Reactivity of 2-Halo-2*H*-azirines. 1. Reactions with Nucleophiles

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Nucleophilic substitution reactions of 2-halo-*2H*-azirines **1a**, **1b**, **1d**, and **1e** with potassium phthalimide and aniline allowed the preparation of new substituted *2H*-azirines **2**−**5**. The reactions of 2-bromo-*2H*-azirine **1a** with methylamine led to the synthesis of α-diimines **7** and **8**. 2-Halo-*2H*-azirines were also established as building blocks for the synthesis of a range of heterocyclic compounds, namely, quinoxalines **10a**−**10d**, 3-oxazoline **14**, and *2H*-[1,4]oxazines **18** and **20**. X-ray crystal structures of α-diimine **7**, 3-oxazoline **14**, and *2H*-[1,4]oxazine **18** are reported.

Introduction

2*H*-Azirines are the smallest unsaturated heterocyclic compounds containing nitrogen. Due to their high reactivity, 2*H*-azirines have been explored extensively for various synthetic purposes.[1]

These heterocycles undergo reactions in which they can function either as a nucleophile or as an electrophile. The *N*-lone pair on the azirine allows the reaction with electrophiles despite the basicity of the nitrogen atom in the azirine being much lower than in simple aliphatic amines. The acid-catalyzed hydrolysis of 2*H*-azirines to give α-amino ketones is one example where the azirine acts as a nucleophile. The polarized carbon−nitrogen double bond is responsible for the electrophilic character of the azirine ring.

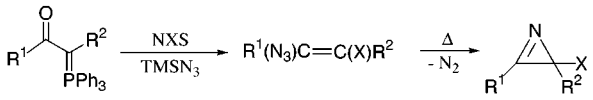
After the initial addition to the imine bond, the reaction of 2*H*-azirines with nucleophiles allows, in some cases, the isolation of the corresponding aziridine, but in other cases, the products are the result of the ring opening and further reactions of the initially formed aziridine.[1,2] The susceptibility of 2*H*-azirines to nucleophilic attack originates in the fact that the addition reaction involves a relief of the ring strain. In fact the strain energy of the 2*H*-azirine ring has been described as being greater than 170 kJ mol^{-1}, and the addition across the imine bond reduces this value by 109 kJ mol^{-1}.[1a]

The study of the reactivity of 2-halo-2*H*-azirines is of particular interest since this system can also undergo halide displacement on reacting with nucleophiles. In contrast with other *2H*-azirine derivatives, the reactivity of 2-halo-2*H*-azirines is almost unexplored. However, studies of the reactivity of 2-chloro-2,3-dimethyl-2*H*-azirine and 2-chloro-2,3-diphenyl-2*H*-azirine revealed the great lability of chlorine in these systems.[3,4]

We have reported a general route to 2-halo-2*H*-azirines starting from α-oxophosphonium ylides which led to new 2-iodo-, 2-bromo-, and 2-chloro-2*H*-azirines (Scheme 1).[5]

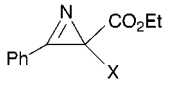
Having access to a broad range of the 2-halo-2*H*-azirines, we decided to study the reactivity of these compounds toward nucleophiles. Our preliminary results confirmed that 2-halo-2*H*-azirines could be used to prepare new 2*H*-azirine derivatives, but they could also lead to the synthesis of other interesting structures.[5b] In this paper we describe the full details of an extensive study of the reactions of 2-halo-2*H*-azirines with nuclephiles.

Scheme 1

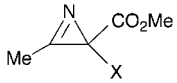


Results and Discussion

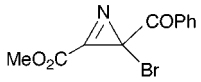
Using the synthetic strategy outlined in Scheme 1, a variety of substituted 2-bromo-2*H*-azirines (**1a**, **1c**, **1e**, and **1f**) and 2-iodo-2*H*-azirines (**1b** and **1d**) were prepared. These 2-halo-2*H*-azirines have electron-withdrawing groups at C-2 but different types of substituents at C-3: 2*H*-azirines **1a** and **1b** have a phenyl group at this position, 2*H*-azirines **1c** and **1d** a methyl group, and 2*H*-azirines **1e** and **1f** an ester group.



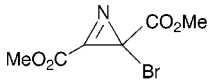
1a X = Br
1b X = I



1c X = Br
1d X = I



1e



1f

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† Departamento de Química.
‡ Departamento de Física.

(1) (a) Padwa, A.; Woolhouse, A. D. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 7, pp 47−93. (b) Nair, V. In *Heterocyclic Compounds*; Hassner, A., Eds.; John Wiley and Sons: New York, 1983; Vol. 42, Part I, pp 215−332.

(2) (a) L'abbé, G.; Van Stappen, P.; Dekerk, J.-P. *J. Chem. Soc., Chem. Commun.* **1982**, 784−785. (b) L'abbé, G.; Van Stappen, P.; Toppet, S.; Germain, G.; Scheefer, G. *Bull. Soc. Chim. Belg.* **1983**, *92*, 193−194. (c) Alves, M. J.; Gilchrist, T. L.; Sousa, J. H. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1305−1310. (d) Gilchrist, T. L.; Mendonça, R. *Synlett* **2000**, 1843−1845.

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(4) Gallagher, T. C.; Storr, R. C. *Tetrahedron Lett.* **1981**, *22*, 2905−2908.

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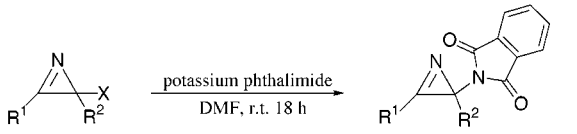
Scheme 2

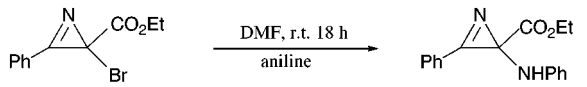


1a R^1 = Ph; R^2 = CO_2Et; X = Br
1b R^1 = Ph; R^2 = CO_2Et; X = I
1d R^1 = Me; R^2 = CO_2Me; X = I
1e R^1 = CO_2Me; R^2 = COPh; X = Br

2 R^1 = Ph; R^2 = CO_2Et 96%*
3 R^1 = Me; R^2 = CO_2Me 28%
4 R^1 = CO_2Me; R^2 = COPh 5%

*from **1a** (35% from **1b**)

Scheme 3



1a **5**, 11%

Our first objective was to evaluate the possibility of having selective nucleophilic substitution of the 2-halo-2*H*-azirines since the nucleophilic addition to the iminic double bond had to be considered. This could allow the use of halide displacement as a source of new 2*H*-azirine derivatives.

We started with the study of the reactivity of 2-bromo-2*H*-azirine **1a** using potassium phthalimide[6] as the nucleophile (Scheme 2). The reaction was carried out at room temperature, in DMF, leading to the synthesis of ethyl 3-phenyl-2-phthalimido-2*H*-azirine-2-carboxylate (**2**) in high yield (96%). The same product (**2**) was obtained in 35% yield from the reaction of 2-iodo-2*H*-azirine **1b** with potassium phthalimide. It was expected that the iodo-2*H*-azirines would undergo halide displacement more easily than the corresponding bromo derivatives. However, the lower stability of the 2-iodo-2*H*-azirine leads to a moderate yield of the nucleophilic substitution product **2**. A new phthalimido-2*H*-azirine derivative (**3**) was also obtained in 28% yield from 2-iodo-2*H*-azirine **1d**. Halide displacement reactions of 2-halo-2*H*-azirine **1e** using potassium phthalimide as the nucleophile led to the synthesis of the corresponding 2-substituted-*2H*-azirine derivatives **4** in low yield (5%). This type of 2-phthalimido-2*H*-azirine derivative is of particular interest since it may allow the development of a methodology for the synthesis of new amino acids.

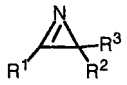
The reaction of 2-bromo-2*H*-azirine **1a** with aniline also gave the product of the nucleophilic substitution, the corresponding 2-phenylamino-2*H*-azirine **5** but this time in low yield (Scheme 3).

The ^{13}C NMR data are very useful for the characterization of 2*H*-azirine derivatives. In particular the ^{13}C NMR spectra of 2-halo-2*H*-azirines show the chemical shift of the sp^3 carbon (C-2) of the azirine ring in the range of 13−63 ppm, depending on the substitution pattern, and this signal is typically of low intensity. The chemical shift of the sp^2 carbon ranges from 155 to 167 ppm.[5] 2*H*-Azirines **2**, **3**, and **5**, obtained from the halide displacement reactions of 2-halo-2*H*-azirines **1a** and **1d** with potassium phthalimide and aniline, show ^{13}C NMR spectra which fit exactly with the characteristics described above for the spectra of 2*H*-azirine derivatives (Table 1).

Table 1. ^{13}C NMR in $CDCl_3$ of the *2H*-Azirines 1a, 1d, 2, 3, and 5

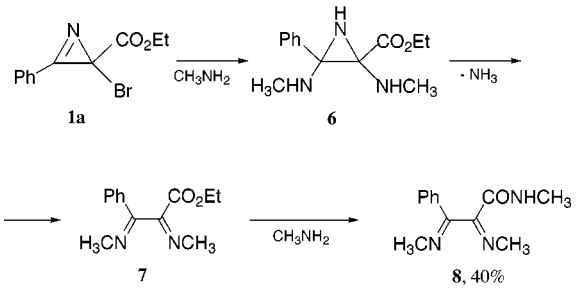
2*H*-azirine	^{13}C NMR (δ, ppm)	2*H*-azirine	^{13}C NMR (δ, ppm)
1a[5c]	44.2 (C-2), 164.5 (C-3)	**3**	41.2 (C-2), 159.9 (C-3)
1d[5c]	13.7 (C-2), 166.6 (C-3)	**5**	30.9 (C-2), 158.9 (C-3)
2	42.9 (C-2), 159.2 (C-3)		

Table 2. ^{13}C NMR in $CDCl_3$ of *2H*-Azirine Derivatives



2*H*-azirines			^{13}C NMR (δ, ppm) (CH_3)
R^1	R^2	R^3	
Ph	H	CH_3	18.9[1b]
Ph	Ph	CH_3	21.0[1b]
H	Ph	CH_3	21.7[1b]
CH_3	Ph	CH_3	12.1, 20.9[1b]
CH_3	Ph	Ph	12.5[1b]
CH_3	Ph	H	12.5[1b]
CH_3	Br	CO_2CH_3	10.7[5c]
CH_3	I	CO_2CH_3	11.4[5c]
CH_3	phthalimido	CO_2CH_3	13.0 (3)

Scheme 4



1a **6** **7** **8**, 40%

On the basis of the comparison of the ^{13}C NMR spectrum of 2*H*-azirine **3** with ^{13}C NMR spectra of other 2*H*-azirines reported in the literature (Table 2), we could rule out the possibility of the halide displacement reaction occurring through an S_N2' process. This pathway would lead to an isomer of 2*H*-azirine **3**, a 2*H*-azirine bearing a methyl group at C-2. However, the ^{13}C NMR spectrum of compound **3** showed the chemical shift assigned to the methyl group consistent with the value expected for a methyl group at C-3 of the 2*H*-azirine ring.

To extend this chemistry, the reaction of 2*H*-azirine **1a** with methylamine was studied. However, in this case, the product was not a substituted 2*H*-azirine, but instead compound **7** was obtained in 6% yield (Scheme 4). The structure of this α-diimine was established by X-ray crystallography (Figure 1).

The 2*H*-azirine **1a** underwent halide displacement and addition to the iminic double bond, giving compound **6**. The opening of the aziridine ring and elimination of ammonia originated the diimine **7**. Performing the reaction in the presence of a large excess of methylamine using either DMF or acetone as solvent, compound **8** was obtained in 36% or 40% yield, respectively. Under these conditions, aminolysis of the ester group led to **8** instead of **7** (Scheme 4).

α-Diimines are a class of compounds which are useful intermediates for the synthesis of heterocycles and are also important in coordination chemistry, which makes

(5) (a) 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. (b) Pinho e Melo, T. M. V. D.; Lopes, C. S. J.; Rocha Gonsalves, A. M. d'A. *Tetrahedron Lett.* **2000**, *41*, 7217−7220. (c) Pinho e Melo, T. M. V. D.; Lopes, C. S. J.; Cardoso, A. L.; Rocha Gonsalves, A. M. d'A. *Tetrahedron* **2001**, *57*, 6203−6208.

(6) Manske, R. H. F. *Org. Synth.* **1932**, *12*, 10−11.

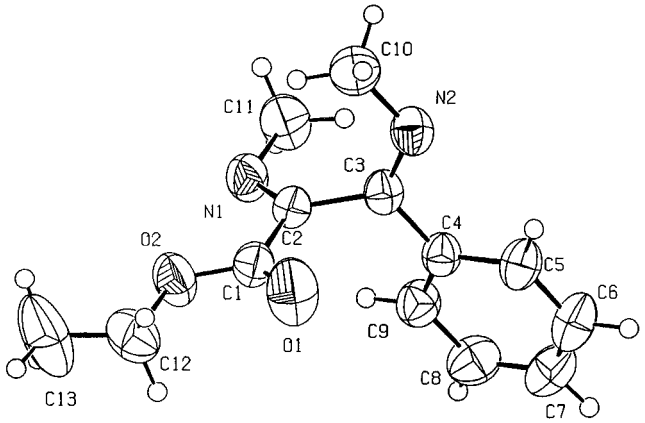
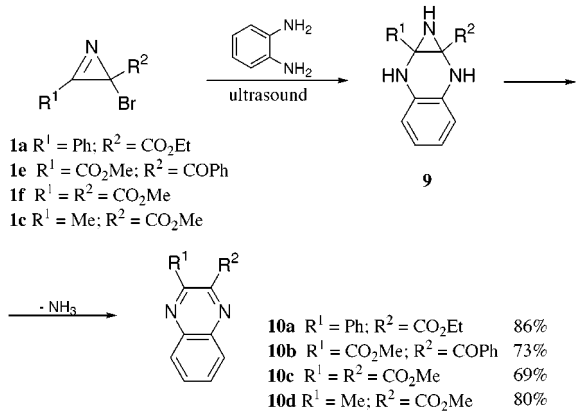


Figure 1. X-ray structure of compound **7**.

Scheme 5



the conversion of 2-halo-2*H*-azirine into this type of compound more appealing.[7]

The preceding results led us to explore the possibility of using doubly nucleophilic reagents to convert 2*H*-azirines into other heterocyclic compounds. 1,2-Phenylenediamine was selected as the nucleophile since its reaction with 2-halo-*2H*-azirines could lead to the synthesis of quinoxalines.

Attempts were made to promote the reaction of azirine **1a** with 1,2-phenylenediamine at room temperature and even at 65 °C, but there was no evidence of the expected product. However, quinoxaline **10a** was obtained in high yield (86%) when the reaction was carried out in an ultrasound bath (Scheme 5). Using the same reaction conditions, 2*H*-azirines **1e**, **1f**, and **1c** also reacted with 1,2-phenylenediamine to give the corresponding quinoxalines **10b** (73%), **10c** (69%), and **10d** (80%).

In a process analogous to the one described for the synthesis of α-diimines, 2*H*-azirines **1a**, **1e**, **1f**, and **1c** underwent halide displacement and addition to the iminic double bond on reacting with 1,2-phenylenediamine, giving **9**. The opening of the aziridine ring followed by the elimination of ammonia led to the quinoxalines (Scheme 5).

The reaction of 2-halo-2*H*-azirines with 1,2-phenylenediamine allowed the preparation of a range of substituted quinoxalines in high yield. The synthesis of these heterocycles is an area of considerable current interest due to their potential biological activity, namely, use in the treatment of epilepsy and Parkinson's and Alzheimer's diseases.[8] This new and efficient route to quinoxalines starting from 2-halo-2*H*-azirines presents itself as a very general method.

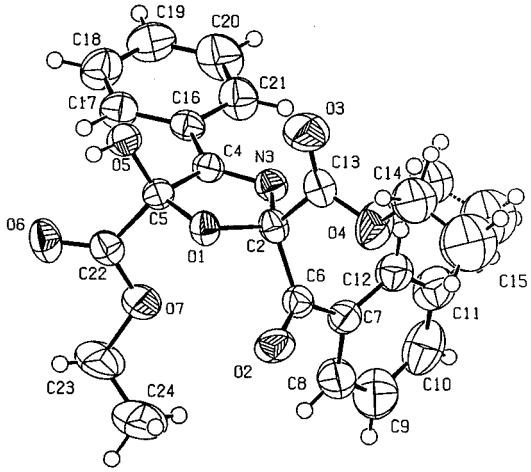
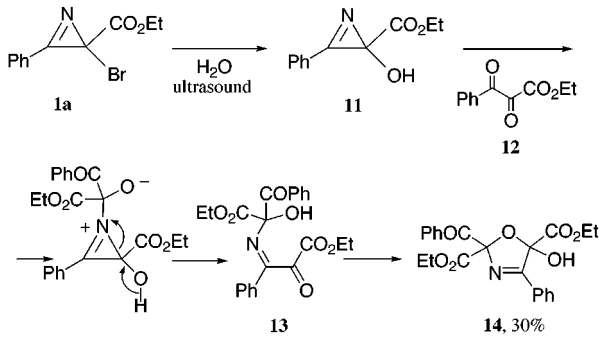


Figure 2. X-ray structure of compound **14**.

Scheme 6



The reactivity of 2-halo-2*H*-azirines with water was also studied. A solution of 2*H*-azirine **1a** in DMF/H_2O gave no reaction after 6 days at room temperature. However, when this reaction was carried out in an ultrasound bath for 2 days, 3-oxazoline **14** could be isolated in 30% yield (Scheme 6).

A single crystal was obtained of this product, and its structure was established by X-ray crystallography (Figure 2). The oxazoline ring is planar within 0.025(2) Å. The angle between the least-squares planes of the phenyl and oxazoline rings is 6.59(18)°. The crystal structure is stabilized by a three-dimensional network of hydrogen bonds between the hydroxyl group and the carbonyl O-2 atom of the benzoyl group with geometry O-5···O-2^{i} 2.834(3) Å, O-5−H-4···O-2^{i} 157.1° (symmetry code i: 2 − *x*, −*y*, −*z*).

Two molecules of opposite chirality were present in the crystal structure: diethyl (*2S*,*5R*)- and (*2R*,*5S*)-2-benzoyl-5-hydroxy-4-phenyl-3-oxazoline-2,5-dicarboxylate (**14a** and **14b**).

The ^{1}H and ^{13}C NMR spectra showed two sets of peaks (1:1 ratio), which clearly indicates that 3-oxazolines **14a** and **14b** were not the only products. A diffraction spectrum of the powder was obtained and compared with a simulation of the diffraction spectra for compounds **14a** and **14b** based on the X-ray diffraction data collected from the single crystal. This allowed us to confirm the

(7) (a) Boger, D. L.; Weinreb, S. N. *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic Press: San Diego, 1987; pp 274−276. (b) Aelterman, W.; De Kimpe, N.; Kulinkovich, O. *Bull. Soc. Chim. Belg.* **1997**, *106*, 703−708.

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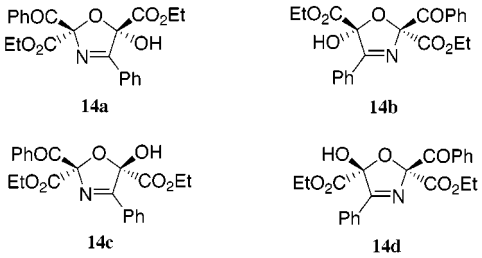
presence of a mixture. We could conclude that the four possible stereoisomers were formed (**14a**, **14b**, **14c**, and **14d**).



2*H*-Azirine **1a** underwent halide displacement on reacting with water, giving 2-hydroxy-2*H*-azirine **11**. Part of this azirine underwent ring opening and hydrolysis, leading to **12**. The reaction of this compound with the remaining 3-hydroxy-2*H*-azirine **11** gave 3-oxazoline **14** (Scheme 6).

Two different synthetic strategies for the preparation of 3-oxazolines using 2*H*-azirines as starting materials have been described. One of them involves the photochemical generation of nitrile ylides from 2*H*-azirines, which participate in dipolar cycloaddition reactions with aldehydes and ketones, giving 3-oxazolines.[9a,b] In the second approach, 3-oxazolines are formed from the reaction of methyl 3-phenyl-2*H*-azirine-2-acetate with aldehydes and acetone in the presence of DABCO.[10] The synthesis of 3-oxazolines described in this work is a novel route to this class of compounds.

The development of a synthetic approach to this class of molecules is of particular interest since various substituted 3-oxazolines show biological activity, namely, fungicidal activity and antidiabetes activity, and some derivatives have been used as artificial flavors.[9]

The reaction of ethanolamine, a doubly nucleophilic reagent, with 2-bromo-2*H*-azirine **1a** was explored. Our first approach was to promote the reaction at room temperature using ethanolamine, 10% in water, with a reaction time of 16 h. One product was obtained in 18% yield. When the reaction was carried out in an ultrasound bath for 4 h, the same product was obtained (7%).

The structure of this compound was established by X-ray crystallography as being 2*H*-[1,4]oxazine **18 (**Figure 3). The angle between the oxazine and phenyl rings is 36.22(8)°. The oxazine ring has a half-chair conformation, with puckering amplitude $Q = 0.484(3)$ Å. The angular puckering coordinates according to Cremer and Pople[11] are $\theta = 51.2(4)°$ and $\varphi = 329.2(4)°$. The phenyl ring is in an equatorial position, whereas the hydroxyl group is axial and the ethyl carboxylate group is in a bissectional position with respect to the oxazine ring. There is an intramolecular hydrogen bond between the hydroxyl group and the carbonyl O of the ethyl carboxylate group atom with geometry O-21···O-23 2.734(3) Å, angle O-21−H-21···O-23 104.90°. The hydroxyl O-21 atom participates in addition as a donor in an intermolecular hydrogen bond with the oxazine N atom of a neighboring molecule such that the molecules are joined in infinite chains parallel to the *c* axis [O-21···N-1^{i} 2.756(3) Å (symmetry code i: $x, -3/2 - y, 1/2 + z$)]. The hydroxyl H atom is therefore shared in a bifurcated hydrogen bond; as expected for such a bond, the sum of the bonding angles defined by the H atom is close to 360.

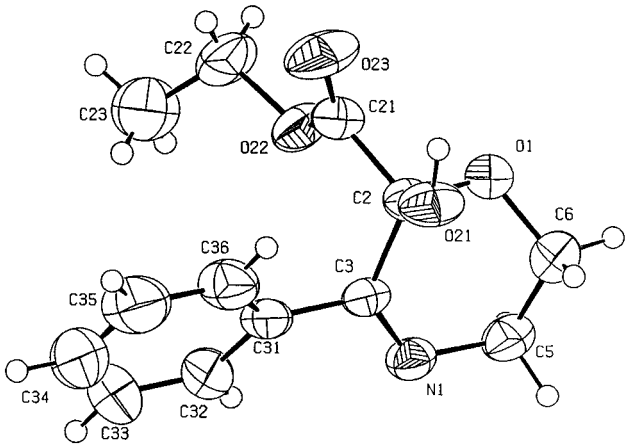
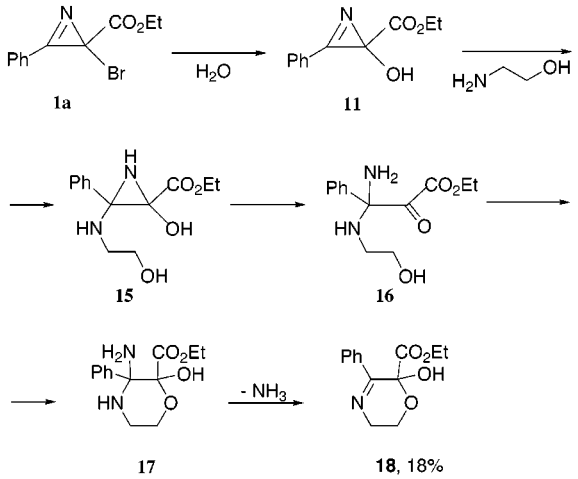


Figure 3. X-ray structure of compound **18**.

Scheme 7



The synthesis of 2*H*-[1,4]oxazine **18** can be rationalized as follows: The presence of water led to a nucleophilic substitution reaction with formation of 2-hydroxy-2*H*-azirine **11** as postulated also in the synthesis of 3-oxazoline **14**. Addition of the amino group from ethanolamine to the iminic double bond of the 2*H*-azirine **11** led to the corresponding aziridine, which underwent a ring-opening reaction. 2*H*-[1,4]Oxazine **18** was formed from the cyclization of this intermediate followed by elimination of ammonia (Scheme 7).

When the reaction of 2*H*-azirine **1a** was performed in the absence of water and using a large excess of ethanolamine, in an ultrasound bath, 2-amino-2*H*-[1,4]oxazine **20** was obtained in 59% yield (Scheme 8). Using these reaction conditions, azirine **1a** underwent halide displacement, and addition to the iminic double bond and the opening of the aziridine thus formed led to the formation of 2*H*-[1,4]oxazine **20**.

This synthesis of 2*H*-[1,4]oxazine **20** could indicate that this compound could be an intermediate when the reaction of 2*H*-azirine **1a** with ethanolamine is performed in the presence of water. In fact, the reaction of **20** with

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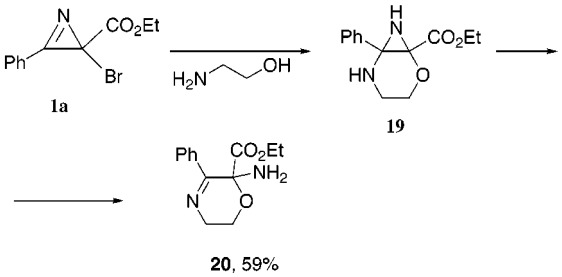
Scheme 8



water in the presence of HBr, which is a byproduct of this process, could lead to compound **18**. However, attempts to convert 2*H*-[1,4]oxazine **20** into 2*H*-[1,4]oxazine **18** by treatment with aqueous hydrobromic acid were unsuccessful. This observation reinforces the mechanism outlined in Scheme 7 for the synthesis of compound **18**.

Conclusion

In this work, we have described the results obtained from the reactions of halo-*2H*-azirines with potassium phthalimide and aniline, which led to products resulting from the halide displacement without evidence of nucleophilic addition to the iminic double bond. Thus, the reaction of 2-halo-2*H*-azirines with these nucleophiles can be used as a source of new azirine derivatives.

The yields obtained in the nucleophilic substitution reactions of 2-halo-2*H*-azirines with phthalimide reflect the relative stability of the 2*H*-azirines. In fact we have previously observed that 2-bromo-2*H*-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 proved to be more stable. The iodo-2*H*-azirines showed lower stability than the corresponding bromo derivatives.[5] In agreement with these observations, the best result was obtained with 2-bromo-3-phenyl-2*H*-azirine-2-carboxylate **1a**, allowing the synthesis of 3-phenyl-2-phthalimido-2*H*-azirine-2-carboxylate **2** in 96% yield.

Interestingly the reactions of 2-bromo-2*H*-azirine **1a** with methylamine led to the preparation of α-diimines **7** and **8**. Halo-*2H*-azirines were also used as building blocks for the synthesis of a 3-oxazoline (**14**) and *2H*-[1,4]-oxazines **18** and **20**.

A new and efficient route to quinoxalines involving the reaction of 2-halo-2*H*-azirines with 1,2-phenylenediamine was developed, allowing the synthesis of a range of quinoxalines (**10a**−**10d**) in high yield.

Experimental Section

General Procedures. ^{1}H NMR spectra were recorded on a Bruker AMX300 instrument operating at 300 MHz. ^{13}C NMR spectra were recorded on a Bruker AMX300 instrument operating at 75.5 MHz. The solvent was deuteriochloroform except where indicated otherwise. IR spectra were recorded on a Perkin-Elmer 1720X FTIR spectrometer. Mass spectra were recorded under electron impact (EI) at 70 eV on a VG Micromass 7070E instrument or where indicated by chemical ionization (CI) with ammonia. Melting points were recorded on a Reichert hot stage and are uncorrected. Flash column chromatography was performed with Merck 9385 silica as the stationary phase. A Bandeline Sonorex, RK 100H ultrasonic bath was used. 2-Halo-*2H*-azirines **1a**−**1f** were prepared as described in the literature.[5c]

General Procedure for the Halide Displacement of 2-Halo-2*H*-azirines with Potassium Phthalimide or Aniline. The 2-halo-2*H*-azirine (1 mol) was dissolved in DMF (10 mL), and potassium phthalimide[7] or aniline (1 mol) was added. The reaction mixture was stirred at room temperature for 18 h. Water (35 mL) was added, and the solution was extracted with chloroform (3 × 10 mL). The combined organic phases were washed with water (20 mL) and dried ($MgSO_4$). The solvent was evaporated, giving the azirine.

Ethyl 3-phenyl-2-phthalimido-2*H*-azirine-2-carboxylate (2): yield 96% from 2*H*-azirine **1a** and 35% from 2*H*-azirine **1b**; mp 144−145 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.21 (3H, t, J = 7.1 Hz), 4.25 (2H, q, J = 7.1 Hz), 7.60−7.78 (5H, m, Ar H), 7.85−7.89 (2H, m, Ar H), 8.22−8.25 (2H, m, Ar H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.1, 42.9 (C-2), 62.7, 121.1, 123.8, 129.2, 131.6, 131.8, 134.49, 134.5, 159.2 (C-3), 167.2, 167.6; MS (EI) *m*/*z* 334 (M^+, 18), 306 (33), 277 (20), 132 (9), 105 (100); HRMS (EI) *m*/*z* 334.0967 ($C_{19}H_{14}N_2O_4$, M^+, 334.0954).

Methyl 3-methyl-2-phthalimido-2*H*-azirine-2-carboxylate (3): oil; yield 28% from 2*H*-azirine **1d** (the reaction time was 2 days); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.81 (3H, s), 3.77 (3H, s), 7.76−7.79 (2H, m), 7.87−7.90 (2H, m); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 13.0, 41.2 (C-2), 53.3, 123.8, 131.7, 134.5, 159.9 (C-3), 167.2, 168.1; HRMS (CI) *m*/*z* 276.0987 ($C_{13}H_{14}N_3O_4$, $[M + NH_4]^+$, 276.0984).

Methyl 2-benzoyl-2-phthalimido-2*H*-azirine-3-carboxylate (4): yield 5%; mp 150−151 °C (from ethyl acetate−hexane); IR (KBr) 13722, 1726, 3384 cm^{-1}. MS (EI) *m*/*z* 348 (M^+, 100), 132 (19), 77 (20); HRMS (CI) *m*/*z* 349.0827 ($C_{19}H_{13}N_2O_5$, $[M + H]^+$, 349.0824).

Ethyl 3-phenyl-2-phenylamino-2*H*-azirine-2-carboxylate (5): yield 11% from 2*H*-azirine **1a**; mp 144−147 °C (from ethyl ether); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.39 (3H, t, J = 7.1 Hz), 4.41 (2H, q, J = 7.1 Hz), 6.85−6.88 (2H, m, Ar H), 7.09−7.13 (1H, m, Ar H), 7.18−7.23 (2H, m, Ar H), 7.37−7.53 (5H, m, Ar H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.2, 30.9 (C-2), 62.2, 119.4, 123.8, 125.8, 128.4, 129.0, 129.6, 130.6, 130.9, 136.6, 137.9, 158.9 (C-3), 167.5.

Reactions of Ethyl 2-Bromo-3-phenyl-2*H*-azirine-2-carboxylate (1a) with Methylamine. Ethyl 1,4-Diaza-1,4-dimethyl-3-phenyl-1,3-butadiene-2-carboxylate (7). The *2H*-azirine **1a** (0.59 g, 2.2 mmol) was dissolved in DMF (10 mL), and methylamine (35% in water, 68.2 mg, 2.2 mmol) was added. The reaction mixture was stirred at room temperature for 5 days. The solvent was evaporated, and the residue was subjected to flash chromatography [with hexane−ethyl acetate (2:1)], giving compound **7** (16 mg, 6%) as a solid: mp 62.5−64 °C (from ethyl ether−hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.30 (3H, t, J = 7.2 Hz), 3.34 (3H, s), 3.37 (3H, s), 4.31 and 4.32 (2H, 2q, J = 7.2 Hz), 7.40−7.45 (3H, m, Ar H), 7.62−7.65 (2H, m, Ar H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 13.9, 41.1, 42.2, 62.3, 126.4, 128.8, 130.9, 134.9, 161.6, 161.8, 163.6; MS (EI) *m*/*z* 232 (M^+, 20), 231 (40), 203 (6), 158 (12), 118 (100), 77 (100); HRMS (EI) *m*/*z* 231.1128 $[M + H]^+$ ($C_{13}H_{15}N_2O_2$, $M - H^+$, 231.1134).

***N*-Methyl-1,4-diaza-1,4-dimethyl-3-phenyl-1,3-butadiene-2-carboxamide (8).** The 2*H*-azirine **1a** (0.2 g, 0.75 mmol) was dissolved in DMF (5 mL), and methylamine (35% in water, 1.75 g, 56.3 mmol) was added. The reaction mixture was stirred at room temperature for 3 h. The solvent was evaporated, and the residue was subjected to flash chromatography [with hexane−ethyl acetate (1:2)], giving compound **8** (59 mg, 36%) as a solid: mp 82−84 °C (from ethyl ether−hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.92 (3H, d, J = 5.3 Hz), 3.24 (3H, s), 3.29 (3H, s), 7.34−7.39 (3H, m, Ar H), 7.58−7.62 (2H, m, Ar H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 25.8, 41.1, 41.2, 126.4, 128.7, 130.7, 135.5, 162.3, 163.6, 164.3; MS (EI) *m*/*z* 217 (M^+, 6), 216 (22), 119 (10), 118 (100), 77 (16); HRMS (CI) *m*/*z* 218.1296 ($C_{12}H_{16}N_3O$, $[M + H]^+$, 218.1293).

Reactions of 2-Halo-2*H*-azirines with 1,2-Phenylenediamine. General Procedure for the Synthesis of Quinoxalines. The *2H*-azirine (1.2 mmol) was dissolved in DMF (10 mL), and 1,2-phenylenediamine (136 mg, 1.2 mmol) was added. The reaction mixture was agitated in an ultrasound bath for 2 h. The solvent was evaporated, and the residue was subjected to flash chromatography [with hexane−ethyl acetate (2:1)], giving the quinoxaline as a solid.

Ethyl 3-phenylquinoxaline-2-carboxylate (10a): yield 86%; mp 51−52 °C (lit.[12] mp 51−53 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.18 (3 H, t, J = 7.1 Hz), 4.34 (2H, q, J = 7.2 Hz), 7.50−7.53 (3H, m, Ph H), 7.72−7.76 (2H, m, Ph H), 7.80−7.90 (2H, m, Ar H, H-6 and H-7), 8.18−8.25 (2H, m, Ar H, H-5 and H-8) [assignment of the aromatic protons made on the basis of a COSY (^{1}H, ^{1}H) spectrum]; ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 13.7 (CH_2CH_3), 62.4 (CH_2CH_3), 128.6 (CH, Ph), 128.7 (CH, Ph), 129.4 and 129.6 (CH, C-5 and C-8), 129.6 (CH, Ph), 130.6 and 131.7 (CH, C-6 and C-7), 137.8 (C), 139.9 (C), 142.3 (C), 145.8 (*C*=N), 152.3 (*C*=N), 166.6 (CO_2Et) [assignment made on the basis of a COSY (^{1}H, ^{13}C) spectrum]; MS (EI) *m*/*z* 278 (M^+, 29), 249 (27), 206 (100), 77 (23); HRMS (CI) *m*/*z* 279.1141 ($C_{17}H_{15}N_2O_2$, $[M + H]^+$, 279.1133).

Methyl 3-benzoylquinoxaline-2-carboxylate (10b): yield 73%; mp 98−100 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.98 (3H, s), 7.49−7.54 (2H, m, Ar H), 7.63−7.67 (1H, m, Ar H), 7.95−7.99 (4H, m, Ar H), 8.19−8.22 (1H, m, Ar H), 8.33−8.36 (1H, m, Ar H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 53.5, 128.7, 129.7, 130.3, 130.4, 132.1, 132.9, 134.0, 135.3, 141.0, 141.4, 143.0, 152.2, 164.8, 192.4; MS (EI) *m*/*z* 292 (M^+, 13), 233 (39), 105 (100), 77 (46); HRMS (CI) *m*/*z* 293.0925 ($C_{17}H_{13}N_2O_3$, $[M + H]^+$, 293.0926).

Dimethyl quinoxaline-2,3-dicarboxylate (10c): yield 69%; mp 132−133 °C (lit.[13] mp 132−133 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.10 (3 H, s), 7.94−7.97 (2 H, m, Ar H), 8.26−8.29 (2 H, m, Ar H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 53.6, 129.9, 132.7, 141.5, 143.9, 165.2; MS (EI) *m*/*z* 246 (M^+, 23), 216 (27), 130 (100), 102 (65); HRMS (CI) *m*/*z* 247.0715 ($C_{12}H_{11}N_2O_4$, $[M + H]^+$, 247.0718).

Methyl 2-methylquinoxaline-3-carboxylate (10d): yield 80%; mp 82−84 °C (lit.[12] mp 79−80 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.98 (3 H, s), 4.08 (3 H, s), 7.74−7.78 (1 H, m, Ar H), 7.81−7.85 (1H, m, Ar H), 8.05−8.07 (1 H, m, Ar H), 8.17−8.20 (1H, m, Ar H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 23.8 (Me), 53.2 (CO_2*Me*), 128.6 and 129.9 (CH, C-5 and C-8), 129.9 and 131.9 (CH, C-6 and C-7), 139.9 (C), 142.8 (C), 143.9 (*C*=N), 153.2 (*C*=N), 166.0 (CO_2Me) [assignment made on the basis of a COSY (^{1}H, ^{13}C) spectrum]; MS (EI) *m*/*z* 202 (M^+, 45), 144 (100), 102 (67), 77 (14), 76 (41); HRMS (CI) *m*/*z* 202.0741 ($C_{11}H_{10}N_2O_2$, M^+, 202.0742).

Reaction of 1a with Water. Diethyl 2-Benzoyl-5-hydroxy-4-phenyl-3-oxazoline-2,5-dicarboxylate (14). The 2*H*-azirine **1a** (0.52 g, 1.94 mmol) was dissolved in DMF (10 mL), and water (60 mg, 3.3 mmol) was added. The reaction mixture was agitated in an ultrasound bath for 2 days. The solvent was evaporated, and the residue was subjected to flash chromatography [with hexanes−ethyl acetate (3:1)], giving **14** (0.117 g, 30%) as a solid: mp 100−102 °C (from ethyl ether−hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.97 (3H, t, J = 7.2 Hz), 1.11 (3H, t, J = 7.2 Hz), 1.14 (3H, t, J = 7.2 Hz), 1.18 (3H, t, J = 7.2 Hz), 4.05−4.35 (8H, m), 5.08 (1H, br s), 5.21 (1H, br s), 7.39−7.55 (10H, m, Ar H), 7.58−7.62 (2H, m, Ar H), 7.96−8.02 (4H, m, Ar H), 8.18−8.26 (4H, m, Ar H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 13.5, 13.7, 62.6, 63.3, 63.5, 63.6, 105.2, 105.5, 109.9, 110.2, 128.2, 128.3, 128.4, 128.5, 128.7, 128.8, 129.0, 129.8, 129.9, 132.5, 132.6, 133.6, 133.7, 134.0, 165.5, 166.7, 167.3, 167.5, 167.9, 168.1, 188.6, 189.7; MS (CI) *m*/*z* 429 $[(M + NH_4)^+$, 4], 412 (37), 307 (56), 290 (100), 208 (21), 105 (11). Anal. Calcd for $C_{22}H_{21}NO_7$: C, 64.23; H, 5.14; N, 3.40. Found: C, 63.86; H, 5.25; N, 3.28.

Reactions of 1a with Ethanolamine. Ethyl 2-Hydroxy-3-phenyl-5,6-dihydro-2*H*-[1,4]oxazine-2-carboxylate (18). The *2H*-azirine **1a** (0.218 g, 0.81 mmol) was dissolved in DMF (5 mL), and ethanolamine (55 mg, 10% in water, 0.8 mmol) was added. The reaction mixture was stirred at room temperature for 16 h. The solvent was evaporated, and the residue was subjected to flash chromatography [with hexane−ethyl acetate (1:2)], giving compound **18** (32 mg, 18%) as a solid. Alternatively the reaction mixture can be agitated in an ultrasound bath for 4 h, giving compound **18** in 7% yield: mp 75−77 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.99 (3H, t, J = 7.1 Hz), 3.95−4.27 (6H, m), 4.52 (1H, s), 7.39−7.44 (3H, m, Ar H), 7.83−7.86 (2H, m, Ar H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 13.4, 47.7, 57.8, 63.1, 89.4, 127.1, 128.2, 130.0, 136.2, 161.3, 169.5; MS (EI) *m*/*z* 249 (M^+, 4), 176 (10), 103 (100), 77 (12).

Ethyl 2-Amino-3-phenyl-5,6-dihydro-2*H*-[1,4]oxazine-2-carboxylate (20). The *2H*-azirine **1a** (0.467 g, 1.74 mmol) was dissolved in DMF (10 mL), and ethanolamine (0.8 g, 13.01 mmol) was added. The reaction mixture was agitated in an ultrasound bath for 3 h. The solvent was evaporated, and the residue was dissolved in dichloromethane. The solution was washed with water (2 × 20 mL) and dried ($MgSO_4$). The solvent was evaporated, giving **20** (0.254 g, 59%) as a solid: mp 69−71 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.04 (3H, t, J = 7.1 Hz), 2.59 (2H, br s), 3.94 (4H, br s), 4.11−4.21 (2H, m), 7.33−7.37 (3H, m, Ar H), 7.88−7.91 (2H, m, Ar H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 13.6, 48.1, 57.6, 62.3, 82.5, 127.6, 128.1, 129.9, 136.4, 163.1, 168.9; HRMS (CI) *m*/*z* 249.1241 ($C_{13}H_{17}N_2O_3$, $[M + H]^+$, 249.1239).

Crystallographic Data. The X-ray data were collected on an Enraf-Nonius CAD-4 single-crystal diffractometer, at 298-(3) K, using graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). Intensities were recorded as full profiles of $\omega-2\theta$ scans. The structures were solved by direct methods as implemented in SHELXS97[14] and refined by full-matrix least-squares using SHELXL97.[15] Examination of the structure with PLATON[16] confirmed the absence of voids in the crystal structures which might be occupied by solvent molecules.

Crystal data for 7: $C_{13}H_{16}N_2O_2$, M = 232.28, crystal dimensions 0.34 × 0.24 × 0.10 mm^3, monoclinic, $P2_1/c$, a = 9.6956(11) Å, b = 8.727(3) Å, c = 15.2982(10) Å, α = 90°, β = 93.840(10)°, γ = 90°, V = 1291.5(5) Å^3, Z = 4, ρ_{calcd} = 1.195 g cm^{-3}, μ = 0.082 mm^{-1}, 2441 reflections measured, 2299 independent, R = 0.046 (1570 reflections with $I > 2\sigma(I)$, R_w = 0.136 for all reflections, GOF = 1.037, 186 parameters, non-H atoms refined anisotropically, H atoms refined as riding, residual density +0.26/−0.20 e Å^{-3}.

Crystal data for 14: $C_{22}H_{21}NO_7$, M = 411.40, crystal dimensions 0.39 × 0.27 × 0.12 mm^3, monoclinic, $P2_1/n$, a = 13.219(2) Å, b = 9.2485(14) Å, c = 17.148(4) Å, α = 90°, β = 90.54(2)°, γ = 90°, V = 2096.3(7) Å^3, Z = 4, ρ_{calcd} = 1.304 g cm^{-3}, μ = 0.098 mm^{-1}, 3845 reflections measured, 3676 independent, R = 0.054 (2298 reflections with $I > 2\sigma(I)$, R_w = 0.154 for all reflections, GOF = 1.183, 274 parameters, one of the ethyl groups (atoms C14 and C15) disordered over two positions with occupancies 0.62(2):0.38(2), non-H atoms refined anisotropically except for those disordered (C14 and C15), which were refined isotropically, H atoms refined as riding, residual density +0.32/−0.36 e A^{-3}.

Crystal data for 18: $C_{13}H_{15}NO_4$, M = 249.26, crystal dimensions 0.37 × 0.34 × 0.20 mm^3, monoclinic, $P2_1/c$, a = 14.155(5) Å, b = 8.165(2) Å, c = 11.741(5) Å, α = 90°, β = 109.17(3)°, γ = 90°, V = 1281.7(8) Å^3, Z = 4, ρ_{calcd} = 1.292 g cm^{-3}, μ = 0.096 mm^{-1}, 2689 reflections measured, 2238 independent, R = 0.045 (1016 reflections with $I > 2\sigma(I)$), R_w = 0.135 for all reflections, GOF = 0.986, 165 parameters, non-H atoms refined anisotropically, H atoms refined as riding, residual density +0.20/−0.20 e Å^{-3}.

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