Synthesis of 3-Substituted Indolizines from the Reaction of Chlorocarbenes with 2-Vinylpyridine

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3-Substituted indolizines have been obtained in a one-step procedure from the reaction of chlorocarbenes with 2-vinylpyridine.

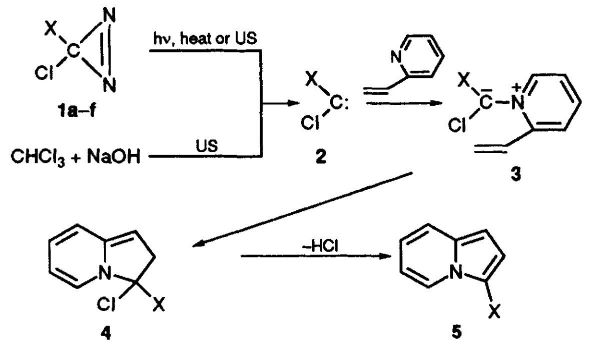
Indolizine has a delocalized 10 π-electron aromatic structure which has a theoretical and practical interest. Most of the work on indolizine has been concerned with the search for drugs and for liquid-screening agents in photographic emulsions.[1,2] Substituted indolizines can be obtained by the reaction of pyridinium ylides with ethylenic compounds to form dihydroindolizines which readily oxidize to the aromatic system.[3] We report here a facile synthesis of 3-substituted indolizines from a variety of chlorocarbenes and 2-vinylpyridine under photolytic, thermal and ultrasound conditions.

The reaction of singlet carbene such as arylchlorocarbene with pyridine to form pyridinium ylide can be envisaged as a Lewis acid-base reaction between the vacant 2p-orbital of the carbene and the non-bonding electrons pair of the nitrogen atom. As expected, these reactions have been found to be very fast and close to diffusion controlled.[4] Typical reaction rate constants have been reported, $k = 10^8$–10^{10} dm^3 mol^{-1} s^{-1}. The absorption spectra of these ylidic species have been well characterized by laser flash photolysis studies.[5] Their absorption at long wavelength (λ 400–600 nm), their long lifetimes ($\tau \sim 10^{-6}$–10^{-4} s) and their high extinction coefficients[5] render them excellent probes in the studies of carbene dynamics.

Our method for the synthesis of 3-substituted indolizine **5** is based on the reaction of electrophilic chlorocarbene, **2**, with 2-vinylpyridine. Since the vinyl double bond attached α to an sp^2-hybridized ring nitrogen is electron deficient, the carbene attacks the lone pair of the nitrogen atom rather than the vinyl double bond. Intramolecular 1,5-dipolar cyclization of the resulting pyridinium ylide, **3**, yields dihydroindolizine, **4**. Hydrogen chloride elimination from **4** gives 3-substituted indolizine **5** (Scheme 1).

Arylchlorocarbenes **2a–c** can be generated from the photolysis, thermolysis and ultrasound (US) irradiation of the corresponding arylchlorodiazirines **1a–c**.[6] Benzylchlorocarbenes **2d–f** can be generated from photolysis and thermolysis of the corresponding benzylchlorodiazirines **1d–f**,[7] which are stable to US. The generation of dichlorocarbene is based on the action of US on the stirred NaOH–CHCl$_3$ solid–liquid system.[8] The chlorocarbenes **2** generated in the above procedures react rapidly with 2-vinylpyridine to give **4**. In all cases, elimination of HCl from **4** to give **5** is very rapid since no trace of **4** was found. Yields of indolizines **5** are presented in Table 1, as well as spectral data which compare well with those previously reported.[9]

In general, arylchlorocarbenes **2a–c** generated from the photolysis of diazirines **1a–c** (λ = 350 nm) gave low yields of indolizines **5a–c**. This is attributed to the filtering effect of **5** which has a very broad absorption band centring at λ 330 nm. Thus, both US and thermolysis gave better yields. In the photolysis of benzylchlorodiazirine **1d**, benzylchlorocarbene **2d** reacts with 2-vinylpyridine to form the expected pyridinium ylide **3d** (λ 380 nm as determined by laser flash photolysis). Apparently, the cyclization of **3** to **4** has a much higher activation energy than the 1,2-hydrogen shift (in the carbene or in the ylide) to form β-chlorostyrenes, hence no indolizine



a; X = Ph,
b; X = *p*-MeC$_6$H$_4$
c; X = *p*-ClC$_6$H$_4$
d; X = PhCH$_2$
e; X = *p*-MeC$_6$H$_4$CH$_2$
f; X = *p*-ClC$_6$H$_4$CH$_2$
g; X = Cl

Scheme 1

Table 1 Spectral data and isolated yields for 3-substituted indolizines **5**

Product 5	X	Method	Yield (%)	^{1}H NMR δ (CDCl$_3$)
a	Ph	*hν*	10[a]	6.4–6.7 (m, 1-H, 6-H, 8-H), 6.83 (d, 2-H, *J* 4 Hz), 7.2–7.7 (m, Ph, 7-H), 8.1–8.4 (m, 5-H)
		Heat	52	
		US	40	
b	*p*-MeC$_6$H$_4$	*hν*	12[a]	2.40 (s, Me), 6.4–6.7 (m, 1-H, 6-H, 8-H), 6.87 (d, 2-H, *J* 4 Hz), 7.2–7.7 (m, C$_6$H$_4$, 7-H), 8.2–8.4 (m, 5-H)
		Heat	52	
		US	54	
c	*p*-ClC$_6$H$_4$	*hν*	11[a]	6.4–6.7 (m, 1-H, 6-H, 8-H), 6.86 (d, 2-H, *J* 4 Hz), 7.2–7.7 (m, C$_6$H$_4$, 7-H), 8.1–8.4 (m, 5-H)[b]
		Heat	52	
		US	47	
d	PhCH$_2$	Heat	27	4.21 (s, CH$_2$), 6.3–6.8 (m, 1-H, 2-H, 6-H, 8-H), 7.0–7.8 (m, Ph, 7-H), 8.5–8.7 (m, 5-H)[c]
e	*p*-MeC$_6$H$_4$CH$_2$	Heat	21	2.30 (s, Me), 4.19 (s, CH$_2$), 6.2–6.8 (m, 1-H, 2-H, 6-H, 8-H), 7.10 (s, C$_6$H$_4$), 7.2–7.9 (m, 5-H, 7-H)
f	*p*-ClC$_6$H$_4$CH$_2$	Heat	21	4.20 (s, CH$_2$), 6.3–6.8 (m, 1-H, 2-H, 6-H, 8-H), 7.0–7.7 (m, C$_6$H$_4$, 5-H, 7-H)[d]
g	Cl	US	13	6.3–6.9 (m, 1-H, 2-H, 6-H, 8-H), 7.2–7.6 (m, 7-H), 7.8–8.1 (m, 5-H)

[a] Isolated yield based on the amount of arylchlorodiazirine used. [b] MS, *m/z* 229 (34), 227 (100), 192 (24), 191 (49), 96 (32). [c] Mp 60.5–61 °C. MS, *m/z* 207 (45), 206 (23), 204 (12), 130 (100), 77 (13), 51 (12). [d] Mp 73.5–74 °C.

5d was observed in photolysis. In thermolysis, the cyclization can compete effectively with the 1,2-H shift thus giving **5d–f** and β-chlorostyrenes in 21 and 38% yields respectively (for 3-chloro-3-*p*-methylbenzyldiazirine **1e**). In the case of dichlorocarbene, the isolated yield of 3-chloroindolizine **5g** is low because it is unstable and turns dark at room temperature.

Photolysis was carried out by irradiation (350 nm) of solutions of chlorodiazirines **1a–c** (0.2 mol dm^{-3}) and 2-vinylpyridine (1 mol dm^{-3}) in hexane at 25 °C for 24 h to give indolizines **5a–c**. For thermolysis reactions solutions of chlorodiazirines **1a–f** (0.1 mol dm^{-3}) and 2-vinylpyridine (0.5 mol dm^{-3}) in absolute benzene were refluxed for 16 h to form indolizines **5a–f**. Ultrasonic irradiation of solutions of chlorodiazirines **1a–c** (0.2 mol dm^{-3}) and 2-vinylpyridine (1 mol dm^{-3}) in hexane was conducted in a round-bottomed flask, equipped with a mechanical stirrer, immersed in a sonic cleaner (Fisher Scientific Solid State Ultrasound FS-9) and simultaneously stirred and irradiated with US for 48 h to give indolizines **5a–c**. 3-Chloroindolizine **5g** was synthesised by ultrasonic irradiation of a mixture of powdered NaOH (0.8 g, 20 mmol) and 2-vinylpyridine (0.21 g, 2.0 mmol) in chloroform (20 ml), placed in a 100 ml, round-bottomed flask equipped with a mechanical stirrer. The flask was immersed in a sonic cleaner and the mixture was simultaneously stirred and irradiated with US for 4 h, the temperature of the bath during US irradiation was 40 °C. In all cases indolizines **5a–g** were isolated by column chromatography (basic alumina) using hexane as an eluent. Indolizines **5d,f** were then recrystallized from hexane.

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