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

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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-2*H*-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 semicondutors. 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-2*H*-azirines [2] we reported the thermolysis of 2-halo-2-acyl-2*H*-azirines (Scheme 1) [2g]. 2-Benzoyl-2-halo-2*H*-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-2*H*-azirines **1**.

The thermolysis of 2*H*-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-2*H*-azirine where the vinylnitrene was trapped with phosphanes [4]. On the other hand, it was known that heating a solution of 3-phenyl-2*H*-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-2*H*-azirine-2-carboxaldehyde at 25 °C with Grubbs' catalyst [5b]. Furthermore, 2-benzoyl-3-phenyl-2*H*-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-2*H*-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-

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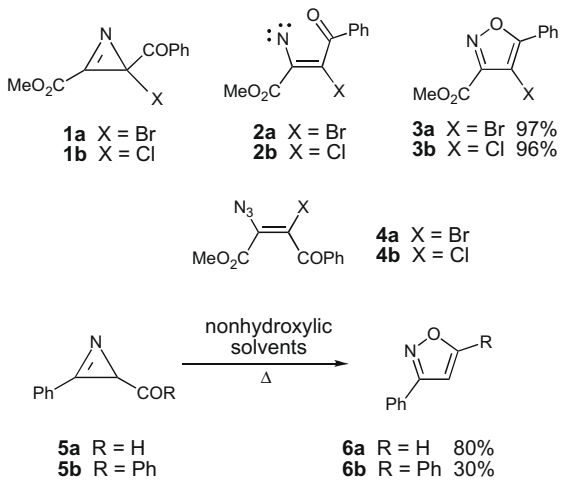
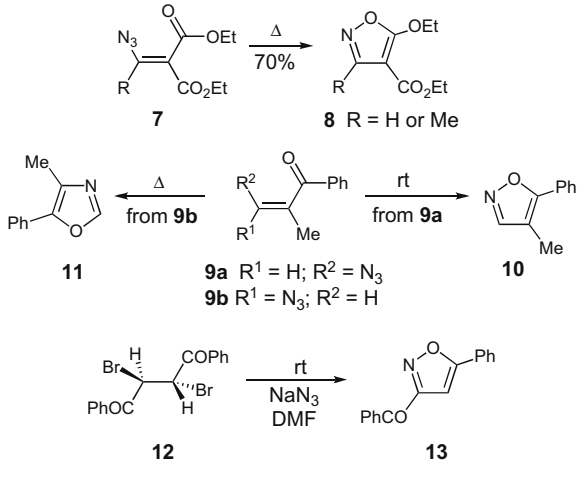


Scheme 1.

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 2*H*-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-2*H*-azirines only oxazoles could be obtained. Nevertheless, this does not account for the fact that the thermolyses of both 3-phenyl-2*H*-azirine-2-carboxaldehyde (**5a**) and 2-benzoyl-3-phenyl-2*H*-azirine (**5b**) afford the corresponding isoxazoles (Scheme 1) [5a,5c]. In fact, the reactivity pattern of 2*H*-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 2*H*-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 2*H*-azirines – methyl 2-chloro-3-methyl-2*H*-azirine-2-carboxylate and methyl 3-methyl-2*H*-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 production 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 2*H*-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.



Scheme 2.

Thermally induced ring expansion reactions of 2-acyl-2*H*-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-2*H*-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-2*H*-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 $C_{11}H_8NO_3Cl$: 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