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Reaction of ethyl 2,2-dimethoxycyclopropanecarboxylates with *m*-CPBA. Discovery of two new related degradative processes leading to β-hydroxyacid derivatives

Vincenzo Piccialli* and M. Liliana Graziano

Dipartimento di Chimica Organica e Biologica, Università degli Studi di Napoli 'Federico II', Via Mezzocannone 16, 80134 Napoli, Italy

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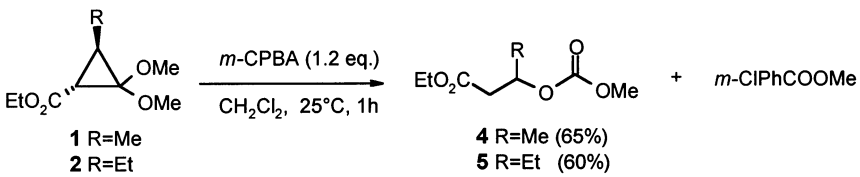
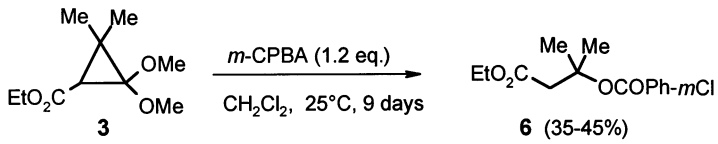
Abstract—The reaction of the 3-alkyl-substituted and 3,3-dialkyl-substituted ethyl 2,2-dimethoxycyclopropanecarboxylates **1**–**3** with *m*-CPBA in CH_2Cl_2 leads to the formation of the β-hydroxyacid derivatives **4**–**6** via two related processes involving the scission of both the C_1–C_2 and C_2–C_3 bonds and consequently to the degradation of the original cyclopropane carbon skeleton (extrusion of the C-2 carbon). *Cis*- and *trans*-2-ethoxycyclopropanecarboxylic acid ethyl esters **9** and **10**, respectively, structurally related to **1**–**3**, are unreactive under the same conditions. A hypothesis explaining the observed reactivity is formulated. © 2000 Published by Elsevier Science Ltd.

Vicinally substituted donor–acceptor cyclopropanes are versatile building blocks in organic synthesis since they are used for the preparation of many types of compounds.[1] We have recently undertaken a plan aimed at testing the reactivity of some of these substances, namely ethyl 2,2-dialkoxycyclopropanecarboxylates, under a variety of oxidising conditions. Previous investigations from our group have led to the finding that RuO_4[2] and $Pb(OAc)_4$[3] are able to oxidatively cleave the reactive C_1–C_2 bond. We now report that 3-alkyl-substituted and 3,3-dialkyl substituted 2,2-dimethoxycyclopropanecarboxylic acid ethyl esters, e.g. **1**–**3** (Schemes 1 and 2), react with *m*-CPBA[4] in CH_2Cl_2 to give the methyl carbonate derivatives **4** and **5** from **1** and **2**, respectively, and the *m*-chlorobenzoate derivative **6** from **3**, through related degradative processes. It is to be noted that the carbon skeleton of the reaction products corresponds to that of the original cyclopropane from which the C-2 carbon has been extruded and is, in the case of compounds **4** and **5**, the carbonyl carbon of the carbonate portion.



Scheme 1.



Scheme 2.

Keywords: *m*-CPBA; ethyl 2,2-dimethoxycyclopropanecarboxylates; methyl carbonates; β-hydroxyacid derivatives; degradative processes.
* Corresponding author. Tel.: 39-81-674111; fax: 39-81-674393; e-mail: vinpicci@unina.it

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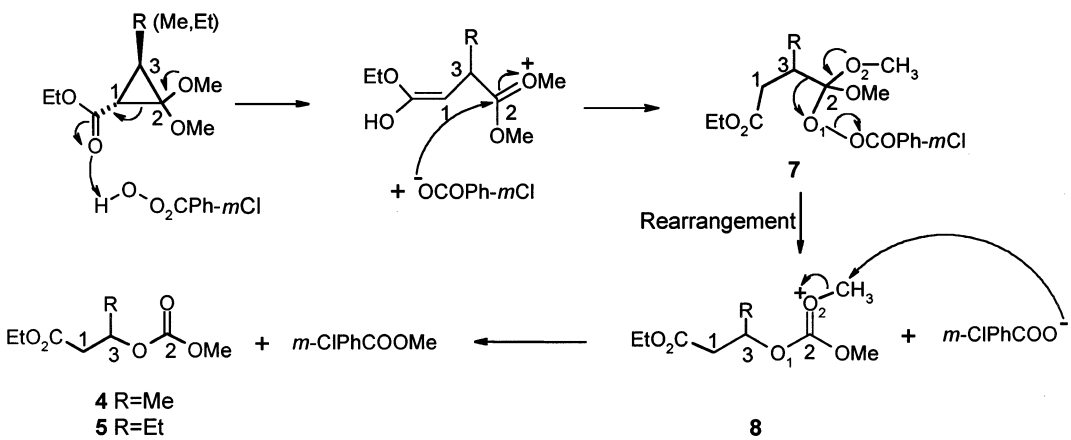
The reactions have been performed by adding the freshly prepared cyclopropane (typically 300 mg) to a solution of *m*-CPBA (1.2 equiv. desiccated overnight over P_2O_5) in anhydrous CH_2Cl_2 (1 mL) with stirring at room temperature. The reaction was complete within a 1 h period in the case of **1** and **2** (TLC monitoring) but required 9 days to proceed to completion for the less reactive cyclopropane **3**. Filtration of the reaction mixture through a short silica gel plug (eluent hexane/Et_2O, 95:5) followed by HPLC (hexane/EtOAc, 93:7) afforded pure samples of compounds **4**–**6**, as well as methyl *m*-chlorobenzoate from the oxidations of **1** and **2**. All the isolated substances gave satisfactory spectral data[5] in full agreement with the assigned structures. While the reaction of compounds **1** and **2** with *m*-CPBA was shown to be reproducible and rather clean, the oxidation of **3** always produces, in addition to the main product **6**, variable amounts of various side-products (unidentified). Worth mentioning, however, is that among these, after a careful HPLC separation of the reaction mixture, the carbonate derivative corresponding to compounds **4** and **5** could not be identified, although it would have been obtained if the oxidation path followed by **3** had been the same as that for **1** and **2**.

Definitive confirmation of the structures of diesters **4**–**6** was provided by synthesis. In particular, methyl carbonate **4** was obtained by borohydride reduction of ethyl acetoacetate ($NaBH_4$/EtOH, 25°C, 15 min, 80%) followed by treatment of the resulting ethyl 3-hydroxybutyrate with methyl chloroformate in pyridine (25°C, 10 min, 90%). Similarly, methyl carbonate **5** was synthesised by reaction of methyl chloroformate with ethyl 3-hydroxyvalerate in pyridine (25°C, 10 min, 95%); the latter compound was in turn obtained via a Reformatsky reaction of ethyl bromoacetate with propanal, as described.[6] *m*-Chlorobenzoate derivative **6** was synthesised by the reaction of *m*-chlorobenzoic acid chloride with ethyl 3-hydroxyisovalerate in pyridine (25°C, 24 h, 80%); ethyl 3-hydroxyisovalerate was in turn synthesised by Reformatsky reaction of ethyl bromoacetate with acetone.[6]

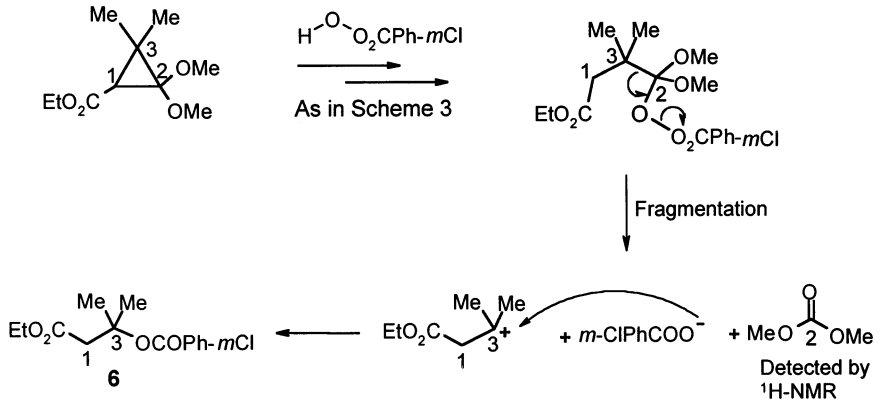
The formation of carbonates **4** and **5** can be explained through the sequence shown in Scheme 3. In the first step, the addition of the OH portion of the percarboxylic acid to the C_1–C_2 bond of the cyclopropane, in a manner similar to that observed for other nucleophilic species (H_2O, MeOH etc.), would generate intermediate **7**. This species could rearrange in such a way that the C_2–C_3 bond shifts from C-2 to O-1 with the simultaneous expulsion of the *m*-chlorobenzoate anion and formation of the stabilised C-2 cation species **8**. This latter would then collapse to the carbonate product via a S_N2 displacement at one of the two OMe groups by the attack of the released *m*-chlorobenzoate, with formation of methyl *m*-chlorobenzoate, a species in turn obtained from the oxidative process. The net result of the above route is that the C-2 carbon of the original cyclopropane ring becomes the carbonyl carbon of a carbonate function linked to the C-3 carbon of a β-hydroxyester derivative.

As for the formation of compound **6** from **3**, it is likely that an intermediate analogous to **7**, obtained as hypothesised above, could form in the first step through the addition of *m*-CPBA across the C_1–C_2 bond (Scheme 4). We reasoned that, at this stage, the presence of two methyl groups at C-3 could favour a fragmentation step that would occur with the expulsion of dimethylcarbonate (DMC) and the *m*-chlorobenzoate anion, as well as the formation of the C-3 tertiary carbocation. Recombination of the two produced ionic species would eventually give the diester product **6**.

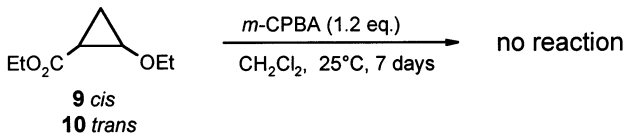
In order to gain evidence supporting the latter mechanistic hypothesis, the reaction of **3** with *m*-CPBA was performed in $CDCl_3$. The advancement of the process was monitored by periodically recording the proton spectrum of the reaction mixture. A singlet peak at δ 3.78 attributable to DMC began to be detectable after some 7 h. Unequivocal assignment of the above resonance to DMC was provided by addition of a trace amount of pure DMC to the reaction mixture that produced the enhancement of the sole peak at δ 3.78. At this time peaks diagnostic for diester **6** were also present.



Scheme 3.



Scheme 4.



Scheme 5.

For a comparative purpose, *cis*- and *trans*-2-ethoxycyclopropanecarboxylic acid ethyl esters (**9** and **10**, Scheme 5) were synthesised as reported[7] and subjected to the same oxidising conditions described above for **1**–**3**; they proved to be unreactive on prolonged treatment (7 days). This result shows that a single alkoxy group at C-2 is not sufficient to confer to the C_1–C_2 bond the electronic characteristics that render it reactive toward *m*-CPBA. Compounds **9** and **10** were also shown to be unreactive towards RuO_4 and $Pb(OAc)_4$ that, on the contrary, are able to cleave cyclopropanes **1**–**3**, as previously reported.[2,3]

As far as we know this is the first report of the *m*-CPBA-induced scission of cyclopropyl compounds.

Acknowledgements

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4. For general accounts on *m*-CPBA reactions, see: (a) *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Ed.; Vol. 7, pp. 357–372. (b) Paquette, L. *Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons: New York, Vol. 2, pp. 1192–1198.
5. Spectral data for compounds **4**–**6**. Compound **4**: FTIR (film) ν_{max} 1741 cm^{-1} (2×CO); ^1H NMR ($CDCl_3$, 200 MHz) δ 5.13 (1H, sextet, $J = 6.5$ Hz, H-3), 4.12 (2H, q, $J = 7.1$ Hz, OCH_2), 3.75 (3H, s, OMe), 2.69 (1H, dd, $J = 15.8$, 7.6 Hz, H_a-1), 2.48 (1H, dd, $J = 15.8$, 5.8 Hz, H_b-1), 1.33 (3H, d, $J = 6.3$ Hz, CH_3 linked at C-3), 1.23 (3H, t, $J = 7.1$ Hz, $OCH_2\underline{CH_3}$). Compound **5**: FTIR (film) ν_{max} 1752 cm^{-1} (2×CO); ^1H NMR ($CDCl_3$, 200 MHz) δ 5.02 (1H, broad quintet, $J = 5.6$ Hz, H-3), 4.12 (2H, q, $J = 6.9$ Hz, OCH_2), 3.75 (3H, s, OMe), 2.59 (2H, AB system further coupled; A part $J = 15.9$, 7.8 Hz, B part $J = 15.9$, 5.3 Hz, H_2-1), 1.68 (2H, quintet, $J = 7.5$ Hz, methylene protons of the Et linked at C-3), 1.22 (3H, t, $J = 6.9$ Hz, $OCH_2\underline{CH_3}$), 0.93 (3H, t, $J = 7.5$ Hz, methyl protons of the Et linked at C-3). Compound **6**: FTIR (film) ν_{max} 1735 cm^{-1} (CO); ^1H NMR ($CDCl_3$, 200 MHz) δ 7.95 (1H, bt, $J = 1.6$ Hz, H-2 of the aromatic ring), 7.88 (1H, dt, $J = 8.0$, 1.6, 1.6 Hz, H-4 or H-6 of the aromatic ring), 7.50 (1H, dt, $J = 8.0$, 1.6, 1.6 Hz, H-6 or H-4 of the aromatic ring), 7.35 (1H, dd, $J = 8.0$, 8.0 Hz, H-5 of the aromatic ring), 4.11 (2H, q, $J = 7.3$ Hz, OCH_2), 2.97 (2H, s, H_2-1), 1.69 (6H, s, 2× CH_3 linked at C-3), 1.18 (3H, t, $J = 7.0$ Hz, $OCH_2\underline{CH_3}$).
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