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for the Preparation
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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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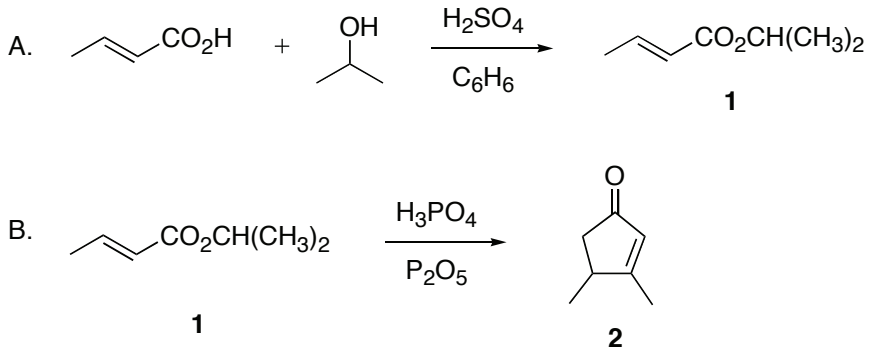
FRAGMENTATION-RECOMBINATION NAZAROV CYCLIZATION: 3,4-DIMETHYLCYCLOPENT-2-EN-1-ONE



Submitted by Keith D. Schwartz and James D. White.[1]
Checked by Shin-ya Tosaki and Masakatsu Shibasaki.

1. Procedure

*A. Isopropyl (E)-but-2-enoate (**1**).* A 500-mL round-bottomed flask is fitted with a Soxhlet extractor containing magnesium sulfate (10 g) in a cellulose extraction thimble. Atop the extractor is a reflux condenser fitted with a rubber septum and an argon line. The flask is charged with crotonic acid (17.00 g, 197.5 mmol), isopropanol (106 mL, 1.39 mol), concentrated sulfuric acid (2.5 mL) and benzene (30 mL) (Note 1). The mixture is heated to reflux over the $MgSO_4$ plug for 18 h and is then cooled to room temperature. Benzene (60 mL) is added, followed by the dropwise addition of a 10% aqueous solution of sodium bicarbonate (100 mL) while stirring. The mixture is transferred to a separatory funnel, the layers are separated, and the aqueous portion is extracted with benzene (3 x 25 mL). The organic layers are combined, washed with brine (50 mL), dried over anhydrous sodium sulfate, and filtered. The solvent is evaporated under vacuum and the resulting yellow oil is purified by distillation (46–48 °C/25 mmHg) to give 17.98–18.00 g (71%) of isopropyl (*E*)-but-2-enoate (**1**) (Note 2) as a colorless oil.

*B. 3,4-Dimethylcyclopent-2-enone (**2**).* A three-necked, 1-L round-bottomed flask is fitted with a mechanical stirrer, a glass stopper, a rubber septum, and an argon line. The flask is charged with phosphoric acid (32.0 g) and phosphorus pentoxide (48.0 g) (Note 1). The mixture is stirred at 100 °C for 1 h, at which time it becomes homogenous. To this mixture is added the neat ester **1** (10.0 g, 78.0 mmol), and the mixture is stirred for 3

min at 100 °C. The mixture is cooled to 0 °C with an ice bath. Diethyl ether (Et_2O, 100 mL) is added followed by the slow addition of saturated aqueous $NaHCO_3$ (150 mL) with vigorous stirring. Solid $NaHCO_3$ is then cautiously added to the mixture in small portions until foaming subsides. The contents of the flask are transferred to a separatory funnel with an additional quantity (50 mL) of Et_2O, the layers are separated, and the aqueous layer is extracted with Et_2O (3 x 60 mL). The organic layers are combined, washed sequentially with water (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, and filtered. The solvent is evaporated under vacuum and the resulting orange colored oil is purified by fractional distillation (68–69 °C/20 mmHg) to give 5.61–5.63 g (65–66 %) of 3,4-dimethylcyclopent-2-enone (**2**) (Note 3) as a colorless oil.

2. Notes

1. Crotonic acid was purchased from TCI and was used as received. Isopropanol was purchased from KANTO CHEMICAL and was used as received. Phosphorus pentoxide powder, phosphoric acid (85 wt. % solution in water), concentrated sulfuric acid, and benzene were purchased from Wako and were used as received. Diethyl ether was purchased from Showa-ether and was used as received.

2. Physical data for isopropyl (*E*)-but-2-enoate: IR (neat, cm^{-1}) 2981, 2940, 1718, 1661; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.25 (d, J = 6.4 Hz, 6 H), 1.86 (dd, J = 7.0, 1.8 Hz, 3 H), 5.05 (septet, J = 6.4 Hz, 1 H), 5.81 (dq, J = 15.6, 1.8 Hz, 1 H), 6.95 (dq, J = 15.6, 7.0 Hz 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 17.9, 21.9, 67.3, 123.3, 144.1, 166.1. Purity was established by gas chromatographic analysis (Restek Rtx-20 column, flow rate 1 mL/min, temperature 45–280 °C ramped at 60 °C/min, retention time 6.49 min).

3. Physical data for 3,4-dimethylcyclopent-2-enone: IR (neat, cm^{-1}) 2965, 2927, 1712, 1684, 1619; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.19 (d, J = 7.3 Hz, 3 H), 2.00 (dd, J = 18.6, 2.1 Hz, 1 H), 2.08 (s, 3 H), 2.64 (dd, J = 18.6, 6.5 Hz, 1 H), 2.81 (ddt, J = 7.3, 6.5, 2.1 Hz, 1 H), 5.88 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 17.0, 18.8, 38.8, 44.2, 130.3, 182.6, 208.9. Purity was established by gas chromatographic analysis (Restek Rtx-20 column, flow rate 1 mL/min, temperature 120–250 °C ramped at 50 °C/min, retention time 7.87 min).

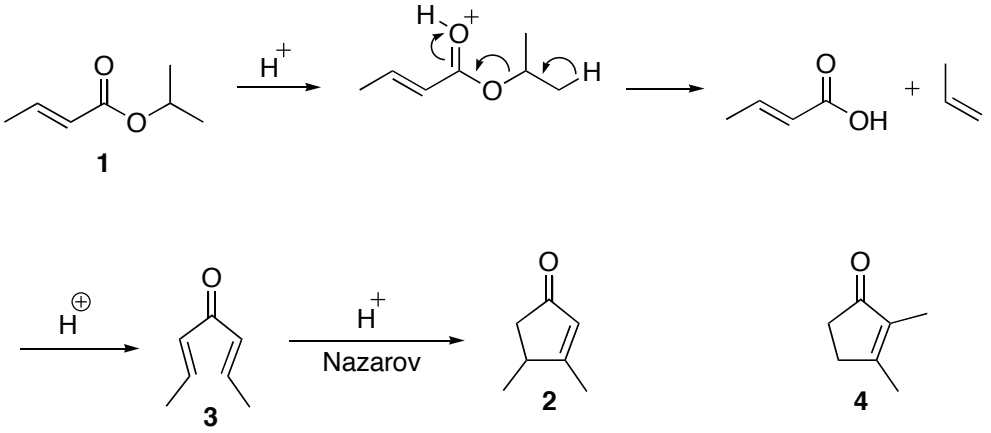
Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The transformation of isopropyl (*E*)-but-2-enoate to 3,4-dimethylcyclopent-2-en-1-one represents an example of a general rearrangement of esters of α,β-unsaturated acids to cyclopentenones catalyzed by polyphosphoric acid at elevated temperature. The reaction was first reported by Conia and Leriverend,[2] and presumably takes place via a fragmentation-recombination-Nazarov cyclization pathway, as shown in Scheme 1. A variety of substituted cyclopent-2-en-1-ones can be prepared by this method; esters of benzoic acid give 1-indanones under the same conditions (see Table 1).

Scheme 1



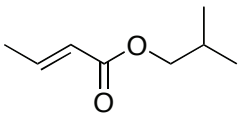
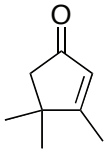
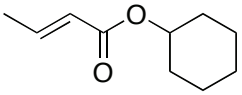
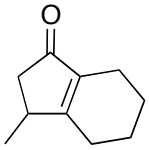
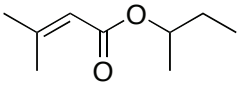
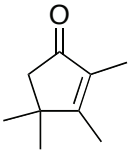
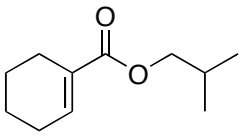
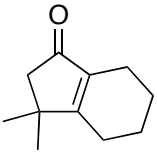
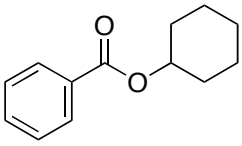
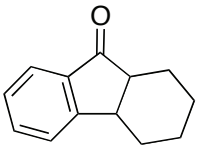
3,4-Dimethylcyclopent-2-en-1-one (**2**) is reported to be formed in 60% yield when hepta-2,5-dien-4-one (**3**) is treated with phosphoric acid and 98% formic acid.[3] However, a later report suggests that the major product from **3** under "Nazarov conditions" (phosphoric acid and formic acid at 90 °C) is 2,3-dimethylcyclopent-2-en-1-one (**4**),[4] a result in accord with an observation made by Nozaki on Nazarov cyclization of nona-3,6-dien-5-one, which gave 2,3-diethylcyclopent-2-en-1-one.[5] Exposure of **3** to fluoro-sulfonic acid at 0 °C gives **2** in 44% yield.[4]

3,4-Dimethylcyclopent-2-en-1-one reacts with an alkyllithium reagent and *p*-toluenesulfonic acid to give 1,2-dimethylcyclopenta-1,3-diene which, as its lithio or potassio derivative, has been employed in a variety of coupling reactions to produce substituted 1,2-dimethylcyclopentadienes.[6]

Bromination of 3,4-dimethylcyclopent-2-en-1-one with *N*-bromo-succinimide gives 4-bromo-3,4-dimethylcyclopent-2-en-1-one (Scheme 2).[7] This compound, upon treatment with triethylamine, generates unstable 3,4-dimethylcyclopentadienone, which undergoes spontaneous self-Diels-Alder cycloaddition to give *endo* adduct **5**.[8]

Table 1

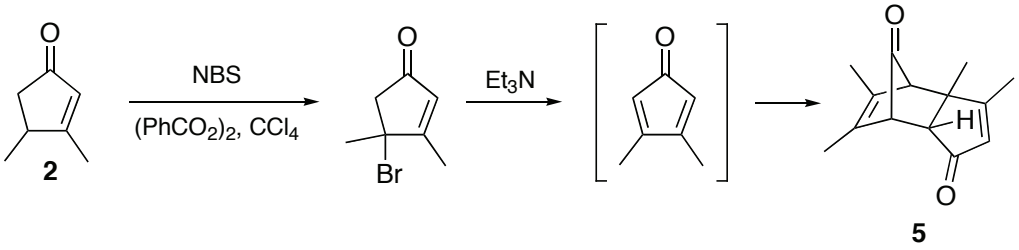
Conversion of α,β-Unsaturated Esters to Cyclopent-2-en-1-ones under Nazarov Conditions[a]

Ester	Product	Yield (%)
		60
		60
		60
		59
		40

a) H_3PO_4, P_2O_5

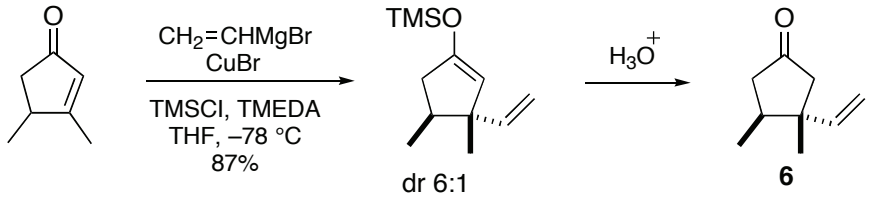
3,4-Dimethylcyclopent-2-en-1-one reacts with sodium azide in the presence of trifluoroacetic acid to give 5,6-dihydro-4,5-dimethyl-2-pyridone, a formal example of a Schmidt reaction leading to ring expansion.[9]

Scheme 2



Finally, conjugate addition of lithium divinylcuprate to 3,4-dimethylcyclopent-2-en-1-one in the presence of trimethylsilylchloride is stereoselective and yields 3-alkyl-3,4-dimethylcyclopentanone **6** after hydrolysis of the silyl enol ether (Scheme 3).[10]

Scheme 3



1. Department of Chemistry, Oregon State University, Corvallis, OR 97331, USA

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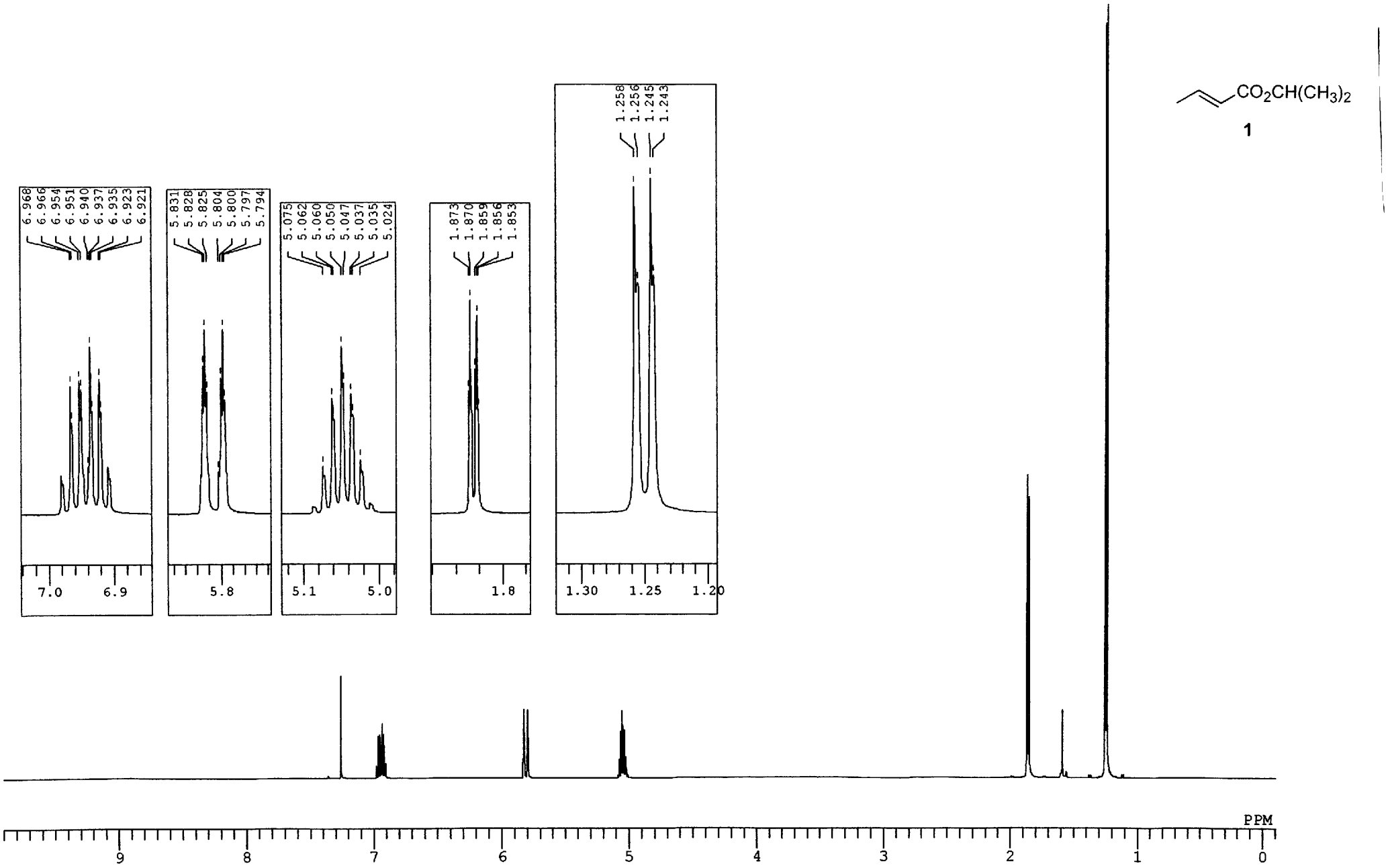
Appendix
Chemical Abstracts Nomenclature (Registry Number)

Crotonic acid: 2-Butenic Acid; (3724-65-0)

Isopropyl (*E*)-but-2-enoate: 2-Butenoic acid, 1-methylethyl ester, (2*E*)-; (6284-46-4)

3,4-Dimethylcyclopent-2-enone: 3,4-Dimethyl-2-cyclopenten-1-one; (30434-64-1)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1.25
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1
PPM
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8
7
6
5
4
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2
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PPM
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7
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