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Cyclopropanes from Allylic Halides. I. Synthesis of Dimethyl 3-(2-Methyl-1-propenyl)-2,2-dimethylcyclopropane-1,1-dicarboxylate and Pyrocin as Precursors of Chrysanthemic Acid

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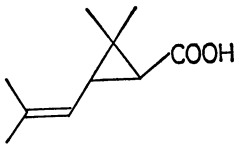
Synopsis. Dimethyl 3-(2-methyl-1-propenyl)-2,2-dimethyl-cyclopropane-1,1-dicarboxylate and pyrocin as precursors of chrysanthemic acid were synthesized by the reaction of (2-halo-2-methylpropylidene)malonate with 2-methyl-1-propenylmagnesium bromide.

Chrysanthemic acid (**1**), an important moiety of pyrethrins and a naturally occurring pesticide, has been a subject of interest as regards its synthesis.[1] In contrast to the nucleophilic substitution reaction of allylic halides taking place at the α- or γ-position, nucleophilic attack with cyanide at the β-carbon of allylic halides **2**



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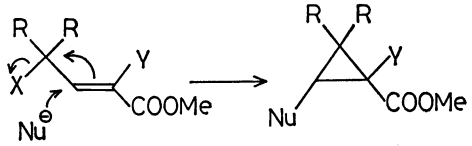
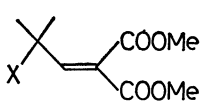
bearing alkoxycarbonyl groups in the γ-position followed by cyclization, giving cyclopropanecarboxylates **3**, was observed.[2] The diverse nature of allylic halides prompted us to examine the reaction of dimethyl (2-halo-2-methylpropylidene)malonate (**4**) with various nucleophiles.



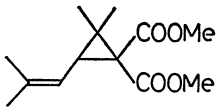
2 **3**

The present paper describes the results obtained in the reaction of **4** with 2-methyl-1-propenylmagnesium bromide[3] as a nucleophile as well as the synthesis of pyrocin (**7b**)[4] using the same starting materials.

(2-Halo-2-methylpropylidene)malonate (**4**) was treated with 2-methyl-1-propenylmagnesium bromide in tetrahydrofuran under the conditions given in Table 1. Chloride **4a** was allowed to react with 2-methyl-1-propenylmagnesium bromide at 24 °C for 45 h to give the desired **5** in 46% yield as well as 11% of **6** and the recovered **4a** (30%) (run 1), whereas the reaction at 45 °C for 18 h resulted in a mixture of 55% of **5**, 19% of **6**, and 14% of **7a** (run 2). When the same reaction was carried out in the presence of catalytic amounts of copper(I) chloride,[5] most of **4a** was consumed within 45 min, giving 51% of **5** and 37% of **6** along with minor product **7a** (4%) (run 3). The presence of a good leaving group in the allylic halide **4** is not sufficient for the reaction, since the same reaction with **4b** (runs 4 and 5) carried out at 24 °C afforded the dehalogenated product **6** principally[6] and **5** showed only 25—32% yields as compared to 46—55% for **5** from **4a**.



4a, X=Cl
b, X=Br



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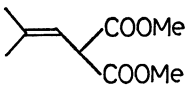

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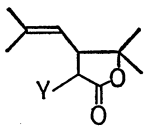
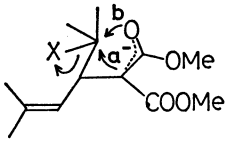


7a, Y=COOMe
b Y=H

The ambident ion **8** is believed to be formed by an unusual nucleophilic reaction of 2-methyl-1-propenide ion on the β-position of **4**. The formation of the cyclopropane ring of **5** can be rationalized by S_N2 type nucleophilic attack of the carbanion of **8** to the γ-position (Path a), while the formation of the parent compound **7a** could be attributed to nucleophilic attack by the enolate ion at the γ-position (Path b).



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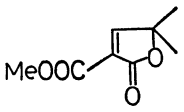
When **4b** was heated to 170 °C for 2 h under nitrogen, the 2-butenolide **9** was obtained in 76% yield. Subsequently, Michael addition of **9** with 2-methyl-1-propenylmagnesium bromide gave **7a** in 85% yield.[7] Demeth oxycarbonylation of **7a** in wet dimethyl sulfoxide-sodium chloride at 170 °C afforded pyrocin (**7b**) smoothly.



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Experimental

All boiling points and melting points were uncorrected, the boiling points indicated being air-bath temperatures. Ir spectra were recorded on a Japan Spectroscopic Co., Ltd., IRA-I infrared recording spectrophotometer with a grating.

Table 1. Reaction of **4a** and **4b** with 2-methyl-1-propenylmagnesium bromide

Run	Substrate (mmol)	>=\MgBr mmol	Additive	Temp °C	Time h	Products, %[a]			
						5	**6**	**7a**	**4**
1	**4a** (0.6)	1.4	none	24	45	46	11	—	30
2	**4a** (4.5)	9.0	none	45	18	55	19	14	—
3	**4a** (0.6)	2.0	CuCl[b]	45	0.75	51	37	4	5
4	**4b** (0.7)	0.8	CuCl[b]	24	0.75	25	47	5	7
5	**4b** (0.6)	1.0	none	24	12	32	56	12	—

a) Isolated Yields. b) Copper(I) chloride (10 mg) was added.

NMR spectra were recorded at 60 MHz on a Hitachi R-24 spectrometer with an internal standard of tetramethylsilan. Elemental analyses were carried out in this laboratory.

Dimethyl (2-Chloro-2-methylpropylidene)malonate (4a). A mixture of dimethyl (2-methylpropylidene)malonate[8] (3.0 g, 16.1 mmol), *t*-butyl hypochlorite[9] (2.0 g, 18.4 mmol), and azobisisobutyronitile (AIBN) (30 mg) in CCl_4 (3 ml) was heated under reflux for 2 h. After removal of the volatile substance, CCl_4 (3 ml), *t*-butyl hypochlorite (2.0 g, 18.4 mmol) and AIBN (30 mg) were added to the residue. The resulting mixture was refluxed for 2 h. The operation was repeated 5 times and the resulting **oil** was distilled to give **4a** (1.78 g, 50%): bp 75—77 °C/3 Torr; IR (neat) 1740 (C=O), 1651 cm^{-1}, (C=C); NMR ($CDCl_3$) δ 1.76 (s, 6, CH_3CCl), 3.77 (s, 6 CH_3), 6.93 (s, 1, HC=C). Found: C, 49.17; H, 6.01%. Calcd for $C_9H_{13}O_4$: C, 48.99; H, 5.94%.

Dimethyl (2-Bromo-2-methylpropylidene)malonate (4b). **4b** was prepared by bromination of dimethyl (2-methylpropylidene)malonate with *N*-bromosuccinimide, bp 92—95 °C/18 Torr, according to the reported procedure.[10]

Dimethyl 2,2-Dimethyl-3-(2-methyl-1-propenyl)cyclopropane-1,1-dicarboxylate (5). The reaction conditions and results are given in Table 1. A typical experimental procedure (run 2) is as follows: To aTHF solution (3 ml) of **4a** (1.0 g, 4.5 mmol) was added dropwise a THF solution (7 ml) of 2-methyl-1-propenylmagnesium bromide,[3] prepared from 2-methyl-1-propenyl bromide (1.22 g, 9.0 mmol) and magnesium (0.22 g, 9.0 mmol) at room temperature. After being stirred for 30 min at this temperature and for 18 h at 45 °C, the mixture was quenched with aqueous 10% NH_4Cl, extracted with ether, washed with brine and dried (Na_2SO_4). Removal of the solvent followed by column chromatography (SiO_2, THF–hexane, 1/20) gave **5** (597 mg, 55%), **6** (160 mg, 19%), and **7a** (143 mg, 14%).

Compound 5: Bp 81—84 °C/10 Torr; IR (neat) 1730 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.23 (s, 3, CH_3), 1.27 (s, 3, CH_3), 1.74 (br s, 6, CH_3C=C), 2.44 (d, 1, J=8 Hz, CH), 3.68 (s, 3, CH_3O), 3.72 (s, 3, CH_3O), 5.02 (diffused d, 1, J=8 Hz, HC=C). Found: C, 64.99; H, 8.59%. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39%.

Compound 6: Bp 73—76 °C/8 Torr: IR (neat) 1735 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.67 (diffused s, 3, CH_3C=C), 1.77 (diffused s, 3, CH_3C=C), 3.71 (s, 6, CH_3O), 4.24 (d, 1, J= 9 Hz, CHCO), 5.43 (diffused d, 1, J=9 Hz, HC=C). Found C, 58.29; H, 7.47%. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58%.

Compound 7a: Mp 81—81.5 °C (hexane–ether, 10/1); IR (Nujol) 1770 (lactone C=O), 1734 (C=O), 1675 cm^{-1} (C=C); NMR ($CDCl_3$) δ 1.27 (s, 3, CH_3), 1.44 (s, 3, CH_3), 1.73 (m, 6, CH_3C=C), 3.48 (d, 1, J=10 Hz, CHC=O), 3.56 (dd, 1, J=5 and 10 Hz, CHC=C), 3.76 (s, 3, CH_3O), 4.98 (diffused d, 1, J=5 Hz, HC=C). Found: C, 63.82; H, 8.05%. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02%.

4,4-Dimethyl-2-methoxycarbonyl-2-butenolide (9). The diester **4b** (940 mg, 3.55 mmol) was heated in a Claisen flask to 170 °C for 2 h under N_2 and then distilled to give **9** (456 mg, 76%): bp 90—95 °C/5 Torr; mp 72—73 °C (hexane); IR (Nujol) 1758 (lactone C=O), 1721 (C=O), 1640 cm^{-1} (C=C); NMR ($CDCl_3$) δ 1.54 (s, 6, CH_3), 3.87 (s, 3, CH_3O), 8.08 (s, 1, HC=C). Found: C, 56.43; H, 5.79%. Calcd for $C_8H_{10}O_4$: C, 56,47; H, 5.92%.

4,4-Dimethyl-3-(2-methyl-1-propenyl)-2-(methoxycarbonyl)butanolide (7a). To a THF solution (3 ml) of **9** (100 mg, 0.95 mmol) was added dropwise a THF solution (2 ml) of 2-methyl-1-propenylmagnesium bromide, prepared from 2-methyl-1-propenyl bromide (135 mg, 1.0 mmol) and magnesium (24 mg, 1.0 mmol) at room temperature. After being stirred for 16 h at this temperature, the mixture was quenched with aqueous 10% NH_4Cl, extracted with ether, washed with brine and dried (Na_2SO_4). Removal of the solvents followed by chromatography (SiO_2, hexane–ether, 20/1) gave **7a** (113 mg, 85%): mp 81—81.5 °C (hexane–ether, 10/1). The IR and NMR spectra were identical with those described above.

Pyrocin (7b). A solution of **7a** (40 mg, 0.18 mmol) in DMSO (1.24 ml) containing NaCl (5 mg) and a few drops of water was heated in a sealed tube at 170 °C for 1 h. The mixture was diluted with water and extracted with ether. The extract was washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. A short-path distillation of the residue gave **7b** (21 mg, 71%): bp 80—85 °C/3 Torr (lit,[4] bp 130—137 °C/17 Torr). The IR and NMR spectra were identical with those reported.[4]

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