Alkylation, Acylation, and Cyclopropanation Reactions of α-Halo Carboxylic Acid Dianions

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We have recently described an updated version of the Darzens glycidic ester condensation which utilizes dianions derived from α-halo carboxylic acids[1]. In carbonyl homologation

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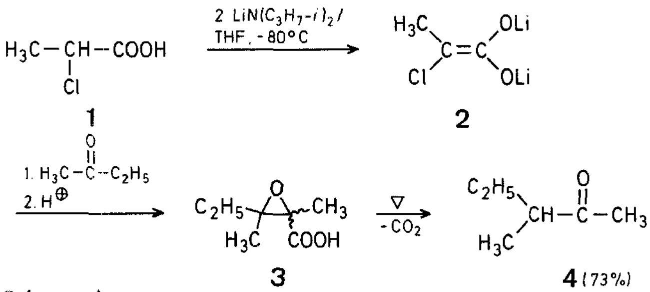
reactions these reagents circumvent the troublesome glycidic ester hydrolysis step (e.g. Scheme A).



Scheme A

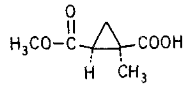
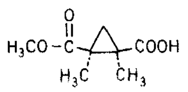
At this time, we report on the reactions of a typical dianion in the series, the dilithium derivative **2** from 2-chloropropanoic acid (**1**), with a sampling of electrophiles other than simple aldehydes and ketones.

The dianion **2** was generated at −80 °C with lithium diisopropylamide in tetrahydrofuran. After five minutes, the electrophile was added and the reaction mixture was allowed to warm to room temperature. The dianion **2** exhibits excellent nucleophilic reactivity towards alkyl halides expected to participate readily in S_N2 reactions (Table). Quenching these reactions at −80 °C results in recovery of starting materials and only a trace of substitution products. The initial product of acylation of **2** with benzoyl chloride decarboxylated during workup to result in 2-chloro-1-phenyl-1-propanone.

Monocarbanions of α-halo esters are known to add to α,β-unsaturated esters in a conjugate manner resulting in the production of cyclopropanedicarboxylates[2]. This reaction generally affords *cis*/*trans*-mixtures. A unique feature observed in the addition of dianion **2** to methyl acrylate and methyl methacrylate is the production of the *cis*-isomer exclusively in 57% and 65% yields, respectively. The product from dianion **2** and methyl methacrylate is initially a mixed acid ester whose ^{1}H-N.M.R. spectrum shows a doublet at $\delta=0.8$ ppm (1 H, $J=2$ Hz) and a coupled doublet at $\delta=2.02$ ppm (1 H, $J=2$ Hz). The two coupled doublets indicate that the cyclopropyl methylene protons are coupled to each other and must be non-equivalent, thus the two carboxylic groups are most likely *cis*. If the two carboxylic groups were *trans*, the methylene protons would be equivalent and would appear as a singlet integrating to two hydrogens. Methylation of the half acid ester with diazomethane afforded the diester which showed an identical pattern. The ^{13}C-N.M.R. spectrum showed only eight absorptions indicating that there was only one isomer present. Reaction of dianion **2** with methyl acrylate produced a product whose ^{1}H-N.M.R. spectrum was much more complicated due to the three non-equivalent cyclopropyl hydrogens. Heating the diacid derivative with acetic anhydride produced a cyclopropyl cyclic anhydride ($\nu_{C=O}=1790$ cm^{-1}) confirming this cyclopropyl diacid product to be the *cis*-isomer. The ^{13}C-N.M.R. spectrum showed only one set of absorptions indicating the presence of only one isomer.

Lithium chelation involving both carboxyl groups may be the origin of the diastereoselectivity. Akabori and Lashii[3] have suggested this type of interaction to explain their results observed in a study of the sodium hydride-promoted addition of methyl chloroacetate to methyl acrylate. In tetrahydrofuran and dichloromethane the major product was the *cis*-diester whereas, in the presence of crown ethers or dimethylformamide solvent, the major product was the thermodynamically more stable *trans*-diester. Presumably the crown ethers or solvents with high dielectric constants associate more strongly with the cation and interfere with chelation by the carboxyl groups.

Table. Reactions of Dianion **2** with Various Electrophiles

Electrophile	Product	Yield [%]
$C_6H_5-CH_2-Cl$	$C_6H_5-CH_2-C(Cl)(CH_3)-COOH$	68
$H_2C=CH-CH_2-J$	$H_2C=CH-CH_2-C(Cl)(CH_3)-COOH$	85
$n-C_4H_9-X$	$n-C_4H_9-C(Cl)(CH_3)-COOH$	73 (X=J) 66 (X=Br)
$C_6H_5-C(=O)-Cl$	$C_6H_5-C(=O)-CH(Cl)-CH_3$	90
$H_2C=CH-COOCH_3$		57
$H_2C=C(CH_3)-COOCH_3$		65

Generation and Reaction of Dianion 2 from 2-Chloropropanoic Acid (1):

Lithium diisopropylamide is generated under argon in an oven-dried flask equipped with a rubber septum by the addition of 1.6 molar butyllithium in hexane (35 ml, 50 mmol) to diisopropylamine (7 ml, 50 mmol) in tetrahydrofuran (150 ml; freshly distilled from lithium aluminum hydride) cooled to −80 °C (Dry Ice/diethyl ether bath). The light yellow solution is stirred at −80 °C for 15 to 20 min, then 2-chloropropanoic acid (**1**; 2.71 g, 25 mmol) dissolved in dry tetrahydrofuran (10 ml) and cooled to −80 °C is added using a stainless steel double-tipped transfer needle and argon pressure. The resulting reaction mixture is stirred for 5 min at −80 °C to insure complete dianion formation. The electrophile (1 equiv) dissolved in tetrahydrofuran is added and the reaction mixture is allowed to warm to room temperature (Table). Reaction products are isolated following a dilute mineral acid workup.

2-Chloro-2-methyl-3-phenylpropanoic Acid:

The product is isolated by distillation as a clear liquid; b.p. 135 °C/0.4 torr which crystallizes upon standing; m.p. 52–53 °C.

$C_{10}H_{11}ClO_2$	calc.	C 60.46	H 5.58
(198.6)	found	60.19	5.40

^{1}H-N.M.R. ($CDCl_3$): $\delta=1.70$ (s, 3 H); 3.34 (s, 2 H); 7.25 (s, 5 H); 12.06 ppm (s, 1 H).

2-Chloro-2-methyl-4-pentenoic Acid:

The acid is isolated as a clear liquid, b.p. 115–116 °C/25 torr.

$C_6H_9ClO_2$	calc.	C 48.50	H 6.10
(148.6)	found	48.75	6.24

^{1}H-N.M.R. ($CDCl_3$): $\delta=1.78$ (s, 3 H); 2.80 (d, 2 H); 5.0–6.2 (m, 3 H); 10.30 ppm (s, 1 H).

2-Chloro-2-methylhexanoic Acid:

The product is a clear liquid; b.p. 64 °C/0.05 torr.

$C_7H_{13}ClO_2$	calc.	C 51.07	H 7.96
(164.6)	found	51.23	8.05

^{1}H-N.M.R. ($CHCl_3$): $\delta=1.80$ ppm (s, 3 H).

2-Chloro-1-phenyl-1-propanone:
Two equivalents of benzoyl chloride are used. The by-product, *N,N*-diisopropylbenzamide, is obtained by extraction of an aqueous work-up mixture prior to acidification. After acidification, extraction with dichloromethane, and distillation, the product is obtained as a clear liquid; b.p. 75 °C/0.2 torr (Lit.[4], b.p. 133 °C/26 torr).

^{1}H-N.M.R. ($CDCl_3$): δ = 1.67 (d, 3 H); 5.17 (q, 1 H); 7.1–8.1 ppm (m, 5 H).

***cis*-1,2-Dimethyl-1,2-cyclopropanecarboxylic Acid:**
The reaction of dianion **2** with methyl methacrylate produces the *monomethyl ester* of the title compound as a clear liquid.

^{1}H-N.M.R. ($CDCl_3$): δ = 0.80 (d, 1 H, J = 2 Hz); 1.41 (s, 6 H); 2.02 (d, 1 H, J = 2 Hz); 3.65 (s, 3 H); 11.83 ppm (s, 1 H).

Upon standing the monoester hydrolyzes to the *diacid*, a white crystalline solid; m.p. 124–125 °C (Lit.[5], m.p. 115–117 °C).

^{1}H-N.M.R. ($CDCl_3$): δ = 0.78 (d, 1 H, J = 2 Hz); 1.14 (s, 6 H); 2.01 (d, 1 H, J = 2 Hz); 12.70 ppm (s, 2 H).

^{13}C-N.M.R. ($CDCl_3$): δ = 16.10 (off resonance decoupled to a quartet, both CH_3); 26.55 (off resonance decoupled to triplet, CH_2); 32.20 (off resonance decoupled to a singlet, both quatenary cyclopropyl carbons); 179.79 ppm (off resonance decoupled to a singlet, both carboxylic acid carbons).

Methylation of the diacid with diazomethane produced the *diester*.

^{1}H-N.M.R. ($CDCl_3$): δ = 0.75 (d, 1 H, J = 2 Hz); 1.38 (s, 6 H); 1.98 (d, 1 H, J = 2 Hz); 3.64 ppm (s, 6 H).

Treatment of the diacid with acetic anhydride gives the *cyclic anhydride*; m.p. 55–56 °C (Lit.[5], m.p. 55–57 °C).

***cis*-1-Methyl-1,2-cyclopropanedicarboxylic Acid:**
The addition of **2** to methyl acrylate affords *cis-2-methoxycarbonyl-1-methylcyclopropanecarboxylic acid* as a clear oil.

^{1}H-N.M.R. ($CDCl_3$): δ = 1.15 (m, 1 H); 1.45 (s, 3 H); 1.9 (m, 2 H); 3.66 (s, 3 H); 11.80 (s, 1 H).

Upon standing this acid hydrolyzes to the *diacid*; m.p. 141–142 °C (Lit.[4], m.p. 139–141 °C).

Heating a sample of the diacid in acetic anhydride on the steam bath results in the formation of the *anhydride*; m.p. 46–47 °C (Lit.[4], m.p. 46–47 °C).

Treatment of the diacid with diazomethane produces cis-*dimethyl 1-methyl-1,2-cyclopropanedicarboxylate*.

^{13}C-N.M.R. ($CDCl_3$): δ = 19.73, 21.03 (CH_3 and CH_2, off resonance decoupling produced overlapping multiplets); 28.64, 28.91 (two carboxyl substituted carbons, off resonance decoupled to an overlapping doublet and singlet, respectively); 52.02, 52.28 (two methyl ester carbons, off resonance decoupled to two overlapping quartets); 171.22, 172.40 ppm (two carboxylic ester carbons off resonance decoupled to two singlets).

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