Ring-opening reactions of cyclopropanes. Part 8.[1] Nitrosation of donor–acceptor cyclopropanes

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The reaction of 2,2-dialkoxycyclopropane-1-carboxylates **1a–d** and monoalkoxycyclopropane **1e** with NOCl gives isoxazoline- and/or isoxazole-3-carboxylates by regioselective ring-opening at C1–C2 bond. A mechanistic interpretation suggests the intermediacy of well-stabilised dipolar species.

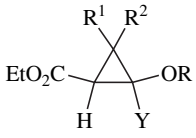
Keywords: donor–acceptor cyclopropanes, nitrosation, isoxazolines, isoxazoles, regioselectivity

Reactivity of vicinally donor-acceptor substituted cyclopropanes is strongly affected by the presence of the activating groups so that they are easily susceptible to heterolytic ring cleavage because of substituent effect to form zwitterionic intermediates.[2] In particular, alkyl 2,2-dialkoxycyclopropane-1-carboxylates, *e.g.* **1a–d** (Fig. 1), undergo regioselective ring-opening at the C1–C2 bond by various unsaturated electrophiles and participate as three-carbon units into [3+2]-type reactions for syntheses of interesting carbo- and heterocycles.[3,4] They also react with saturated reagents as selenenyl compounds[1] or sulfides[5a] or halogens[5b] as well as with oxidants as RuO_4[6a], $Pb(OAc)_4$[6b] and *m*-CPBA[6c]. Activation works also for 2-monoalkoxycyclopropane **1e,** even to a minor extent, and regioselective C1–C2 ring opening has been recently observed in the reaction with halides.[5b] In all the cases, ring-openings start with the attack of the electrophile at C1 with formation of well-stabilised ionic intermediates. Continuing our investigation on the chemistry of activated cyclopropanes **1,** we have now examined the reaction with nitrosyl reagents NOX (X= Cl, BF_4). So far data on cyclopropane nitrosation deal with the reaction of aryl-[7] or *N*-arylsubstituted[8] or halogenated[9] cyclopropanes with $NOBF_4$[7a,9] or with $NaNO_2/CF_3COOH$[7b] or $NaNO_2$ /CH_3COOH[8]. Gaseous NO has also been used in a 9,10-dicyanoanthracene-sensitised photoreaction.[10]

Results and discussion

In a typical experiment, NOCl was bubbled for 30 min into a CCl_4 solution of the cyclopropane kept at –20 °C under strictly anhydrous conditions.[11] The mixture was then allowed to stand at room temperature until compound **1** disappearance (^{1}H NMR). After solvent removal, reaction products were isolated by silica gel chromatography of the residue.

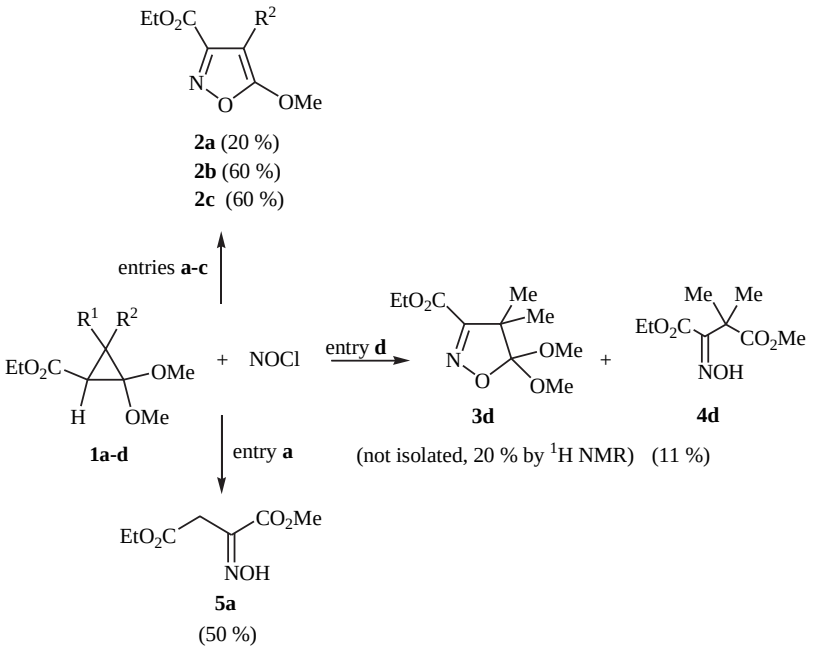
Dialkoxyderivatives **1a–d** reacted within 30–240 min and gave the products reported in Scheme 1. Isoxazoles **2a–c**



1

	Y	R	R^1	R^2
a	OMe	Me	H	H
b	OMe	Me	H	Me
c	OMe	Me	H	Et
d	OMe	Me	Me	Me
e	H	Et	H	H

Fig. 1



2a (20 %)
2b (60 %)
2c (60 %)

entries **a-c**

1a-d

+ NOCl

entry **d**

3d (not isolated, 20 % by ^{1}H NMR)

+

4d (11 %)

entry **a**

5a (50 %)

Scheme 1 Solvent: CCl_4; reaction times: 60 min for **a**, 40 min for **b**, 30 min for **c**, 240 min for **d**.

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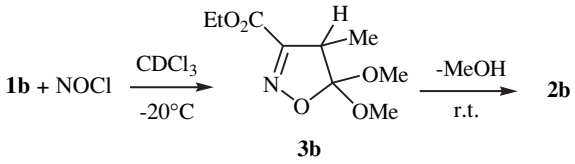
were obtained from the derivatives **1a–c** and were isolated in 20–60% yields and fully characterised (Scheme 1). In particular, the ^{13}C spectrum showed a singlet in the typical δ range 156–157 due to the quaternary carbon of C=N group while in the proton spectrum the singlet due to the OMe linked to an aromatic system appeared in the δ region 4.0–4.2. Moreover, structures of **2a**[12] and **2b**[13] were confirmed by comparing the physical and ^1H NMR data, respectively, with those reported in the literature. A complex mixture of products was obtained from C3-disubstituted derivative **1d** which reacted within 240 min.[14] Careful NMR analysis showed the presence, among the others, of transient signals (*ca* 20%) which could be attributed to the isoxazoline **3d** by comparing them with those of **3b** (see below). By chromatography the only identifiable product was the oxime **4d**. (Scheme 1). Control experiments showed that, when the reaction of **1b**, chosen as representative, was performed at –20 °C using $CDCl_3$ as solvent, the NMR spectrum of the mixture recorded at this temperature showed the presence of the isoxazoline **3b** which was carefully characterised (Scheme 2). In addition to the singlet at δ 157.0 due to the C=N carbon, the ^{13}C spectrum exhibited a singlet at δ 125.6 attributable to the quaternary carbon of the orthoester function which was confirmed by the presence in the proton spectrum of the singlets at δ 3.35 and 3.47 of the two 5-OMe. Upon warming to room temperature isoxazoline **3b** converted to the isoxazole **2b** and MeOH (by ^1HNMR).

In the reaction of **1a** oxime **5a** was also found in addition to **3a** (Scheme 1). Control experiments showed that this oxime was formed by nitrosation of the alkene **6a** (Scheme 3)**,** deriving from isomerisation of **1a** (see below). **5a** structure was also confirmed by converting the product to the isoxazolone **7** (Scheme 3)**.**

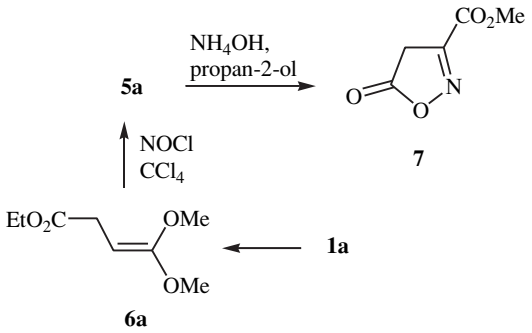
According to the previous data,[1-6] the results clearly indicate that compounds **1a–d** undergo the attack of the electrophile NO^+ at C1 with the regioselective breakage of C1–C2 bond and formation of the stabilised cations **8a–d** (Scheme 4). The latter by intramolecular ring closure lead, by loss of HCl, to the isoxazolines **3** which for entries **a–c** rapidly aromatise into the corresponding isoxazoles **2a–c** due to the acid conditions.[15] The derivative **3d** which cannot aromatise partly decomposes partly converts to oxime **4d**. The presence of HCl should be responsible for the isomerisation of cyclopropane **1a** to the alkene **6a**. Indeed, it is known that 2,2-dialkoxycyclopropane-1-carboxylates, especially those 3-unsubstituted, may rearrange thermally or under acid conditions into open-chain compounds as **6a**, and the addition to the alkene often competes with that to the parent cyclopropane.[1,2,5] The addition of NOCl to the double bond of the alkene **6a** leads to the oxime **5a** probably through the well-stabilised species **9a** which differently from the intermediate **8a** cannot rearrange to a cyclic structure and, hence, leads, via a S_N2 type displacement,[16] to the oxime **5a** and MeCl (Scheme 4).

The reaction of both *cis*- and *trans*-**1e**, conducted as above for **1a–d,** required a longer time (20 h) as expected due to the lower activation of one alkoxy group. As shown in Scheme 5, it led to compound **3e** and also to **10e** and **11e** (< 50% total yield).[17] It is likely that the intermediate cation **8**e, besides cyclising to isoxazoline **3e**, leads, via a carbonyl intermediate **12e**, to hydroxyisoxazoline **10e** and, via loss of HNO, to the unsaturated aldehyde **11e** (Scheme 6).

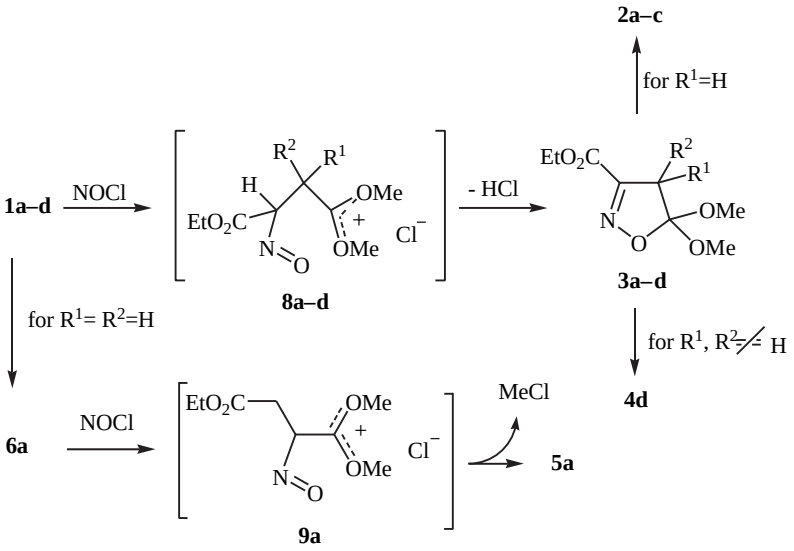
Due to its high hygroscopic property, $NOBF_4$ cannot be employed as nitrosating agent with cyclopropanes **1a–d** since the reaction led, after the work-up, to the corresponding open compounds.[11] The reaction was successful with more stable cyclopropane **1e** which gave the isoxazole **13e** in 48%, (Scheme 7), likely due to the strong acid conditions. It is significant that just this compound was found when either



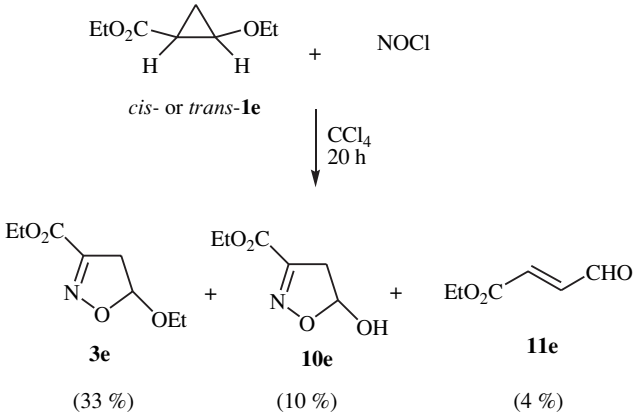
Scheme 2



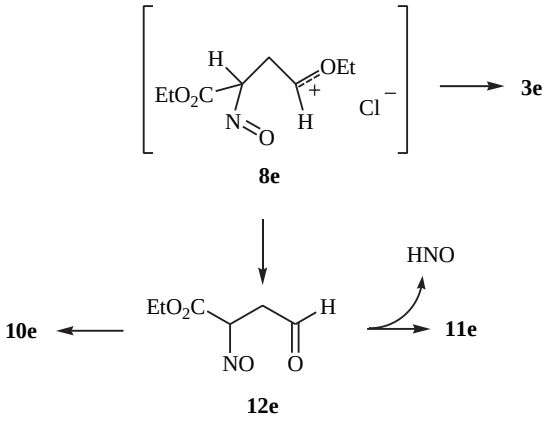
Scheme 3



Scheme 4



Scheme 5



Scheme 6

isoxazoline **3e** or **10e** were treated with $NOBF_4$ in the same manner as **1e**.

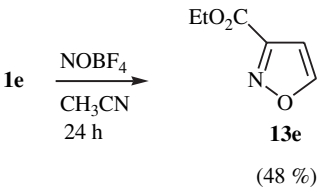
In conclusion, the work represents a further contribution to the chemistry of cyclopropane systems and confirms the tendency of activated derivatives as **1** to undergo regioselective ring-opening at C1–C2 bond under mild conditions due to the push–pull combination of the *gem*-dialkoxy (or alkoxy) and alkoxycarbonyl groups. In this context, it is to be noted that methyl cyclopropanecarboxylate (commercially available) which has not got this substituent pattern was recovered unchanged by prolonged treatment (even after 48 h) either with NOCl or $NOBF_4$ under the same conditions as used for **1**.

Due to the efficient and very flexible method to construct cyclopropanes such as **1**,[18] the obtaining, although in moderate yields, of isoxazole-3-carboxylates **3a**–**c** and **13e** through the suitable choice of the nitrosating agent represents a further simple entry to functionalised isoxazoles. This heterocyclic system is of particular interest due to the biological activity of diverse derivatives.[19] In addition to the classical 1,3-dipolar cycloaddition of nitrile oxides to alkynes,[20] compounds as **3** or **13** have been prepared occasionally[13] or by patent pathways.[12,21]

Experimental

General procedures

IR spectra were recorded on a Perkin Elmer 1760/X-FT spectrophotometer using $CHCl_3$ as solvent. ^1H and ^{13}C NMR spectra were recorded with a Varian (INOVA) 500 MHz spectrometer using $CDCl_3$ as solvent and Me_4Si as internal standard. *J* values are given in Hz. DEPT techniques were employed to determine the multiplicity in the ^{13}C NMR spectra. Low-resolution electron–impact mass spectra were obtained operating at 70 eV on a GCMS-QP5050A (Shimadzu). CCl_4 and CH_3CN used in the reactions were anhydrous. Silica gel [0.063-0.20 mm (Macherey-Nagel)] and light petroleum (b.p. 40–60 °C) were used for column chromatography. Cyclopropanes **1a**[11a], *trans*-**1b**[11a], *trans*-**1c**,[11b] **1d**[11a], *cis*- and *trans*-**1e**[22] were prepared according to literature methods[18] using copper(II) acetylacetonate as catalyst. Alkene **6a** was prepared by heating the cyclopropane **1a** in a sealed ampoule at 130 °C for 4 h.[11a] NOCl was prepared by passing hydrochloric acid into sodium nitrite according to the literature procedure,[23] and was bubbled under flow of N_2 into the solution to be treated after passing the gases through three drying tubes containing sodium nitrite (to absorb hydrogen chloride), potassium chloride (to absorb nitrogen dioxide) and anhydrous calcium chloride. $NOBF_4$ (Fluka) was recrystallised from acetonitrile at –20 °C , followed by filtration in a dry box and vacuum drying (caution: very hygroscopic, after opening must be stored over P_4O_{10}). Caution: all the operations with either NOCl or $NOBF_4$ are to be performed in a hood.



Scheme 7

Nitrosation of cyclopropanes **1a–d**; *General procedure*

The reactions were carried out by bubbling NOCl and N_2 into 0.1M solutions of cyclopropanes **1a–d** in dry CCl_4 at –20 °C. The gases were dried passing through drying tubes filled with anhydrous calcium chloride. After 30 min, the flow was stopped and the brownish-red solutions were kept at room temperature until the disappearance of the cyclopropane. The completion of the reaction was confirmed by ^1H NMR analysis of a sample of the tetrachloride solution, recorded in $CDCl_3$. Then, the solvent was removed under reduced pressure and the residue chromatographed on silica gel. All products were fully characterised by spectral means. Known compounds were identified by comparing the physical data with those reported in the literature; unpublished spectral data have been described.

The reaction of **1a** was complete within 60 min. Chromatography using light petroleum/Et_2O (9:1) and Et_2O gave compounds **2a** (20%) and oxime **5a** (50%), respectively.

Ethyl 5-methoxyisoxazole-3-carboxylate (**2a**): M.p. 46–48 °**C** [m.p. 45–47 °C][12]; IR ($CHCl_3$): ν (cm^{-1}) 1734,1609; ^1H NMR ($CDCl_3$): δ 1.40 (t, *J* = 7.0, 3H, CH_3), 4.03 (s, 3H, OCH_3), 4.42 (q, *J* = 7.0, 2H, OCH_2), 5.65 (s, 1H, CH); ^{13}C NMR ($CDCl_3$) δ 14.1 (q), 59.2 (q), 62.1 (t), 78.1 (d), 157.9 (s) 159.9 (s), 175.1 (s);

4-Ethyl 1-methyl 2-(hydroxyimino)butanedioate (**5a**): Oil; IR ($CHCl_3$): ν (cm^{-1}) 3556, 3226,1735,1571; ^1H NMR ($CDCl_3$): δ 1.19 (t, *J* = 7.2, 3H, CH_3,), 3.68 (s, 2H, CH_2), 3.86 (s, 3H, OCH_3), 4.18 (q, *J* = 7.2, 2H, OCH_2), 11.1 (s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ: 13.9 (q), 30.3 (t), 52.8 (q), 61.3 (t), 145.7 (s), 163.4 (s), 168.1 (s). Anal. calcd for $C_7H_{11}NO_5$ (189.17): C, 44.44; H, 5.86; N, 7.41. Found C, 44.30; H, 5.73; N, 7.27 %.

The reaction of cyclopropane *trans*-**1b** was complete within 40 min and led by chromatography (light petroleum/Et_2O (9:1) as eluent) to *ethyl 5-methoxy-4-methylisoxazole-3-carboxylate*-**2b** as viscous oil (m.p. 8 °C)[13] in 60 % yield: ^{13}C NMR ($CDCl_3$): δ 5.8 (q), 14.1 (q), 58.3 (q), 61.7 (t), 90.0 (s), 156.7 (s), 160.7 (s), 170.5 (s).

The reaction of cyclopropane *trans*-**1c** was complete within 30 min and led by chromatography [light petroleum/Et_2O (9:1) as eluent] to *ethyl 4-ethyl-5-methoxyisoxazole-3-carboxylate*-**2c** as oil in 60 % yield: IR ($CHCl_3$): ν (cm^{-1}) 1736, 1637; ^1H NMR ($CDCl_3$): δ 1.12 (t, *J* = 7.5, 3H, CH_2CH_3), 1.42 (t, *J* = 7.0, 3H, OCH_2CH_3), 2.49 (q, *J* = 7.5, 2H, CH_2), 4.14 (s, 3H, OCH_3), 4.42 (q, *J* = 7.0, 2H, OCH_2); ^{13}C NMR ($CDCl_3$): δ 14.0 (q), 14.1 (q), 14.3 (t), 58.3 (q), 61.7 (t), 96.2 (s), 156.4 (s), 160.6 (s), 170.4 (s). Anal. calcd for $C_9H_{13}NO_4$ (199.20): C, 54.26; H, 6.58; N, 7.03. Found C, 51.21; H, 6.98; N, 7.52 %.

The reaction of **1d** was complete within 240 min. The residue, analysed by ^1H NMR, showed the presence of a complex mixture of products among which an unstable compound was present. Over time the signals of this product decreased while those of other products increased, and, after 1 h, only the latter were present. To this intermediate we tentatively assigned the structure **3d** by comparing the value of the MeO singlet at δ 3.43 (6H) with those of **3b** (see below). The yield of isoxazoline **3d** was deduced by a careful analysis of the reaction mixture by integrating the methoxy singlet at δ 3.43

(6H) respect to the OCH_2 signals for all mixture products (δ range 4.18–4.30). Chromatography of the mixture, eluting with Et_2O, gave the oxime **4d** (11%) as the only identified product.

Ethyl5,5-dimethoxy-4,4-dimethyl-4,5-dihydroisoxazole-3-carboxylate (**3d**): ^{1}H NMR (selected signals) ($CDCl_3$): δ 3.43 (s, 6H, 2 OMe), 4.21 (q, *J* = 7.0, 2H, OCH_2). Missing signals overlap with those of the other products of the mixture.

4-Ethyl 1-methyl 3-(hydroxyimino)-2,2-dimethylbutanedioate (**4d**): Oil; IR ($CHCl_3$): ν (cm^{-1}) 3409, 1739, 1684; ^{1}H NMR ($CDCl_3$): δ 1.27 (s) and 1.30 (t, *J* = 7.1) (together 9H, 3 CH_3), 3.74 (s, 3H, OCH_3), 4.25 (q, *J* = 7.1, 2H, OCH_2), 7.51 (brs, 1H, OH); ^{13}C NMR ($CDCl_3$): δ 13.9 (q), 22.1 (q), 47.8 (s), 53.0 (q), 63.0 (t), 168.4 (s), 169.6 (s), 175.0 (s). Anal. calcd for $C_9H_{15}NO_5$ (217.22): C, 49.76; H, 6.96; N, 6.45. Found C, 49.82; H, 6.92; N, 6.38 %.

Ethyl 5,5-dimethoxy-4-methyl-4,5-dihydroisoxazole-3-carboxylate (**3b**): The reaction of **1b** was carried out at –20 °C as above using $CDCl_3$ as solvent. After completion of the reaction, ^{1}H NMR analysis of the mixture performed at this temperature showed the presence of **3b:** ^{1}H NMR ($CDCl_3$): δ 1.20 (d, *J* = 7.2, 3H, $CHCH_3$), 1.37 (t, *J* = 7.0, 3H, OCH_2CH_3), 3.35 (s) and 3.36 (q, *J* = 7.2) (together 4H, OCH_3 and CH), 3.47 (s, 3H, OCH_3), 4.34 (q, *J* = 7.0, 2H, OCH_2); ^{13}C NMR ($CDCl_3$): δ 10.9 (q), 13.8 (q), 43.3 (d), 50.4 (q), 52.0 (q), 62.1 (t), 125.6 (s), 157.0 (s), 159.6 (s).

Upon warming to room temperature the signals of **3b** disappeared while those of **2b** and MeOH appeared.

Nitrosation of alkene (**6a**): The reaction of the alkene **6a** with NOCl was carried out and monitored as above reported for **1a**. After 60 min, the ^{1}H NMR spectrum showed the presence of only oxime **5a**.

Methyl 5-oxo-4,5-dihydroisoxazole-3-carboxylate (**7**): To a solution of oxime **5a** (0.29 mmol) in propan-2-ol (0.29 M) was added 0.1 ml of NH_4OH (32% solution in water). After 48 h the reaction mixture was acidified with H_2SO_4, extracted with CH_2Cl_2 and the organic layer was anhydrified with Na_2SO_4. After removal of the solvent, the spectrum ^{1}H NMR of the residue showed the presence of only compound **7** which was isolated as oil in 60% yield by silica gel chromatography eluting with Et_2O/light petroleum (4:1): IR ($CHCl_3$): ν (cm^{-1}) 1789; ^{1}H NMR ($CDCl_3$): δ 3.68 (s, 2H, CH_2), 3.97 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$): δ 33.1 (t), 53.5 (q), 157.2 (s), 158.5 (s), 172.7 (s). Anal. calcd for $C_5H_5NO_4$ (143.10): C, 41.96; H, 3.52; N, 9.79. Found C, 41.87; H, 3.60; N, 9.70 %.

Nitrosation of cyclopropanes trans- and cis (**1e**): The reaction of *cis*-isomer **1e** with NOCl was carried out and monitored as described for **1a–d**. After completion of the reaction (20 h, ^{1}H NMR), the solvent was removed under reduced pressure and the residue chromatographed on silica gel using light petroleum/Et_2O (9:1) as eluent giving compounds **3e** (33%), **11e** (4%) and **10e** (10%), successively. All products were fully characterised by spectral means. Unpublished spectral data for known compounds **3e**[24] and **11e** (b.p. 75–76 °C/ 15 torr)[25] have been described.

Ethyl 5-ethoxy-4,5-dihydroisoxazole-3-carboxylate (**3e**): Oil; IR ($CHCl_3$): ν (cm^{-1}) 1724; ^{1}H NMR ($CDCl_3$): δ 1.21 (t, *J* = 7.0, 3H, OCH_2CH_3), 1.35 (t, *J* = 7.0, 3H, $CO_2CH_2CH_3$), 3.07 (dd, *J* = 18.5, 2.0) and 3.22 (dd, *J* = 18.5, 7.0) (together 2H, H-4), 3.60 and 3.89 (2m, 2H, OCH_2), 4.34 (m, 2H, CO_2CH_2), 5.69 (dd, *J* = 7.0, 2.0, 1H, H-5) ; ^{13}C NMR ($CDCl_3$): δ 14.1 (q), 14.9 (q), 40.1 (t), 62.1 (t), 64.3 (t), 104.8 (d), 151.9 (s), 160.3(s).

Ethyl 5-hydroxy-4,5-dihydroisoxazole-3-carboxylate (**10e**): Oil; IR ($CHCl_3$): ν (cm^{-1}) 3591, 3440, 1722; ^{1}H NMR ($CDCl_3$): δ 1.36 (t, *J* = 7.0, 3H, CH_3), 3.10 (dd, *J* = 18.6, 1.8) and 3.27 (dd, *J* = 18.6, 7.0) (together 2H, H-4), 3.47 (brs, 1H, OH), 4.35 (q, *J* = 7.2, 2H, OCH_2), 6.06 (dd, *J* = 7.0, 1.8, 1H, H-5); ^{13}C NMR ($CDCl_3$): δ 14.0 (q), 40.8 (t), 62.3 (t), 99.8 (d), 151.5 (s), 160.2 (s). Anal. calcd for $C_6H_9NO_4$ (159.14): C, 45.28; H, 5.70; N, 8.80. Found C, 45.20; H, 5.76; N, 8.68 %.

Ethyl 4-oxobutenoate (E) (**11e**): ^{1}H NMR ($CDCl_3$): δ 1.33 (t, *J* = 7.0, 3H, CH_3), 4.34 (q , *J* = 7.0, 2H, OCH_2), 6.72 (d, *J* = 16.0, 1H, H-2), 6.95 (dd, *J* = 16.0, 7.5, 1H, H-3), 9.76 (d, *J* = 7.5, 1H, H-4); ^{13}C NMR ($CDCl_3$): δ 14.1 (q), 61.7 (t), 139.4 (d), 140.3 (d), 166.8 (s), 192.4 (d).

The reaction of cyclopropane *trans*-**1e** with NOCl was carried out as described for **1a–d** and gave the same products of the reaction of cyclopropane *cis*-**1e.**

Reaction of cyclopropanes **1a–d** *with* $NOBF_4$: To a 0.06M solution of $NOBF_4$ (0.5 mmol) in dried CH_3CN at –23 °C under nitrogen atmosphere, a 0.2 M solution of cyclopropanes **1** in dried CH_3CN was added dropwise with stirring in a period of 20 min. After an additional stirring for 30 min, the reaction mixture was warmed to room temperature. After 24 h the reaction mixture was quenched with water followed by neutralisation with 10% aq. NaOH and extraction with CH_2Cl_2. The organic layer was anhydrified with Na_2SO_4. After removal of the solvent, the ^{1}H NMR spectra of the residues showed only the presence of the corresponding ethyl methyl butanedioates.[11a]

Reaction of cyclopropanes trans- and cis- (**1e**) *with* $NOBF_4$: The reaction of *cis*-isomer **1e** with $NOBF_4$ was carried out and monitored as described for **1a–d**. The spectrum of the mixture showed the presence of only isoxazole **13e** which was isolated by chromatography on silica gel, eluting with light petroleum/Et_2O (9:1) in 48% yield and identified by comparing the proton signals with those reported.[20] The reaction of *trans*-**1e** with $NOBF_4$ was carried out as described for **1a–d** and gave the same product and in similar yield as *cis*-**1e**.

Ethyl isoxazole-3-carboxylate (**13e**):[20] ^{13}C NMR ($CDCl_3$): δ 14.0 (q), 62.2 (d), 105.2 (d), 155.6 (s), 159.9 (d), 165.0 (s).

Reaction of isoxazolines **3e** *and* **11e** *with* $NOBF_4$: When either isoxazoline **3e** or **11e** were treated with $NOBF_4$ as above reported for **1e**, the ^{1}H NMR spectrum showed the only presence of isoxazole **13e**.

Reaction of methyl cyclopropanecarboxylate with nitrosyl reagents: When the title cyclopropane (purchased from Aldrich) was treated with NOCl or $NOBF_4$ as above reported for **1** and worked up after 24 h, the ^{1}H NMR spectrum showed the only presence of starting compound.

NMR spectra were run on a 500 Varian INOVA spectrometer (INCA Laboratory of Naples) at the Centro di Metodologie Chimico-Fisiche-Università di Napoli Federico II.

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as **4** were found even for entries **a**–**c.** Evidently in these cases cyclization surpasses completely the S_N2 displacement.

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