Synthesis of α-Carboxy-γ-butyrolactones by Rearrangement of *capto-dative* Cyclopropanes on Silica Surfaces

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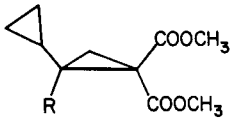
Received August 31, 1981

The rearrangement of some cyclopropanes featuring electron-withdrawing and electron releasing substituents on vicinal carbons of the trimethylene ring to α-carboxy-γ-lactones upon contact with silica gel at room temperature has been discovered. One or two alkyl ester groups were chosen as electron attractor substituents while one or two cyclopropyl units were used for the release of electron density. It was observed that the lactone forming process is strongly dependent upon these substituents to the extent that only two ester groups and at least one cyclopropane will confer enough vulnerability to the tetra-substituted cyclopropane for the rearrangement to take place. A comparative study of the lactonization by means of contact with silica and alkaline hydrolysis was performed and some mechanistic considerations are put forth.

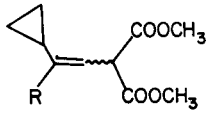
J. Heterocyclic Chem., **19**, 369 (1982).

The synthesis of α-methylene butyrolactones has received a great deal of attention in recent years (1) chiefly because of the tumor-inhibiting activity displayed by several natural products containing this five membered ring in their structure (2). In some instances appropriately activated cyclopropanes have served as useful precursors of α-methylene-γ-butyrolactones, particularly in cases where the trimethylene ring had electron withdrawing substituents such as esters. These groups imbue the cyclopropane with those characteristics expected for an electrophile giving rise to its interaction with nucleophiles such as amines, hydroxide ion and some carbanions. The resulting ring opened products featured an active nucleophile four carbons removed from the carbonyl group of the initial ester synthon, which is a well known combination for the production of γ-lactams, γ-lactones, and cyclopentenes. These syntheses make use of the peculiar



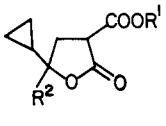
1: R = $CH(CH_2)_2$

4: R = CH_3



2: R = $CH(CH_2)_2$

6: R = CH_3

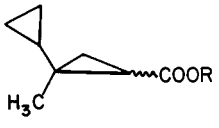


3a: $R^1 = CH_3$, $R^2 = CH(CH_2)_2$

3b: $R^1 = H$, $R^2 = CH(CH_2)_2$

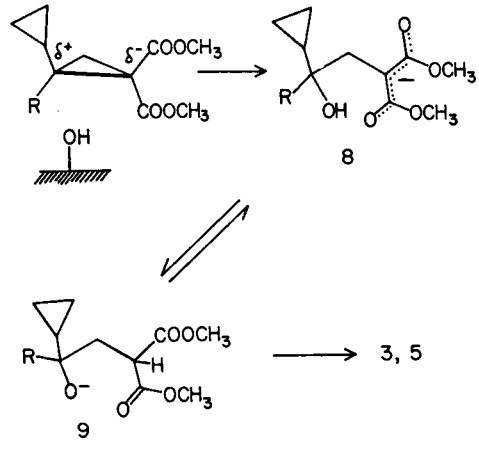
5a: $R^1 = R^2 = CH_3$

5b: $R^1 = H$, $R^2 = CH_3$



7a: $R = C_2H_5$

7b: R = H



symmetry of a spiroacylal diester linkage which confers vulnerability towards nucleophiles in the cyclopropane, since simple ester substitution is insufficient for inducing the required electrophilicity (3). Two conceptually related transformations based on the rearrangement of cyclopropyl carbinyl systems are also on record (4,5).

We hypothesized that the introduction of electron donor substituents in addition to the electron withdrawing units, located on vicinal carbons of cyclopropane as to allow for conjugative effects through the ring, would impart increased reactivity, *i.e.* less demanding reaction conditions, in the ring unraveling reactions of trimethylene involved *inter alia* in lactonization processes. Below we report that this conception is feasible and that simple exposure of active cyclopropanes to untreated silica gel at room temperature is enough to promote rearrangement-cyclization. Our interest in *capto-dative* cyclopropanes (6) stems on the one hand from their ability to undergo 1,3-sigmatropic rearrangement under mild conditions to furnish heterocyclic products in high yield (7) and to give synthetically useful ring opening products (8), on the other.

When 2,2-dicyclopropylcyclopropane diester (**1**), obtained in 88% yield from dicyclopropylethylene and dimethyldiazomalonate (9), was chromatographed through silica gel Si-60 (70-230 mesh) in pentane-methylene chloride, the eluted material showed no signs of the starting cyclopropane. The less polar fraction (55%) displayed an AB system at δ 4.46 and 5.40 ppm (J = 10 Hz) expected for a dimethyldicarboxylate-methynevinyl-methyne combination in the nmr spectrum, and other spectroscopic features corresponding to structure **2**. Further elution furnished a second product (45%) (96% total recovery yield) showing two carbonyl bands at 1735 and 1770 cm^{-1} in the infrared spectrum which strongly suggested a γ-lactone structure. Additional evidence was gathered from the cyclic ABM system in the proton nmr spectrum and other analytical evidence (*vide infra*) in the assignment of structure **3a** to this compound.

2-Methyl-2-cyclopropylcyclopropane diester (**4**), featuring one activating group only on the donor end of cyclopropane (10) required ten days of exposure to silica gel in chloroform to give the corresponding lactone **5a** in a mixture with a small amount of the starting trimethylene (**4**) (5%). Longer treatment did not change appreciably the composition of the mixture except for partial hydrolysis of the ester group to give (**5b**). Nevertheless, the production of the lactone could be rendered nearly quantitative by chromatographic separation of its precursor (**4**) followed by a second extended contact with silica. Notably, no β,γ-unsaturated diester (**6**) was formed within our limits of detection (<0.5%). Along the same lines, a mixture of *Z* and *E* 2-methyl-2-cyclopropyl-1-ethoxycarbonylcyclopropane (**7a**) was recovered unchanged after fifteen days of contact with silica in chloroform.

The construction of γ-lactones **3a** and **5a** from the electrophilic cyclopropanes **1** and **4** must involve a hydrolytic step whereby the heterocyclic oxygen atom is incorporated. The combination of the hydroxyl groups contained in untreated silicas (11) and the Lewis acidity associated with this solid support would provide the required nucleophile as well as additional activation of the electron captor end of cyclopropane. Indeed, simple hydrolysis with potassium hydroxide of compound **1** furnished the carboxylic acid **3b** in nearly quantitative yield. That this process is strongly dependent on the presence of electron donors was evidenced by the much slower lactonization of compound **4** upon basic hydrolysis, and the absence of γ-lactones in the hydrolysis of simple cyclopropane diesters (3). At the same time the importance of the captor substituents in combination with electron donors on cyclopropane was further emphasized by the total lack of rearrangement during the hydrolysis of **7a**, whereby only **7b** was produced. In addition, the fact that the ester group is preserved during the treatment of **1** and **4** with silica implies an *ab initio* attack of hydroxide ion on carbon C-2 of cyclopropane, thus exposing the unique situation of a trimethylene ring such as **1** and **4** being more electrophilic than the carbonyl carbon of an ester.

The intermediacy of β,γ-unsaturated esters such as **2** in the production of lactones cannot be ruled out if one considers this possibility within the context of the recently reported acid promoted transformation of α,β-unsaturated diesters to γ-lactones (12) and the thermal isomerization of α,β- to β,γ-unsaturated esters by way of a 1,5-hydrogen transfer (13). However, compound **2** was stable under reaction conditions other than protic acid treatment upon which it underwent, not unexpectedly, uncontrolled decomposition.

Finally, the fact that the cyclopropyl substituents on carbon C-2 remained unchanged throughout the lactonization process allows one to discard the intervention of diradical species during the trimethylene ring unraveling step (14). Consequently, the collected evidence strongly favors a sequence of events represented by the series **1**→**8**→**9**→**3a** to account for the observed rearrangement.

EXPERIMENTAL

Infrared spectra were measured on a Perkin-Elmer 337 spectrophotometer using polystyrene film as calibration standard; nmr spectra were obtained from a Varian Associates EM-390 instrument operating at 90 MHz, using tetramethylsilane as internal standard and in deuteriochloroform solutions unless otherwise stated. Boiling and melting points are uncorrected. Dimethyl diazomalonate was prepared from dimethyl malonate and tosyl azide as reported earlier (15) and was purified by distillation (63-64°/0.8 torr). Dicyclopropylethylene was synthesized from dicyclopropyl ketone as reported previously (16). Elemental analyses were performed by Drs. Malissa and Reuter in Germany.

2,2-Dicyclopropyl-1,1-dimethoxycarbonylcyclopropane (**1**).

A solution of dimethyl diazomalonate (1.6 g, 10 mmoles) and 1,1-dicyclopropylethylene (1.65 g, 15 mmoles) in dry benzene (20 ml) was added dropwise over a period of two hours to a stirred suspension of bis(acetoacetonato)copper(II) (72 mg) in benzene (2 ml) at reflux temperature under a nitrogen atmosphere. After the addition was complete, heating was continued for an additional 22 hour period while the disappearance of diazomalonate was monitored by the $C{=}N_2$ band at 2150 cm^{-1} in the infrared spectrum. Then, the reaction mixture was cooled to 5° and passed rapidly through a short path neutral alumina act III column to remove the catalyst. Evaporation of solvents and distillation *in vacuo* of the remaining crude material gave pure compound **1**, bp 94-95°/0.1 torr, yield, 2.09 g (88%); ir (neat): 1730 (s), 1230 (m), 1030 (m) cm^{-1}; nmr: δ 0.28-0.75 (m, 8H, 4 × CH_2 of cyclopropanes), 0.90-1.18 (m, 2H, cyclopropyl methynes), 1.18 (s, 2H, CH_2 of tetrasubstituted cyclopropane), 3.69 (s, 6H, OCH_3) ppm.

Anal. Calcd. for $C_{13}H_{18}O_4$: C, 65.51; H,7.62; O, 27.87. Found: C, 65.39; H, 7.65; O, 27.95.

1,1-Dicyclopropyl-3,3-dimethoxycarbonylpropene (**2**) and 5,5-Dicyclopropyl-2-oxo-3-methoxycarbonyltetrahydrofuran (**3a**).

Compound **1** was dissolved in pentane-dichloromethane (3:1) and chromatographed through a column of Silica Gel Si-60 (70-230 mesh) (60 g). Elution with this mixture of solvents gave 1.58 g (oil) of material identified as compound **2**; ir (neat): 3070 (m), 3000 (s), 2940 (s), 1740 (s), 1650 (s), 1255 (s), 1150 (s) cm^{-1}; nmr: δ 0.35-0.70 (m, 8H, cyclopropane methylenes), 3.76 (s, 6H, CH_3O), 4.46 (d, 1H, J = 10 Hz, $CH(COOCH_3)_2$), 5.40 (d, 1H, J = 10 Hz, $HC\text{-}CH(COOCH_3)_2$) ppm.

Anal. Calcd. for $C_{13}H_{18}O_4$: C, 65.51; H, 7.62; O, 27.87. Found: C, 65.54; H, 7.60; O, 27.81.

Further elution with dichloromethane furnished 1.22 g of thick colorless oil corresponding to compound **3a**; ir (neat): 1770 (s), 1730 (s), 1200 (s), 1160 (s) cm^{-1}; nmr (carbon tetrachloride): δ 0.30-0.60 (m, 8H, cyclopropyl methylenes), 0.8-1.20 (m, 2H, cyclopropyl methynes), 2.30 (AB part of an ABM pattern, 2H, J_1 = 9.0, J_2 = 12 Hz, CH_2 of C-4), 3.30 (part M of an ABM pattern, 1H, $J_1 = J_2$ = 9.0 Hz, CH of C-3), 3.75 (s, 3H, $COOCH_3$) ppm.

Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.26; H, 7.20; O, 28.55. Found: C, 64.31; H,7.18; O, 28.53.

5,5-Dicyclopropyl-2-oxotetrahydro-3-furoic Acid (**3b**).

Compound **1** was heated at reflux temperature (1.6 g) in a 10% solution of potassium hydroxide in methanol-water (10:1) for an eight-hour period. Careful acidification (*p*H 2) of the cold reaction mixture (5°), extraction with ether, treatment with aqueous sodium bicarbonate, and evaporation of solvent gave a thick oil (1.45 g, 96%) that crystallized on standing, mp (pentane-methylene chloride) 66-67°; ir (potassium bromide): 3200 (broad, m), 1770 (broad, s); nmr: δ 0.30-0.70 (m, 8H, CH_2 of cyclopropanes), 0.85-1.30 (m, 2H, CH of cyclopropanes), 2.30 (AB part of an ABM system, 2H, J_1 = 9.0, J_2 = 13.5 Hz, CH_2 of C-4), 3.66 (M part of an ABM system, 1H, J = 9.0 Hz, CH at C-3) ppm.

Anal. Calcd. for $C_{11}H_{14}O_4$: C, 62.83; H, 6.72. Found: C, 62.83; H, 6.70.

2-Methyl-2-cyclopropyl-1,1-dimethoxycarbonylcyclopropane (**4**).

A solution of dimethyl diazomalonate (3.15 g, 20 mmoles) and 2-cyclopropylpropene (2.45 g, 30 mmoles) in dry benzene (40 ml) was added dropwise to a stirred refluxing suspension of bis(acetoacetonato)-copper(II) (160 mg) in benzene (2 ml) under a nitrogen atmosphere. Heating was continued for an additional 22 hour period after the addition was complete. The cold reaction mixture (5°) was then filtered through a pad of neutral alumina act III to remove the catalyst, solvents were evaporated and the residue distilled under vacuum to give the desired cyclopropane **4**, bp 77-78°/0.1 torr, yield, 3.57 g (84%); ir (neat): 2990 (s), 2940 (s), 1725 (s), 1425 (s), 1240 (s), 1110 (s), 875 (s) cm^{-1}; nmr: δ 0.1-0.6 (m, 4H, CH_2 of cyclopropyl substituent), 0.85-1.15 (m, 1H, CH), 1.06 (s, 2H, CH_2 of tetrasubstituted cyclopropane), 1.17 (s, 3H, CH_3-C), 3.53 and 3.56 (s, 3H each, $COOCH_3$) ppm.

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.23; H, 7.60; O, 30.16. Found: C, 62.19; H,7.61; O, 30.22.

5-Methyl-5-cyclopropyl-2-oxo-3-methoxycarbonyltetrahydrofuran (**5a**).

Compound **4** (1.8 g) was dissolved in chloroform (30 ml) and introduced in a chromatography column filled with silica gel Si-60 (70-230 mesh) (40 g) in chloroform, and it was allowed to stand at room temperature for a period of ten days. The material in the column was eluted with chloroform, solvents were evaporated and the residue (1.71 g) was chromatographed through a column of silica gel (25 g). Elution with benzene gave the starting material (95 mg, 5%) and further elution with benzene-chloroform 1:1 furnished pure compound **5a** (1.61 g, 95%) as a thick colorless oil; ir (neat): 1770 (s), 1730 (s), 1440 (s), 1260 (s), 1200 (s), 1150 (s), 1090 (m), 1020 (m) cm^{-1}; nmr: δ 0.30-0.60 (m, 4H, CH_2 of cyclopropyl substituent), 0.90-1.30 (m, 1H, CH of cyclopropane), 1.40 and 1.50 (2 × s, 3H, CH_3-C of *cis*- and *trans*-epimers), 2.49 (AB part of a ABM system, 2H, J_1 = 9.0, J_2 = 12.0 Hz, CH_2 of C-4), 3.83 (part M of an ABM system, 1H, J = 9.0 Hz, CH-COO), 3.83 (s, 3H, $COOCH_3$). ppm.

Anal. Calcd. for $C_{10}H_{14}O_4$: C, 60.58; H, 7.12; O, 32.30. Found: C, 60.63; H, 7.12; O, 32.36.

5-Methyl-5-cyclopropyl-2-oxotetrahydro-3-furoic Acid (**5b**).

Compound **4** was heated at reflux temperature (1.5 g) in a 20% solution of potassium hydroxide in methanol-water (10:1) for a twelve-hour period. The resulting white slurry was cooled to 5° and poured into a cold 5% aqueous solution of hydrochloric acid (200 ml) and extracted with ether. The organic layer was washed with a 3% solution of potassium bicarbonate and water, then dried over magnesium sulfate and evaporated to give the oily lactone carboxylic acid **3b**; ir (neat): 3450 (broad, s), 2950 (s), 1760 (broad, s), 1390 (s), 1225 (s), 1130 (s), 1020 (s), 950 (s), 930 (s) cm^{-1}; nmr: δ 0.40-0.70 (m, 4H, CH_2 of cyclopropane), 1.0-1.3 (m, 1H, CH of cyclopropane), 1.40 and 1.50 (2 × s, 3H, CH_3C of *cis*- and *trans*-epimers), 2.46 (AB part of an ABM system, J_1 = 9, J_2 = 13 Hz, CH_2 at C-4), 3.83 (part M of an ABM system, 1H, J = 9 Hz, CH-COO), 8.63 (s (broad)), 1H, COOH) ppm.

Anal. Calcd. for $C_9H_{12}O_4$: C, 58.67; H, 6.57; O, 34.76. Found: C, 58.59; H, 6.76; O, 35.11.

Z,E-2-Methyl-2-cyclopropyl-1-ethoxycarbonylcyclopropane (**7a**).

A solution of ethyl diazoacetate (2.5 g, 0.022 mole) and methylcyclopropylethylene (2.90 g, 0.035 mole) dissolved in dry benzene (35 ml) was added dropwise to a refluxing suspension of bis(acetoacetonato)-copper(II) (85 mg) in benzene (3 ml) under a nitrogen atmosphere. After the addition was complete, heating was continued for an additional 30 minute period. The cold reaction mixture was passed through a pad of neutral alumina act III and solvents were evaporated. The clear residue was distilled under vacuum to give pure compound **7a** as a colorless oil, bp 90° (bath)/0.25 torr, yield, 2.92 g (79%); ir (neat): 2970 (s), 1730 (s), 1310 (s), 1250 (s), 1160 (s), 1020 (s), 970 (s) cm^{-1}; nmr: δ 1.00 (s, 3H, CH_3-C of the *E*- epimer), 1.23 (s, 3H, CH_3-C of *Z*- epimer), 1.23 (t, 2H, J = 7.0 Hz, CH_3CH_2O), 4.03 (q, 2H, J = 7.0 Hz, CH_3CH_2O) ppm.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.38; H, 9.59; O, 19.03. Found: C, 71.27; H, 9.62; O, 19.11.

Acknowledgement.

The financial support of the Consejo Nacional de Investigaciones Científicas y Tecnológicas CONICIT of Venezuela is gratefully acknowledged.

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