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Bromination and iodination of donor–acceptor cyclopropanes. Evidence for an ET mechanism

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Abstract—Ethyl 2,2-dimethoxycyclopropanecarboxylates **1a–d** react easily with Br_2 and I_2 in CCl_4 or CH_2Cl_2 leading, in high yields, to 1-ethyl-4-methyl 2-halobutanedioates **2** and **3**, respectively. Bromination in the presence of pyridine, NBS, trimethyl phosphate, and iodination with ICl and ICl/pyridine has been also performed. A common SET mechanism may be proposed for both halogenations; depending on the reaction conditions, bromination can also occur via acid-catalysed or S_E2 routes. The reaction of the 2-ethoxyanalogues *cis*-**12** and *trans*-**12** with the same halogens proceeds in a similar manner, giving 3-formyl-2-haloesters along with the corresponding diethylacetals as main products. Iodination of **12** with the catalytic system NaI/*m*-CPBA/18-crown-6 has also been investigated.

Vicinally substituted donor–acceptor cyclopropanes are versatile building blocks in organic synthesis.[1] Our group has long been involved in the study of the reactivity of ethyl 2,2-dimethoxycyclopropanecarboxylates. In particular, we have recently shown that these compounds react easily with saturated electrophiles such as sulfenyl[2a] and benzeneselenenyl[2b] chlorides and with oxidising reagents such as RuO_4,[3a] $Pb(OAc)_4$,[3b] and *m*-CPBA,[3c] leading to synthetically useful compounds via regioselective ring-opening at the C1–C2 bond.

We now report that ethyl 2,2-dimethoxycyclopropanecarboxylates **1a–d**, and structurally related ethyl 2-ethoxyanalogues *cis*- and *trans*-**12**, react easily with Br_2 and I_2 leading, via scission of the reactive C_1–C_2 bond, to haloderivatives, generally in good yields.

In a typical experiment, to the cyclopropane (2.5 mmol) dissolved in CCl_4 or CH_2Cl_2 (1 mL) was added Br_2 (2.5 mmol) or a solution of I_2 dissolved in the same solvent. The reaction was complete within a few minutes with disappearance of the halogen colour. Removal of the solvent followed by HPLC (hexane/EtOAc, 96:4) gave pure reaction products.[4]

Scheme 1 depicts the results for cyclopropanes **1a–d**. As shown, C-2 bromosuccinates **2** and C-2 iodoanalogues **3** were the only reaction products except for the bromination of unsubstituted cyclopropane **1a** which also led to the isomeric C-3 bromocompound **4** and, in a minor amount, to the C-2,C-3-dibromoderivative **5**. Note that almost equimolecular amounts of *syn*- and *anti*-**2b**,**c** and **3b**,**c** were formed in the reactions of C-3 monoalkylated cyclopropanes **1b** and **1c**.

Since both isomers within the diastereomeric pairs **2b**, **2c**, **3b**, and **3c** exhibited the same value of the vicinal coupling constant, assignment of the configuration of compounds composing each pair was carried out on the basis of the straightforward comparison of ^1H NMR spectral data with those exhibited by the corresponding thio- and seleno-analogues.[2] In particular, as reported for the latter,[2] the *syn*-isomers all show the singlet resonance due to CO_2Me upshifted by about 0.05 ppm compared with that for the corresponding *anti*-isomers. The configuration of compounds composing the pair **2b** was also chemically confirmed by stereoselective conversion of *syn*- and *anti*-**2b** into *anti*- and *syn*-1-ethyl 4-methyl 2-phenylsulphenylbutandioate,[2a] respectively, via the well-known[5] S_N2 reaction with PhSNa in dioxane.

The results obtained for **1a–d** might be explained in terms of the two classical competitive corner and edge attacks of an electrophile at the cyclopropane ring as shown in Scheme 2 for *trans*-**1b**,**c**.[6] The S_E2 corner

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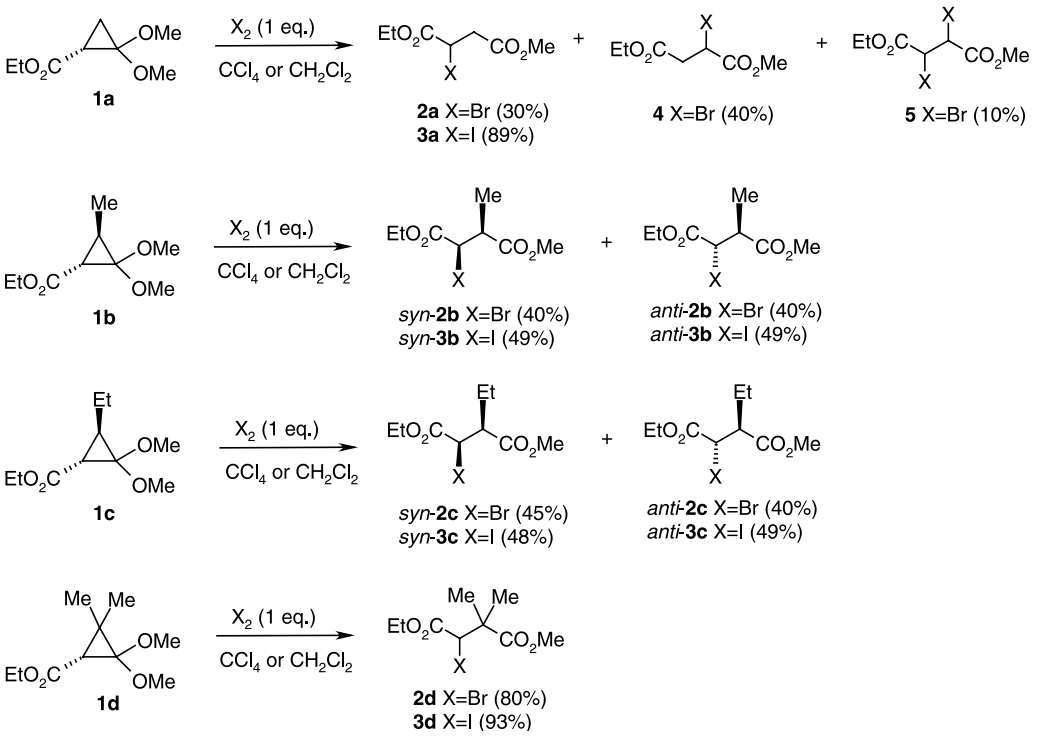
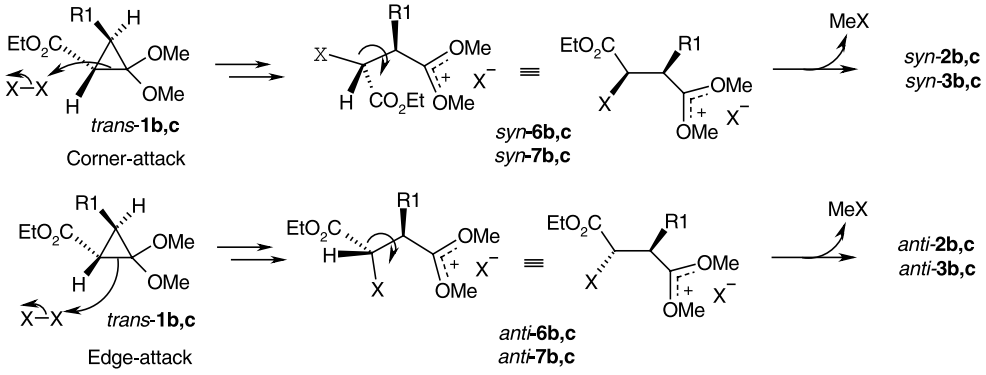


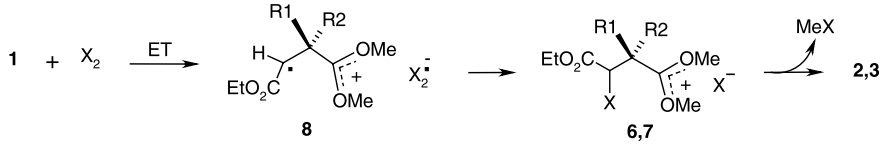
Scheme 1.



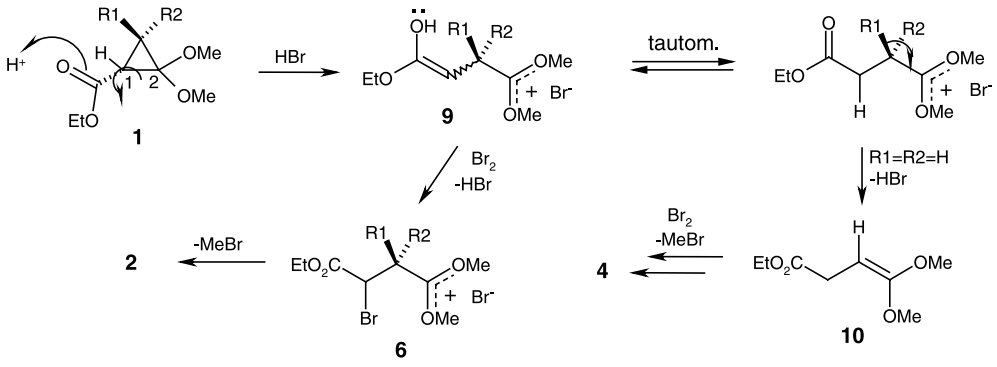
Scheme 2.

attack gives inversion of configuration at the C-1 centre, delivering the *syn*-isomer, while the edge mode proceeds with retention at C-1 and formation of the *anti* isomer, via the stabilised cations **6** and **7**.

The obtention of almost equal amounts of the *syn*- and *anti*-**2b**,**c** and **3b**,**c** could be explained assuming that both above routes are operating with a very similar rate. Though in principle possible, this seems to be, however, not plausible in that for cyclopropanes **1a**–**d** the corner attack is generally predominant,[2] and the direct attack of the halogen, especially of iodine, should be subject to steric hindrance. An electron transfer (ET) mechanism appears to be more plausible. In particular, as depicted in Scheme 3, the transfer of an electron from the C1–C2 bond of the cyclopropane to the halogen would generate the well-stabilised cation radical **8.** The radical centre, that is likely to be planar,[7] would undergo halogenation from both sides of the plane, leading to an equimolecular mixture of the C-2



Scheme 3.



Scheme 4.

diastereomeric compounds **2** or **3** via **6**, **7**. It is to be noted that I_2 and mixed halogens such as ICl, may iodinate activated aromatic compounds via an ET mechanism,[8] and that similar routes have been proposed in the bromination of some bicyclobutanes[9a] and bicyclohexane[9b] derivatives. Moreover, donor-substituted cyclopropanes can give radical cations.[10]

The presence of HBr in Br_2 could, however, promote a competitive mechanism for bromination, as shown in Scheme 4. Thus, compounds **2** would be formed via the acid-catalysed ring opening to the enols **9** followed by bromine addition on both faces of the double bond and MeBr loss. This route also explains the obtention of almost equimolecular amount of *syn*- and *anti*-isomers **2b**,**c**. Support for this path is provided by formation of **4** which should originate from bromine addition to the alkene **10** in turn derived from the easy acid-catalysed isomerisation[2] of **1a**, as shown in Scheme 4.

In order to gain further insight into the mechanism of the above processes, the halogenation of **1a**–**d** was carried out under different conditions. Table 1 lists the results obtained for cyclopropane **1b**. As shown, iodination with ICl alone or in the presence of pyridine (entries 7 and 8), able to trap possible acid traces, gave results similar to those obtained with I_2. On the other hand, also bromination with Br_2 in trimethyl phosphate (HBr-free bromine)[11] (entry 5) afforded the same results obtained with Br_2. These evidence confirm that indeed an ET mechanism could be operating for both processes (Scheme 3). In contrast, the ratio of the diastereomers dramatically changes from 1/1 to 5/1 or 6/1 using Br_2 in the presence of pyridine or NBS, respectively, (entries 2 and 3). Besides the HBr-trapping ability, these additives are able, particularly pyridine, to generate complexes with Br_2 which are considered the effective brominating agents.[12] Due to their reduced redox potential, it is difficult for these complexes to undergo ET reactions. Therefore, a direct ring attack of these complexes would occur in a manner similar to that shown in Scheme 2, with a preference for the corner mode, which leads to *syn*-**2b**. Control experiments showed that the same result was obtained by using the preformed complex pyridine–bromine (i.e. pyridinium perbromide).[13] Finally, the presence of 2,4,6-tri-*tert*-butylphenol (TTBP) (entry 4), a free radical inhibitor,[14] did not affect the course of the bromination, suggesting no radical involvement.

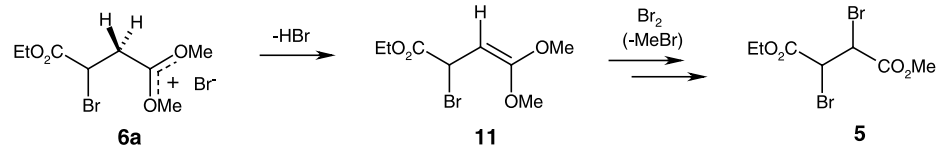
The same trend was observed for *trans*-**1c**. Interestingly, the unsubstituted cyclopropane **1a** did not afford the C-3 bromoderivative **4** under all three HBr-free conditions, confirming the role of the acid catalysis in its formation. Compound **5**, instead, was obtained under all the brominating conditions. Its formation can be rationalised assuming bromine addition to the alkene **11** (Scheme 5) formed through HBr loss from **6a**, an intermediate species common to all the proposed mechanistic routes.

Bromination and iodination of related ethyl 2-ethoxycyclopropanecarboxylates *cis*- and *trans*-**12** (Scheme 6) led to mixtures of the 3-formyl-2-haloesters **13** and the diethylacetals **14** in addition to variable amounts of the conjugated product **15** (50–60% total yield).[4] The latter likely derives from **13** by HX loss occurring during the process or subsequent work-up. Mass balance for this reaction indicated a loss of material. Attempts to optimise the process by varying the halogen concentration or using other solvents gave scarcely significative results. On the assumption that the loss of material could be due to the volatility of the products, a less volatile derivative of *cis*-**12** was synthesised from it by

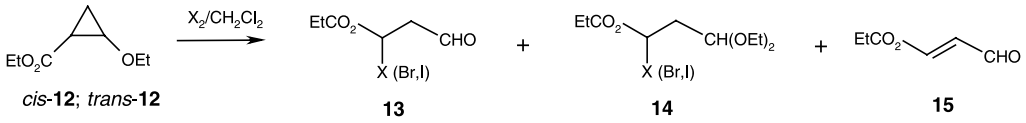
Table 1. Reactions of cyclopropane **1b** under different halogenating conditions

Entry	Condition[a]	Solvent[b]	Product (%)[c]	*syn*/*anti*[d]
1	Br_2	CCl_4	**2b** (80)	1/1
2	Py-Br_2[e]	CH_2Cl_2	**2b** (80)	5/1
3	NBS-Br_2[e]	CH_2Cl_2	**2b** (90)	6/1
4	Br_2-TTBP[f]	CCl_4	**2b** (78)	1/1
5	HBr-free Br_2[g]	CCl_4	**2b** (70)	1/1
6	I_2	CH_2Cl_2	**3b** (98)	1/1
7	ICl	CH_2Cl_2	**3b** (94)	1/1
8	Py-ICl[e]	CH_2Cl_2	**3b** (93)	1/1

[a] Equimolecular amount of halogenating agent.
[b] 0.2 M solution except for entry 6 (0.02 M).
[c] Isolated (HPLC) yield.
[d] Evaluated by ^1H NMR.
[e] **1b**:Py (or NBS) = 1:1.
[f] **1b**:TTBP = 3:1.
[g] 1 M solution of Br_2 in trimethyl phosphate.



Scheme 5.



Scheme 6.

alkaline hydrolysis (K_2CO_3/MeOH–H_2O (95:5), reflux, 48 h) followed by esterification with tetradecanol (1 equiv.) in the presence of $DMAP_{(cat.)}$/DCC (1.2 equiv.) in CH_2Cl_2. Unfortunately, halogenation of this substance also gave only a slightly higher mass recovery. Finally, iodination of *cis*-**12** was carried out using the catalytic system NaI (5 equiv.)/*m*-CPBA (2 equiv.)/18-crown-6 (0.1 equiv.) in CH_2Cl_2 at rt. Only a modest 5–10% higher mass recovery was obtained in this case as well, while yields for **13** and **14** appeared to be essentially unaffected.

It is likely that routes similar to those invoked for compounds **1a**–**d** could be involved in the formation of halocompounds **13** while it remains an intriguing question how could the acetal species **14** be formed. The presence of two OEt goups at C-3 (acetal function) suggests that two molecules of cyclopropane are required for each molecule of **14** to be formed but how incorporation of the second OEt group in the acetal function could occur is still unclear.

In conclusion, the uncatalysed ring-opening of donor–acceptor cyclopropanes by halogens proceeds at the C1–C2 bond regio- but not stereoselectively; however, the stereochemical course of bromination can be addressed under suitable conditions. The reaction products appear to be prone to further synthetic manipulations that would deserve further attention. It is to be noted that continuous attention is devoted to bromination of cyclopropanes;[15] while, on the contrary, iodination has been performed in very few cases and in the presence of catalysts,[16a] and has generally been limited to derivatives where the cyclopropane ring is part of a highly strained molecular framework.[16b]

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