 68.5~69.5°C. (lit. mp 69.0~70.5°C^{6c}). IR (nujol) 1470, 1380, 1070 cm⁻¹. NMR (CCl₄) δ 1.2~1.5 (30 H, br), 3.85 ppm (8 H, s).

2.6 2,15-Hexadecanedione (5).

The diacetal (4) (1 g, 2.8 mmol) was added to 5% hydrochloric acid (10 ml) and the mixture was stirred for 15 h at room temperature. The mixture was extracted with ether. The extract was washed with water, dried (Na₂SO₄), and concentrated to give (5) in quantitative yield. The compound (5) was purified by recrystallization from methanol to give pure (5) as colorless needles, mp 83~84°C (lit. mp 83~84°C¹⁰). IR (nujol) 1710 cm⁻¹. NMR (CCl₄) δ 1.1~1.7 (20 H, br), 2.05 (6 H, s), 2.2~2.5 ppm (4 H, m).

3 Results and Discussion

3.1 The Claisen condensation of the sulfone (1) and ethyl 4,4-(ethylenedioxy)valerate.

Under a nitrogen atmosphere, condensation of the dianion of sulfone (1) generated with two equivalents of LDA at -78°C with ethyl 4,4-(ethylenedioxy)valerate in THF gave the sulfone (2) in quantitative yield, with as high as 95% purity by NMR. The yield of the sulfone (2) decreased when excess LDA was used, and the starting sulfone (1) and ethyl 4,4-(ethylenedioxy) valerate were recovered.

3.2 Reductive elimination of the sulfonyl group and the cleavage of the sulfone (2).

Aluminum amalgam was found to be suitable for desulfonylation of the sulfone (2) to give 2,2,15,15-bis(ethylenedioxy)-5,12-hexadecanedione (3) in 90% yield. When the sulfone (2) was treated with sodium amalgam in ethanol instead of aluminum amalgam, no sulfonyl group of the sulfone (2) was eliminated reductively. Sulfone (1) and ethyl 4,4-(ethylenedioxy)valerate were obtained since the cleavage of the sulfone (2) predominated.

In the other examples of this cleavage, ethyl 4-oxo-5-(*p*-toluenesulfonyl)-7-decenoate (6)¹¹⁾ was cleaved by treating sodium amalgam in ethanol to form diethyl succinate and 1-(*p*-toluenesulfonyl)-*cis*-3-hexene (7). However, 2,2-ethylenedioxy-6-(*p*-toluenesulfonyl)-8-undecen-5-one (8) was reduced to 2,2-ethylenedioxy-8-undecen-5-one (9) in good yield (Scheme-2). The sulfone (8) was obtained from the sulfone (7) and ethyl 4,4-(ethylenedioxy)valerate using LDA as a base in good yield. But, when excess base was used, the yield of the sulfone (8) decreased.

Scheme-2 The cleavage of the sulfone (6) and reductive elimination of the sulfonyl group of the sulfone (8) using sodium amalgam in ethanol.

The sulfonyl group of these sulfones, (6) and (8), were eliminated reductively with aluminum amalgam in good yield. Because the aluminum amalgam is neutral, it is useful for the reductive elimination of the sulfonyl group of alkali-sensitive compounds¹³⁾, such as the sulfone (2), (6), and (8).

3.3 Synthesis of 2,15-hexadecanedione.

The diketone (3) was carried out Wolff-Kishner reduction to give the diacetal (4) in 90% yield.

The diacetal (4) was acidified with 5% hydrochloric acid at room temperature to give 2,15-hexadecanedione (5) in quantitative yield.

As mentioned above, all the compounds, (1) ~ (5), were easily purified by the recrystallization, and 2,15-hexadecanedione was obtained from the sulfone (1) *via* 4 steps in 69% overall yield.

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アルキルスルホンを用いる 2,15-ヘキサデカンジオンの合成

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香料として重要な *dl*-ムスコンの合成中間体の1つである 2,15-ヘキサデカンジオンを新しい方法で収率よく合成した。1,6-ビス(*p*-トルエンスルホニル)ヘキサン(1)と 4,4-(エチレンジオキシ)吉草酸エチルとの Claisen 縮合により, 2,2,15,15-ビス(エチレンジオキシ)-6,11-ビス(*p*-トルエンスルホニル)-5,12-ヘキサデカンジオン(2)を定量的収率で得た。(2)のスルホニル基を還元除去したあと, Wolff-Kishner 還元によってカルボニル基を除去, 続いてジアセタールを加水分解して 2,15-ヘキサデカンジオンを(1)からの全収率 69%で得た。2,15-ヘキサデカンジオンから *dl*-ムスコンへは, 古くは, Stoll が, 最近では, 辻らが報告している。