Synthesis of Civetone from Palm Oil Products

Yuen-May Choo*, **Kay-Eng Ooi** and **Ing-Hong Ooi**
Palm Oil Research Institute of Malaysia, 50720 Kuala Lumpur, Malaysia

Metathesis of ethyl oleate, catalyzed by WCl_6 and $SnMe_4$, provided diethyl 9-octadecenedioate (the desired starting material for the synthesis of civetone) in 99% yield. Dieckmann condensation of diethyl 9-octadecenedioate gave 2-ethoxycarbonyl-9-cycloheptadecenone (63% yield), the hydrolysis–decarboxylation reaction of which yielded civetone (93%). Identification of all products was by ^1H nuclear magnetic resonance, infrared and mass spectroscopic data. This is the first report of the synthesis of civetone from palm oil-derived products.

KEY WORDS : Civet, civetone, diethyl 9-octadecenedioate, 2-ethoxycarbonyl-9-cycloheptadecenone, ethyl oleate, metathesis, palm oil.

Civetone (9-*cis*-cycloheptadecenone), commonly known as civet, is a major macrocyclic ketone found in the glandular secretion of civet cats. Civetone is a 17-membered macrocyclic ketone carrying musk odor, which attains a pleasant smell in extreme dilution. Due to the flexibility of the large ring, civetone is expected to be present as *cis* and *trans* isomers. However, this compound occurs in nature as the *cis*-form (1).

Civetone is of commercial importance as a fragrance material due to its characteristic odor and is widely used in the perfumery industry as the base component for compounding of perfumes. Civetone had been successfully synthesized (2–8); however, due to the many steps involved, poor yields and scarcity of the starting materials, it has not been produced on a commercial scale. For instance, starting from phloionic acid, *cis*-civetone was synthesized in eleven steps with an overall yield of only 2.8%.

In this paper we report the successful synthesis of civetone from ethyl oleate prepared from palm oil. We also report the identification of the intermediate product, 2-ethoxycarbonyl-9-cycloheptadecenone, which has not yet been reported.

EXPERIMENTAL PROCEDURES

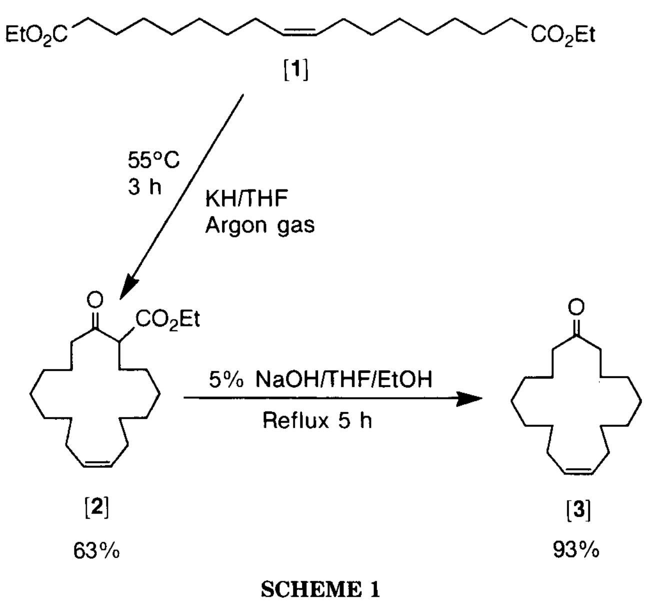
Materials. WCl_6 and $SnMe_4$ were purchased from Aldrich Chemical Co. (Milwaukee, WI). The reagent KH (20% dispersion in mineral oil) was procured from Fluka (Buchs, Switzerland). WCl_6 was purified by vacuum sublimation under nitrogen gas at 200°C. Benzene and toluene were purchased from Merck (Darmstadt, Germany) and were dried over $CaCl_2$ and distilled onto 3Å molecular sieves. Tetrahydrofuran (THF) (BDH, Poole, United Kingdom) was distilled from metallic sodium under an inert gas atmosphere. Other solvents were of reagent grade and used directly. Analytical thin-layer chromatography (TLC) was performed on Merck Analtech glass-backed plates, precoated with silica gel (UV_{254}, 0.25 mm thickness, Merck 9385, 230–400 mesh).

Methods. ^1H Nuclear magnetic resonance (NMR) spectra were obtained on JEOL JNM-PMX60 SI and JNM-FX100 spectrometers (JEOL, Tokyo, Japan) with tetramethylsilane as internal standard. Infrared (IR) spectra were recorded in chloroform on a Hitachi (Hitachi, Ltd., Tokyo, Japan) 270-30 spectrometer. Electron impact–mass spectra (EI–MS) were obtained from a JEOL JMS-DX303 spectrometer.

Preparation of ethyl oleate. Oleic acid of 99% purity, isolated from hydrolytic splitting of palm oil, was esterified with dry ethanol in the presence of catalytic amounts of concentrated sulfuric acid at 110°C for 2 h. The pure ethyl oleate obtained was distilled under reduced pressure.

Metathesis of ethyl oleate. The vacuum-sublimed pure WCl_6 (shiny, dark-blue crystals, 0.39 g, 6.6 mol%) was transferred, under nitrogen, into a 100-mL, two-necked round-bottomed flask and weighed; 20 mL of dry benzene was then added. $SnMe_4$ (0.19 g, 7.2 mol%) was added slowly from a pipette into the reaction flask at room temperature (28°C). The mixture was allowed to stir for 10 min. A solution of ethyl oleate (4.66 g, 0.015 mol) in 8 mL dry benzene was added all at once, and the resulting mixture was stirred for another 10 min. The mixture was heated at 70°C (oil bath) for another 20 h. At the end of the reaction, 10 mL of 10% NaOH was added to quench the reaction. The mixture was extracted with 2 × 60 mL diethyl ether/petroleum ether (60–80°C) (1:4, vol/vol). The organic layer was successively washed with 5N HCl solution, saturated $NaHCO_3$ solution, brine solution and dried over Na_2SO_4. The dry extract was filtered, and the excess solvent was removed by rotary evaporator at 40°C. The crude and concentrated products were initially checked by TLC for their purity. Silica-gel column chromatography with diethyl ether/petroleum ether (60–80°C) as eluent afforded the isolation of two desired products, 9-octadecene and diethyl 9-octadecenedioate (1) (Scheme 1).

9-Octadecene. Metathesis of ethyl oleate with catalyst $WCl_6/SnMe_4$ has provided 9-octadecene in 97% yield. ^1H



SCHEME 1

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*To whom correspondence should be addressed at Chemistry and Technology Division, Palm Oil Research Institute of Malaysia, P.O. Box 10620, 50720 Kuala Lumpur, Malaysia.

NMR ($CDCl_3$) δ 5.43–5.35 (*m*, olefinic proton, 2H), 1.99 (*m*, 4H), 1.27 (*m*, 24H), 0.94–0.83 (*t*, 6H). IR (NaCl) υ_{max}: 3012, 2964, 2932, 1470, 970 cm^{-1}; EI-MS showed *m/e* at 252 (M^+), 224, 209, 195, 181, 168, 154, 139, 125, 111, 98, 82, 71, 54.

Diethyl 9-octadecenedioate [1]. From the metathesis reaction, [1] was isolated by silica-gel column at 99% yield. ^1H NMR ($CDCl_3$) δ 5.46–5.13 (*m*, olefinic proton, 2H), 4.02 (*qt*, $J = 7$ Hz, 4H), 2.37–1.75 (*m*, 8H), 1.74–0.71 (*m*, 20H). IR (NaCl) υ_{max}: 2988, 2936, 2864, 1742, 1468, 1450, 1376, 1352, 1318, 1304, 1276, 1248, 1182, 1116, 1100, 1038, 972, 666 cm^{-1}. EI-MS showed *m/e* at 368 (M^+).

Dieckmann condensation of diethyl 9-octadecenedioate. Potassium hydride KH (0.27 g, 6.7 mmol) in mineral oil was washed under argon three times with dry pentane in a two-necked, round-bottomed flask. Dry THF (40 mL) was then introduced into the flask. A solution of diethyl 9-octadecenedioate (0.44 g, 1.2 mmol) in 10 mL dry THF was added dropwise under argon over 2 h into the KH suspension with stirring at 55°C. The mixture was stirred for 1 h and then carefully poured into a suspension of ice, NH_4Cl and diethyl ether/petroleum ether (60–80°C) (1:4, vol/vol) to destroy the excess KH. The reacted mixture was extracted with 2 × 60 mL diethyl ether/petroleum ether (60–80°C) (1:5, vol/vol). The combined organic layer was washed with brine solution and dried over Na_2SO_4. The dry extract was filtered, and the excess solvent was removed by a rotary evaporator. Purification of the crude product on silica-gel column with 1% diethyl ether in petroleum ether (40–60°C) afforded 2-ethoxycarbonyl-9-cycloheptadecenone [2] in 63% yield.

2-Ethoxycarbonyl-9-cycloheptadecenone [2]. ^1H NMR ($CDCl_3$) δ 5.33–5.24 (*m*, olefinic proton, 2H), 4.19–4.04 (*qt*, 2H), 3.44 (*t*, 1H), 2.48–2.34 (*m*, 2H), 2.16–0.89 (*m*, 27H). IR (NaCl) υ_{max}: 2932, 2860, 1750, 1718, 1648, 1614, 1464, 1448, 1404, 1372, 1346, 1302, 1272, 1242, 1180, 1126, 1118, 1098, 1078, 1060, 1036, 970, 724 cm^{-1}. EI-MS showed *m/e* at 322 (M^+), 304, 276, 248, 230, 215, 197, 181, 166, 151, 136, 121, 98, 82, 67.

Synthesis of civetone. 2-Ethoxycarbonyl-9-cycloheptadecenone (0.30 g, 0.93 mmol) was dissolved in a solution containing 5% NaOH/ethanol/THF (7.5:15:7.5, vol/vol/vol) and refluxed (80°C) for 5 h. After cooling to 0°C and made slightly acidic with concentrated H_2SO_4, the acidified mixture was refluxed for 10 min. The solvents were removed *in vacuo*, and the residue was extracted with 2 × 60 mL diethyl ether/petroleum ether (60–80°C) (1:4, vol/vol). The extract was then washed with saturated $NaHCO_3$ solution, brine solution and dried over Na_2SO_4. Filtration followed by solvent removal *in vacuo* afforded a colorless oil. Chromatography of this oil on silica gel with eluent of 1% diethyl ether in petroleum ether (60–80°C) gave civetone [3] (0.22 g, 0.86 mmol, 93%) as a colorless oil with a musk odor.

Civetone [3]. ^1H NMR ($CDCl_3$) δ 5.43–5.35 (*m*, olefinic proton, 2H), 2.44–2.30 (*m*, 4H), 2.16–2.03 (*m*, 4H) 2.03–1.28 (*m*, 20H). IR (NaCl) υ_{max}: 3008, 2932, 2860, 1716, 1464, 1444, 1368, 970, 674 cm^{-1}. EI-MS showed *m/e* at 250 (M^+), 232, 207, 189, 175, 161, 148, 135, 122, 108, 94, 80, 68, 55.

RESULTS AND DISCUSSION

The metathesis of ethyl oleate has been successfully carried out with the $WCl_6/SnMe_4$ catalytic system. The molar ratio of substrate-to-catalyst used affects the rate of reaction. Too much catalyst suppresses the conversion. Accordingly, an optimum of 6.3 mole% of WCl_6 was found to yield 97% of 9-octadecene and 99% diethyl 9-octadecenedioate for the metathesis of ethyl oleate, based on the reacted material of ethyl oleate. These metathesis products, together with unreacted ethyl oleate, could easily be separated on a silica-gel column by gradient elution. The 9-octadecene was first eluted with petroleum ether, followed by ethyl oleate. Diethyl 9-octadecenedioate was eluted with 4% diethyl ether in petroleum ether.

Diethyl 9-octadecenedioate was then subjected to a two-step reaction sequence, i.e., a Dieckmann condensation reaction followed by a hydrolysis–decarboxylation reaction. The intermediate keto ester product obtained was confirmed as 2-ethoxycarbonyl-9-cycloheptadecenone, which was obtained in 63% yield. Lower yields of the intermediate have been observed when there were traces of moisture. Occasionally only hydrolysis products of the diesters could be detected from the action of KOH derived from the hydration of KH. Nevertheless, careful purification and drying of THF is required to give an optimum yield. The hydrolysis–decarboxylation of the intermediate gave a high yield (93%) of civetone, as shown in Scheme 1.

The characteristic spectroscopic data of all three products, i.e., diethyl 9-octadecenedioate [1], 2-ethoxycarbonyl-9-cycloheptadecenone [2] and civetone [3], are presented in Table 1 for comparison. The stretching absorptions of the carbonyl group C=O of all these compounds occurred at 1742, 1750 and 1718 and 1716 cm^{-1} respectively. Thus, there is only one type of C=O stretching in [1] and [3], whereas two carbonyl stretchings were seen in [2], i.e., 1750 and 1718 cm^{-1} for C=O of the ester and 1718 cm^{-1} for the ketone, respectively. From the proton NMR spectra, all three compounds have the olefinic protons (H-C=C-H), with chemical shift resonance at δ 5.1–5.5 ppm. Along with the IR and ^1H NMR spectroscopic data, mass spectra were also used to confirm the respective molecular masses and some characteristic fragment ions. The molecular ion of the diester [1] appeared at *m/e* 368, with diagnostic peaks of an ester scattered at lower fragments. Similarly, the intermediate [2] showed its molecular ion *m/e* at 322, and civetone [3] gave rise to a strong molecular ion at *m/e* 250.

TABLE 1

Spectroscopic Characteristic Data of Compounds 1, 2 and 3

Compounds	^1H NMR[a] (δ/ppm)	IR[a] (cm^{-1})	M^+ (*m/e*)
1	5.33–5.24	1750 and 1718	322
2	5.46–5.13	1742	368
3	5.43–5.35	1716	250

[a]NMR, nuclear magnetic resonance; IR, infrared.

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