Tetrahedron Vol 29, pp 1179 to 1183 Pergamon Press 1973 Printed in Great Britain

THREE-MEMBERED RING FORMATION—IV
SELECTIVE SYNTHESES OF HALOGENOCYCLOPROPANEDICARBOXYLIC ESTERS POSSESSING DIFFERENT ALCOHOL RESIDUES

Y. KAWAKAMI,* K. TAJIMA and T. TSURUTA
Department of Synthetic Chemistry, Faculty of Engineering, The University of Tokyo, Bunkyo-ku, Tokyo, Japan

(*Received in Japan* 16 *September* 1972; *Received in UK for publication* 19 *December* 1972)

Abstract—Selective syntheses for some 1-halogeno-2-alkyl-*cis*-1,2-cyclopropanedicarboxylic esters were studied. In a ring formation between α-halogenoacetic and α-propylacrylic esters, lithium hydride was a much better condensing agent than sodium hydride for the selective syntheses of cyclopropanedicarboxylic ester possessing two different alcohol residues. A greater reactivity was found at the ester group linked to carbon 1 than that linked to carbon 2 in transesterification by alkali metal *t*-butoxide and also in its partial hydrolysis by KOH. This is presumably ascribed to the difference in the inductive effects of alkyl group and the Cl atom.

INTRODUCTION

As reported[1-3] a new type of ring closure is possible in the reaction of α-chloroacrylic ester with some organozinc compounds, resulting in the formation of cyclopropanedicarboxylic ester. A study of the reactivity of dimethyl 1-chloro-2-alkyl-*cis*-1,2-cyclopropanedicarboxylate, toward alkali metal t-butoxide, revealed that transesterification is strongly controlled by the nature of alkali metal.

This prompted an investigation into which ester group of the cyclopropanedicarboxylate is more liable to transesterification. Several cyclopropanedicarboxylic esters possessing two different ester groups were prepared and their NMR spectra studied.

RESULTS AND DISCUSSION

In the reaction of dimethyl 1-chloro-2-methyl-*cis*-1,2-cyclopropanedicarboxylate with alkali metal t-butoxide (alkali metal = K, Na and Li) in t-butyl alcohol, two products, A and B, were detected by VPC.

The NMR spectra of A and B are shown in Fig 1.

The NMR spectra show that one methoxy Me group disappeared in A, while both of the two methoxy Me groups disappeared in B. Corresponding to this, one singlet and two singlets appeared in A and B, respectively, which were assigned to t-butyl groups involved in the t-butyl ester groups. Therefore, A and B were concluded to be products of transesterification, in which one OMe group and two OMe groups were exchanged, respectively, by t-butoxy group of the alkali metal t-butoxide.

The results of elementary analyses of A and B are as follows:

A:	Found	C: 53·21; H: 6·80; Cl: 14·00
	Calc. for $C_{11}H_{17}ClO_4$	C: 53·20; H: 6·85; Cl: 14·25
B;	Found	C: 58·25; H: 8·00; Cl: 12·12
	Calc. for $C_{14}H_{23}ClO_4$	C: 57·9; H: 7·92; Cl: 12·20

The ratio of A and B formed was varied according to the nature of the alkali metal used as shown in Table 1.

Table 1. Reaction of alkali metal t-butoxide with dimethyl 1-chloro-2-methyl-*cis*-1,2-cyclopropanedicarboxylate[a]

Metal	Reaction time (hr)[b]	Mixed ester (A) (%)	Di-t-butyl ester (B) (%)
K	4	9·8	90·2
Na	15	41·3	58·7
Li	15	93·7	6·3

[a]30° in t-BuOH.
[b]Starting diester was all consumed.

Both the ester Me groups of the cyclopropanedicarboxylic ester were exchanged by potassium t-butoxide, whereas only one ester Me group was exchanged by lithium t-butoxide with high selectivity. Similar results were obtained with dimethyl 1-chloro-2-propyl-*cis*-1,2-cyclopropanedicarboxylate.

The NMR spectrum of dimethyl 1-chloro-2-propyl-*cis*-1,2-cyclopropanedicarboxylate (1) is shown in Fig 2.

Two singlets observed at 3·62 ppm and 3·54 ppm were assigned to the two non-equivalent carbo-

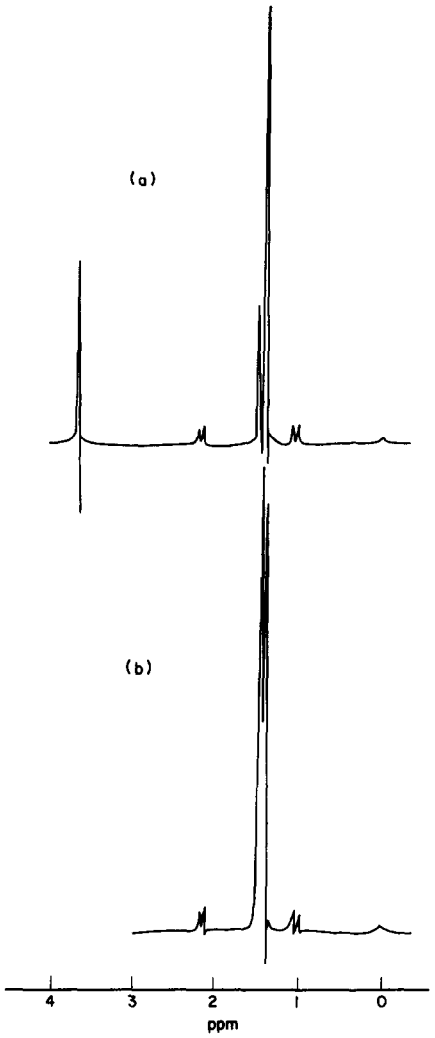


Fig 1. NMR spectra of A and B.
(a) A (b) B

methoxy Me groups, though no mutual correspondence between them has been ascertained. To establish the correspondence between them. cyclopropanedicarboxylate possessing different ester groups were prepared from dichloroacetic and α-propylacrylic esters.

The reaction of ethyl dichloroacetate with methyl α-propylacrylate in the presence of lithium hydride was interrupted by adding methanol or ethanol. The gaschromatogram of the reaction mixture is shown in Fig 3a. C, D and E were separated from one another by preparative gaschromatography. In the same way, reaction products C, D' and E were separated from a reaction of methyl dichloroacetate with ethyl α-propylacrylate.

The products distribution varied markedly according to the choice of alcohol for interrupting the ring formation reaction.

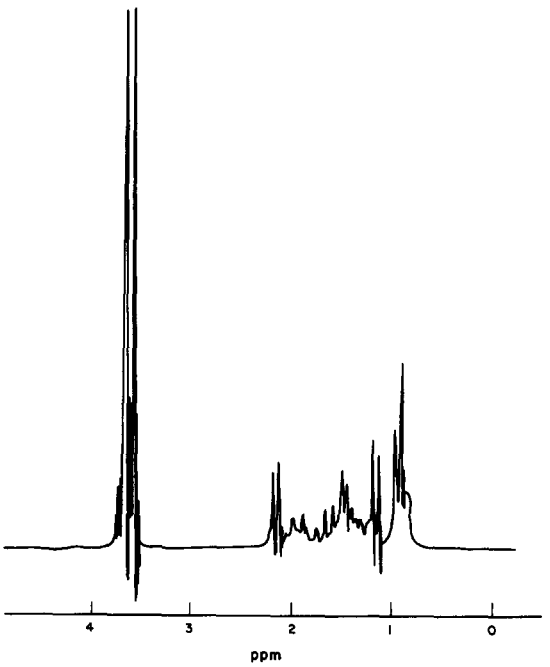


Fig 2. NMR spectrum of dimethyl 1-chloro-2-propyl-*cis*-1,2-cyclopropanedicarboxylate.

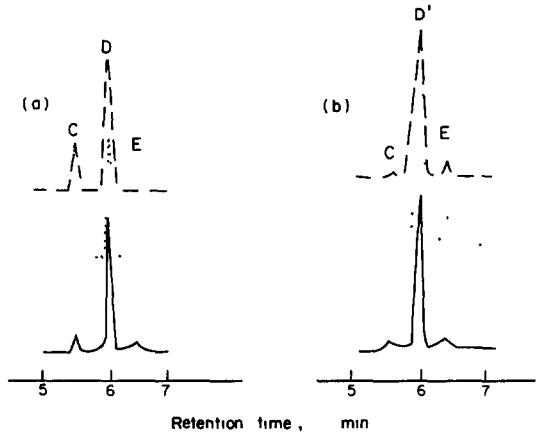


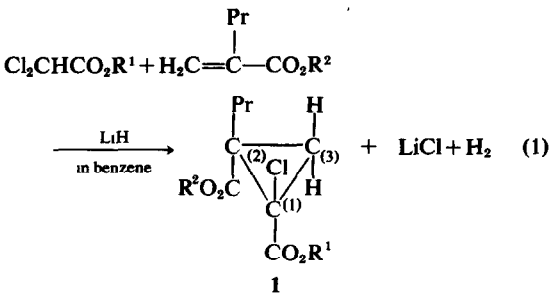
Fig 3. Gaschromatograms of the reaction mixture
(a) Reaction mixture of ethyl dichloroacetate with methyl α-propylacrylate
(b) Reaction mixture of methyl dichloroacetate with ethyl α-propylacrylate.
Analysed by a column packed with silicone DC 550, carrier H_2 45 ml/min. at 180°
-------- reaction mixture after killing by methanol
--------- reaction mixture after killing by ethanol
——— reaction mixture before killing by alcohol

As shown in Table 2, the selectivity with respect to the ester groups in reaction (1) was very high when the reaction was stopped by the alcohol with the same ester group as dichloroacetate.

Table 2. Product distribution of cyclopropanedicarboxylate

No	R^1	R^2	Killing agent	Products distribution (%) C([1])	D([2])	D'([3])	E([6])	Total yield (%)
1	Me	Et	MeOH	12	0	77	11	33
			EtOH	0	5	47	48	33
2	Et	Me	MeOH	59	41	0	0	37
			EtOH	0	90	0	10	37

R^1 and R^2 indicate the alcohol residue of dichloroacetate and α-propylacrylate, respectively.



1

From the NMR spectra, C and E were identified as 1 and diethyl 1-chloro-2-propyl-*cis*-1,2-cyclopropanedicarboxylate (4), respectively. The NMR spectra of D and D' are shown in Fig 4.

The NMR spectra indicated that either D or D' should correspond to one of the two esters, *cis*-1-carboethoxy-2-carbomethoxy-1-chloro-2-propylcyclopropane (2), or *cis*-2-carboethoxy-1-carbomethoxy-1-chloro-2-propyl-cyclopropane (3).

All these results (Table 2) are satisfactorily explained by assuming the ester group attaching to carbon 1 to be much more liable to transesterification. For instance, 2, which was originally formed in reaction (2), was presumably changed to 1 (in 59% yield) after being treated with methanol as killing agent. On the other hand, only a small fraction (12%) of the dicarboxylic ester (3) formed originally in reaction 3 was changed to 1, because of the poor reactivity of the ester group attaching to carbon 2.

Transesterification between dichloroacetic and α-propylacrylic esters did not take place in the presence of lithium hydride. Therefore, it was concluded that D (product from reaction 2) and D' (product from reaction 3) were 2 and 3, respectively. The two NMR signals at 3·62 ppm and 3·54 ppm should also be assigned to the methoxy methyls of compound 1 linked with carbon 1 and carbon 2, respectively.

Results obtained with NaH as a condensation agent are shown in Table 3.

In this Table some results with EtZnCl are also listed. As seen in Table 3, broad products distribution was always present in the reaction with NaH, in spite of any choice of alcohol as the killing agent,

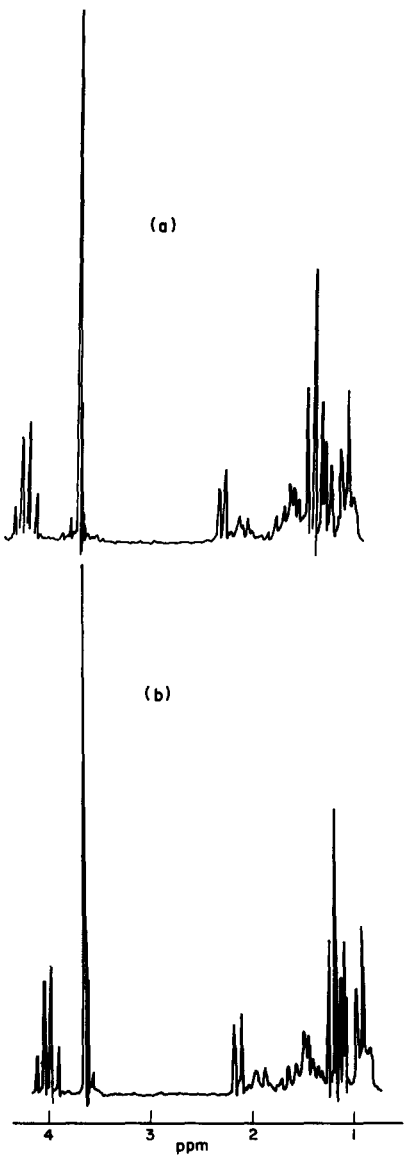
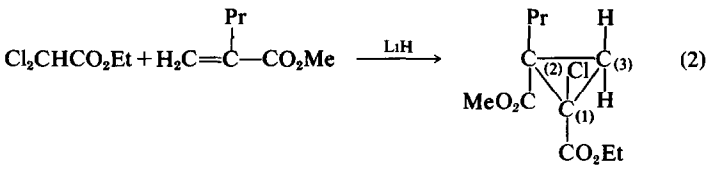
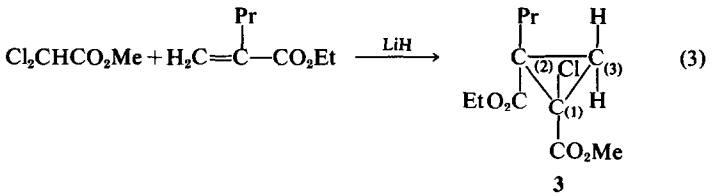


Fig 4. NMR spectra of D and D'
(a) D (b) D'



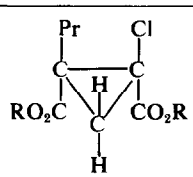
(2)



(3)

Table 3. Syntheses of cyclopropanedicarboxylate

No	Method	R^1	R^2	Killing agent	Products distribution (%) 1	2[h]	3[h]	4	Total yield (%)
1	NaH[a]	Me	Me	MeOH	100	0	0	0	70
2	NaH	Me	Et	MeOH	38	17	33	12	53
				EtOH	22	15	20	43	53
3	NaH	Et	Me	MeOH	41	28	26	5	54
				EtOH	7	28	20	45	54
4	NaH	Et	Et	MeOH	30	16	34	20	51
				EtOH	0	0	0	100	51
5	EtZnCl[a]	Me[b]	Me[b]	H_2O–HCl	100	0	0	0	50[c]
6	EtZnCl[a]	Me[d]	Et[d]	H_2O–HCl	25	22	31	22	43[e]
7	EtZnCl[a]	Et[f]	Et[f]	H_2O–HCl	0	0	0	100	38[g]

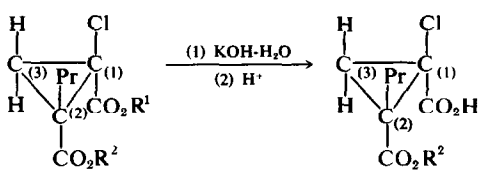
[a]The reaction: $EtZnCl + 2CH_2{=}C(Cl){-}CO_2R \longrightarrow$  $+ ZnCl_2$,

[b]Methyl α-chloroacrylate(MCA) was used.
[c]Value based on 1/2[MCA].
[d]Equimoles of methyl α-chloroacrylate and ethyl α-chloroacrylate (ECA) were used
[e]Based on [MCA].
[f]ECA was used.
[g]Based on 1/2[ECA].
[h]The ratio was determined by NMR.

a fact which visualizes the superiority of LiH to NaH as condensation agent for the selective preparation of cyclopropanedicarboxylic esters having different alcohol residues.

In keeping with the higher reactivity of ester group linked to carbon 1, products from partial hydrolysis of **1**, **2**, **3** and **4** with equimolar amounts of KOH were shown to be monoesters in which the ester group linked to carbon 1 was selectively hydrolysed.

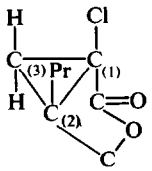
The higher reactivity of the CO group of the ester at carbon 1 was also confirmed in a reaction



(4)

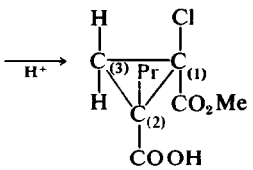
between 1-chloro-2-propyl-*cis*-1,2-cyclopropanedicarboxylic acid anhydride (**6**) and ethylzinc methoxide. The acid anhydride (**6**) was prepared from the dicarboxylic acid by treating with acetic an-

hydride.[4] In the reaction of the anhydride with EtZnOMe, *cis*-2-carbohydroxy-1-carbomethoxy-1-chloro-2-propylcyclopropane (**7**) was produced, which was an addition product of the OMe group to the CO carbon linked to carbon 1.



+ EtZnOMe

6



+ $Zn(OH)_2 + EtH$ (5)

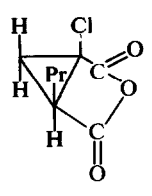
7

Reactions (4) and (5) provide appropriate methods for the preparation for the both types of the cyclopropanedicarboxylic acid monoesters (**5** and **7**).

The difference in the reactivity of the two ester groups linked to carbons 1 and 2 was ascribed to the difference in the inductive effects of the propyl group and the Cl atom (σ^*: $PrCH_2$-, −0·13; $ClCH_2$-, +1·05).[5]

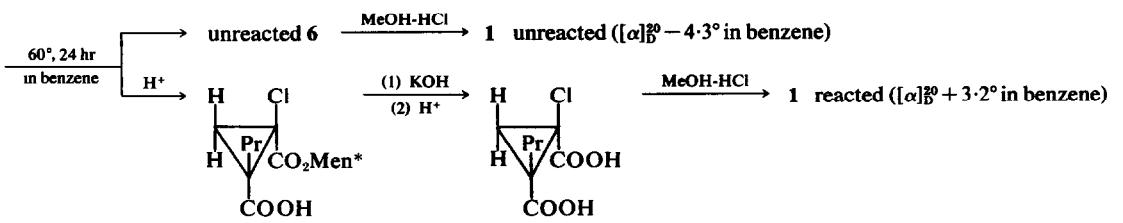
In connection with reaction (5), asymmetric transformation was attempted with ethylzinc-*l*-menthoxide (**8**).

The reactions were carried out with a one to two mole ratio of **8** and **6**. The reaction process was as follows:



+ EtZnO-Men*

6



The results of asymmetric transformation are also shown in the above scheme. Since the reaction site of **6** with EtZnOR was confirmed to be the CO carbon linked to carbon 1, it was concluded that the attack of ethylzinc-*l*-menthoxide must have taken place in preference of one antipode of the stereoisomeric site around carbon 1.

EXPERIMENTAL

Reagents. Commercial methyl dichloroacetate and ethyl dichloroacetate were purified by distillation. Methyl α-propylacrylate and ethyl α-propylacrylate were prepared according to the literature.[6] t-BuOH was dried with BaO. Alkali metal t-butoxides were prepared by adding alkali metal into t-BuOH. Commercial Et_2Zn was purified by distillation. Ethylzinc menthoxide and ethylzinc methoxide were prepared by Noltes' method.[7]

The NMR spectra were recorded by the high resolution NMR spectrometer model JNM-4H-100 (JEOL).

The reaction of **6** *to* **1**. This was carried out at 50° with one to two mole ratios of **8** and **6**. After 24 hr, unreacted **6** was distilled off *in vacuo* and the reaction was stopped by HCl and the mixture extracted by diethyl ether. After the solvent was distilled off, the residue was hydrolysed by excess KOH, and the mixture twice extracted with diethyl ether. The system was acidified by HCl to pH 5·0–6·0 and again extracted with diethyl ether. After the solvent was distilled off, the residue was esterified with MeOH-HCl to **1**. Unreacted **6** was also converted to **1**.

REFERENCES

[1] Y. Kawakami and T. Tsuruta, *Tetrahedron Letters* 1173 (1971)
[2] Y. Kawakami and T. Tsuruta, *Ibid*, 1959 (1971)
[3] T. Tsuruta, Y. Kawakami and R. Tsushima, *Makromol. Chem.* **149** 135 (1971)
[4] L. L. McCoy, *J. Org. Chem.* **25**, 2078 (1960)
[5] R. W. Taft, Jr., *Steric Effects in Organic Chemistry* (Edited by M. S. Newman) Chap. 13. Wiley, New York (1956)
[6] C. Mannich and K. Ritsert, *Ber. Dtsch Chem. Ges* **57**, 1116 (1924)
[7] J. G. Noltes and J. Boersma, *J Organometal. Chem.* **12**, 425 (1968); G. E. Coates and D. Ridley, *J. Chem. Soc.* 1870 (1965)