Diketene and Acetylated Meldrum's Acid: Agents for a Facile Teprenone Synthesis *via* Carroll Rearrangement

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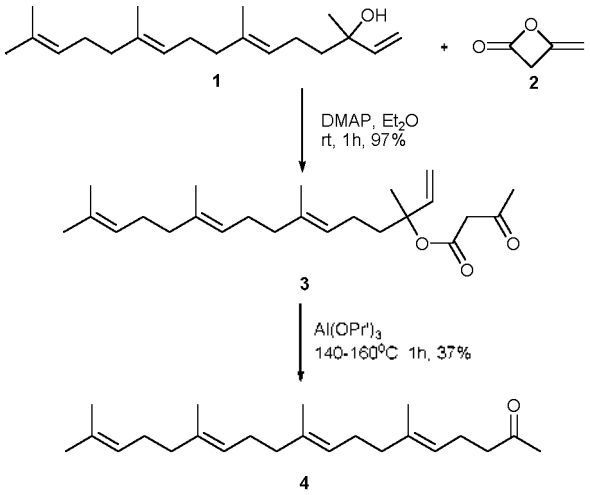
Received March 11, 2009, Accepted July 30, 2009

Key Words: Carroll rearrangement, Anti-ulcer drug, Teprenone, Diketene, Acetylated meldrum's acid

Teprenone (6,10,14,18-tetramethylnonadeca-5,9,13,17-tetraen-2-one) commonly called geranylgeranyl acetone is a drug developed in Japan that has been clinically tested for its effectiveness in the treatment of gastric ulcers.[1] It acts as a protecting agent *via* its stimulatory action on gastric mucus synthesis and secretion and its inhibitory action on neutrophil infiltration and enhanced lipid peroxidation in the gastric mucosal tissue.[2] Aside from this well-known use of teprenone, there have been a number of other applications of this drug either as an additive or as an active ingredient. Teprenone is tested for treating some eye problems like glaucoma.[3] It was also thought to increase hepatic and gastric blood flow.[4] One study showed that it has potent antiviral activity,[5] while others showed that it inhibit melanin production making it as active ingredient in whitening embellisher.[6] Most recently it was applied for prevention and treatment of classic and motile heat injury to human and animal.[7] These myriad and growing applications of teprenone showed that it is important to develop a facile synthetic way to produce it in large scale. There are many synthetic approaches published for teprenone however, most of them proffer several drawbacks. For instance, two Korean patents[8] used Julia-Lythgoe olefination method; it has lengthy steps involving hazardous chemicals with low overall yield. Other methods involved the reaction of different alkyl acetoacetates with various alcohols such as geranyllinalool,[9] geranylgeraniol[10] or nerolidol[11] undergoing Carroll rearrangement. These methods either used complex and expensive catalysts, expensive starting material like geranylgeraniol, higher temperature, difficult to handle chemicals, and tedious reaction conditions. There is also one method published which involved lengthy procedure with much lower overall yield than the others.[12] Having all these drawbacks available for all of these known routes, we came out for a new method, which somehow eliminates some of these weaknesses.

The easiest way to make teprenone is *via* Carroll rearrangement. Thus, we decided to find appropriate reagents that could facilitate Carroll rearrangement such that it will produce teprenone in a facile manner in which the results we report herein. β-Ketoesters readily undergo Carroll rearrangement and some literature published demonstrated that it can be straightforwardly generated from the reaction of tertiary alcohol and diketene with catalytic amount of DMAP.[13] Thus we considered geranyl linalool (**1**), a tertiary alcohol, and diketene (**2**) to make β-keto-ester intermediate, **3** followed by Carroll rearrangement to produce teprenone, **4** (Scheme 1). We found that aluminium isopropoxide was the best catalyst for the rearrangement (Table 1).

We did not optimize the yield for stage 2 of the two-step synthesis because we simply want to know the most probable catalyst among these choices for Carroll rearrangement. With this result, we decided to do a one-pot synthesis of teprenone (Scheme 2) in which we succeeded. We found that the reaction for 5.5 h at 130 °C with slightly excess diketene (2.5 equiv.) and 0.10 equiv of $Al(OPr^i)_3$ would give 72% teprenone in its



Scheme 1. Two-step Synthesis

Table 1. Catalysts for Carroll Rearrangement

Entry[a]	Catalyst	Time (hr)	Yield (%)[b]
1	$FeCl_3 \cdot 6H_2O$	1	Intractable mixture
2	ZrO_2	4	Intractable mixture
3	TiO_2	3	Intractable mixture
4	$Mg(ClO_4)_2$	1	Intractable mixture
5	$B(OCH_3)_3$	1	8
6	SiO_2	6	18
7	$Ti(OPr^i)_4$	1	23
8	$Al(OPr^i)_3$	1	37

[a]Reaction temperature: 140 - 160 °C, [b]Un-optimized yield.

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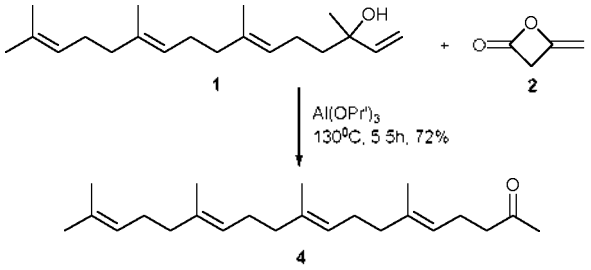
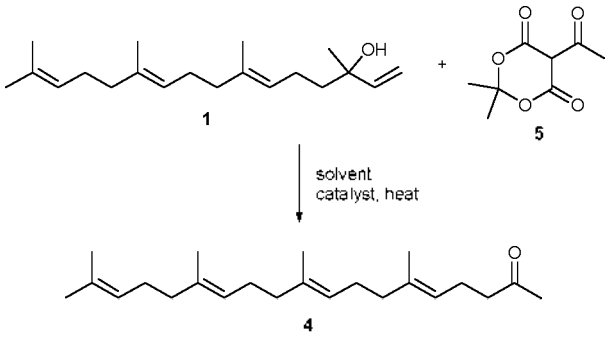


Scheme 2. One-pot Teprenone Synthesis



Scheme 3. One-step Synthesis of Teprenone using Acetylated Meldrum's acid

pure *E* form. We verified this configuration with the reported NMR data. This condition is appropriate for industrial application because it makes use of relatively lower temperature than other known methods and only use slightly excess of reagent. However, though this procedure is easy and has high yield, it has one drawback viz diketene is unstable making it difficult to handle. Hence, we considered another agent.

Surveying the literature, we found that acetylated Meldrum's acid (**5**) has comparable reactivity with diketene towards alcoholysis.[14] It is easy to handle and stable making it a perfect choice. Thus, we considered it as shown in Scheme 3. This acetylated meldrum's acid (**5**) readily reacts with tertiary alcohol, geranyl linalool (**1**), *via* nucleophilic attack to produce acetoacetic moiety, which then undergoes Carroll rearrangement to produce teprenone. We have considered several parameters to find the optimum conditions that would produce (*E*)-teprenone in best yield. We found that the same equivalent as that of diketene was necessary with *p*-xylene solvent and 0.10 equiv of Al(OPr^i)$_3$ at 160 °C oil bath temperature for 6 h were essential to obtain the maximum yield (76%). Doing the reaction under neat condition or with other solvent such as toluene makes the yield lower.

We also tried several Lewis acids as catalyst to assist the reaction (Table 2). Used of transition metal catalysts (Table 2, entries 5, 8, 9, and 10) gave poor yield. The proton NMR spectrum of by-products was presumably a combination of un-rearranged product and polymerized starting material. Likewise, the boron complex (Table 2, entries 3 and 4) gave even worst results. All the starting material disappeared after 3 h of reaction however; the teprenone spot was hardly visible. Perhaps it reacted on a different manner contrary to the expected one. On the other hand, aluminum oxide and silicon oxide catalysts

Table 2. Catalysts for Carroll Rearrangement using Acetylated Meldrum's Acid

Entry	Catalyst[a]	Time (hr)	Yield (%)[b]
1	Al(OPr^i)$_3$	6	76
2	Al_2O_3	6	41
3	$B(OCH_3)_3$	3	3
4	BF_3·Et_2O	3	Intractable mixture
5	$FeCl_3$·$6H_2O$	6	13
6	$Mg(ClO_4)_2$	6	8
7	SiO_2	6	52
8	TiO_2	6	39
9	Ti(OPr^i)$_4$	6	21
10	ZrO_2	6	20

[a]Used 0.10 equiv.; [b]Used the optimum conditions abovementioned.

gave quite good result relatively (Table 2, entries 2 and 7). Presumably, these catalysts were also capable of accelerating the reaction in the same manner as aluminum isopropoxide. Nevertheless, among these catalysts tried aluminum isopropoxide gave the best yield.

In conclusion, we have developed new routes for teprenone by introducing new agents for Carroll rearrangement. Both diketene and acetylated Meldrum's acid are efficient agents for rearrangement, the former produced (*E*)-teprenone at lower temperature while the latter offer stability and ease of handling as advantages. These one-step processes overcome the complication caused by multi-step reaction. Indeed, either of these strategies is practical for industrial purposes because it employs mild reaction conditions, easy handling and higher reaction yield.

Experimental Section

General. All reagents used were purchased and used as it is. Analytical TLC was conducted on E. Merck 60 F254 aluminum-backed silica gel plates (0.2 mm). Developed plates were visualized using UV light or *p*-anisaldehyde staining solution. Flash column chromatography was performed using Merck silica gel 60 (230 - 400 mesh). ^{1}H and ^{13}C NMR spectra were obtained using Varian 300 spectrometer (300 and 75 MHz respectively) with TMS as internal standard. Coupling constants (J) were given in Hz and all chemical shifts are in ppm. IR spectra were recorded on Brucker Alpha ATR-ZnSe. HRMS were obtained on a JMS 700 spectrometer.

(3,7,11,15-Tetramethylhexadeca-1,6,10,14-tetraen-3-yl)-3-oxobutanoate, 3. Geranyl linalool, **1** (1.65 mL, 5 mmol) and 4-DMAP (0.061 g, 0.50 mmol) were added to the flask containing Et_2O (20 mL) as solvent. Diketene, **2** (0.97 mL, 12.53 mmol) was added to the same flask. The reaction mixture was stirred at room temperature for 1 h. When the reaction was completed based on TLC, the solvent was evaporated until the volume was reduced to one-fourth of the original volume. The mixture was diluted with CH_2Cl_2 and washed with brine solution. The organic phase was collected, dried with anhydrous $MgSO_4$ and concentrated using rotary evaporator. The residue was purified using silica gel column chromatography with hexane:

ethyl acetate (10:1 v/v, R_f = 0.25) eluent system to give colorless oil product (1.82 g) in 97% yield. IR (ATR eco ZnSe): 1103, 1148, 1240, 1643, 1718, 1740, 2855, 2917, 2968 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.59 (s, 12 H, 16, 17, 18, 19-CH_3), 1.68 (s, 3 H, 20-CH_3), 182 (m, 2 H, 4-CH_2), 1.98 (m, 10 H, 5, 8, 9, 12, 13-CH_2), 2.27 (s, 3 H, 24-CH_3), 3.40 (s, 2 H, 22-CH_2), 5.09 (m, 3 H, 6, 10, 14-CH), 5.15 (d, J = 3.3 Hz, 1 H, 1-CHa), 5.19 (d, J = 9.6 Hz, 1 H, 1-CHb), 5.99 (dd, J = 10.5, 17.4 Hz, 1 H, 2-CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.18, 16.24, 17.94, 21.45, 22.42, 23.52, 23.97, 25.96, 26.77, 26.97, 30.43, 39.88, 39.94, 40.09, 40.53, 51.40, 83.36, 84.81, 90.88, 113.10, 114.03, 123.60, 123.79, 124.33, 124.60, 131.52, 135.25, 135.80, 135.92, 141.27, 142.32, 166.06, 172.32, 175.43, 201.12 (includes tautomer); HRMS *m/z* (EI+) calcd. for $C_{24}H_{38}O_3$ 374.2821, found 374.2824.

(*E*-6,10,14,18-Tetramethylnonadeca-5,9,13,17-tetraen-2-one), 4. Procedure A: Preformed β-ketoester, **3** (0.3229 g, 0.81 mmol) and $Al(OPr^i)_3$ (0.0170 g, 0.081 mmol) were added to the flask. The reaction mixture was stirred at 140 - 160 °C for 1 h. When the reaction was completed based on TLC, the mixture was diluted with CH_2Cl_2 and washed with brine solution. The residue was purified using silica gel column chromatography with hexane:ethyl acetate (50:1 v/v) eluent system to give colorless oil (0.0992 g) in 37% yield.

Procedure B: Geranyl linalool (0.263 mL, 0.800 mmol), diketene (0.153 mL, 2 mmol) and $Al(OPr^i)_3$ (0.0163 g, 0.080 mmol) were added to a flask having a condenser attached to it. The temperature was gradually increased to 130 °C using oil bath. When the reaction was completed based on TLC, full vacuum was applied to eliminate the remaining diketene. The reaction mixture was diluted with 5% Na_2CO_3 solution to quench the remaining $Al(OPr^i)_3$.[15] The reaction mixture was purified by silica gel column chromatography with CH_2Cl_2 eluent solvent to give colorless oil (0.1904 g) in 72% yield.

Procedure C: In a flask geranyl linalool (0.300 mL, 0.9109 mmol), acetylated Meldrum's acid, **5** (0.3920 g, 2.2773 mmol) and $Al(OPr^i)_3$ (0.0186 g, 0.0911 mmol) were dissolved in 4.63 mL of *p*-xylene. The flask was immersed in a pre-heated oil bath (160 °C) and stirred for 6 hr. The mixture was allowed to cool down to room temperature and the solvent was evaporated using rotary evaporator. Saturated Na_2CO_3 solution was added to the residue and the crude product was extracted with CH_2Cl_2. The organic phase was dried with anhydrous $MgSO_4$, filtered and concentrated. The residue was purified using silica gel column chromatography with hexane : ethyl acetate (40 : 1 v/v) eluent system and hexane: ethyl acetate (10:1 v/v) monitoring eluent system to obtain a colorless oil (0.2294 g, 76%). ^1H NMR (300 MHz, $CDCl_3$) δ 1.60 (s, 12 H, 20, 21, 22, 23-CH_3), 1.68 (s, 3 H, 19-CH_3), 2.01 (m, 12 H, 7, 8, 11, 12, 15, 16-CH_2), 2.14 (s, 3 H, 1-CH_3), 2.26 (m, 2 H, 3-CH_2), 2.45 (m, 2 H, 4-CH_2), 5.09 (m, 4 H, 5, 9, 13, 17-CH).

Acknowledgments. K. A. D. C. and E. Y. B. greatly appreciate the Korean Ministry of Education through the second stage of BK21 project for Hanyang University graduate program for the financial support.

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15. This dilution step is necessary to make the separation easy because the mixture is too concentrated.