

Practical Synthesis of (Z)-Civetone Utilizing Ti-Dieckmann Condensation

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Received: April 2, 2002; Accepted: April 22, 2002

Abstract: An efficient, practical, and stereocontrolled synthesis of (Z)-civetone (**1**), a representative musk perfume, has been performed utilizing a Ti-Dieckmann (intramolecular Ti-Claisen) condensation of dimethyl (Z)-9-octadecenedioate (**3**) as the key step. This cyclization reaction has some advantages compared with the traditional basic Dieckmann condensation such as higher concentration (100–300 mM), lower reaction temperature (0–5 °C), shorter reaction time (1–3 h), use of environmentally benign (low toxicity and safe) reagents (TiCl₄ and Et₃N or Bu₃N), and economical reagents and solvents. 15-, 17-, and 19-membered saturated β -ketoesters (**6–8**) were also prepared by the present method.

Keywords: civetone; cyclization; Dieckmann condensation; macrocycles; Ti-Claisen condensation; titanium

Practical syntheses of natural macrocyclic musks, especially muscone and civetone, are one of the most important topics in the perfume industry.^[1] These two representative natural musks originally come from glandular secretions of musk deer and civet cat, respectively. The Washington treaty, Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES), however, claims that harvesting musk constitutes ill treatment of wild animals. (Z)-Civetone (**1**) is an attractive ingredient of civet cat musk^[2] and has been one of the most challenging synthetic targets for producing macrocyclic musks due to its unique symmetrical 17-membered structure.

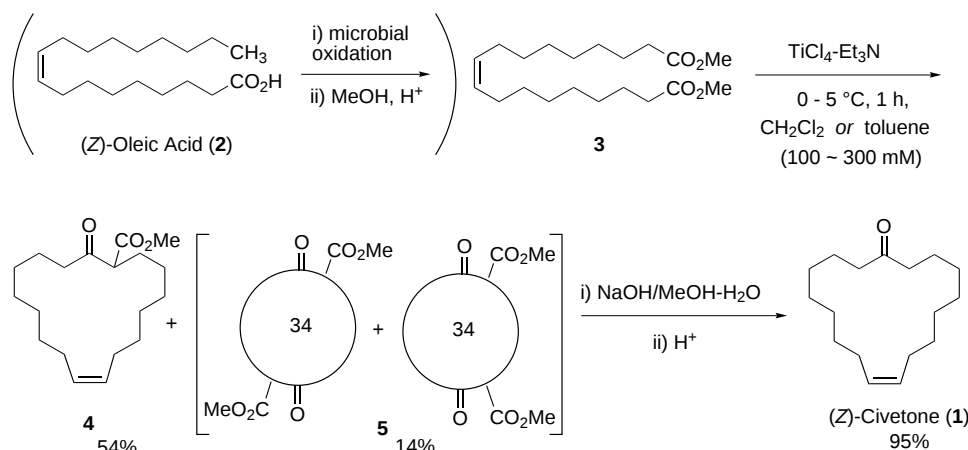
Several hitherto reported syntheses of **1**, however, are limited by the laboratory methods used because of their low yields and/or multi-step procedures.^[3] Recently, we reported a short step synthesis of (E)-rich civetone utilizing the Ti-Claisen condensation and ring-closing metathesis.^[4] In addition to the high cost of Grubbs'

metathesis catalyst, the ring closure has a serious problem of requiring high dilution conditions (*ca.* 4 mM), which is undesirable for large-scale production. Moreover, most of the known syntheses, including ours, are not stereocontrolled. There are two stereocontrolled examples; (1) Tsuji and Mandai's method,^[5] which requires 17 steps starting from nitromethane and butadiene and (2) Fürstner and Seidel's method,^[6] which seems to be one of the most efficient to date (5 steps), but requires a high dilution technique for the ring closing metathesis. Here we wish to disclose a practical synthesis of (Z)-civetone (**1**) utilizing the Ti-Dieckmann (intramolecular Ti-Claisen) condensation,^[7] which would be a back to front version of our precedent method.^[4] (Scheme 1).

Dimethyl (Z)-9-octadecenedioate (**3**) was prepared by the known microbial oxidation (*Candida tropicalis*) of cheap and available (Z)-oleic acid (**2**), followed by esterification in MeOH with the complete retention of (Z)-geometry.^[8] The Ti- and Zr-Claisen condensations exhibit powerful reactivity to realize C-C bond formation between various carboxylic esters.^[9] This characteristic merit would promise a large ring closing with higher concentrations and speed, and indeed Ti-Dieckmann cyclization of **3** was successfully performed to give the key 17-membered ring β -ketoester **4** (Table 1).

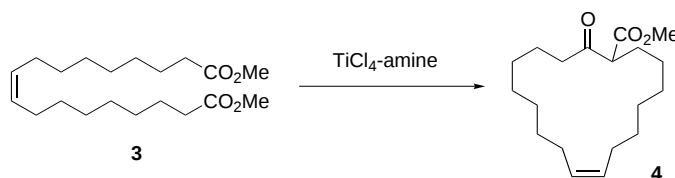
There are some advantages compared with the traditional Dieckmann condensations using the basic system (KH or KHMDS reagent/THF solvent); (a) higher concentrations (100–300 mM), lower reaction temperature (0–5 °C), and shorter reaction time (1–3 h), than those of the basic methods^[10] (25 mM, 60 °C, 2–10 h); (b) use of environmentally benign (low toxicity and safe) reagents; and (c) more economical and practical reagents and solvents (it is not necessary to use the strict dryness conditions required for the THF solvent). Yields of the Ti-Dieckmann condensations are, however, slightly lower than those of the basic method (63%).^[10b]

A 20-g scale (dimethyl ester **3**) reaction could be carried out in a 1.0-L vessel, which is an approximately 4



Scheme 1. Synthetic route to (Z)-civetone (**1**).

Table 1. Ti-Dieckmann condensation of dimethyl (Z)-9-octadecenedioate (**3**).



Entry	Equiv. of TiCl ₄	Amine (Equiv.)	Solvent	Conc. [mM]	Temp. [°C]	Addition time [h]	Yield [%] ^[a]		
							3 ^[b]	4	5
1	1.2	Bu ₃ N (1.4)	CH ₂ Cl ₂	100	0–5	1	45	23	5
2	2.4	Bu ₃ N (3.0)	CH ₂ Cl ₂	100	0–5	1	7	41	22
3	2.8	Bu ₃ N (3.0)	CH ₂ Cl ₂	100	0–5	1	trace	52	13
4	2.8	Et ₃ N (3.0)	CH ₂ Cl ₂	100	0–5	1	trace	54	14
5	2.8	Et ₃ N (3.0)	toluene	100	0–5	1	5	44	17
6	2.8	Et ₃ N (3.0)	CH ₂ Cl ₂	300	0–5	3	trace	47	16
7	2.8	Et ₃ N (3.0)	CH ₂ Cl ₂	50	0–5	1	15	37	22
8	2.8	Et ₃ N (3.0)	CH ₂ Cl ₂	100	–15 – –10	1	trace	42	33
9	2.8	Et ₃ N (3.0)	CH ₂ Cl ₂	100	10–15	1	22	34	17
10	2.8	Et ₃ N (3.0)	CH ₂ Cl ₂	100	0–5	3	trace	54	12

^[a] Isolated yields.

^[b] Recovery.

to 25-fold higher concentration than the related known systems.^[4,10] In this Ti-Dieckmann cyclization, both Bu₃N and Et₃N were available for the amine and CH₂Cl₂ was a slightly better solvent than toluene. The major by-product is a double-sized, 34-membered diester **5**.

An important technical note is that conformity of the molar ratio should be maintained to realize smooth condensation using a microfeeder apparatus equipped with dual syringes. That is, two lots of solutions were prepared: one was a mixture of dimethyl ester **3** and amine (Bu₃N or Et₃N) in solvent (CH₂Cl₂ or toluene) and the other was TiCl₄ in the same solvent. To keep the molar ratio balance of the reactants and reagents, these solutions were simultaneously and proportionally added to a solvent placed beforehand in the reaction vessel. If

this protocol was not followed, significant competitive intermolecular oligomerization occurred. Finally, hydrolysis and decarboxylation of β-ketoester **4** gave the desired (Z)-civetone (**1**) in 95% yield by the reported method.^[4,10b]

Ti-Dieckmann cyclizations of 15-, 17-, and 19-membered saturated β-ketoesters **6–8** were also performed by the present method (Table 2). In the case of **6**, however, the 30-membered diester predominated over the 15-membered β-ketoester. Major by-products in the other cases of **7** and **8** were double-sized, 34- and 38-membered diesters, respectively.

In conclusion, we achieved the first simple and practical synthesis of (Z)-civetone (**1**) utilizing the Ti-Dieckmann condensation, which is a promising candi-

Table 2. Ti-Dieckmann condensation of saturated dimethyl dicarboxylic esters **6** – **8**.^[a]

Entry	Ester	Equiv. of TiCl ₄	Equiv. of Et ₃ N	Addition time [h]	Yield (%) ^[b]	
					a	b
1	6 (n = 15)	2.8	3.0	1	8	31
2	6 (n = 15)	3.5	3.7	3	15	41
3	7 (n = 17)	2.8	3.0	1	33	18
4	7 (n = 17)	3.5	3.7	3	45	12
5	8 (n = 19)	3.5	3.7	3	46	11

^[a] These reactions were carried out in CH₂Cl₂ (100 mM) at 0–5 °C.

^[b] Isolated yields.

date for the industrial production of (Z)-civetone (**1**) and provides a novel methodology for large carbon ring construction.

Experimental Section

Ti-Dieckmann Condensation of Dimethyl (Z)-9-Octadecenedioate (**3**)

Procedure A: Two lots of solutions (A) and (B) were prepared: (A) TiCl₄ (9.23 mL, 84.0 mmol) diluted with CH₂Cl₂ (147 mL) under an argon atmosphere and (B) mixed solution of dimethyl (Z)-9-octadecenedioate (**3**; 10.21 g, 30 mmol) and Et₃N (9.11 g, 90 mmol) in CH₂Cl₂ (133 mL). Solutions (A) and (B) were simultaneously and proportionally added to a stirred CH₂Cl₂ solvent (30 mL) at 0–5 °C during 1 h under an argon atmosphere, using a microfeeder apparatus equipped with dual syringes (Note: this procedure is critical as described in the text.). After completion of the feed, the mixture was further stirred for 15 min at the same temperature. Then, water (100 mL) was added to the stirring mixture for 5 min with vigorously stirring, which was evaporated using a rotary evaporator to remove CH₂Cl₂. The resultant mixture was extracted with toluene (150 mL × 3), and the combined organic phase was washed with water, brine, dried (Na₂SO₄) and concentrated. The obtained crude oil (9.83 g) was purified by SiO₂-column chromatography (hexane:AcOEt = 20:1) to give 2-methoxycarbonyl-(Z)-9-cycloheptadecenone (**4**; 4.83 g, 52%) and 2,17(or 19)-bis(methoxycarbonyl)-(Z,Z)-cyclotetradecatriacota-9,26-diene-1,17-dione (**5**; 1.27 g, 14%).

Procedure B: Two lots of solutions (A) and (B) were prepared: (A) TiCl₄ (18.46 mL, 168 mmol) diluted with CH₂Cl₂ (138 mL) under an argon atmosphere and (B) mixed solution of dimethyl (Z)-9-octadecenedioate (**3**; 20.42 g, 60 mmol) and Et₃N (18.22 g, 180 mmol) in CH₂Cl₂ (110 mL). (A) and (B) was simultaneously and proportionally added to a

stirred CH₂Cl₂ solvent (360 mL) at 0–5 °C during 1 h under an argon atmosphere, using a microfeeder apparatus (Note: this proportionality is critical as described in the text). After completion of the feed, the mixture was further stirred for 15 min at the same temperature. Similar work-up as for procedure A gave the desired product **4** (9.93 g, 54%) and (**5**; 2.54 g, 14%).

4: Colorless oil. ¹H NMR (400 MHz, CDCl₃): δ = 1.18–1.44 (16H, m), 1.53–1.71 (2H, m), 1.75–1.87 (1H, m), 1.88–2.09 (5H, m), 2.52 (2H, t, *J* = 6.8 Hz), 3.49 (0.93H, dd, *J* = 9.0 Hz, 5.4 Hz; keto form), 3.70 (2.79H, s; keto form), 3.75 (0.21H, s; enol form), 5.28–5.40 (2H, m), 12.72 (0.07H, s; enol form); ¹³C NMR (100 MHz, CDCl₃): δ = 23.34, 26.58, 26.79, 27.05, 27.95, 27.99, 28.08, 28.15, 28.35, 28.45, 28.98, 29.01, 41.54, 52.24, 58.42, 130.07, 130.14, 170.22 (keto form), 175.51 (enol form), 206.34; IR (neat): ν = 2928, 1748, 1713, 1437, 1242 cm⁻¹.

5: Colorless oil. ¹H NMR (300 MHz, CDCl₃): δ = 1.18–1.41 (32H, m), 1.47–1.68 (4H, m), 1.77–1.89 (4H, m), 1.93–2.08 (8H, m), 2.40–2.62 (4H, m), 3.45 (1H, t, *J* = 7.3 Hz), 3.45 (1H, t, *J* = 7.3 Hz), 3.71 (6H, s), 5.26–5.40 (4H, m); ¹³C NMR (75 MHz, CDCl₃): δ = 23.36, 27.01, 27.03, 27.38, 28.21, 28.74, 28.77, 28.87, 28.90, 28.95, 29.03, 29.04, 29.43, 29.49, 41.77, 41.89, 52.19, 58.78, 58.84, 129.78, 129.83, 129.86, 129.90, 170.35, 205.51; IR (neat): ν = 2928, 1746, 1715, 1437, 1200 cm⁻¹.

Hydrolysis and Decarboxylation of 2-Methoxycarbonyl-(Z)-9-cycloheptadecenone (**4**)

Aqueous 10%-NaOH (36 mL, 90 mmol) was added to a stirred solution of 2-methoxycarbonyl-(Z)-9-cycloheptadecenone (**4**; 9.25 g, 30 mmol) in MeOH (36 mL) at 20–25 °C, and the mixture was refluxed for 1 h. After cooling down, the mixture was made slightly acidic (pH ~ 1) with 10% H₂SO₄, followed by refluxing for 30 min. The mixture was evaporated under reduced pressure to remove MeOH. Then residue was extracted with ether (100 mL × 3), and the combined organic phase was washed with water, brine, dried (Na₂SO₄) and

concentrated. The obtained crude oil (7.60 g) was purified by SiO₂-column chromatography (hexane:AcOEt = 40:1) to give the desired (*Z*)-civetone (**1**); yield: 7.12 g (95%); colorless crystals; mp 31.0–32.0 °C; ¹H NMR (400 MHz, CDCl₃): δ = 1.24–1.39 (16H, m), 1.57–1.67 (4H, m), 1.96–2.06 (4H, m), 2.40 (4H, t, *J* = 6.7 Hz), 5.30–5.39 (2H, m); ¹³C NMR (100 MHz, CDCl₃): δ = 23.84, 26.68, 28.11, 28.19, 28.58, 29.01, 42.41, 130.12, 212.50; IR (neat): ν = 2926, 1713, 1460, 1364, 718 cm⁻¹.

Acknowledgements

This research was partially supported by a Grant-in-Aid for Scientific Research on Priority Areas (A) "Exploitation of Multi-Element Cyclic Molecules" and on Basic Areas (C) from the Ministry of Education, Culture, Sports, Science and Technology, Japan, and by the Cosmetology Foundation in Japan.

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