Synthesis of 2-halo-2*H*-azirines

Teresa M. V. D. Pinho e Melo,* Cláudia S. J. Lopes, Ana L. Cardoso and
António M. d'A. Rocha Gonsalves

Departamento de Química, Faculdade de Ciências e Tecnologia, Universidade de Coimbra, 3004-535 Coimbra, Portugal

Abstract—α-Oxophosphonium ylides react with *N*-chlorosuccinimide, *N*-bromosuccinimide and *N*-iodosuccinimide in the presence of azidotrimethylsilane giving the corresponding haloazidoalkenes which were completely converted to the 2-halo-2*H*-azirines on heating in heptane. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

We have previously described a non-classical Wittig reaction which offers a route to some simple tetrasubstituted alkenes of a type that was poorly represented in the literature.[1] Diethyl 2-oxo-3-triphenylphosphoranylidene-butanedioate **1a** reacts with chlorine and bromine in the presence of a range of nucleophiles giving 2,3-disubstituted diethyl butenedioates with elimination of triphenylphosphine oxide (Scheme 1). The reaction of *N*-bromosuccinimide and *N*-chlorosuccinimide in methanol or in the presence of azidotrimethylsilane also gave 2,3-disubstituted diethylbutenedioates. Several of the reactions were highly stereoselective whereas others gave both (*E*) and (*Z*) isomers.

The study of the reactivity of ylides **1b–d** towards reagent systems XY (electrophile/nucleophile), where X≠Y, clearly indicates that the electrophile binds exclusively to the carbon of the phosphoranylidene group of the starting ylide and the oxygen which is eliminated in the process is always from the keto carbonyl group.[2]

1b R^1 = CO$_2$Et; R^2 = CO$_2$Me
1c R^1 = CO$_2$Me; R^2 = CO$_2$Et
1d R^1 = Ph; R^2 = CO$_2$Et
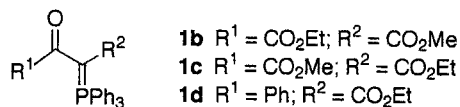
We postulated that isomeric halonium ions were intermediates in the formation of the observed products. These halonium ions could interconvert by way of an acyclic cation. The opening of the two halonium ions by a nucleophile would lead to the isomeric alkenes after the elimination of triphenylphosphine oxide (Scheme 2).
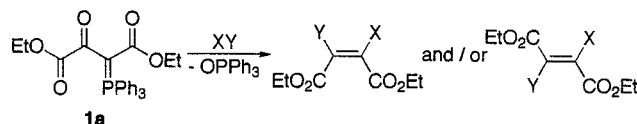
Scheme 1.

The formation of an halophosphonium salt as an intermediate is in agreement with the known halogenation of α-oxophosphonium ylides which gives the corresponding halophosphonium salt **2**[3] (Scheme 3).

On the other hand, one example is known of an intramolecular non-classical Wittig reaction of the type described above. In fact the reac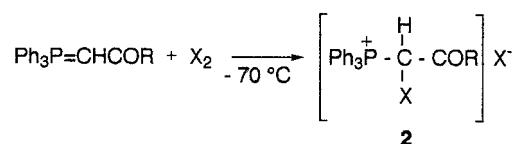tion of α-oxophosphonium ylides, bearing a terminal carboxylic acid group acting as the nucleophile, with halogenating agents leads to the formation of *E*- and *Z*-halo enol lactones.[4,5] The cyclization is also thought to proceeds via a halophosphonium salt followed
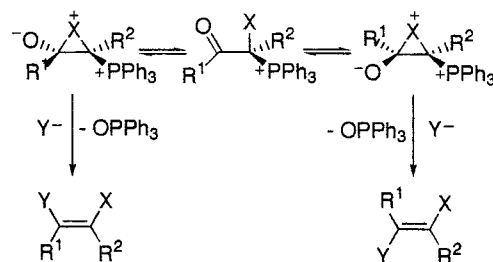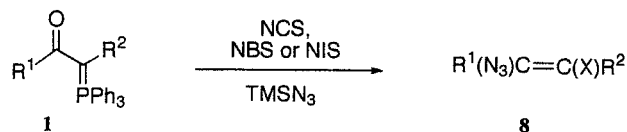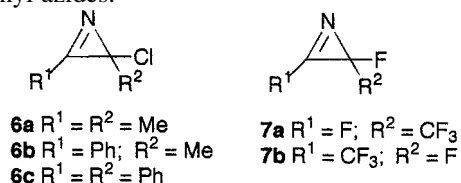

Scheme 2.

Scheme 3.
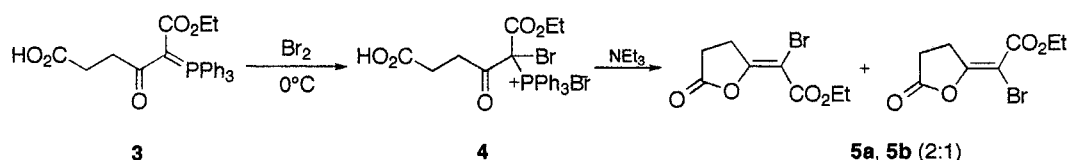
Scheme 4.

by loss of triphenylphosphine oxide. Scheme 4 illustrates one case where it is possible to isolate the bromophosphonium salt **4** if the reaction of ylide **3** with bromine is promoted at 0°C. Treatment of **4** with triethylamine gives the corresponding bromo enol lactones.[5]

One aspect of particular interest in this methodology for the synthesis of tetrasubstituted alkenes is the possibility of preparing haloazidoalkenes from the reaction of phosphorus ylides with *N*-halosuccinimide in the presence of azidotrimethylsilane since these compounds were potential precursors of 2-halo-2*H*-azirines.

2*H*-Azirines are unsaturated three-membered heterocycles which are used for various synthetic purposes due to their high reactivity.[6] The most general method of synthesis of 2*H*-azirines is the thermal or photochemical decomposition of vinyl azides involving vinyl nitrenes as intermediates.[6–9] There are very few literature reports of halo substituted azirines.[8,9] The reaction of iodine azide[8a,b] or chlorine azide[8c] with chloroalkenes followed by elimination of hydrogen iodide or hydrogen chloride gives the corresponding chlorovinyl azides which can be converted into chloroazirines (**6a–c**). There are also a few examples of fluorinated 2*H*-azirines, such as **7a** and **7b**, prepared from fluorovinyl azides.[9a,b]

6a $R^1 = R^2 = Me$
6b $R^1 = Ph$; $R^2 = Me$
6c $R^1 = R^2 = Ph$

7a $R^1 = F$; $R^2 = CF_3$
7b $R^1 = CF_3$; $R^2 = F$

In the course of our work we have found that haloazido-alkenes prepared from phosphorus ylides can be easily converted into the corresponding 2-halo-2*H*-azirines.[10,11] In this paper, we describe this general route to 2-halo-2*H*-azirines starting from phosphorus ylides which allowed the synthesis of the first examples of 2-bromo- and 2-iodo-2*H*-azirine derivatives.

2. Results and discussion

Aiming the synthesis of a variety of 2-halo-2*H*-azirines in order to evaluate the scope of the synthetic methodology, a variety of stabilised ylides were selected. α-Oxoalkylidene-tri-phenylphosphoranes bearing two carboxylate substituents (**1a** and **1f**), derivatives with a phenyl and a carboxylate group (**1d** and **1e**), ylide **1g** with a carboxylate group and a benzoyl group and ylide **1h** with a methyl and a carboxylate group as substituents were prepared using synthetic procedures described in the literature.[12–14]

These ylides reacted with *N*-halosuccinimide in the presence of azidotrimethylsilane giving the corresponding haloazidoalkenes **8a–f** and **8h–n** (Scheme 5). The alkene **8g** could not be isolated since the reaction of ylide **1e** with *N*-bromosuccinimide and azidotrimethylsilane led directly to the synthesis of 2-bromo-2*H*-azirine **9g** in 89% yield. Alkenes **8d–f** could be characterised by IR spectroscopy but attempts to purify these alkenes in order to get the complete characterisation data led to the isolation of the corresponding 2*H*-azirines. These results indicate that the conversion of 3-azido-2-halo-3-phenylpropenoates to

1a $R^1 = R^2 = CO_2Et$
1d $R^1 = Ph$; $R^2 = CO_2Et$
1e $R^1 = Ph$; $R^2 = CO_2Me$
1f $R^1 = R^2 = CO_2Me$
1g $R^1 = CO_2Me$; $R^2 = COPh$
1h $R^1 = Me$; $R^2 = CO_2Me$

8a $R^1 = R^2 = CO_2Et$; X = Cl	90%
8b $R^1 = R^2 = CO_2Me$; X = Cl	75%
8c $R^1 = R^2 = CO_2Me$; X = Br	89%
8d $R^1 = Ph$; $R^2 = CO_2Et$; X = Cl	98%
8e $R^1 = Ph$; $R^2 = CO_2Et$; X = Br	60%
8f $R^1 = Ph$; $R^2 = CO_2Et$; X = I	65%
8g $R^1 = Ph$; $R^2 = CO_2Me$; X = Br	-----
8h $R^1 = Ph$; $R^2 = CO_2Me$; X = I	37%
8i $R^1 = CO_2Me$; $R^2 = COPh$; X = Cl	40%
8j $R^1 = CO_2Me$; $R^2 = COPh$; X = Br	44%
8l $R^1 = CO_2Me$; $R^2 = COPh$; X = I	43%
8m $R^1 = Me$; $R^2 = CO_2Me$; X = Br	93%
8n $R^1 = Me$; $R^2 = CO_2Me$; X = I	73%

Scheme 5.

Table 1. ^{13}C NMR in CDCl$_3$ of the haloazidoalkenes (δ in ppm)

Alkene	C–X	C–N$_3$
8a	114.8	136.8
8b[a]	114.3	137.6
8c	105.4	138.9
8h	73.5	153.9
8i	129.6	134.3
8j	117.6	133.9
8m	99.9	143.9
8n	72.9	146.1

[a] Major component

Table 2. ^{13}C NMR in CDCl$_3$ of the 2H-azirines **9a–e**, **9g–j**, **9m** and **9n** (δ in ppm)

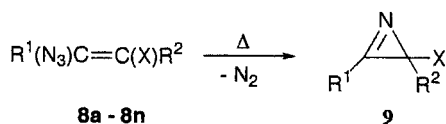| 2H-Azirine	C-2	C-3
9a	63.3	154.7
9b	54.6	155.0
9c	42.9	155.0
9d	54.0	163.5
9e	44.2	164.5
9g	43.7	164.4
9i	54.4	166.4
9j	42.8	165.9
9m	43.4	166.9
9n	13.7	166.6

2-halo-3-phenyl-2H-azirine-2-carboxylate is extremely favourable.

The reactions with N-chlorosuccinimide and N-bromosuccinimide were completed after 5 min. However, the reaction with N-iodosuccinimide required the use of excess of this halogenating agent and was only completed after 4.5 h.

The majority of these reactions showed high stereoselectivity leading to the synthesis of the alkenes as single isomers (**8d–n**). However, the 2-azido-3-halobut-2-enedioates (**8a–c**) were obtained as mixtures of E/Z isomers.

The ^{13}C NMR spectra of the haloazidoalkenes show the C–X carbon between 72.9 and 129.6 and the C–N$_3$ between 133.9 and 146.1 ppm (Table 1). In the case of the 2-azido-3-chlorobut-2-enedioates (**8a–c**) the assignment was made on the basis of a comparison of its ^{13}C NMR spectra with those of dimethyl azidofumarate and dimethyl azidomaleate.[7] The completed assignment of the ^{13}C NMR spectrum of methyl 2-azido-3-bromo-3-benzoylprop-2-enoate **8j** was supported by ^{1}H–^{1}H COSY and ^{1}H–^{13}C COSY spectra.

Alkenes **8a–f** and **8h–n** are easily converted into the corresponding 2-halo-2H-azirines (**9a–f**, **9h–n**) on heating in heptane for 2–3 h (Scheme 6). The reaction can be followed by TLC and by IR by monitoring the disappearance of the band corresponding to the azido group of the starting azidoalkenes ($\nu\sim$2110–2120 cm^{-1}). 2-Chloro-2H-azirines

and 2-bromo-2H-azirines were obtained in high yield (89–99%) whereas the yields obtained in the synthesis of the 2-iodo-2H-azirine derivatives ranged from 36 to 85%.

The ^{13}C NMR spectra of the 2-chloro- and 2-bromo-2H-azirines show the sp^2 carbon between 155.0 and 166.9 ppm and the sp^3 carbon between 43 and 63 ppm depending on the substitution pattern. Compounds **9b** and **9i** show the signal for the sp^3 carbon coincident with the signal for the methyl group. Methyl 2-iodo-3-methyl-2H-azirine-3-carboxylate **9n** shows the sp^2 carbon at 166.6 ppm and the sp^3 carbon at 13.7 ppm (Table 2).
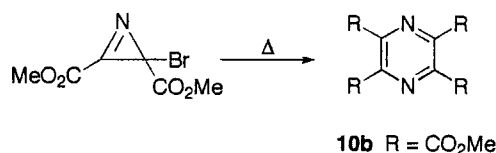
On attempting to obtain mass spectra of 2-halo-2H-azirines **9a–c**, using chemical ionisation with ammonia, we could only observe the spectra of the corresponding pyrazine-2,3,5,6-tetracarboxylate (**10a** and **10b**).

10a R = Et
10b R = Me
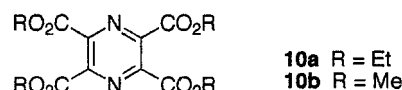
To confirm this observation tetramethyl pyrazine-2,3,5,6-tetracarboxylate **10b** was prepared by heating a solution of dimethyl 2-bromo-2H-azirine-2,3-dicarboxylate **9c** in heptane for 17 h (Scheme 7). Using this procedure pyrazine **10b** was obtained in low yield (2%).

The comparison of the mass spectrum of pyrazine **10b** with the mass spectra obtained from azirines **9b** and **9c** confirmed that they were identical. This result allowed us to conclude that 2-halo-2H-azirines **9a–c** undergo auto-condensation to give pyrazine-2,3,5,6-tetracarboxylates when subjected to the conditions required to obtain the mass spectra.

Chloro- and bromo-2H-azirines with electron withdrawing groups at C-3 decomposed in the condensed phase within 2–3 days at room temperature whereas azirines with a phenyl or methyl group at C-3 showed more stability.

$R^1(N_3)C{=}C(X)R^2$ $\xrightarrow[- N_2]{\Delta}$

8a - 8n → **9**

9a $R^1 = R^2 = CO_2Et$; X = Cl   98%
9b $R^1 = R^2 = CO_2Me$; X = Cl   99%
9c $R^1 = R^2 = CO_2Me$; X = Br   98%
9d $R^1 = Ph$; $R^2 = CO_2Et$; X = Cl   97%
9e $R^1 = Ph$; $R^2 = CO_2Et$; X = Br   97%
9f $R^1 = Ph$; $R^2 = CO_2Et$; X = I   36%
9g $R^1 = Ph$; $R^2 = CO_2Me$; X = Br   89%
9h $R^1 = Ph$; $R^2 = CO_2Me$; X = I   77%
9i $R^1 = CO_2Me$; $R^2 = COPh$; X = Cl   97%
9j $R^1 = CO_2Me$; $R^2 = COPh$; X = Br   98%
9l $R^1 = CO_2Me$; $R^2 = COPh$; X = I   36%
9m $R^1 = Me$; $R^2 = CO_2Me$; X = Br   99%
9n $R^1 = Me$; $R^2 = CO_2Me$; X = I   85%

Scheme 6.

10b R = CO$_2$Me

Scheme 7.

The iodo-2*H*-azirines showed lower stability than the corresponding chloro and bromo derivatives.

3. Conclusion

This work has provided a very general and efficient route to 2-halo-2*H*-azirines starting from phosphorus ylides. A range of 2-chloro-, 2-bromo- and 2-iodo-2*H*-azirines bearing a variety of substituents were obtained including derivatives having electron withdrawing groups at C-2 and C-3 (**9a**–**c**, **9i**, **9j** and **9l**), 2-halo-2*H*-azirines bearing electron withdrawing groups at C-2 and a phenyl at C-3 (**9d**–**h**) and 2-halo-2*H*-azirine derivatives having an electron withdrawing group at C-2 and a methyl group at C-3 (**9m** and **9n**).

4. Experimental

^{1}H NMR spectra were recorded on a Bruker AMX300 instrument operating at 300 MHz. ^{13}C spectrum were recorded on a Brucker AMX300 instrument operating at 75.5 MHz. The solvent is deuteriochloroform except where indicated otherwise. IR spectra were recorded on a Perkin–Elmer 1720X FTIR spectrometer. Mass spectra were recorded under electron impact at 70 eV on a VG Micromass 7070E instrument or where indicated, by chemical ionisation with ammonia (CI). Mp's were recorded on a Reichert hot stage and are uncorrected. Flash column chromatography was performed with Merck 9385 silica as the stationary phase. Phosphorus ylides were prepared using general procedures described in the literature (**1a**,[12] **1f**,[12] **1d**,[13] **1e**,[13] **1g**[13] and **1h**[14]).

4.1. General procedure for the synthesis of chloro- and bromoazidoalkenes

The ylide (4.5 mmol) was dissolved in dichloromethane (50 mL) and a solution of azidotrimethyilsilane (0.71 g, 6.5 mmol) and *N*-chloro- or *N*-bromosuccinimide (6.5 mmol) in dichloromethane (100 mL) was added. The reaction was complete after 5 min. The residue obtained upon removal of the solvent was purified by column chromatography and gave the vinyl azide.

4.1.1. Diethyl 2-azido-3-chlorobut-2-enedioate 8a. The title compound was purified by column chromatography [ethyl acetate/hexane (3:1)] and isolated directly as an oil as a mixture of isomers (90%). ν_{max} (film) 1601, 1734 and 2125 cm^{-1}; δ_H 1.25–1.39 (m, 6H), 4.28 and 4.38 (q, together 4H); δ_C 13.8, 13.9, 62.7, 63.2, 114.8 (C–Cl), 136.8 (C–N$_3$), 160.6 and 161.8. Accurate mass (CI): 247.036. C$_8$H$_{10}$ClN$_3$O$_4$ requires 247.036.

4.1.2. Dimethyl 2-azido-3-chlorobut-2-enedioate 8b. The title compound was purified by column chromatography [dichloromethane] (75%). δ_H [both isomers (32:68)] 3.83 and 3.86 (s, together 3H), 3.91 and 3.95 (s, together 3H). *Major isomer* (isolated from the mixture by crystallization): mp 48–50°C (from pentane) (Found: C, 33.07; H, 2.79; N, 18.60. C$_6$H$_6$ClN$_3$O$_4$ requires C, 32.88; H, 2.74; N, 19.18%); ν_{max} (KBr) 1678, 1709, 1721 and 2137 cm^{-1}; δ_H 3.83 (3H,

s) and 3.91 (3H, s); δ_C 63.5, 63.7, 114.3 (C–Cl), 137.6 (C–N$_3$), 161.2 and 162.3. Accurate mass (CI): 220.012 [MH]$^+$. C$_6$H$_7$ClN$_3$O$_4$ requires 220.012.

4.1.3. Dimethyl 2-azido-3-bromobut-2-enedioate 8c. The title compound was purified by column chromatography [dichloromethane] and was isolated directly as an oil (89%). ^{1}H NMR [both isomers (24:76)] 3.83 and 3.84 (s, together 3H), 3.92 and 3.93 (s, together 3H). *Major isomer* (isolated from the mixture by crystallization): mp 49–50°C (from ethyl ether/pentane); ν_{max} (KBr) 1599, 1737 and 2120 cm^{-1}; δ_H 3.83 (3H, s) and 3.92 (3H, s); δ_C 53.9, 54.0, 105.4 (C–Br), 138.9 (C–N$_3$), 161.4 and 163.4. Accurate mass (CI): 263.961 [MH]$^+$. C$_6$H$_7$BrN$_3$O$_4$ requires 263.961.

4.1.4. Ethyl 3-azido-2-chloro-3-phenylpropenoate 8d. The title compound was purified by column chromatography [ethyl acetate/hexane (3:1)] and was isolated directly as an oil (98%). It can be characterized by IR spectroscopy [ν_{max} (film) 1697, 1734, 2120 and 2986 cm^{-1}] and ^{1}H NMR [δ_H 1.26 (3H, t) and 4.12 (2H, q)]. Attempts to purify this alkene in order to get more characterization data led to the isolation of the corresponding 2*H*-azirine.

4.1.5. Ethyl 3-azido-2-bromo-3-phenylpropenoate 8e. The title compound was purified by column chromatography [ethyl acetate/hexane (3:1)] and was isolated directly as an oil (60%). It can be characterized by IR spectroscopy [ν_{max} (film) 1695 and 2135 cm^{-1}]. Attempts to purify this alkene in order to get more characterization data led to the isolation of the corresponding 2*H*-azirine.

4.1.6. Methyl 2-azido-3-chloro-3-benzoylpropenoate 8i. The title compound was purified by column chromatography [ethyl acetate/hexane (6:1)] and was isolated directly as a solid (40%). Mp 62–64°C. (Found: C, 49.0; H, 2.7; N, 15.8. C$_{11}$H$_8$ClN$_3$O$_3$ requires C, 49.7; H, 3.0; N, 15.8%), ν_{max} (KBr) 1674, 1732 and 2137 cm^{-1}; δ_H 3.58 (3H, s), 7.48 (2H, t, *J*=16 Hz, Ar–H), 7.60–7.64 (1H, m, Ar–H) and 7.87–7.89 (2H, m, Ar–H); δ_C 53.1, 129.0, 129.4, 129.6 (C–Cl), 134.1, 134.3 (C–N$_3$), 160.4 and 187.5. Accurate mass (CI): 283.059 [M+NH$_4$]$^+$. C$_{11}$H$_{12}$ClN$_4$O$_3$ requires 283.059.

4.1.7. Methyl 2-azido-3-bromo-3-benzoylpropenoate 8j. The title compound was purified by column chromatography [ethyl acetate/hexane (6:1)] and was isolated directly as a solid (44%). Mp 73–74°C. (Found: C, 42.6; H, 2.6; N, 13.4. C$_{11}$H$_8$BrN$_3$O$_3$ requires C, 42.6; H, 2.6; N, 13.6%). ν_{max} (film) 1601, 1663, 1732 and 2124 cm^{-1}; δ_H 3.57 (3H, s), 7.48–7.53 (2H, m, Ar–H, H–C-*m*), 7.60–7.63 (1H, m, Ar–H, H–C-*p*) and 7.87–7.91 (2H, m, Ar–H, H–C-*o*); δ_C 53.2 (CH$_3$), 117.6 (C–Br), 128.8 (Ar, C-*m*), 129.4 (Ar, C-*o*), 131.2 (Ar, C-*ipso*), 133.9 (C–N$_3$), 134.1 (Ar, C-*p*), 159.9 (*C*O$_2$CH$_3$) and 188.1 (*C*OPh). Accurate mass (CI): 327.009 [M+NH$_4$]$^+$. C$_{11}$H$_{12}$BrN$_4$O$_3$ requires 327.009.

4.1.8. Methyl 3-azido-2-bromobut-2-enoate 8m. The title compound was purified by column chromatography [dichloromethane] and was isolated directly as an oil (93%). ν_{max} (film) 1673, 1745 and 2131 cm^{-1}; δ_H 2.30 (3H, s), 3.74 (3H, s); δ_C 20.1, 52.8, 99.9 (C–Br), 143.9

(C–N$_3$) and 162.6. Accurate mass (CI): 219.972 [MH]$^+$. C$_5$H$_7$BrN$_3$O$_2$ requires 219.972.

4.2. General procedure for the synthesis of the iodoazidoalkenes

The ylide (4.5 mmol) was dissolved in dichloromethane (50 mL) and a solution of azidotrimethyilsilane (0.71 g, 6.5 mmol) and *N*-iodosuccinimide (13 mmol) in dichloromethane (100 mL) was added. The reaction was complete after 4.5 h. The residue obtained upon removal of the solvent was purified by column chromatography [ethyl acetate/hexane (1:2)] giving the vinyl azide.

4.2.1. Ethyl 3-azido-2-iodo-3-phenylpropenoate 8f. 65%. ν_{max} (film) 1691, 2114 and 2983 cm^{-1}; δ_H 0.92 (3H, t), 3.95 (2H, q), 7.27–7.31 (2H, m, Ar–H), 7.46–7.51 (1H, m, Ar–H) and 7.61–7.69 (2H, m, Ar–H).

4.2.2. Methyl 3-azido-2-iodo-3-phenylpropenoate 8h. 37%. ν_{max} (film) 1693, 1716, 2135 and 2999 cm^{-1}; δ_H 3.51 (3H, s), 7.26–7.29 (2H, m, Ar–H), 7.43–7.49 (1H, m, Ar–H) and 7.59–7.65 (2H, m, Ar–H); δ_C 52.9, 73.5 (C–I), 153.9 (C–N$_3$) and 172.5.

4.2.3. Methyl 2-azido-3-iodo-3-benzoylpropenoate 8l. 43%. ν_{max} (film) 1660, 1724 and 2125 cm^{-1}; δ_H 3.57 (3H, s) and 7.47–7.90 (5H, m, Ar–H).

4.2.4. Methyl 3-azido-2-iodo-but-2-enoate 8n. The titled compound was isolated directly as an oil (73%). ν_{max} (film) 1709 and 2110 cm^{-1}; δ_H 2.43 (3H, s) and 3.81 (3H, s); δ_C 23.7, 63.1, 72.9 (C–I), 146.1 (C–N$_3$) and 164.6.

4.3. General procedure for the synthesis of 2*H*-azirines

A solution of the vinyl azide (2.0 mmol) in heptane (10 mL) was heated under reflux for 2–3 h (the reaction was monitored by TLC). The reaction mixture was cooled and the solvent evaporated giving the azirine.

4.3.1. Diethyl 2-chloro-2*H*-azirine-2,3-dicarboxylate 9a. The title compound was isolated directly as an oil (98%). ν_{max} (film) 1628 and 1733 cm^{-1}. δ_H 1.29 (3H, t), 1.43 (3H, t), 4.26 (2H, q) and 4.50 (2H, q); δ_C 13.9, 14.0, 63.3 (C-2), 63.9, 64.6, 154.67 (C-3), 162.7 and 165.4; *m/z* (CI) [Tetraethyl pyrazine-2,3,5,6-tetracarboxylate] 386 [M+NH$_4$]$^+$ (12%), 369 [MH]$^+$ (5), 302 (10), 285 (100) and 203 (16).

4.3.2. Dimethyl 2-chloro-2*H*-azirine-2,3-dicarboxylate 9b. The title compound was isolated directly as an oil (99%). ν_{max} (film) 1652 and 1755 cm^{-1}. δ_H 3.85 (3H, s) and 3.90 (3H, s); δ_C 54.39, 54.57 (C-2 and CH$_3$), 155.0 (C-3), 162.6 and 165.7; *m/z* (CI) [Tetramethyl pyrazine-2,3,5,6-tetracarboxylate] 330 [M+NH$_4$]$^+$ (16%), 313 [MH]$^+$ (6), 194 (62), 175 (52) and 160 (100).

4.3.3. Dimethyl 2-bromo-2*H*-azirine-2,3-dicarboxylate 9c. The title compound was isolated directly as an oil (98%). ν_{max} (film) 1653 and 1749 cm^{-1}. δ_H 3.85 (3H, s) and 4.09 (3H, s); δ_C 42.9 (C-2), 54.5, 155.0 (C-3), 163.1 and 165.3; *m/z* (CI) [Tetramethyl pyrazine-2,3,5,6-tetra-

carboxylate] 330 [M+NH$_4$]$^+$ (100%), 313 [MH]$^+$ (28), 194 (27), 175 (35) and 160 (26).

4.3.4. Ethyl 2-chloro-3-phenyl-2*H*-azirine-2-carboxylate 9d. The title compound was isolated directly as an oil (97%). ν_{max} (film) 1745 and 2984 cm^{-1}; δ_H 1.27 (3H, t), 4.27 (2H, q), 7.60–7.66 (2H, m, Ar–H), 7.70–7.76 (1H, m, Ar–H) and 7.93–7.97 (2H, m, Ar–H); δ_C 13.9, 54.0 (C-2), 63.2, 119.6, 129.6, 130.7, 134.9, 163.5 (C-3) and 167.3. Accurate mass (CI): 241.074 [M+NH$_4$]$^+$. C$_{11}$H$_{14}$ClN$_2$O$_2$ requires 241.074.

4.3.5. Ethyl 2-bromo-3-phenyl-2*H*-azirine-2-carboxylate 9e. The title compound was isolated directly as an oil (97%). (Found: C, 49.24; H, 5.76; N, 5.22. C$_{11}$H$_{10}$BrNO$_2$ requires C, 49.24; H, 5.75; N, 5.67%). ν_{max} (film) 1742 and 2984 cm^{-1}; δ_H 1.28 (3H, t), 4.27 (2H, q), 7.61–7.66 (2H, m, Ar–H), 7.71–7.77 (1H, m, Ar–H) and 7.95–7.99 (2H, m, Ar–H); δ_C 14.1, 44.2 (C-2), 63.6, 119.8, 129.7, 130.9, 135.1, 164.5 (C-3) and 166.7; *m/z* (EI) M$^+$ 268 (35%), 241 (20), 222 (10), 196 (18), 188 (86) and 89 (100).

4.3.6. Ethyl 2-iodo-3-phenyl-2*H*-azirine-2-carboxylate 9f. The title compound was isolated directly as an oil (36%). δ_H 1.28 (3H, t), 4.22 (2H, q), 7.60–7.65 (2H, m, Ar–H), 7.71–7.74 (1H, m, Ar–H) and 7.91–7.94 (2H, m, Ar–H). Accurate mass (CI): 333.009 [M+NH$_4$]$^+$. C$_{11}$H$_{14}$IN$_2$O$_2$ requires 333.010.

4.3.7. Methyl 2-bromo-3-phenyl-2*H*-azirine-2-carboxylate 9g. 89%, directly from ylide 1c and after purification by column chromatography with ethyl acetate/hexane (1:2). (Found: C, 47.46; H, 3.11; N, 5.48. C$_{10}$H$_8$BrNO$_2$ requires C, 47.27; H, 3.17; N, 5.51%). ν_{max} (film) 1670, 1759 and 2954 cm^{-1}; δ_H 3.82 (3H, s), 7.62–7.67 (2H, m, Ar–H), 7.72–7.78 (1H, m, Ar–H) and 7.95–7.99 (2H, m, Ar–H); δ_C 43.7 (C-2), 54.2, 119.7, 129.7, 131.0, 135.2, 164.4 (C-3) and 167.2.

4.3.8. Methyl 2-iodo-3-phenyl-2*H*-azirine-2-carboxylate 9h. 77%. ν_{max} (film) 1756 cm^{-1}; δ_H 3.82 (3H, s), 7.63–7.68 (2H, m, Ar–H), 7.73–7.79 (1H, m, Ar–H) and 7.94–7.98 (2H, m, Ar–H). Accurate mass (EI): 301.9666. C$_{10}$H$_9$INO$_2$ requires 301.9678.

4.3.9. Methyl 2-benzoyl-2-chloro-2*H*-azirine-3-carboxylate 9i. The title compound was isolated directly as an oil (97%). ν_{max} (film) 1680, 1748 and 2961 cm^{-1}. δ_H 3.85 (3H, s), 7.56–7.64 (2H, m, Ar–H), 7.73–7.81 (1H, m, Ar–H) and 8.17–8.22 (2H, m, Ar–H); δ_C 54.4 (C-2 and CH$_3$), 129.6, 129.9, 133.8, 136.5, 164.3, 166.4 (C-3) and 179.1. Accurate mass (EI): 237.019. C$_{11}$H$_8$ClNO$_3$ requires 237.019.

4.3.10. Methyl 2-benzoyl-2-bromo-2*H*-azirine-3-carboxylate 9j. The title compound was isolated directly as an oil (98%). (Found: C, 47.29; H, 2.81; N, 4.58. C$_{11}$H$_8$BrNO$_3$ requires C, 46.84; H, 2.86; N, 4.97. ν_{max} (film) 1674, 1748 and 2834 cm^{-1}; δ_H 3.87 (3H, s), 7.60–7.65 (2H, m, Ar–H), 7.70–7.82 (1H, m, Ar–H) and 8.21–8.25 (2H, m, Ar–H); δ_C 42.8 (C-2), 54.6, 129.5, 129.9, 133.8, 136.5, 164.6, 165.9 (C-3) and 178.8; *m/z* (EI) [M(^{81}Br)$^+$],

283 (36%), [M(^{79}Br)$^+$], 281 (36%), 128 (8), 105 (100) and 77 (91).

4.3.11. Methyl 2-benzoyl-2-iodo-2H-azirine-3-carboxylate 9l. 36%. δ_H 4.10 (3H, s), 7.47–7.56 (3H, m, Ar–H) and 8.00–8.07 (2H, m, Ar–H). Accurate mass (EI): 328.9549. $C_{11}H_8NO_3I$ requires 328.9547.

4.3.12. Methyl 2-bromo-3-methyl-2H-azirine-2-carboxylate 9m. The title compound was isolated directly as an oil (99%). ν_{max} (film) 1693 and 1747 cm^{-1}. δ_H 2.58 (3H, s) and 3.77 (3H, s); δ_C 10.74, 43.44 (C-2), 53.95, 166.91 (C-3) and 167.49. Accurate mass (CI): 208.992 [M+NH$_4$]$^+$. $C_5H_{10}BrN_2O_2$ requires 208.992.

4.3.13. Methyl 2-iodo-3-methyl-2H-azirine-3-carboxylate 9n. 85%, ν_{max} (film) 1734 cm^{-1}. δ_H 2.56 (3H, s) and 3.80 (3H, s); δ_C 11.4, 13.7 (C-2), 54.3, 166.6 (C-3) and 167.7; *m/z* (CI) 257 [M+NH$_4$]$^+$ (1%), 239 (2), 224 (10), 130 (4) and 86 (26). The 2-iodo-2H-azirine **9n** was converted into its halide displacement product on reacting with potassium phthalimide as described previously:[11] methyl 2-phthalimido-3-methyl-2H-azirine-2-carboxylate δ_H 2.81 (3H, s), 3.77 (3H, s), 7.76–7.79 (2H, m) and 7.87–7.90 (2H, m); δ_C 13.0, 41.2 (C-2), 53.3, 123.8, 131.7, 134.5, 159.9 (C-3), 167.2 and 168.1. Accurate mass (CI): 276.098 [M+NH$_4$]$^+$. $C_{13}H_{14}N_3O^4$ requires 276.098.

4.3.14. Tetramethyl pyrazine-2,3,5,6-tetracarboxylate 10b. 2%. A solution of the dimethyl 2-bromo-2H-azirine-2,3-dicarboxylate **9c** (2.0 mmol) in heptane (10 mL) was heated under reflux for 17 h. The residue obtained upon removal of the solvent was purified by column chromatography [ethyl acetate/hexane (1:1)] giving the pyrazine. Mp 180–182°C (lit.[15] mp 181–182°C). ν_{max} (film) 1664 and 1745 cm^{-1}. δ_H 4.04 (12H, s); δ_C 53.8, 145.1 and 163.4. Accurate mass (CI): 313.066 [M+NH$_4$]$^+$. $C_{12}H_{13}N_2O_8$ requires 313.067.

References

1. Rocha Gonsalves, A. M. d'A; Cabral, A. M. T. D. P. V.; Pinho e Melo, T. M. V. D.; Gilchrist, T. L. *Synthesis* **1997**, 673–676.
2. Pinho e Melo, T. M. V. D.; Rocha Gonsalves, A. M. d'A.; Carrapato, S. M. S.; Taborda, A. M. O. M. P. *Molecules* **1999**, *4*, 219–231.
3. Denney, D. B.; Ross, S. T. *J. Org. Chem.* **1962**, *27*, 998–1000.
4. Murphy, P. J.; Lee, S. E. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3049–3066.
5. Abell, A. D.; Hoult, D. A.; Morris, K. M.; Taylor, J. M.; Trent, J. O. *J. Org. Chem.* **1995**, *58*, 1531–1537.
6. (a) Backes, J. *Methoden der Organischen Chemie (Houben-Weyl)*, Vol. E16; Georg Thieme Verlag: Stuttgart, 1992; pp 316–369. (b) Padwa, A.; Woolhouse, A. D. *Comprehensive Heterocyclic Chemistry*, Vol. 7; Pergamon: Oxford, 1984; pp 47–93.
7. L'abbé, G.; Dekerk, J.-P.; Van Stappen, P. *Bull. Soc. Chim. Belg.* **1981**, *90*, 1073–1074.
8. (a) Ciabattoni, J.; Cabell, Jr., M. *J. Am. Chem. Soc.* **1971**, *93*, 1482–1483. (b) Padwa, A.; Blacklock, T. J.; Carlsen, P. H. J.; Pulwer, M. *J. Org. Chem.* **1979**, *44*, 3281–3287. (c) Gallagher, T. C.; Sasse, M. J.; Storr, R. C. *Chem. Commun.* **1979**, 419–420. (d) Gallagher, T. C.; Storr, R. C. *Tetrahedron Lett.* **1981**, *27*, 2905–2908. (e) Hamana, H.; Sugasawa, T. *Chem. Lett.* **1985**, 571–574.
9. (a) Banks, R. E.; McGlinchey, M. J. *J. Chem. Soc. (C)* **1970**, 2172–2175. (b) Banks, R. E.; Moore, G. J. *J. Chem. Soc. (C)* **1966**, 2304–2307. (c) Morawietz, J.; Sander, W. *J. Org. Chem.* **1996**, *61*, 4351–4354.
10. Pinho e Melo, T. M. V. D.; Rocha Gonsalves, A. M. d'A.; Lopes, C. S. J.; Gilchrist, T. L. *Tetrahedron Lett.* **1999**, *40*, 789–792.
11. Pinho e Melo, T. M. V. D.; Lopes, C. S. J.; Rocha Gonsalves, A. M. d'A. *Tetrahedron Lett.* **2000**, *41*, 7217–7220.
12. Aitken, R. A.; Hérion, H.; Janosi, A.; Raut, S. V.; Seth, S.; Shannon, I. J.; Smith, F. C. *Tetrahedron Lett.* **1993**, *34*, 5621–5622.
13. Aitken, R. A.; Hérion, H.; Janosi, A.; Karodia, N.; Raut, S. V.; Seth, S.; Shannon, I. J.; Smith, F. C. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2467–2471.
14. Wasserman, H. H.; Ennis, D. S.; Blum, C. A.; Rotello, V. M. *Tetrahedron Lett.* **1992**, *33*, 6003–6006.
15. (a) Williams, J. R.; Cossey, J. J.; Adler, M. *J. Org. Chem.* **1972**, *37*, 2963–2965. (b) Mager, H. I. X.; Berends, W. *Recl. Trav. Chim. Pays-Bas* **1960**, *79*, 282–284.