4-Halo-1,3-oxazoles: Unambiguous structural assignment of 2-halo-2-benzoyl-2H-azirine-3-carboxylates thermal ring expansion products

Susy Lopes, Cláudio M. Nunes, Rui Fausto, Teresa M.V.D. Pinho e Melo *

Department of Chemistry, University of Coimbra, P-3004-535 Coimbra, Portugal

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ABSTRACT

IR spectroscopy in cryogenic argon matrix of methyl 4-chloro-5-phenyl-1,3-oxazole-2-carboxylate and methyl 4-chloro-5-phenylisoxazole-3-carboxylate was applied for the structural assignment of these isomeric heterocycles. It was demonstrated that methyl 2-benzoyl-2-halo-2H-azirine-3-carboxylates undergo thermal ring expansion to give 4-halo-5-phenyl-1,3-oxazole-2-carboxylates and not the isomeric isoxazoles.

1. Introduction

Oxazoles and isoxazoles are isomeric heterocyclic compounds having a remarkable number of applications and have been demonstrated to be very versatile building blocks in organic synthesis [1]. The wide range of biological activities of isoxazoles and oxazoles includes pharmacological properties such as hypoglycemic, analgesic, anti-inflammatory, anti-bacterial, anti-tumoral and HIV-inhibitory activity. Some isoxazole derivatives display agrochemical properties, namely herbicidal and soil fungicidal activity, and have applications as pesticides and insecticides. Isoxazoles have also been used as dyes, electric insulating oils, high temperature lubricants and polyisoxazoles have applications as semiconductors. The oxazole ring occurs naturally and the total synthesis of natural products with a wide variety of biological activities containing oxazole moiety is an area of intense research. Other applications of oxazole derivatives include the use as pesticides, fluorescent whitening agents, lubricants, dyes and pigments. Therefore, there is considerable interest of having available efficient routes to these heterocycles and to better understand their reactivity.

In relation with our ongoing research on the synthesis and reactivity of 2-halo-2H-azirines [2] we reported the thermolysis of 2-halo-2-acyl-2H-azirines (Scheme 1) [2g]. 2-Benzoyl-2-halo-2H-azirine-3-carboxylates (1) underwent ring expansion giving products in high yield which were identified as being 4-haloisoxazoles 3.

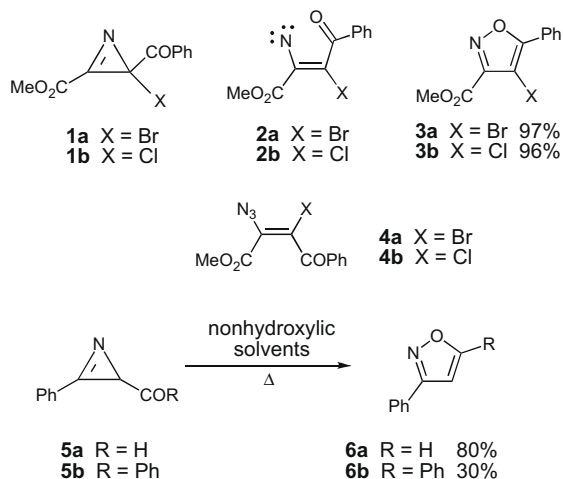The same products were also obtained in high yield from the thermolysis of haloazidoalkenes 4 via intermediate 2-benzoyl-2-halo-2H-azirines 1.

The thermolysis of 2H-azirines usually results in cleavage of the N–C2 single bond giving a transient vinylnitrene, the reverse of the cyclization of vinylnitrenes used to prepare 2H-azirines [3]. Evidence for the existence of this intermediate comes from the thermal ring opening of 2,3-diaryl-2-cyano-2H-azirine where the vinylnitrene was trapped with phosphanes [4]. On the other hand, it was known that heating a solution of 3-phenyl-2H-azirine-2-carboxaldehyde (5a) at 200 °C leads to 3-phenylisoxazole (6a) in high yield [5a]. The same isoxazole can also be obtained in 90% yield by treatment of 3-phenyl-2H-azirine-2-carboxaldehyde at 25 °C with Grubbs' catalyst [5b]. Furthermore, 2-benzoyl-3-phenyl-2H-azirine (5b) affords the corresponding isoxazole 6b upon heating in non-hydroxylic solvents [5c]. These observations led us to rationalize the thermal reaction of 2-benzoyl-2-halo-2H-azirine-3-carboxylates (1) as being the conversion into isoxazoles 3 via vinyl nitrenes 2 (Scheme 1).

Isoxazoles have also been obtained from (Z)-β-azido-α,β-unsaturated ketones and esters (7 and 9a) (Scheme 2) [5d,5e]. Hassner et al. also observed that meso-1,2-benzoylethylene dibromide 12 reacts with two equivalents of sodium azide to give 3-benzoyl-5-phenylisoxazole 13 via a vinyl azide intermediate [5f]. However, the thermal induced reaction of (E)-β-azido-α,β-unsaturated ketone 9b gives the corresponding 1,3-oxazole 11 [5e]. The different outcome of the thermolysis of the (Z)- and (E)-β-azido-α,β-unsaturated ketones led the authors to propose a concerted mechanism for the synthesis of isoxazoles starting from (Z)-β-azido-α,β-unsat-
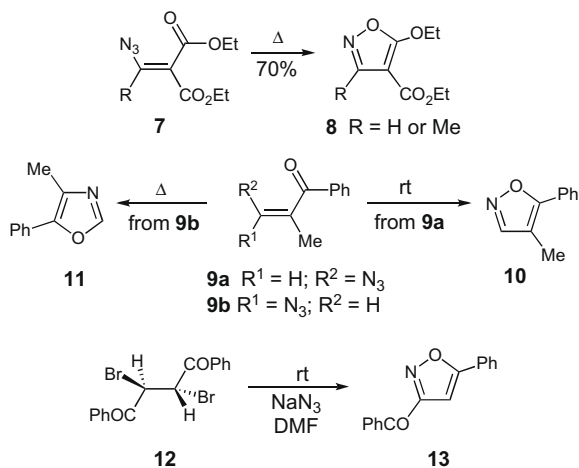
* Corresponding author.
  E-mail address: tmelo@ci.uc.pt (T.M.V.D. Pinho e Melo).

Scheme 1.

urated ketones. In the case of the (E)-β-azido-α,β-unsaturated ketones the concerted mechanism would not be possible due to the configuration of the alkene. Therefore, the formation of 2H-azirine intermediates was postulated followed by ring expansion reaction to oxazole, which would require a C2—C3 bond cleavage. These observations could lead to the conclusion that starting from 2-acyl-2H-azirines only oxazoles could be obtained. Nevertheless, this does not account for the fact that the thermolyses of both 3-phenyl-2H-azirine-2-carboxaldehyde (**5a**) and 2-benzoyl-3-phenyl-2H-azirine (**5b**) afford the corresponding isoxazoles (Scheme 1) [5a,5c]. In fact, the reactivity pattern of 2H-azirine derivatives has been shown to be more difficult to establish a priori then initially supposed, since it is significantly dependent on the nature of the substituents.

In fact, under thermal conditions the reactivity expected for 2H-azirines is the cleavage of the N—C2 single bond giving a transient vinylnitrene whereas the photolysis should lead to the cleavage of the C2—C3 bond giving nitrile ylide intermediates [1,3]. However, we have previously studied the UV induced photochemical reactions of two aliphatic 2H-azirines – methyl 2-chloro-3-methyl-2H-azirine-2-carboxylate and methyl 3-methyl-2H-azirine-2-carboxylate – isolated in argon matrices [6a–c]. For both compounds, irradiation with $\lambda > 235$ nm led to the observation of two primary photoprocesses: the expected C2–C3 bond cleavage, with production of nitrile ylides, but also the N–C2 bond cleavage, with produc-

tion of methylated ketene imines. Inui and Murata also demonstrated that both C2—C3 and N—C2 bonds can be cleaved upon photolysis of matrix-isolated 2H-azirines bearing an aromatic substituent at C2 [6d,6e]. They concluded that the tendency toward the N—C2 bond cleavage increases with the electron-withdrawing ability of the ring substituents.

Thermally induced ring expansion reactions of 2-acyl-2H-azirines leading to oxazoles have also been reported, although these transformations required a base- or Lewis acid-catalysis or the use of organometallic catalysts [5c,7].

Matrix isolation infrared spectroscopy is extremely powerful to undertake detailed structural and photochemical studies. Once the substance under investigation is isolated in a cryogenic inert matrix, in situ irradiation can be undertaken and the progress of the reaction probed spectroscopically. The use of criteriously chosen irradiation conditions can selectively induce a given reaction path, enabling a detailed characterization of the related intermediates. Thus, we decided to use matrix isolation infrared spectroscopy to carry out the structural and vibrational characterization as well as the study of the photochemistry of 4-haloisoxazoles.

The chloro compound obtained from the thermolysis of methyl 2-benzoyl-2-chloro-2H-azirine-3-carboxylate (**1b**) was selected for our study. The monomeric structure isolated in low temperature argon matrix was studied by FT-IR spectroscopy, supported by theoretical calculations undertaken at the DFT(B3LYP)/6-311++G(d,p) level of theory. For our surprise the theoretically predicted spectrum for isoxazole **3b** did not match the experimental IR spectrum. Indeed, the results described below will demonstrate that the studied compound can not be methyl 4-chloro-5-phenylisoxazole-3-carboxylate (**3b**) but instead we are in the presence of methyl 4-chloro-5-phenyl-1,3-oxazole-2-carboxylate (**15**) (MCPOC).

2. Experimental

^{1}H NMR spectra were recorded on a Bruker Avance 300 instrument operating at 300 MHz. ^{13}C NMR spectra were recorded on a Bruker Avance 300 instrument operating at 75.5 MHz. The solvent is deuteriochloroform except where indicated otherwise. IR spectra were recorded on a PerkinElmer 1720X FTIR spectrometer. Mass spectra were recorded on a HP GC 6890/MSD5973 instrument under electron impact (EI) except where indicated otherwise. Microanalyses were performed using an EA 1108-HNS-O Fisons instrument. Mp were recorded on a Reichert hot stage and are uncorrected. Flash column chromatography was performed with Merck 9385 silica as the stationary phase.

2.1. General procedure for the synthesis of 1,3-oxazoles 15 and 18 from 2-halo-2H-azirines

The 2-halo-2H-azirine [2b] (2.81 mmol) was dissolved in toluene (10 ml) and the reaction mixture was heated at reflux for 5 h. The solvent was evaporated giving the 1,3-oxazole as a solid.

2.1.1. Methyl 4-chloro-5-phenyl-1,3-oxazole-2-carboxylate 15 [8]
Compound **15** was obtained as a solid (96%), mp 71–72 °C. IR (KBr) 1529, 1738, 2959 cm^{-1}; ^{1}H NMR 4.04 (3H, s), 7.47–7.51 (3H, m, Ar-H), 7.98–8.01 (2H, m, Ar-H); ^{13}C NMR 53.5, 125.6, 125.9, 126.6, 129.0, 130.2, 147.8, 148.7, 155.3; MS (EI) m/z 239 [M(^{37}Cl)+] (34), 237 [M(^{35}Cl)+] (100), 177 (17), 128 (8), 105 (55), 77 (59). Anal. Calcd. for C$_{11}$H$_8$NO$_3$Cl: C, 55.60; H, 3.39; N, 5.89. Found: C, 55.66; H, 3.32; N, 5.92%.

2.1.2. Methyl 4-bromo-5-phenyl-1,3-oxazole-2-carboxylate 18
Compound **18** was obtained as a solid (97%), mp 66–68 °C. IR (KBr) 1737, 2958 cm^{-1}; ^{1}H NMR 4.04 (3H, s), 7.48–7.51 (3H, m, Ar-H), 8.03–8.06 (2H, m, Ar-H); ^{13}C NMR 4.04 (3H, s), 7.48–7.51

Scheme 2.

(3H, m, Ar-H), 8.03–8.06 (2H, m, Ar-H); MS (EI) *m/z* 283 [M(^{81}Br)+] (100), 281 [M(^{79}Br)+] (100), 223 (18), 221 (18), 105 (55), 77 (89). Anal. Calcd. for $C_{11}H_8NO_3Br$: C, 46.84; H, 2.86; N, 4.97. Found: C, 47.24; H, 3.12; N, 5.29%.

2.2. General procedure for the synthesis of 1,3-oxazoles *15* and *18* from haloazidoalkenes

The azidoalkene [2b] (1 mmol) was dissolved in toluene (10 ml) and the reaction mixture was heated under reflux for 7 h. The solvent was evaporated and the residue was washed with cooled ethyl ether giving the 1,3-oxazole as a solid.

2.2.1. Methyl 4-chloro-5-phenyl-1,3-oxazole-2-carboxylate *15* (98%)
Identified by comparison with the specimen isolated earlier.

2.2.2. Methyl 4-bromo-5-phenyl-1,3-oxazole-2-carboxylate *18* (95%)
Identified by comparison with the specimen isolated earlier.

2.3. Methyl 4-chloro-5-phenylisoxazole-3-carboxylate *3b*

A solution of methyl 5-phenylisoxazole-3-carboxylate *17* (70 mg, 0.345 mmol) and NCS (85 mg, 0.64 mmol) in 2.3 mL of 7% fuming nitric acid in acetic acid was irradiated for 40 min in the microwave reactor (CEM Focused Synthesis System, Discover S-Class) with the temperature set to 160 °C. After cooling to room temperature, water (15 mL) was added and the mixture extracted with CH_2Cl_2 (2 × 15 mL). The organic phase was dried (MgSO4) and evaporated off. The crude product was purified by flash chromatography [ethyl acetate–hexane (1:5)] to give *3b* as a white solid (59%). mp 62–63 °C. IR (KBr) 1221, 1441, 1738, 2957 cm^{-1}; ^{1}H NMR 4.03 (3H, s), 7.52–7.55 (3H, m), 8.03–8.06 (2H, m);^{13}C NMR 53.1, 106.0, 125.6, 126.6, 129.0, 131.2, 153.3, 159.1, 165.8; MS (EI) *m/z* 237 (M$^+$, 99), 206 (14), 105 (100), 77 (68), 59 (78); HRMS (CI) *m/z* 237.0200 ($C_{11}H_8NO_3Cl$ [M$^+$], 237.0193).

2.4. Infrared spectroscopy

Matrix isolation of 1,3-oxazole *15* (MCPOC) and isoxazole *3b* (MCPIC): The IR spectra were collected, with 0.5 cm^{-1} spectra resolution, using a Mattson (Infinity 60AR series) or a Nicolet 6700 Fourier transform infrared spectrometer, equipped with a deuterated triglycine sulphate (DTGS) detector and a Ge/KBr beamsplitter.

To avoid interference from atmospheric H_2O and CO_2, a stream of dry nitrogen continuously purged the optical path of the spectrometers. All experiments were performed using an APD Cryogenics closed-cycle helium refrigeration system with a DE-202A expander.

To deposit the matrices, the compound to be studied was sublimated (*T* = 323 K) using a specially designed mini-furnace thermoelectrically heatable placed inside the cryostat and co-deposited with a large excess of the matrix gas (argon N60 obtained from Air Liquide) onto the CsI optical substrate of the cryostat cooled to 10 K.

2.5. Computational methodology

The quantum chemical calculations were performed with Gaussian 03 (Revision B.01) program [10] at the DFT level of theory, using the split valence triple-ζ 6-311++G(d,p) basis set and the three-parameter B3LYP density functional, which includes Becke's gradient exchange correction [11] and the Lee, Yang and Parr correlation functional [12].

Geometrical parameters of the relevant conformations were optimized using the Geometry Direct Inversion of the Invariant

Subspace (GDIIS) method [13]. In order to assist the analysis of the experimental spectra, vibrational frequencies and IR intensities were also calculated at the same level of approximation. The computed harmonic frequencies were scaled down by two factors (0.9894 for MCPOC and 0.9817 for MCPIC) to correct them for the effects of basis set limitations, neglected part of electron correlation and anharmonicity effects. The optimized structures of all conformers described in this study were confirmed to correspond to true minimum energy conformations on the potential energy surface investigated.

3. Results and discussion

Two low energy conformers of MCPOC were predicted to exist by the calculations (Fig. 1). The IR spectrum of matrix-isolated 1,3-oxazole *15* is presented in Figs. 2 and 3 along with the calculated spectra for the two most stable conformers. The comparison of the IR spectrum of the product of the thermolysis of methyl 2-benzoyl-2-chloro-2H-azirine-3-carboxylate (*1b*) with the theoretically predicted spectrum of MCPOC allow us to unambiguously establish the structure as being methyl 4-chloro-5-phenyl-1,3-oxazole-2-carboxylate (*15*).

In the present case, the formation of oxazole *15* from 2H-azirine *1b* can be explained considering the thermal cleavage of the C2-C3 to give nitrile ylide *14* followed by recyclization giving oxazole *15* as the final product (Scheme 3). Since the oxazole is obtained in
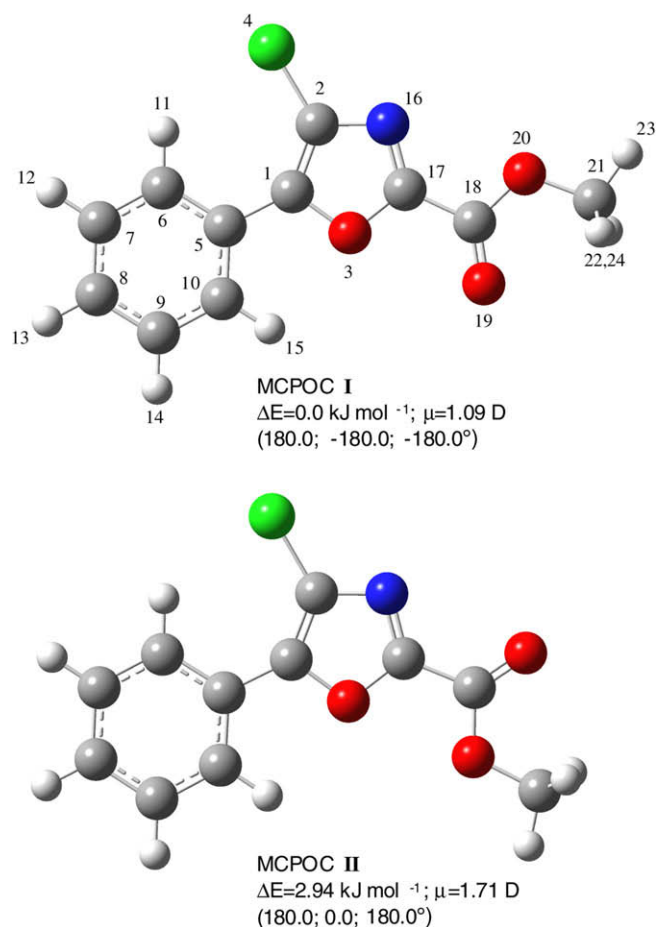

Fig. 1. Conformers of methyl 4-chloro-5-phenyl-1,3-oxazole-2-carboxylate (*15*) (MCPOC) with atom numbering. Relative energies and dipole moments are also provided, as well as the C_6—C_5—C_1—O_3, N_{16}=C_{17}—C_{18}=O_{19} and C_{17}—C_{18}—O_{20}—C_{21} dihedral angles.
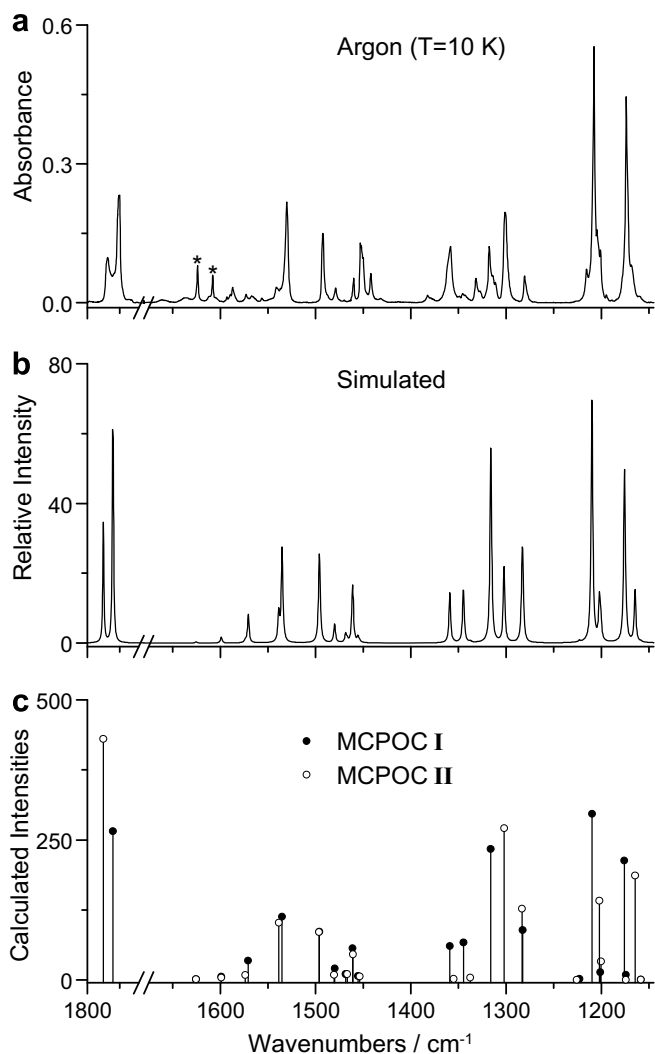
Fig. 2. Infrared spectra of MCPOC (**15**) (1800–1145 cm^{-1} region): (a) spectrum of MCPOC isolated in an argon matrix (sublimation temperature: 323 K; substrate temperature: 10 K), (b) simulated population-weighted (at 323 K) spectrum of MCPOC using Lorentzian functions with 2 cm^{-1} half bandwidth and centred at the DFT(B3LYP)6-311++G(d,p) calculated wavenumbers for the two relevant conformers of MCPOC; and (c) theoretical spectra for the two conformers of MCPOC. Calculated wavenumbers were scaled by 0.9894. Bands marked with an asterisk are due to monomeric water impurity.

Fig. 3. Infrared spectra of MCPOC (**15**) (1145–530 cm^{-1} region): (a) spectrum of MCPOC isolated in an argon matrix (sublimation temperature: 323 K; substrate temperature: 10 K), (b) simulated population-weighted (at 323 K) spectrum of MCPOC using Lorentzian functions with 2 cm^{-1} half bandwidth and centred at the DFT(B3LYP)6-311++G(d,p) calculated wavenumbers for the two relevant conformers of MCPOC; and (c) theoretical spectra for the two conformers of MCPOC. Calculated wavenumbers were scaled by 0.9894.

high yield (98%) we can conclude that only the reaction pathway **B** is observed.

Another relevant conclusion can be drawn from this study. In fact, the mechanism of formation of the 2*H*-azirine ring from the haloazidoalkene **4b** must be a concerted process since the formation of a vinylnitrene intermediate should lead to the competitive formation of the isoxazole **3b**.

Recently, Li et al. reported the bromination of isoxazoles with *N*-bromosuccinimide in acid solvents using microwave irradiation [14]. The work included the synthesis of methyl 4-bromo-5-phenylisoxazole-3-carboxylate (**3a**). The authors observed that the ^{13}C NMR spectrum of this compound did not match the NMR data previously reported by us for the product of the thermolysis of 2-benzoyl-2-bromo-2*H*-azirine-3-carboxylate **1a** [2g]. This led the authors to confirm the structure of 4-bromo-5-phenylisoxazole-3-carboxylate **3a** by single crystal X-ray crystallography. This was another evidence that indicates that the thermolysis of 2-benzoyl-2-halo-2*H*-azirine-3-carboxylates **1** leads to oxazoles and not to isoxazoles.
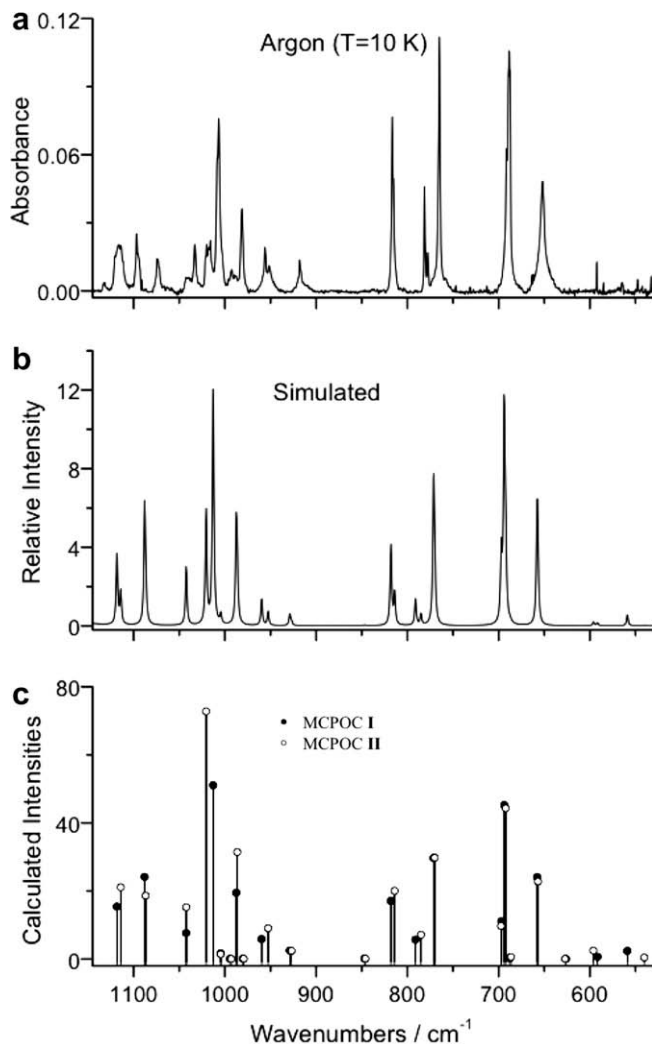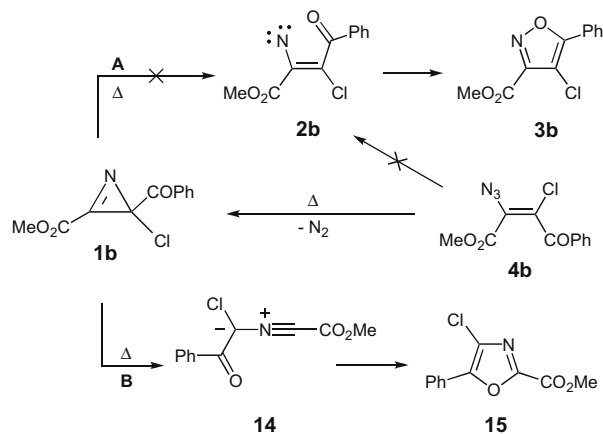

Scheme 3.

Scheme 4.

MCPIC I
$\Delta E=0.0$ kJ mol^{-1}; $\mu=1.52$ D
(-20.3; 10.8; -178.6°)

MCPIC II
$\Delta E=3.87$ kJ mol^{-1}; $\mu=4.09$ D
(-21.1;-153.7; -180°)

MCPIC III
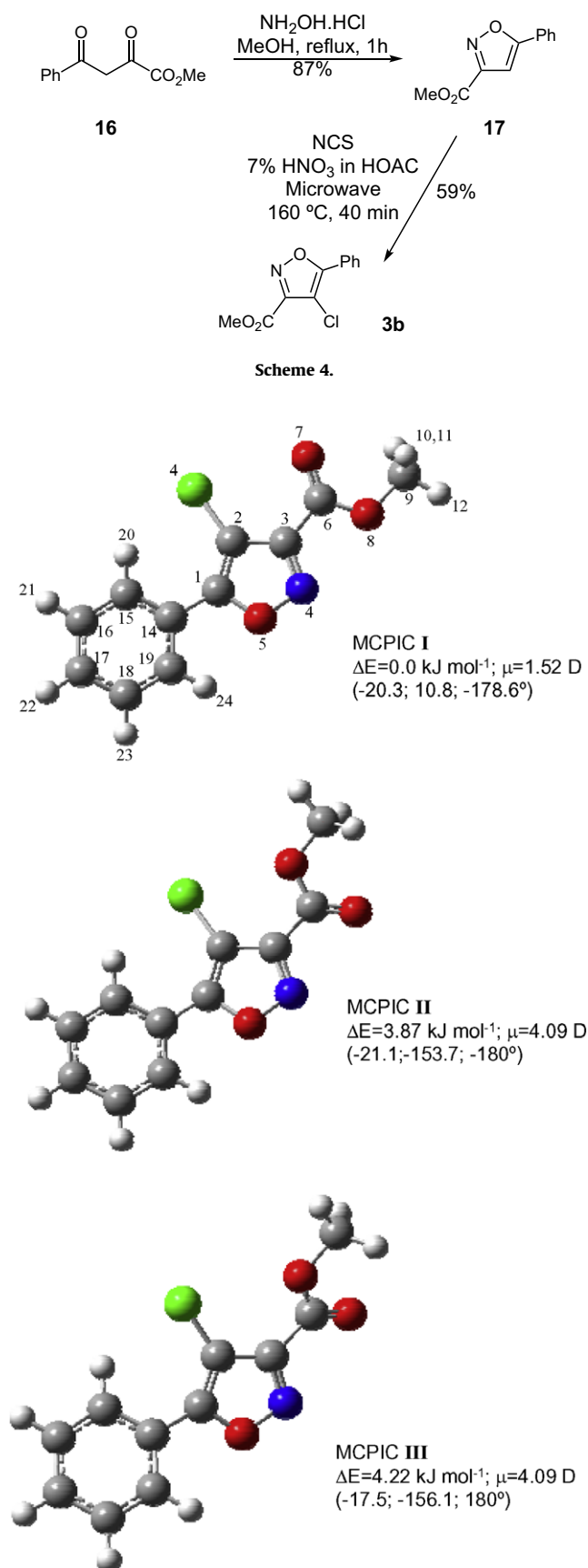$\Delta E=4.22$ kJ mol^{-1}; $\mu=4.09$ D
(-17.5; -156.1; 180°)

Fig. 4. Conformers of methyl 4-chloro-5-phenylisoxazole-3-carboxylate (3b) (MCPIC) with atom numbering. Relative energies and dipole moments are also provided, as well as the C$_{15}$—C$_{14}$—C$_1$—C$_2$, O$_7$=C$_6$—C$_3$—C$_2$ and C$_9$—O$_8$—C$_6$—C$_3$ dihedral angles.
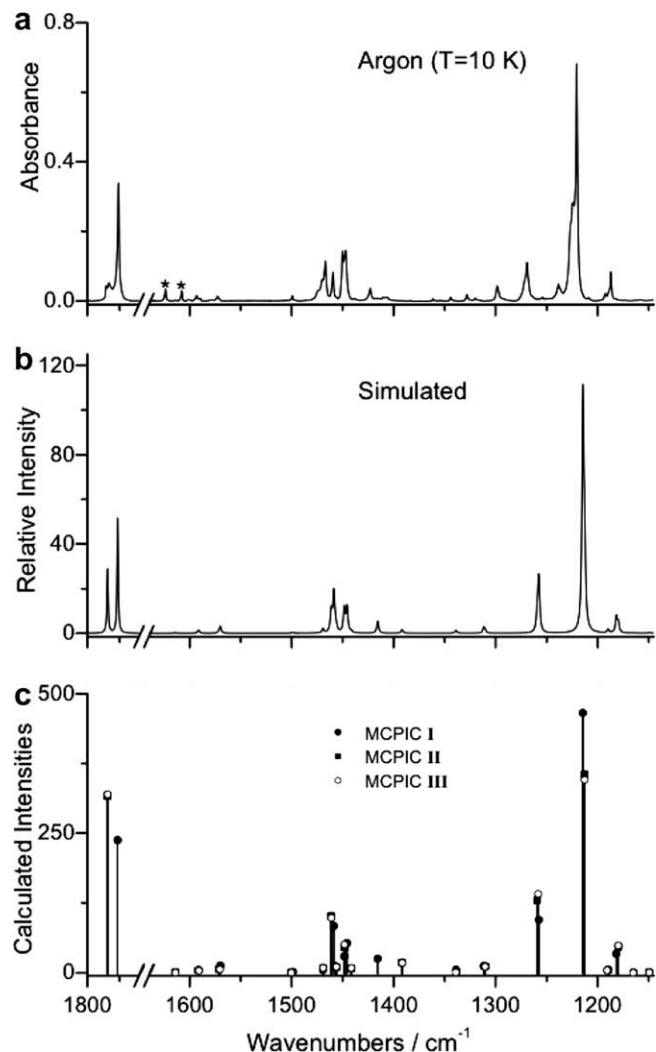

Fig. 5. Infrared spectra of MCPIC (3b) (1800–1145 cm^{-1} region): (a) spectrum of MCPIC isolated in an argon matrix (sublimation temperature: 323 K; substrate temperature: 10 K), (b) simulated population-weighted (at 323 K) spectrum of MCPIC using Lorentzian functions with 2 cm^{-1} half bandwidth and centred at the DFT(B3LYP)6-311++G(d,p) calculated wavenumbers for the three relevant conformers of MCPIC; and (c) theoretical spectra of the three conformers of MCPIC. Calculated wavenumbers were scaled by 0.9817. Bands marked with an asterisk are due to monomeric water impurity.

In order to get further support to the structural assignment we decided to prepare 4-chloro-5-phenylisoxazole-3-carboxylate 3b to study the compound by matrix-isolation FTIR. The synthesis of isoxazole 3b is outlined in Scheme 4. The starting methyl 5-phenylisoxazole-3-carboxylate (17) was prepared by cyclization of 2,4-dioxo-4-phenylbutanoate (16) with hydroxylamine hydrochloride [9]. We applied the general procedure described by Li et al.[14] for the synthesis of 4-chloro-5-phenylisoxazole-3-carboxylate 3b but using NCS instead of NBS. Using 5% fuming nitric acid in acetic acid as solvent the solution of isoxazole 17 was irradiated in the microwave reactor with the temperature set to 150 °C for 25 min giving the desired product in 45% yield. However, the yield could be improved to 59% carrying out the microwave irradiation at 160 °C for 40 min and using 7% fuming nitric acid in acetic acid.

Three different low energy conformers of 4-chloro-5-phenylisoxazole-3-carboxylate 3b (MCPIC) were predicted to exist by the calculations (Fig. 4). The IR spectrum of matrix-isolated 4-chloro-5-phenylisoxazole-3-carboxylate 3b (MCPIC) is shown in Figs. 5 and 6. The assignment of the observed bands was carried out by
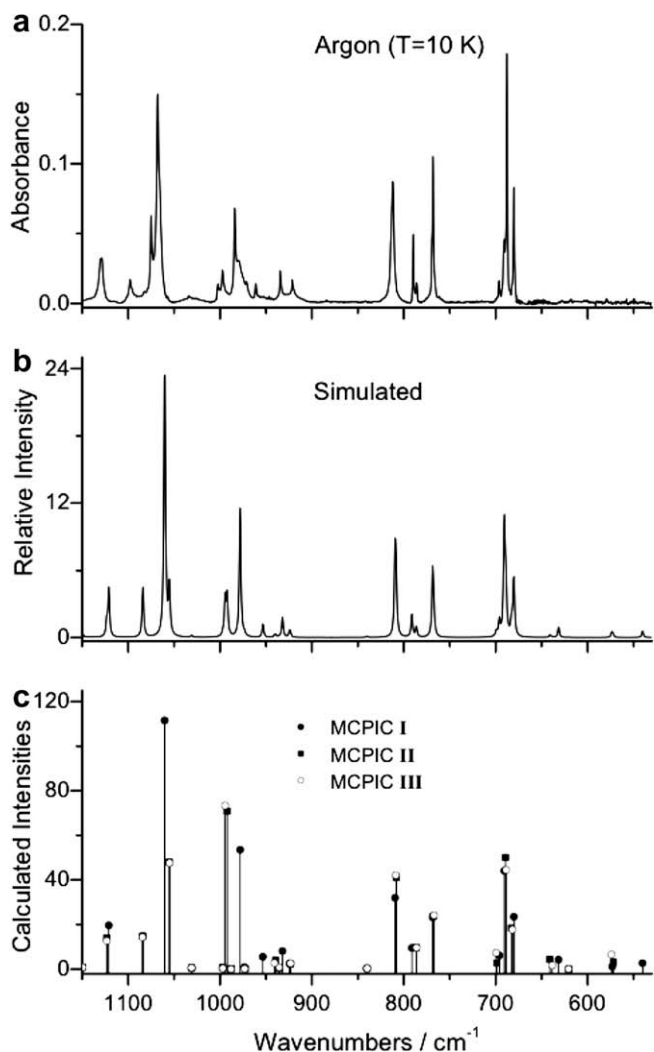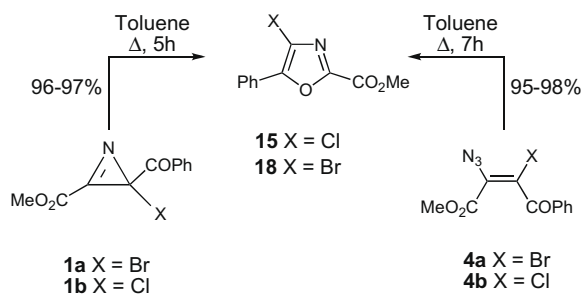
Fig. 6. Infrared spectra of MCPIC (**3b**) (1145–530 cm^{-1} region): (a) spectrum of MCPIC isolated in an argon matrix (sublimation temperature: 323 K; substrate temperature: 10 K), (b) simulated population-weighted (at 323 K) spectrum of MCPIC using Lorentzian functions with 2 cm^{-1} half bandwidth and centred at the DFT(B3LYP)6-311++G(d,p) calculated wavenumbers of the three relevant conformers of MCPIC; and (c) theoretical spectra of the three conformers of MCPIC. Calculated wavenumbers were scaled by 0.9817.

Scheme 5.

comparison with the theoretically predicted simulated spectrum, which nicely fits the observed spectrum (see Figs. 5 and 6). This spectrum of MCPIC is significantly distinct from that of the product resulting from the thermolysis of **1b** (which, as already shown, corresponds to the 1,3-oxazole **15**).

In order to give further insight into the unusual thermolysis process of the studied 2-benzoyl-2H-azirine, we now also examined the possibility of occurrence of initial formation of the isoxazole, followed by isomerization to the oxazole ring, since the thermal rearrangement of 4-acylisoxazoles to 4-acyloxazoles is known [15]. In reference [15] the synthesis of the oxazoles from the corresponding isoxazoles was rationalized considering ring contraction reaction to give a 2H-azirine intermediate, followed by a ring expansion process via C2—C3 bond cleavage and cyclization. Therefore, the thermolysis of 2-benzoyl-2-chloro-2H-azirine-3-carboxylate **1b** could also involve the formation of isoxazole **3b** followed by the rearrangement to oxazole **15**. However, this possibility was rolled out, since upon heating at reflux for 5 h a solution of isoxazole **3b** in toluene no reaction was observed.

4. Conclusion

It is clear from the analysis of the matrix-isolated 4-chloro-5-phenyl-1,3-oxazole-2-carboxylate **15** and methyl 4-chloro-5-phenylisoxazole-3-carboxylate **3b** FTIR spectra that this technique allows to distinguish easily these isomeric heterocycles. Therefore, it has been demonstrated that methyl 2-benzoyl-2-halo-2H-azirine-3-carboxylates **1** undergo thermal ring expansion to give 4-halo-5-phenyl-1,3-oxazole-2-carboxylates (**15** and **18**) in high yield. These 1,3-oxazoles can also be obtained in high yield from haloazidoalkenes **4** (Scheme 5).

Acknowledgment

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