

Reactivity of 2-Halo-2H-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

2H-Azirines are the smallest unsaturated heterocyclic compounds containing nitrogen. Due to their high reactivity, 2H-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 2H-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.

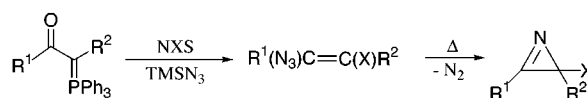
After the initial addition to the imine bond, the reaction of 2H-azirines with nucleophiles allows, in some cases, the isolation of the corresponding aziridine, but in other cases, the products are the result of the ring opening and further reactions of the initially formed aziridine.^{1,2} The susceptibility of 2H-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 2H-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-2H-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-2H-azirines is almost unexplored. However, studies of the reactivity of 2-chloro-2,3-dimethyl-2H-azirine and 2-chloro-2,3-diphenyl-2H-azirine revealed the great lability of chlorine in these systems.^{3,4}

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

Having access to a broad range of the 2-halo-2H-azirines, we decided to study the reactivity of these compounds toward nucleophiles. Our preliminary results con-

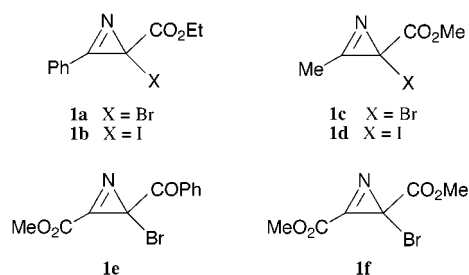
Scheme 1



firmed that 2-halo-2H-azirines could be used to prepare new 2H-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-2H-azirines with nucleophiles.

Results and Discussion

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



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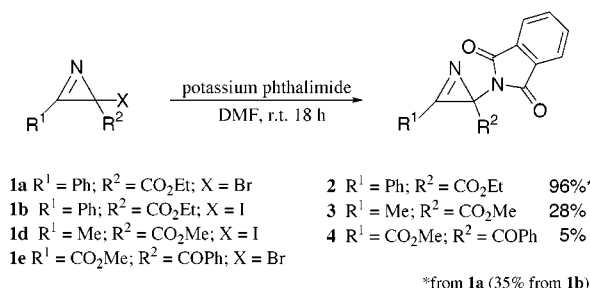
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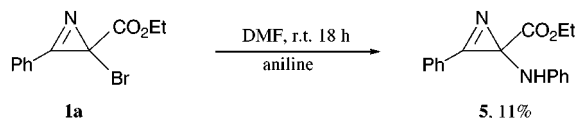
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Scheme 2



Scheme 3



Our first objective was to evaluate the possibility of having selective nucleophilic substitution of the 2-halo-2H-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 2H-azirine derivatives.

We started with the study of the reactivity of 2-bromo-2H-azirine **1a** using potassium phthalimide⁶ 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-2H-azirine-2-carboxylate (**2**) in high yield (96%). The same product (**2**) was obtained in 35% yield from the reaction of 2-iodo-2H-azirine **1b** with potassium phthalimide. It was expected that the iodo-2H-azirines would undergo halide displacement more easily than the corresponding bromo derivatives. However, the lower stability of the 2-iodo-2H-azirine leads to a moderate yield of the nucleophilic substitution product **2**. A new phthalimido-2H-azirine derivative (**3**) was also obtained in 28% yield from 2-iodo-2H-azirine **1d**. Halide displacement reactions of 2-halo-2H-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-2H-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-2H-azirine **1a** with aniline also gave the product of the nucleophilic substitution, the corresponding 2-phenylamino-2H-azirine **5** but this time in low yield (Scheme 3).

The ¹³C NMR data are very useful for the characterization of 2H-azirine derivatives. In particular the ¹³C NMR spectra of 2-halo-2H-azirines show the chemical shift of the sp³ 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 sp² carbon ranges from 155 to 167 ppm.⁵ 2H-Azirines **2**, **3**, and **5**, obtained from the halide displacement reactions of 2-halo-2H-azirines **1a** and **1d** with potassium phthalimide and aniline, show ¹³C NMR

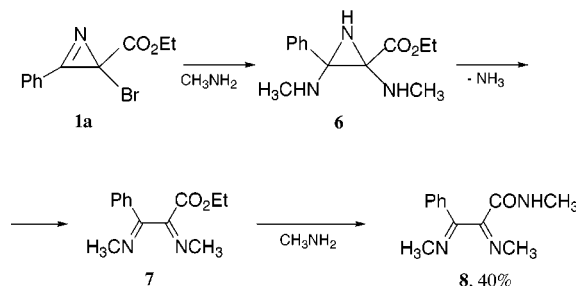
Table 1. ¹³C NMR in CDCl₃ of the 2H-Azirines **1a**, **1d**, **2**, **3**, and **5**

2H-azirine	¹³ C NMR (δ, ppm)	2H-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. ¹³C NMR in CDCl₃ of 2H-Azirine Derivatives

2H-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 ₂ CH ₃	10.7 ^{5c}
CH ₃	I	CO ₂ CH ₃	11.4 ^{5c}
CH ₃	phthalimido	CO ₂ CH ₃	13.0 (3)

Scheme 4



spectra which fit exactly with the characteristics described above for the spectra of 2H-azirine derivatives (Table 1).

On the basis of the comparison of the ¹³C NMR spectrum of 2H-azirine **3** with ¹³C NMR spectra of other 2H-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 2H-azirine **3**, a 2H-azirine bearing a methyl group at C-2. However, the ¹³C 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 2H-azirine ring.

To extend this chemistry, the reaction of 2H-azirine **1a** with methylamine was studied. However, in this case, the product was not a substituted 2H-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 2H-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

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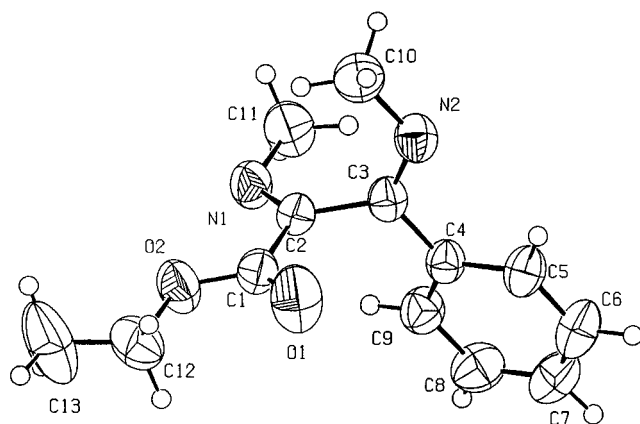
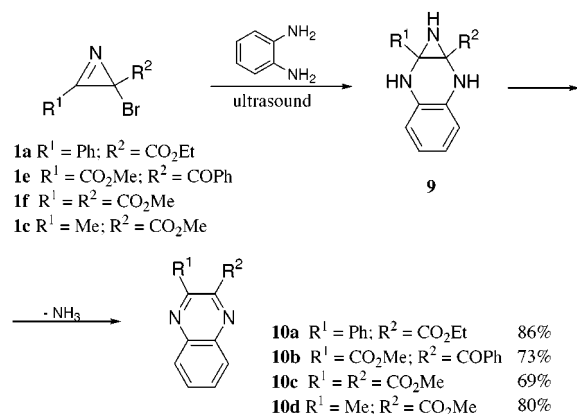


Figure 1. X-ray structure of compound 7.

Scheme 5



the conversion of 2-halo-2H-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 2H-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, 2H-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, 2H-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-2H-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-2H-azirines presents itself as a very general method.

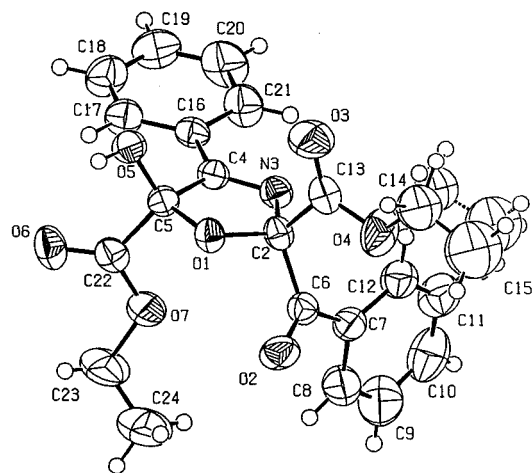
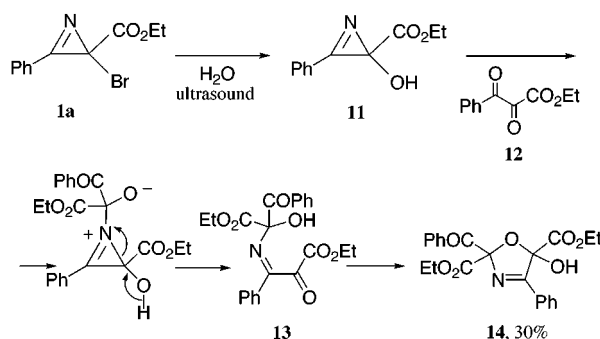


Figure 2. X-ray structure of compound 14.

Scheme 6



The reactivity of 2-halo-2H-azirines with water was also studied. A solution of 2H-azirine **1a** in DMF/H₂O 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-2ⁱ 2.834(3) Å, O-5-H-4...O-2ⁱ 157.1° (symmetry code i: 2 - x, -y, -z).

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

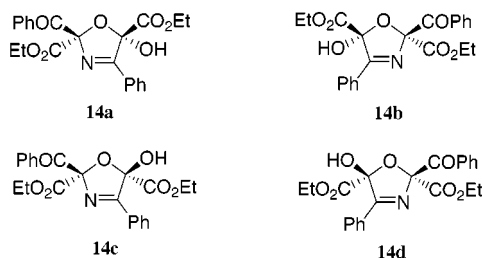
The ¹H and ¹³C NMR spectra showed two sets of peaks (1:1 ratio), which clearly indicates that 3-oxazolines **14a** and **14b** were not the only products. A diffraction spectrum of the powder was obtained and compared with a simulation of the diffraction spectra for compounds **14a** and **14b** based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

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



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

Two different synthetic strategies for the preparation of 3-oxazolines using 2H-azirines as starting materials have been described. One of them involves the photochemical generation of nitrile ylides from 2H-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-2H-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-2H-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 2H-[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 Pople¹¹ are $\theta = 51.2(4)^\circ$ and $\varphi = 329.2(4)^\circ$. 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 intermo-

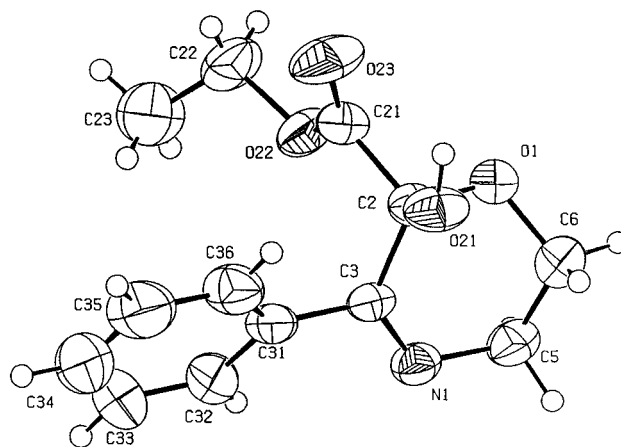
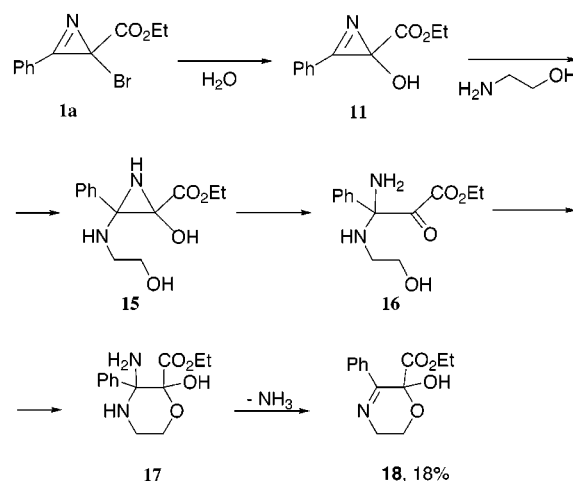


Figure 3. X-ray structure of compound **18**.

Scheme 7



lecular 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 [$O-21 \cdots N-1^i$ 2.756-(3) Å (symmetry code: $x, -3/2 - y, 1/2 + z$)]. 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.

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

When the reaction of 2H-azirine **1a** was performed in the absence of water and using a large excess of ethanolamine, in an ultrasound bath, 2-amino-2H-[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 2H-[1,4]oxazine **20**.

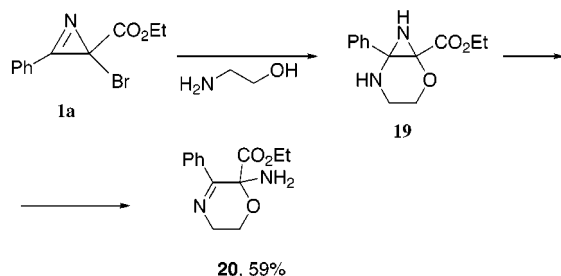
This synthesis of 2H-[1,4]oxazine **20** could indicate that this compound could be an intermediate when the reaction of 2H-azirine **1a** with ethanolamine is performed in the presence of water. In fact, the reaction of **20** with

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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 2H-[1,4]oxazine **20** into 2H-[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-2H-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-2H-azirines with phthalimide reflect the relative stability of the 2H-azirines. In fact we have previously observed that 2-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 proved to be more stable. The iodo-2H-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-2H-azirine-2-carboxylate **1a**, allowing the synthesis of 3-phenyl-2-phthalimido-2H-azirine-2-carboxylate **2** in 96% yield.

Interestingly the reactions of 2-bromo-2H-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-2H-azirines with 1,2-phenylenediamine was developed, allowing the synthesis of a range of quinoxalines (**10a–10d**) in high yield.

Experimental Section

General Procedures. ¹H NMR spectra were recorded on a Bruker AMX300 instrument operating at 300 MHz. ¹³C 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-2H-azirines with Potassium Phthalimide or

Aniline. The 2-halo-2H-azirine (1 mol) was dissolved in DMF (10 mL), and potassium phthalimide⁷ 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 $\times$ 10 mL). The combined organic phases were washed with water (20 mL) and dried (MgSO₄). The solvent was evaporated, giving the azirine.

Ethyl 3-phenyl-2-phthalimido-2H-azirine-2-carboxylate (2): yield 96% from 2H-azirine **1a** and 35% from 2H-azirine **1b**; mp 144–145 °C; ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 (C₁₉H₁₄N₂O₄, M⁺, 334.0954).

Methyl 3-methyl-2-phthalimido-2H-azirine-2-carboxylate (3): oil; yield 28% from 2H-azirine **1d** (the reaction time was 2 days); ¹H NMR (CDCl₃, 300 MHz) δ 2.81 (3H, s), 3.77 (3H, s), 7.76–7.79 (2H, m), 7.87–7.90 (2H, m); ¹³C NMR (CDCl₃, 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 (C₁₃H₁₄N₃O₄, [M + NH₄]⁺, 276.0984).

Methyl 2-benzoyl-2-phthalimido-2H-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 (C₁₉H₁₃N₂O₅, [M + H]⁺, 349.0824).

Ethyl 3-phenyl-2-phenylamino-2H-azirine-2-carboxylate (5): yield 11% from 2H-azirine **1a**; mp 144–147 °C (from ethyl ether); ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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-2H-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); ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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]⁺ (C₁₃H₁₅N₂O₂, M – H⁺, 231.1134).

N-Methyl-1,4-diaza-1,4-dimethyl-3-phenyl-1,3-butadiene-2-carboxamide (8). The 2H-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); ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 (C₁₂H₁₆N₃O, [M + H]⁺, 218.1293).

Reactions of 2-Halo-2H-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); ¹H NMR (CDCl₃, 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 (¹H, ¹H) spectrum]; ¹³C NMR (CDCl₃, 75.5 MHz) δ 13.7 (CH₂CH₃), 62.4 (CH₂CH₃), 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 (CO₂Et) [assignment made on the basis of a COSY (¹H, ¹³C) spectrum]; MS (EI) m/z 278 (M⁺, 29), 249 (27), 206 (100), 77 (23); HRMS (CI) m/z 279.1141 (C₁₇H₁₅N₂O₂, [M + H]⁺, 279.1133).

Methyl 3-benzoylquinoxaline-2-carboxylate (10b): yield 73%; mp 98–100 °C; ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 (C₁₇H₁₃N₂O₃, [M + H]⁺, 293.0926).

Dimethyl quinoxaline-2,3-dicarboxylate (10c): yield 69%; mp 132–133 °C (lit.¹³ mp 132–133 °C); ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 (C₁₂H₁₁N₂O₄, [M + H]⁺, 247.0718).

Methyl 2-methylquinoxaline-3-carboxylate (10d): yield 80%; mp 82–84 °C (lit.¹² mp 79–80 °C); ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 75.5 MHz) δ 23.8 (Me), 53.2 (CO₂Me), 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 (CO₂Me) [assignment made on the basis of a COSY (¹H, ¹³C) spectrum]; MS (EI) m/z 202 (M⁺, 45), 144 (100), 102 (67), 77 (14), 76 (41); HRMS (CI) m/z 202.0741 (C₁₁H₁₀N₂O₂, M⁺, 202.0742).

Reaction of 1a with Water. Diethyl 2-Benzoyl-5-hydroxy-4-phenyl-3-oxazoline-2,5-dicarboxylate (14). The 2H-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); ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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, 167.9, 168.1, 188.6, 189.7; MS (CI) m/z 429 [(M + NH₄)⁺, 4], 412 (37), 307 (56), 290 (100), 208 (21), 105 (11). Anal. Calcd for C₂₂H₂₁NO₇: 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-2H-[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; ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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-2H-[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 (MgSO₄). The solvent was evaporated, giving **20** (0.254 g, 59%) as a solid: mp 69–71 °C; ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 (C₁₃H₁₇N₂O₃, [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 K α radiation (λ = 0.71073 Å). Intensities were recorded as full profiles of ω –2 θ scans. The structures were solved by direct methods as implemented in SHELXS97¹⁴ and refined by full-matrix least-squares using SHELXL97.¹⁵ Examination of the structure with PLATON¹⁶ confirmed the absence of voids in the crystal structures which might be occupied by solvent molecules.

Crystal data for 7: C₁₃H₁₆N₂O₂, M = 232.28, crystal dimensions 0.34 × 0.24 × 0.10 mm³, 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) Å³, 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: C₂₂H₂₁NO₇, M = 411.40, crystal dimensions 0.39 × 0.27 × 0.12 mm³, 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) Å³, 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 Å⁻³.

Crystal data for 18: C₁₃H₁₅NO₄, M = 249.26, crystal dimensions 0.37 × 0.34 × 0.20 mm³, 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) Å³, 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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