Preparation of Some α-Substituted Cyclopropanecarboxylic Acids *via* Dichlorocarbene

By

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Some α,β-unsaturated esters (**1**), including *trans*-crotonate, *trans*-α-methoxycrotonate, *trans*-α-fluorocrotonate, *trans*-cinnamate, *trans*-α-chlorocinnamate, *cis*- and *trans*-α-fluorocinnamates, fumarate, and maleate, were allowed to react with dichlorocarbene, generated by the thermal decomposition of sodium trichloroacetate at 120–160°C, to give the corresponding β,β-dichlorocyclopropanecarboxylates (**2**) in fair to good yields (38–88%). The additions of dichlorocarbene to these esters were stereospecific. A similar reaction of *n*-butyl acrylate gave only a very low yield (6%) of the dichlorocarbene adduct, probably because of the accompanying polymerization of the starting ester. The reduction of 1-unsubstituted or 1-methoxy-substituted 2,2-dichloro-3-methylcyclopropanecarboxylate with tri-*n*-butyltin hydride at 90°C yielded both the completely reduced (**3**) and the partially reduced esters (**4** and **5**). That of 1-fluoro-substituted ester gave only the completely reduced product. These cyclopropanecarboxylates (**2** and **3**) were hydrolyzed with potassium hydroxide to give the corresponding free acids (**6** and **7**) in good yields (72–92%). The properties (bp, mp, n_D, pmr spectral data, etc.) of the cyclopropanecarboxylic acids and esters thus prepared are described.

It has already been reported that dihalocarbene can react with some α,β-unsaturated esters to yield the corresponding *gem*-dihalocyclopropanecarboxylates. Phenyl (trihalomethyl) mercury[1], sodium trihaloacetate[2], and haloform in the presence of alkali hydroxide and quaternary ammonium or phosphonium halide[3] have been used as carbene precursors.

The α-substituted cyclopropanecarboxylates hitherto prepared by this method are, however, limited to α-methyl-, α-*n*-butyl-, and α-phenyl-substituted ones. It is of much interest, therefore, to examine the applicability of this method for the preparation of other α-substituted cyclopropanecarboxylates, especially those having

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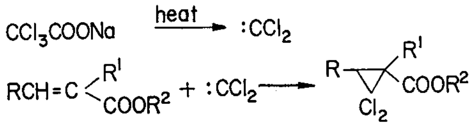
an electronegative α-substituent such as fluorine or chlorine, very few of which have ever been known to date.

This paper will deal with the results of the attempts to prepare some such α-substituted cyclopropanecarboxylates by the reaction of sodium trichloroacetate[4] with α-substituted α, β-unsaturated esters, followed by the reduction of the products with tri-n-butyltin hydride. The preparation of the corresponding free acids by hydrolysis of the esters will be described.

Results and Discussion

Reaction of Sodium Trichloroacetate with α, β-Unsaturated Esters. Sodium trichloroacetate was allowed to react with eleven α, β-unsaturated esters (**1a-k**) at 85-160°C with or without solvent. The products were isolated by distillation under reduced pressure, and were identified by their pmr, ir, and mass spectra. The reaction scheme is shown below, and the results are summarized in Tables 1 and 2.



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a : R=Me, R¹=H, R²=Me (trans)
b : R=Me, R¹=OMe, R²=Me (trans)
c : R=Me, R¹=F, R²=Me (trans)
d : R=Ph, R¹=H, R²=Me (trans)
e : R=Ph, R¹=Cl, R²=Me (trans)
f : R=Ph, R¹=F, R²=Me (trans)
g : R=Ph, R¹=F, R²=Me (cis)
h : R=COOMe, R¹=H, R²=Me (trans)
i : R=COOMe, R²=H, R²=Me (cis)
j : R=Me, R¹=H, R²=Et (trans)
k : R=H, R¹=H, R²=n-Bu

Table 1. Reaction of Sodium Trichloroacetate with α, β-Unsaturated Esters

Starting Material	Solvent	Reaction Temp.(°C)	Reaction Time(hr)	Yield (%)	Product
1a	None	120	2	65.1	**2a**
1b	None	120	4.5	69.5	**2b**
1c	None	120	4.5	48.3	**2c**
1d	None	150	2	73.6	**2d**
1e	None	160	4	59.4	**2e**
1f	None	150	2	65.6	**2f**
1g	None	140	2	74.8	**2g**
1h	None	140	2.5	41.8	**2h**
1i	None	140	2.5	37.9	**2i**
1j	None	125	2.5	87.7	**2j**
1k	DME	85	15	6.0	**2k**

Table 2. Properties of Dichlorocyclopropanecarboxylates

Compound	Bp(°C/mmHg)	n_D^t(t, °C)	Pmr		ν C=O
			Concn	δ (ppm) and *J* (Hz)	
2a	88–91/17[a]	1.4620(22.5)[b]	100%	1.40 (d, 3H, *J*=6.6), 1.87–2.48 (m, 2H), 3.82 (s, 3H)	1740
2b	100–106/13	1.4686(19.0)	100%	1.25 (d, 3H, *J*=6.6), 2.42 (q, 1H, *J*=6.6), 3.60 (s, 3H), 3.83 (s, 3H)	1740
2c	92–94/19	1.4578(29.0)	100%	1.31 (d, 3H, *J*=6.6), 2.52 (dq, 1H, *J*=6.6, 7.8), 3.88 (s, 3H)	1740
2d	102–110/0.6	58–59[c]	17% in CCl_4	2.75 (d, 1H, *J*=8.4), 3.42 (d, 1H, *J*=8.4), 3.82 (s, 3H), 7.30 (s, 5H)	1725
2e	123–125/1.2	1.5499(20.0)	100%	3.77 (s, 3H), 3.83 (s, 1H), 7.28 (s, 5H)	1740
2f	137–141/5.5	1.5390(18.0)	100%	3.67 (d, 1H, *J*=7.8), 3.90 (s, 3H), 7.33 (s, 5H)	1740
2g	110–113/1.0	1.5340(22.5)	100%	3.44 (d, 1H, *J*=22.8), 3.56 (s, 3H), 7.20 (s, 5H)	1750
2h	112–115/2.0	1.4820(26.0)	100%	3.70 (s, 2H), 3.80 (s, 6H)	1750, 1735
2i	109–111/2.0	1.4766(26.0)	100%	3.69 (s, 2H), 3.79 (s, 6H)	1755, 1740
2j	87–90/12	1.4655(23.0)	100%	1.30 (t, 3H, *J*=7.2), 1.37 (d, 3H, *J*=6.6), 1.70–2.45 (m, 2H), 4.22 (q, 2H, *J*=7.2)	1740
2k	99–100/21	1.4779(23.0)	40% in CCl_4	0.97 (t, 3H, *J*=6.0), 1.18–2.25 (m, 6H), 2.50 (dd, 1H, *J*=6.2, 10.0), 4.14 (t, 2H, *J*=6.0)	1740

a) Lit.[1] 50/2–3. b) Lit.[1] 1.4648 (25.0). c) MP (°C). Anal. Calcd for $C_{11}H_{10}O_2Cl_2$: C, 53.90% ; H, 4.11% ; Cl, 28.93%. Found : C, 54.27% ; H, 4.23% ; Cl, 28.60%.

The products formed by the dichlorocarbene addition to the α, β-unsaturated esters having a β-substituent gave a gas chromatogram composed of one peak. This suggests the formation of only one geometrical isomer, *i. e.*, the stereospecific nature of the reaction. The analysis of the pmr spectra of the products also proved the retention of configuration throughout the reaction.

It should be noted that dichlorocarbene, generally regarded as an electrophile, could add to such an electron-deficient double bond as in α-fluoro-, α-chloro-, or α-methoxyacrylates. Probably, the higher temperature employed for the carbene generation makes the carbene less sensitive to the electronic effect of α-substituents in comparison with those generated under milder conditions.

Attempts were made to prepare methyl 1-methoxy-2, 2-dichloro-3-phenylcyclopropanecarboxylate (**2**, R=Ph, R^1=OMe, R^2=Me) in a similar way, but were unsuccessful for reasons not known at present.

The very low yield of **2k** is believed to be due to the accompanying polymerization of **1k** under the reaction conditions. No carbene adduct was obtained when the reaction was carried out at 120°C without solvent.

Reduction of β, β-Dichlorocyclopropanecarboxylates with Tri-n-butyltin Hydride. Some of the methyl β, β-dichlorocyclopropanecarboxylates thus prepared (**2a-c**) were reduced with tri-*n*-butyltin hydride at 90°C in the presence of azobisisobutyronitrile (AIBN)[5,6].

The results are summarized in Tables 3 and 4. As seen from Table 3, both

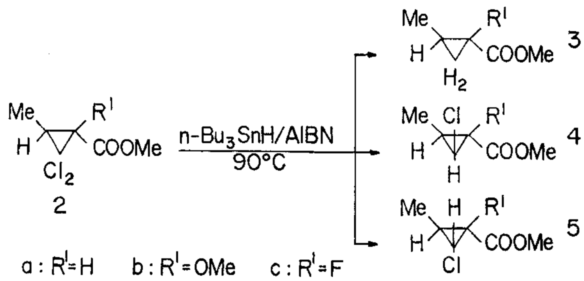


Table 3. Reduction of β, β-Dichlorocyclopropanecarboxylates with Tri-*n*-butyltin Hydride

Starting Material	Molar Ratio (Hydride/Ester)	Reaction Time (hr)	Yield (%)		Isomer Ratio[a] (4/5)
			3	4+5	
2a	3.0	12	36.1	53.9	65/35
2b	1.0	9	6.0	62.3	63/37
2b	2.3	9	26.7	30.6	65/35
2b	3.0	9	68.7	29.6	62/38
2b	4.0	24	67.8	28.9	65/35
2c	3.0	12	38.8	0.0	——

a) Determined by glpc before distillation.

Table 4. Properties of Reduction Products

Compound	Bp(°C/mmHg)	n_D^t(t, °C)	Pmr		ν C=O
			Concn	δ (ppm) and *J* (Hz)	
3a	53–54/40	1.4172 (24.0)	100%	0.23–0.80 (m, 1H), 1.10 (d, 3H, *J*=4.2), 1.20–2.22 (m, 3H), 3.62 (s, 3H)	1725
4a	78–80/40	——	100%	0.30–0.73 (m, 1H), 1.18 (d, 3H, *J*=5.0), 1.40–1.94 (m, 2H), 3.63 (s, 3H)	1720
5a	78–80/40	——	100%	0.30–0.73 (m, 1H), 1.21 (d, 3H, *J*=5.0), 1.40–1.94 (m, 2H), 3.67 (s, 3H)	1720
3b	64–65/13	1.4344 (21.0)	100%	0.52–0.77 (m, 1H), 1.26–1.95 (m, 2H), 1.15 (d, 3H, *J*=5.4), 3.39 (s, 3H), 3.67 (s, 3H)	1730
4b	87–88/13	——	100%	1.16 (d, 3H, *J*=6.6), 1.43–2.27 (m, 1H), 3.09 (d, 1H, *J*=6.2), 3.55 (s, 3H), 3.71 (s, 3H)	1733
5b	87–88/13	——	100%	1.20 (d, 3H, *J*=6.6), 1.43–2.27 (m, 1H), 3.30 (d, 1H, *J*=2.4), 3.44 (s, 3H), 3.76 (s, 3H)	1733
3c	64–66/55	1.4082 (29.0)	100%	0.58–0.91 (m, 1H), 1.21 (d, 3H, *J*=4.2), 1.29–2.08 (m, 2H), 3.74 (s, 3H)	1728

Table 5. Hydrolysis of Cyclopropanecarboxylates

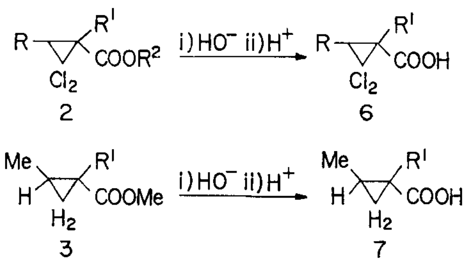
Starting Material	Yield (%)	Product								
		Structure	Carbon (%)		Hydrogen (%)		Chlorine (%)		Fluorine (%)	
			Calcd	Found	Calcd	Found	Calcd	Found	Calcd	Found
2b	83.8	**6b**	36.20	36.30	4.05	4.11	35.63	35.47	——	——
2c	78.1	**6c**	32.11	31.82	2.70	2.57	37.92	38.04	10.16	10.16
2d	91.3	**6d**	51.98	51.72	3.49	3.48	30.69	30.91	——	——
2e	90.5	**6e**	45.23	45.40	2.66	2.70	40.06	40.01	——	——
2f	86.4	**6f**	48.22	48.40	2.83	2.84	28.47	28.71	7.63	7.76
2g	92.3	**6g**	48.22	48.00	2.83	2.88	28.47	28.33	7.63	7.56
2j	72.2	**6j**	35.53	35.58	3.58	3.51	41.96	41.82	——	——
3b	72.0	**7b**	55.37	54.75	7.75	7.78	——	——	——	——
3c	76.2	**7c**	50.84	51.28	5.98	6.21	——	——	16.09	15.83

of the completely reduced esters (**3**) and the partially reduced ones (**4** and **5**) were generally formed under the reaction conditions, except in the case of **2c**.

Structural assignments for the partially reduced esters (**4** and **5**) were made from their pmr spectra, based on the relative magnitudes of the coupling constants between the vicinal ring protons for **4b** and **5b**, and on the relative magnitudes of the δ-values corresponding to the methyl and methoxycarbonyl groups for **4a** and **5a** (see Table 4 and Experimental).

The isomer ratio (**4b**/**5b**) found in the partially reduced 1-methoxy ester was nearly identical, irrespective of the amount of the hydride used. The simplest way to account for this fact is to assume that the equilibration between the two pyramidal forms of the α-chlorocyclopropyl radical precedes their hydrogen abstraction. Very probably, the rate of their inversion of configuration is increased by the higher reaction temperature (90°C) more pronouncedly than the rate of their hydrogen abstraction. At lower temperatures (<30°C), the rate of hydrogen abstraction is expected to be faster than, or at least comparable to, the rate of inversion[7].

Hydrolysis of Cyclopropanecarboxylates. The hydrolysis of the esters (**2b**-**g**, **2j**, **3b**-**c**) with potassium hydroxide in 50% aqueous ethanol gave the corresponding acids in good yields. The results are shown in Tables 5 and 6. The attempted hydrolysis with hydrochloric acid in acetic acid gave little or no acids.



Conclusion

As a method for preparing α-substituted cyclopropanecarboxylic acids or their esters, the one described here seems to be superior in the simplicity of the procedure as well as in the ready accessibility of the starting materials.

Studies on the stereochemical behavior of α-substituted cyclopropyl radicals are now in progress by using these acids as their precursors.

Experimental

All melting and boiling points are uncorrected. Proton magnetic spectra were

Table 6. Properties of Cyclopropanecarboxylic Acids

Compound	Bp(°C/mmHg)	n_D^t(t, °C)	Mp(°C)	Pmr	
				Concn[a]	δ (ppm) and *J* (Hz)
6b	114–118/2.0	—	75–75.5	63%	1.26 (d, 3H, *J*=6.6), 2.42 (q, 1H, *J*=6.6), 3.73 (s, 3H), 11.21 (s, 1H)
6c	91–91.5/1.8	—	42–43	20%	1.32 (d, 3H, *J*=6.6), 2.52 (dq, 1H, *J*=6.6, 7.8), 11.40 (s, 1H)
6d	152–157/2.4	—	114.5–115[b]	11%	2.83 (d, 1H, *J*=8.4), 3.50 (d, 1H, *J*=8.4), 7.35 (s, 5H), 10.68 (s, 1H)
6e	144/2.0	—	102–103	10%	3.89 (s, 1H), 7.44 (s, 5H), 10.49 (s, 1H)
6f	136–141/1.5	—	101–102	40%	3.73 (d, 1H, *J*=7.8), 7.36 (s, 5H), 12.51 (s, 1H)
6g	131/3.0	—	100–101	8%	3.50 (d, 1H, *J*=22.8), 7.26 (s, 5H), 9.30 (s, 1H)
6j	89–92/0.5	—	63–64	24%	1.43 (d, 3H, *J*=6.6), 1.81–2.56 (m, 2H), 11.80 (s, 1H)
7b	82–83/1.2	1.4487 (22.0)	c)	100%	0.58–0.89 (m, 1H), 1.19 (d, 3H, *J*=5.4), 1.31–1.91 (m, 2H), 3.45 (s, 3H), 12.04 (s, 1H)
7c	63–65/1.9	1.4254 (28.5)	—	100%	0.58–1.10 (m, 1H), 1.25 (d, 3H, *J*=4.2), 1.35–2.03 (m, 2H), 12.34 (s, 1H)

a) In CCl_4. b) Lit.[2] 110°C. c) Solid at −20°C.

obtained with a T-60 or an EM-360 nmr spectrometer of Varian Associates. The δ-values are expressed in ppm downfield from internal TMS. Infrared spectra were recorded on a Shimadzu IR-27 infrared spectrometer. For the glpc analyses, two kinds of 3 mm × 3 m columns (7% Silicone Grease or 7% Apiezon Grease L on Celite 545) were used. All α, β-unsaturated esters were prepared by known methods.

Preparation of β, β-Dichlorocyclopropanecarboxylates (**2a-k**). In a flask, fitted with a thermometer, a magnetic stirrer and a reflux condenser, was placed 0.1 mol of an α, β-unsaturated ester. It was heated with stirring at 120-160°C, and 0.15 mol of sodium trichloroacetate was gradually added. The reaction mixture was stirred at the same temperature for 2 to 4.5 hours, cooled, and poured into water. The product was extracted with ether, and the extracts were dried over anhydrous sodium sulfate. After evaporation of the ether, the residue was distilled under reduced pressure. For *n*-butyl acrylate (**1k**), which gave only polymeric material under the above conditions, the reaction was effected at 85°C for 15 hours in the presence of 25 m*l* of DME. The results are shown in Tables 1 and 2.

The yields listed in Table 1 are those calculated on the basis of the starting ester consumed. Recoveries were 71.1% for **1a**, 35.0% for **1b**, 14.3% for **1c**, 26.0% for **1d**, 32.2% for **1e**, 21.6% for **1f**, 46.5% for **1g**, 40.0% for **1h**, 36.1% for **1i**, 65.1% for **1j**, and 0.0% for **1k**.

Reduction of β, β-Dichlorocyclopropanecarboxylates (**3a-c**) *with Tri-n-butyltin Hydride.* In a flask, fitted with a thermometer, a magnetic stirrer, an inlet tube for nitrogen and a reflux condenser, was placed a mixture of 0.1 mol of a β, β-dichlorocyclopropanecarboxylate, 0.1-0.4 mol of tri-*n*-butyltin hydride, and a small amount of azobisisobutyronitrile (AIBN). The mixture was stirred at 90°C for 9 to 24 hours under nitrogen, and then was distilled under reduced pressure. The results are shown in Tables 3 and 4. The reaction of **3c** was very exothermic and gave no partially reduced products.

The isomer ratio for **4a**/**5a** given in Table 3 is only tentative, because the structural assignment for **4a** and **5a** is based on the assumption that in chlorocyclopropanes, the δ-value for β-methyl cis to Cl is smaller than the one trans to Cl, and that the δ-value for β-methoxycarbonyl cis to Cl is larger than the one trans to Cl, as is observed for **4b** and **5b** (see Table 4).

Hydrolysis of Cyclopropanecarboxylates (**2b-g**, **2j**, **3b-c**). The hydrolysis was effected by stirring 0.1 mol of an ester with a 10% solution of potassium hydroxide (0.15-0.20 mol) in 100-150 m*l* of 50% aqueous ethanol at room temperature for 24 hours. Distillation, followed by recrystallization from petroleum ether, gave the corresponding free acid. The results are summarized in Tables 5 and 6. The yields given in Table 5 are those calculated from the amount of the ester consumed. Recoveries were 1.7% for **2b**, 0.0% for **2c**, 36.7% for **2d**, 55.8% for **2e**, 12.0%

for **2f**, 34.9% for **2g**, 14.0% for **2j**, 1.3% for **3b**, and 0.0% for **3c**.

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