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Improved procedure for cyclization of vinyl azides into 3-substituted-2*H*-azirines

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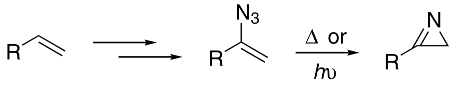
Abstract—A significantly improved procedure for the preparation of 3-substituted 2*H*-azirines has been developed. By cyclization of the corresponding vinyl azides in low boiling solvents in closed vessels at elevated temperature, high purity, short reaction time and simple isolation of the product were achieved. © 2003 Elsevier Science Ltd. All rights reserved.

Azirines are highly reactive three-membered unsaturated nitrogen-containing heterocycles that have found an increased use in organic synthesis.[1] They take part in various chemical transformations since they can act as dienophiles and dipolarophiles as well as electrophiles and nucleophiles.[2] The ring strain and the reactive π-bond account for the high reactivity of the azirine moiety and make it an attractive intermediate in the synthesis of complex alkaloids.[2] In order to further develop the chemistry of the 2*H*-azirines a convenient method for their preparation is of great importance.

Several methods for the synthesis of various 2*H*-azirines have been described.[2] A frequently used method employs vinyl azides,[3–5] which can be converted into the corresponding 2*H*-azirines by thermolysis or photolysis (Scheme 1).[5–8]

For the thermal conversion of vinyl azides into 2*H*-azirines, elevated temperatures are needed. The most commonly used solvent has been toluene, but others such as dioxane and heptane, all with a boiling point between 98 and 110°C, have also been applied.[6,9,10] At these temperatures reaction times of 1.5 to 10 h are commonly required to accomplish complete conversion of the vinyl azides and it has been observed that it is sometimes difficult to separate the formed azirine from the solvent. To circumvent this the reaction can be performed at lower temperature, allowing the use of solvents with low boiling point, but with substantially longer reaction times, typically 1–7 days, as a result.[11] Since azirines are thermally unstable,[4] with some decomposition even at ambient temperature,[12] prolonged heating should be avoided. This is to suppress undesired polymerization which is a known side reaction in the formation of azirines.[8,13] In an ongoing project we needed a ready access to a variety of azirines. As a result, an optimization of the thermolysis was undertaken and herein our results are detailed.



Scheme 1.

From earlier work in our research group a convenient improvement of existing methods for thermolysis of vinyl azides into azirines has emerged.[14] The vinyl azides are simply heated in low boiling solvents. In order to reach the necessary temperature to facilitate ring closure and to avoid prolonged reaction times the reaction must be performed in a closed vessel. While it has been possible to use pentane or Et_2O for some vinyl azides,[15] 2-azidoacrylic esters do not tolerate these solvents. The resulting ester-substituted azirines decompose more easily than alkyl- or aryl-substituted ones and the cyclizations are often accompanied by considerable amounts of byproduct formation. Consequently, azidoacrylic ester **1a** was selected as substrate for the thermolysis optimization study.

The cyclization of azide **1a** in CH_2Cl_2 at different temperatures clearly showed that higher reaction temperature for a shorter time was more efficient than a lower temperature which required a longer reaction

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time for complete consumption of **1a** (compare entries 1, 2 and 3, Table 1). At prolonged reaction time, byproduct formation increased and the yield of azirine **2a** after 6 h at 100°C was 43% with 13% of **1a** still remaining. After 20 min at 150°C no starting material was present and **2a** was obtained in 85% yield.[16] For the reactions run at 100 and 125°C it was also noted that the amount of **2a** remained constant after a short time (2 h and 30 min, respectively) despite continued heating and consumption of **1a**.

The results in Table 2 show the solvent dependence of the thermolysis of vinyl azide **1a**. Three solvent types were represented by CH_2Cl_2, toluene and Et_2O.[17] All reactions were run at 150°C for 20 min at which time all the azide was consumed. In toluene product **2a** was obtained in 52% yield, whereas in Et_2O no product was detected (entries 1 and 2). In both cases byproducts were clearly visible in the ^1H NMR spectra of the crude reaction mixtures. However, the thermolysis in CH_2Cl_2 gave acceptable results (entry 3) and this solvent was selected for further optimizations.

Table 1. Temperature dependence[a]

Entry	Temp. (°C)	Time (min)	Yield of **2a**[b] (%)
1	100	360	43[c]
2	125	75	69
3	150	20	85

[a] Reaction conditions: 0.1 M of **1a** in CH_2Cl_2.
[b] Measured by ^1H NMR.
[c] With 13% of azide remaining.

Table 2. Solvent dependence[a]

Entry	Solvent	Yield of **2a**[b] (%)
1	Toluene	52
2	Et_2O	0
3	CH_2Cl_2	85

[a] Reaction conditions: 0.1 M of **1a** in solvent at 150°C for 20 min.
[b] Measured by ^1H NMR.

The concentration of the vinyl azide is an important parameter in the thermolysis reaction and a wide range of concentrations (0.006–0.42 M) have been reported in the literature.[5,10] In order to find the optimal conditions, three concentrations were studied, 0.10, 0.25 and 0.5 M of **1a**. In all cases vinyl azide **1a** was completely consumed, but with large variations in the yield of azirine **2a** (Table 3). At 0.10 M of **1a** the yield of **2a** was 85%, falling to 36% at 0.25 M and at 0.50 M only 2% of the azirine could be detected (entries 1, 2 and 3).

The optimized conditions with 0.1 M vinyl azide in dichloromethane at 150°C for 20 min proved to work well also for azides **1b**–**h** which were chosen in order to demonstrate the generality of the reaction conditions (Fig. 1 and Table 4). All compounds gave the corresponding azirines **2b**–**h** in good to excellent yields and with high purity.

We report in this paper the development of an improved and general method for the preparation of 3-substituted 2*H*-azirines. The major advantages with this method are the high yields, the short reaction times and the convenient isolation of the products.

General procedure for preparation of 3-substituted-2*H*-azirines: The vinyl azide **1a** (140 mg, 0.69 mmol) was

Table 3. Concentration dependence[a]

Entry	Concentration (M)	Yield of **2a**[b] (%)
1	0.10	85
2	0.25	36
3	0.50	2

[a] Reaction conditions: The azirine was heated in CH_2Cl_2 at 150°C for 20 min.
[b] Measured by ^1H NMR.

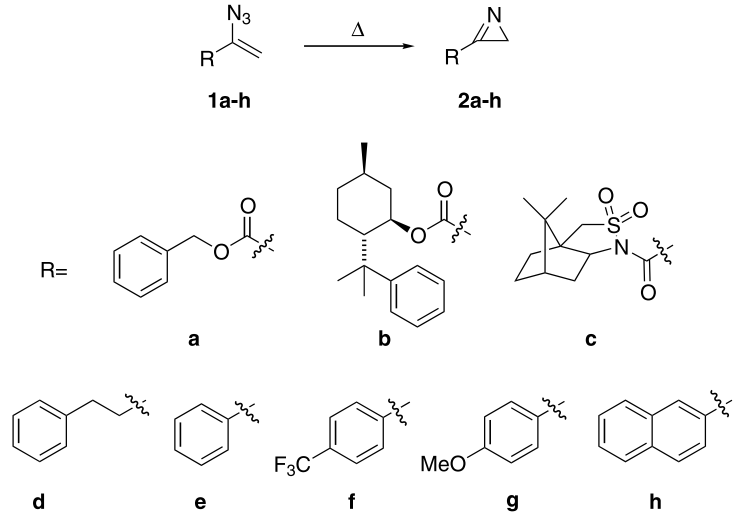

Figure 1.

Table 4. Thermolysis of vinyl azides **1a**–**1h**[a]

Entry	Product	Yield[b] (%)
1	**2a**	85
2	**2b**	>95
3	**2c**	>95
4	**2d**	84
5	**2e**	95
6	**2f**	>95
7	**2g**	74
8	**2h**	82

[a] Reaction conditions: The azirines were heated in CH_2Cl_2 at 150°C for 20 min.

[b] Measured by ^1H NMR.

dissolved in dry CH_2Cl_2 (6.9 mL) and heated in a glass tube fitted with a screw cap for 20 min (150°C, preheated oil bath) and then cooled in an ice bath. CAUTION: Heating of azides may cause explosion. Evaporation gave **2a** as a pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.48 (5H, m), 5.42 (2H, s), 1.97 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 158.6, 134.0, 129.0, 128.9, 128.8, 68.6, 24.2.

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15. Azides **1d** and **1e** cyclized well in pentane (125°C, **2h**), **1g** and **1h** in Et_2O under the same conditions.
16. 1,4-Di-*tert*-butylbenzene (0.2 equiv.) was added before workup and used as the standard to determine the yields by ^1H NMR spectroscopy.
17. Other solvents such as $CHCl_3$, CH_2Cl_2, pentane and THF have also been used, with results in line with those presented in Table 2.