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A New Cyclobutane Ring Contraction: the Base-Induced Rearrangement of an α-Bromocyclobutanecarboxylic Ester

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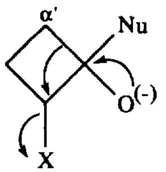
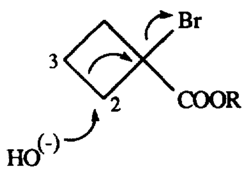
Abstract: Contrary to previous reports, reactions of methyl α-bromocyclobutanecarboxylate **6b** with potassium hydroxide or carbonate lead exclusively to 1-(hydroxymethyl)cyclopropanecarboxylic acid **7**.

The easy interconversions which occur among cyclobutane, cyclopropane and open-chain related frameworks have been extensively studied.[1] Thus the stereospecific rearrangement of α-halo- or α-tosyloxy cyclobutanones into cyclopropanecarboxylic acid derivatives, has been shown to involve addition of nucleophiles (*e.g.*, H_2O, EtOH, EtONa, NaOH, NH_3, $LiAlH_4$, CH_3MgI, ...) to the carbonyl carbon atom. Thus is produced the intermediary **1** which then undergo a concerted displacement of the halide (or tosyloxy) group X, concomitant with 1,2-migration of the Cα'-C carbonyl bond, *i.e.* following the mechanism of the so-called *semi-benzilic rearrangement*.[2]





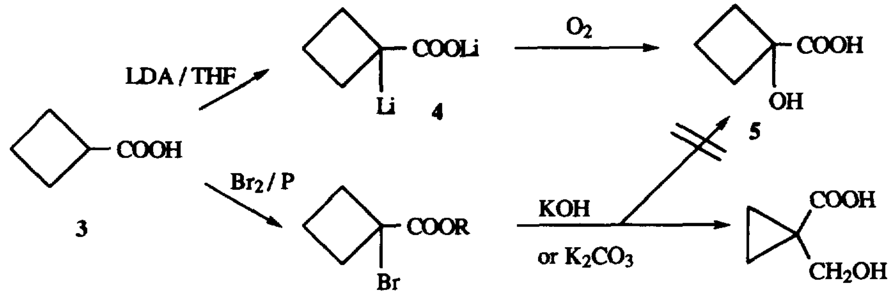
1 X = Cl, Br, TsO
Nu = HO, NH_2, RO, H, R

2

We report herein the unexpected but related ring contraction of an α-bromocyclobutanecarboxylic acid and ester, likely involving the intermediary **2**. For our current investigations we needed the 1-hydroxy cyclobutanecarboxylic acid **5** as starting material. Reported approaches to this required α-hydroxy acid involve either the acid-induced hydrolysis of cyclobutanone cyanohydrin,[3] the direct oxidation by oxygen of the enolate anion **4** derived from cyclobutanecarboxylic acid **3**[4] by treatment with 3 equiv. of lithium diisopropylamide,[5] or the bromination of **3** followed by reaction with aqueous potassium hydroxide [6] or aqueous potassium carbonate.[7]

Effectively, as reported, slow addition of 2 equiv. of bromine to acid **3**[4] in the presence of 10% of dry amorphous phosphorus, followed by heating at 90°C for 3 h, led after pouring the mixture into an excess of water or methanol, to α-bromocyclobutanecarboxylic acid **6a** (55%) or methyl ester **6b** (90%),[8] respectively. However, reactions of the bromoester **6b** either with refluxing aqueous potassium hydroxide or with potassium carbonate solutions do not lead, as previously claimed,[6,7] to the α-hydroxy acid **5**[3,4] but exclusively to the 1-(hydroxymethyl)cyclopropanecarboxylic acid **7**.[9]

Moreover, formation of **7** was also observed upon treatment of **6b** with a 0.1 M solution of KOH in water at room temperature: 18% after 3 hours and quantitatively within 18 hours, respectively. This β-hydroxyacid which constitutes an useful synthon, has been isolated in 95% yield after liquid chromatography; it was previously obtained in 43% yield from potassium permanganate partial oxidation of 1,1-bis(hydroxymethyl) cyclopropane.[10]



6a R = H (55%)
b Me (90%)

7 (95%)

Comparatively, solvolysis of **6b** in refluxing glacial acetic acid containing 1.1 equiv. of silver acetate was not so selective[1,2] and led to methyl 1-acetoxymethylcyclopropanecarboxylate (43%), besides 12% of a homoallylic isomer from ring opening.[11] Most probably the base induced ring contraction **6b** → **7** involves the intermediary **2**, which undergoes displacement of the bromine atom concerted with an 1,2-migration of the C_2-C_3 bond and nucleophilic substitution at C_2 either by a hydroxide or carbonate anion, or also likely intramolecularly by a carboxylate anion.

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8. B.p.: 74°C/17 mm ; IR ($CDCl_3$) : 3010, 2960, 2850, 1740 ($\nu_{C=O}$), 1440 cm^{-1} ; ^{1}H NMR (250 MHz, $CDCl_3$) δ : 1.80 - 1.92 (m, 1H) ; 2.18 - 2.23 (m, 1H), 2.25 - 2.67 (m, 2H), 2.84 - 2.96 (m, 2H), 3.79 (s, 3H) ; ^{13}C NMR (50 MHz) δ : 16.37, 36.93, 52.68, 53.68, 171.47 ; MS (CI, NH_3) (m/z) : 210 (M^++18, 86), 212 (M^++18, 76).
9. IR ($CDCl_3$) : 3600, 3000 and 1700 ($\nu_{C=O}$) cm^{-1} ; ^{1}H NMR (250 MHz, $CDCl_3$) δ : 0.96 (dd, J = 7.1 and 4.3 Hz, 2H) ; 1.35 (dd, J = 7.1 and 4.3 Hz), 3.64 (s, 2H), 5.10 (broad s, 2H) ; ^{13}C NMR (62.8 MHz) δ : 14.61, 25.47, 65.31, 180.35 ; MS (CI, NH_3) (m/z) : 134 (M^++18, 100).
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