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Synthesis and reactivity of 2-halo-2*H*-azirines towards nucleophiles

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Abstract

Nucleophilic substitution reactions of 2-halo-2*H*-azirine with potassium phthalimide and aniline allowed the preparation of new substituted 2*H*-azirines. The reactions of 2-bromo-3-phenyl-2*H*-azirine-2-carboxylate with methylamine led to the synthesis of α-diimines and from the reaction with water, a 3-oxazoline was obtained. © 2000 Published by Elsevier Science Ltd.

Keywords: 2*H*-azirines; α-diimines; 3-oxazoline.

The chemistry of highly reactive 2*H*-azirines has 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. Reactions with nucleophiles always involve the initial addition to the imine bond.[1,2] In some cases the corresponding aziridine can be isolated but in other cases the products result from the formation of aziridine followed by ring opening and further reactions.

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 2*H*-azirines 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]

Having reported previously a general route to 2-halo-2*H*-azirines,[4] in this paper we describe the use of this synthetic methodology for the preparation of new 2-halo-2*H*-azirines, including the first examples of 2-iodo-2*H*-azirines, and a study of their reactivity towards nucleophiles.

The 2-bromo-2*H*-azirines **3a**[4] and **3d** were prepared from the alkenes **2a** and **2d** which were obtained from the reaction of ylides **1a** and **1c** with *N*-bromosuccinimide and azidotrimethylsilane (Scheme 1). The reaction of ylides **1a** and **1b** with *N*-iodosuccinimide and azidotrimethylsilane

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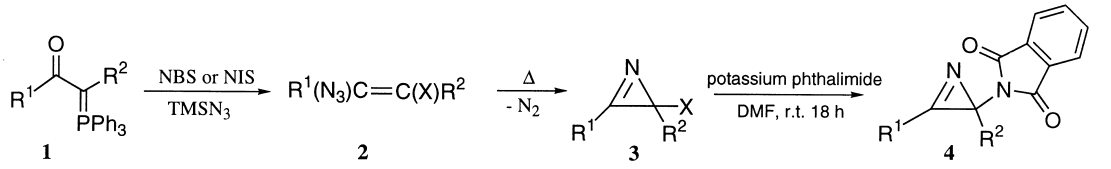
gave the corresponding iodoazidoalkenes **2b** and **2c**. These compounds were converted to the 2-iodo-2*H*-azirines **3b** and **3c**.



1 **2** **3** **4**

1a R^1 = Ph; R^2 = CO_2Et
1b R^1 = Me; R^2 = CO_2Me
1c R^1 = CO_2Me; R^2 = COPh

2a, 3a R^1 = Ph; R^2 = CO_2Et; X = Br
2b, 3b R^1 = Ph; R^2 = CO_2Et; X = I
2c, 3c R^1 = Me; R^2 = CO_2Me; X = I
2d, 3d R^1 = CO_2Me; R^2 = COPh; X = Br

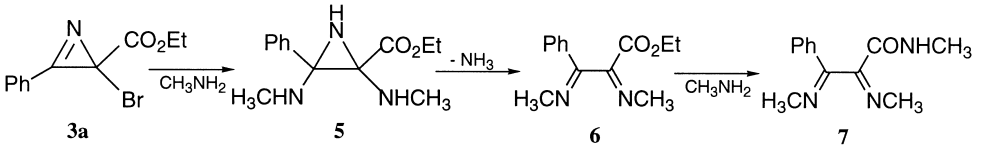
4a R^1 = Ph; R^2 = CO_2Et
4b R^1 = Me; R^2 = CO_2Me
4c R^1 = CO_2Me; R^2 = COPh

Scheme 1.

We started with the study of the reactivity of 2-halo-2*H*-azirine using potassium phthalimide as the nucleophile, which could allow the development of a methodology for the synthesis of new amino acids. (Scheme 1). The reaction of 2-bromo-2*H*-azirine **3a** led to the synthesis of ethyl 3-phenyl-2-phthalimido-2*H*-azirine-2-carboxylate **4a** in high yield[5] (96%). The same product (**4a**) was obtained in 35% yield from the reaction of 2-iodo-2*H*-azirine **3b** 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 led to a moderate yield of compound **4a**. A new phthalimido-2*H*-azirine derivative (**4b**) was also obtained in 28% yield from 2-iodo-2*H*-azirine **3c**. The halide displacement reactions of 2-halo-2*H*-azirine **3d** led to the synthesis of the corresponding 2-substituted-2*H*-azirine derivatives **4c** in low yield.

2-Phenylamino-2*H*-azirine could also be prepared from the reaction of 2-bromo-2*H*-azirines **3a** and **3d** with aniline.

To extend this chemistry the reaction of 2*H*-azirine **3a** with methylamine was studied. The product was not a substituted 2*H*-azirine but instead compound **6** was obtained[6,7] (6%). The 2*H*-azirine **3a** underwent halide displacement and addition to the iminic double bond to give **5**. Opening of the aziridine ring and elimination of ammonia gave the α-diimine **6**. In the presence of a large excess of methylamine, using DMF or acetone as a solvent, compound **7** was obtained in 36 and 40% yield, respectively (Scheme 2).

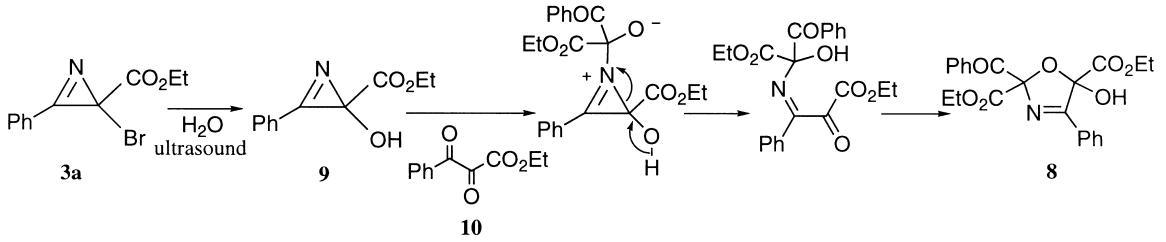


3a **5** **6** **7**

Scheme 2.

The reactivity of 2-halo-2*H*-azirines towards water was studied. A solution of 2*H*-azirine **3a** 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 **8** could be isolated in 30% yield[7,8]

(Scheme 3). 2*H*-Azirine **3a** underwent halide displacement giving 3-hydroxy-2*H*-azirine **9**. Part of this azirine underwent ring opening and hydrolysis leading to **10**. The reaction of this compound with the remaining 3-hydroxy-2*H*-azirine **9** gave 3-oxazoline **8**. This synthesis is an alternative route to the known synthetic strategies for the preparation of 3-oxazolines using 2*H*-azirines as starting material.[9a,9b,10]



Scheme 3.

In conclusion, we have described the results obtained from the reactions of halo-2*H*-azirines with nucleophiles. With potassium phthalimide and aniline the products resulted from the halide displacement and there was no 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 2*H*-azirine derivatives.

The reactions of 2-bromo-2*H*-azirine **3a** with methylamine allowed the preparation of α-diimines, important intermediates for the synthesis of heterocycles and in coordination chemistry.[11] A useful approach to the synthesis of 3-oxazolines was also achieved. They are interesting heterocyclic compounds since several derivatives show biological activity.[9]

Acknowledgements

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5. 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 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 2-phthalimido-3-phenyl-2H-azirine-2-carboxylate* **4a** (96% from 2*H*-azirine **3a** and 35% from 2*H*-azirine **3b**). M.p. 144–145°C. ^{1}H NMR ($CDCl_3$, 300 MHz): 1.21 (3H, t), 4.25 (2H, q), 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): 14.1, 42.9 (C-2), 62.7, 121.1, 123.8, 129.2, 131.6, 131.8, 134.5, 134.49, 159.2 (C-3), 167.2 and 167.6; MS (EI) 334 (M^+, 18%), 306 (33), 277 (20), 132 (9) and 105 (100).

6. *Ethyl 1,4-diaza-1,4-dimethyl-3-phenyl-1,3-butadiene-2-carboxylate* **6**. The 2*H*-azirine **3a** (0.59 g, 2.2 mmol) was dissolved in DMF (10 ml) and methylamine (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 the compound **6** (16 mg, 6.2%) as a solid. M.p. 62.5–64°C (from ethyl ether–hexane). ^{1}H NMR ($CDCl_3$, 300 MHz): 1.30 (3H, t, *J* 7.2 Hz), 3.34 (3H, s), 3.39 (3H, s), 4.31 and 4.32 (2H, 2×q, 7.2 Hz), 7.40–7.43 (3H, m, Ar-H) and 7.61–7.65 (2H, m, Ar-H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): 13.9, 41.1, 42.2, 62.3, 126.4, 128.8, 130.9, 134.9, 161.6, 161.8, 163.6; MS (EI) 232 (M^+, 20%), 231 (40), 203 (6), 158 (12), 118 (100) and 77 (100); HRMS (EI) 231.1128 $[M–H]^+$ ($C_{13}H_{15}N_2O_2$ M–H^+, 231.1134).
7. The structures of this α-diimine **6** and 3-oxazoline **8** were established by X-ray crystallography. These results will be disclosed in a joint paper by the authors together with Beja, A. M.; Paixão, J. A.; Silva, M. R.; Alte da Veiga, L. (Departamento de Física, Faculdade de Ciências e Tecnologia, Universidade de Coimbra, Portugal).
8. *Diethyl 2-benzoyl-5-hydroxy-4-phenyl-3-oxazoline-2,5-dicarboxylate* **8**. The 2*H*-azirine **3a** (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 stirred in an ultrasound bath for 2 days. The solvent was evaporated and the residue was subjected to flash chromatography [with hexane:ethyl acetate (3:1)] giving **8** (0.117 g, 30%) as a solid. M.p. 99.7–102°C (from ethyl ether–hexane). 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. ^{1}H NMR ($CDCl_3$, 300 MHz): 0.97 (3H, t), 1.11 (3H, t), 1.14 (3H, t), 1.18 (3H, t), 4.05–4.35 (8H, m), 5.08 (1H, bs), 5.21 (1H, bs), 7.39–7.55 (10H, m, Ar-H), 7.58–7.62 (2H, m, Ar-H), 7.96–8.02 (4H, m, Ar-H) and 8.18–8.26 (4H, m, Ar-H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): 13.45, 13.69, 62.64, 63.27, 63.54, 63.61, 105.17, 105.47, 109.85, 110.17, 128.23, 128.29, 128.44, 128.47, 126.71, 126.74, 128.95, 129.83, 129.86, 132.54, 132.59, 133.58, 133.70, 133.96, 165.51, 166.74, 167.34, 167.50, 167.87, 168.05, 188.64 and 189.67.
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