

Synthesis of 2-Halo-2*H*-Azirines from Phosphorus Ylides

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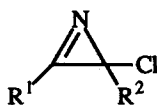
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Abstract: α -Oxophosphonium ylides (**3a–3e**) react with *N*-chlorosuccinimide and *N*-bromosuccinimide in the presence of azidotrimethylsilane giving the corresponding haloazidoalkenes (**4a–4g**) with elimination of triphenylphosphine oxide. These compounds were completely converted to the 2*H*-azirines **5a–5g** on heating in heptane. © 1999 Elsevier Science Ltd. All rights reserved.

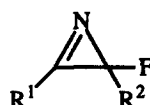
2*H*-Azirines **1** are unsaturated three-membered heterocycles which are used for various synthetic purposes due to the high reactivity of such molecules.¹ The most general method of synthesis of 2*H*-azirines is the thermal or photochemical decomposition of vinyl azides involving vinyl nitrenes as intermediates.^{1–4} There are very few literature reports of halo substituted azirines.^{3,4} The reaction of iodine azide ^{3a,b} or chlorine azide^{3c} with chloroalkenes followed by elimination of hydrogen iodide or hydrogen chloride gives the corresponding chlorovinyl azides which can be converted into chloroazirines (**1a–1c**). There are also a few examples of fluorinated 2*H*-azirines, such as **2a** and **2b**, prepared from fluorovinyl azides.^{4a,b} No bromo-2*H*-azirines have been reported before.



1a R¹ = R² = Me

1b R¹ = Ph; R² = Me

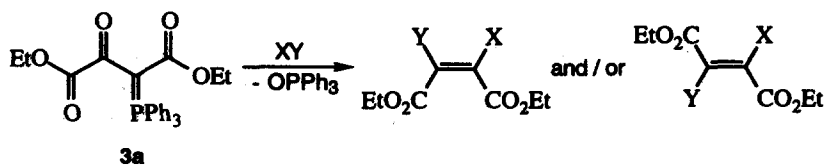
1c R¹ = R² = Ph



2a R¹ = F; R² = CF₃

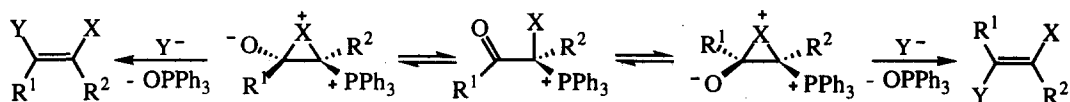
2b R¹ = CF₃; R² = F

In this paper we describe a new and general route to 2-halo-2*H*-azirines starting from phosphorus ylides. We have recently reported the synthesis of tetrasubstituted alkenes by the reaction of phosphorus ylide **3a** with chlorine and bromine in the presence of nucleophiles⁵ (Scheme 1). Similar reactions occur between ylide **3a** and *N*-chlorosuccinimide and *N*-bromosuccinimide in the presence of methanol or azidotrimethylsilane.



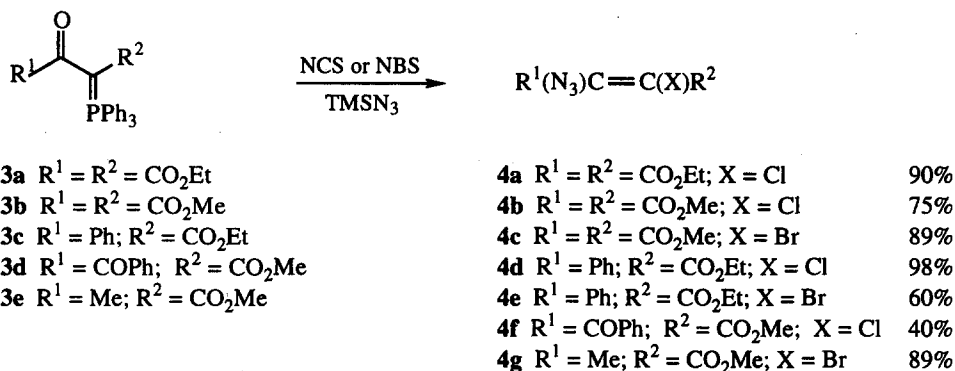
Scheme 1

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 2

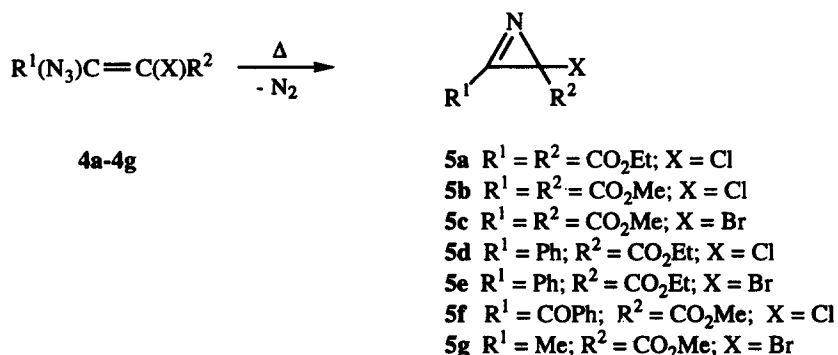
Of particular interest is the possibility of preparing haloazidoalkenes from phosphorus ylides with *N*-chlorosuccinimide and *N*-bromosuccinimide in the presence of azidotrimethylsilane since these compounds are potential precursors of 2-halo-2*H*-azirines. In fact ylide **3a** can be used to prepare alkenes **4a**.⁵ We decided to study the possibility of extending our reaction to other phosphorus ylides in order to obtain a range of haloazidoalkenes. Ylides **3b** - **3e**⁶ were converted into the corresponding alkenes in good yield (Scheme 3). The products **4b**, **4c** and **4g** were obtained as a mixture of *E* / *Z* isomers whereas alkenes **4d**, **4e** and **4f** were obtained as single isomers.⁷



Scheme 3

Alkenes **4a** - **4g** are easily and completely converted into the corresponding 2*H*-azirines (**5a** - **5g**) on heating in heptane for 2-3 hours⁸ (Scheme 4). 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 (ν ~ 2110 - 2120 cm⁻¹). The ¹³C NMR spectra of the 2*H*-azirines show the sp² carbon between 155 and 166 ppm and the sp³ carbon between 43 and 63 ppm depending on the substitution pattern. Compounds **5b** and **5f** show the signal for the sp³ carbon coincident with the signal for the methyl group (Table).

L'abbé *et al.*² studied the thermolysis of dimethyl azidobutenedioate and found that starting from the *Z* isomer only dimethyl 2*H*-azirine-2,3-dicarboxylate was formed while the *E* isomer gave a mixture of the azirine and methyl 5-methoxyisoxazole-3-carboxylate. However in our study we always obtained quantitative conversions of the alkenes which means that both isomers give the corresponding 2*H*-azirine.



Scheme 4

Table ¹³C NMR in CDCl₃ of the 2*H*-azirines **5a-5g**.

Azirine	Yield	¹³ C NMR (δ in ppm)
5a	98%	13.89, 13.96, 63.25 (C-2), 63.94, 64.62, 154.67 (C-3), 162.70 and 165.36
5b	99%	54.39, 54.57 (C-2 and CH ₃), 155.02 (C-3), 162.58 and 165.74
5c	98%	42.90 (C-2), 54.48, 155.01 (C-3), 163.11 and 165.29
5d	97%	13.94, 53.99 (C-2), 63.23, 119.56, 129.55, 130.72, 134.96, 163.52 (C-3) and 167.25
5e	97%	14.06, 44.19 (C-2), 63.56, 119.78, 129.78, 130.94, 135.09, 164.51 (C-3) and 166.71
5f	97%	54.37 (C-2 and CH ₃), 129.63, 129.95, 133.83, 136.54, 164.25, 166.39 (C-3) and 179.06
5g	99%	10.74, 43.44 (C-2), 53.95, 166.91 (C-3) and 167.49

This work has provided the synthesis of a range of isolable but unstable 2-halo-2*H*-azirines including 2-halo-2*H*-azirines bearing electron withdrawing groups at C-2 and C-3 (**5a**, **5b**, **5c** and **5f**), 2-halo-2*H*-azirines bearing electron withdrawing groups at C-2 and a phenyl at C-3 (**5d** and **5e**) and a 2-halo-2*H*-azirine derivative having an electron withdrawing group at C-2 and a methyl group at C-3. 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. The route to halo-2*H*-azirines starting from phosphorus ylides presents itself as a very general method.

Acknowledgements:

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- Ylide **3c** was prepared as described in Aitken, R. A.; Héron, H.; Janosi, A.; Raut, S. V.; Seth, S.; Shannon, I. J.; Smith, F. C. *Tetrahedron Lett.* **1993**, 34, 5621–5622. Ylides **3b** and **3d** were prepared by the procedure described in reference 5 for ylide **3a**; Ylide **3e** was prepared as described in Wasserman, H. H.; Ennis, D. S.; Blum, C. A.; Rotello, V. M. *Tetrahedron Lett.* **1992**, 33, 6003–6006.
- General procedure for the synthesis of the alkenes*: The ylide (4.5 mmol) was dissolved in dichloromethane (50 mL) and a solution of azidotrimethylsilane (0.71 g, 6.5 mmol) and *N*-chlorosuccinimide 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 (CH₂Cl₂) and gave the vinyl azide. *Dimethyl 2-azido-3-chlorobutenedioate 4b* m.p. 48–50 °C (from pentane) (Found: C, 33.07; H, 2.79; N, 18.60. C₆H₆ClN₃O₄ requires C, 32.88; H, 2.74; N, 19.18%); ν (KBr) 1678, 1709, 1721 and 2137 cm⁻¹; δ (200 MHz, CDCl₃) 3.83 (3H, s) and 3.92 (3H, s); δ (¹³C) 63.48, 63.68, 114.33, 137.63, 161.21 and 162.34.
- General procedure for the synthesis of the 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. *Methyl 2-bromo-2-methyl-2H-azirine-3-carboxylate 5g* was isolated directly as an oil. δ (200 MHz, CDCl₃) 2.58 (3H, s) and 3.77 (3H, s); δ (¹³C) 10.74, 43.44, 53.95, 166.91 and 167.49; m/z 208.9928 [M+NH₄]⁺ (C₅H₁₀BrN₂O₂ requires M, 208.9926).