Formation of Indolizines by the Addition of α-Chloroacrylonitrile to Pyridinium Ylides: Regioselectivity and Hammett Correlation

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Cycloaddition of pyridinium ylides to α-chloroacrylonitrile give indolizines: the regioselectivity of the reaction can be rationalized in terms of nucleophilic attack by the ylides on the olefin.

Indolizine, a heterocyclic system with $10\,\pi$ delocalized electrons, is of current synthetic interest. Methods for construction of the nucleus have been reviewed;[1] 1,3-dipolar cycloaddition is one of the most general of such methods. However, where pyridinium ylides react with ethylenic compounds, dihydro-indolizines are isolated as intermediates and these can be catalytically converted into the indolizines. We report here the direct formation of 3-aryl-1-cyanoindolizines from the 1,3-cyclo-addition of pyridinium ylides to α-chloroacrylonitrile (ClACN), and the absolute rate constants for this reaction. Pyridinium ylides are generated from the photolysis of 3-aryl-3-chloro-diazirines in the presence of pyridine.

The diazirines (**1a**—**d**), synthesized according to Graham's method,[2] upon photolysis at 355 nm yield the corresponding carbenes (**2a**—**d**). The absorption spectra of these carbenes have been well characterized[3,4] by laser flash photolysis (LFP). In the presence of pyridine, LFP[4] of the diazirines (**1a**—**d**) produce new transient absorption spectra which are attributed to

Table. Rate constants for ylide formation and for quenching of ylides by ClACN at 25 °C

Species monitored	(3a)	(3b)	(3c)	(3d)
$\lambda_{max.}$/nm	430	460	480	605
$k_{ylide}/10^8\,dm^3\,mol^{-1}$	1.58 ± 0.05	2.90 ± 0.30	3.35 ± 0.29^a	75.0 ± 1.0
$k_q/10^5\,dm^3\,mol^{-1}$	188 ± 3	146 ± 4	77.2 ± 3.7	2.34 ± 0.10

[a] Value taken from J. E. Jackson, N. Soundarajan, M. S. Platz, M. T. H. Liu, *J. Am. Chem. Soc.*, 1988, **110**, 5595.

the ylides (**3a**—**d**) (Scheme). The absorption spectra of these transients ($\lambda_{max.}$ given in the Table) show a bathochromic shift when compared with the spectra of the corresponding aryl-chlorocarbenes. The extinction coefficients for ylides (**3a**—**d**) may be estimated by the relative actinometry method:[5]

$$\varepsilon_1 = \frac{\Delta OD_1 \Phi_2}{\Delta OD_2 \Phi_1}$$

where ΔOD_1 and ΔOD_2 are the optical density of the ylide absorption and that of the triplet-triplet absorption of benzophenone in benzene[6] ($\varepsilon_2 = 7.63 \times 10^3\,dm^3\,mol^{-1}\,cm^{-1}$, $\lambda_2 = 530\,mm$) respectively. The quantum yield for intersystem crossing in benzophenone Φ_2 is known to be unity. The quantum yield of the formation of the ylide, Φ_1, is the product of the quantum yield for the decomposition of diazirine (assumed to be 1)[7] multiplied by the yield of ylide formed from carbene and pyridine, Φ_{ylide}.

This yield can easily be shown to be quantitative from the expression: $\Phi_{ylide} = k_{ylide}\,[\text{pyridine}]/(k_{ylide}[\text{pyridine}] + k_{carbene\,decay})$. Thus, the extinction coefficients for ylides (**3a**), (**3b**), (**3c**), and (**3d**) in iso-octane were found to be 0.64, 1.35, 1.41, and $1.64 \times 10^4\,dm^3\,mol^{-1}\,cm^{-1}$ respectively.

The rate constant for ylide formation, k_{ylide}, is determined by plotting the rate of growth of the ylide absorption, $k_{growth} = k_{carbene\,decay} + k_{ylide}[\text{pyridine}]$, as a function of pyridine concentration. Hammett analysis of log k_{ylide} with σ_p constants gave a ρ value of $+1.5 \pm 0.10$. The positive ρ value is consistent with the electrophilic addition of carbene to pyridine. It is noteworthy that the arylchlorocarbenes bearing electron-donating as well as electron-withdrawing substituents add to pyridine whereas only those with the latter add to acetone to give carbonyl ylides.[8,9]

The ylides (**3a**—**d**) decay slowly ($\tau_0 \sim 300\,\mu s$) in the absence of quenchers. The addition of an ethylenic quencher, ClACN, accelerates ylide decay and since $1/\tau = 1/\tau_0 + k_q[\text{ClACN}]$, the k_q values are obtained (Table) from the slopes of plots of $1/\tau$ vs [ClACN]. Hammett correlation of the k_q values yielded a ρ value of -1.80 ± 0.10.

Irradiation of a mixture of diazirine (**1c**) (500 mg, 3.3 mmol), pyridine (12 mmol), and ClACN (3.3 mmol) in iso-octane (10
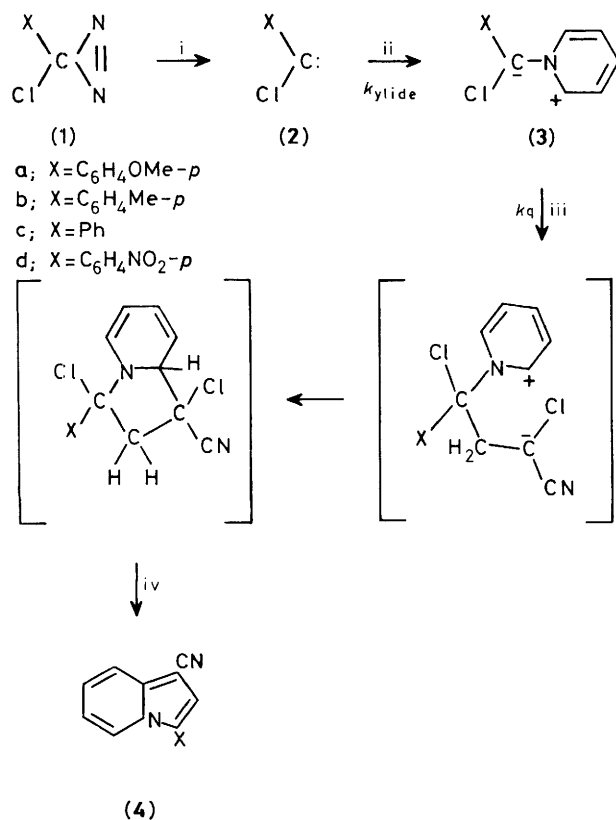
Scheme. *Reagents and conditions:* i, *hv*, $-N_2$; ii, pyridine; iii, Cl(CN)C=CH$_2$; iv, -2HCl

ml) at 350 nm and 25 °C for 18 h resulted in the formation of 1-cyano-3-phenylindolizine (4c)* (40% isolated yield). Only one regioisomer is formed. The carbon-13 chemical shift data allow an unambiguous assignment for structure (4c). Confidence in this assignment was obtained by noting the quaternary carbon at 82.94 p.p.m. which is consistent with the cyano effect at C-1 in the indolizine.[10] As a consequence of the regioselectivity and a negative Hammett ρ value in the cycloaddition, a mechanism is proposed in which the rate-determining-step is a nucleophilic attack of the ylide on the olefin. This mechanism is further substantiated by the fact that the ylide (3c) is quenched by acrylonitrile ($k = 4.4 \times 10^5 \text{ dm}^3 \text{ mol}^{-1}$) or 1,1-dichloroethylene ($k = 3.6 \times 10^4 \text{ dm}^3 \text{ mol}^{-1}$) but it is unreactive towards electron-rich olefins such as tetramethylethylene. For efficient formation of indolizine, it is therefore essential to employ electron deficient olefins possessing a good leaving group for spontaneous aromatization.

Changing the starting material from phenylchlorodiazirine to

(5)   (6)

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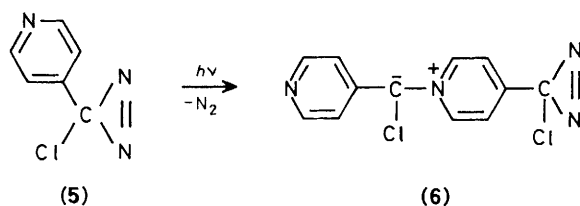
* The isolated yield for (4c) is 40% based on initial amount of diazirine used. The chemical yield calculated on the consumed diazirine is 90% since the diazirine is not totally used up in the photolysis due to the filtering effect of (4c).

$\nu_{max.}$ 2 200, 1 500, 742 and 690 cm^{-1}; m/z 218 (M^+, 100), 217 (14), 216 (13), 190 (10), and 28 (10); $\lambda_{max.}$ nm (ε dm^3 mol^{-1} cm^{-1}), 206 (1.05 × 10^4), 256 (7.8 × 10^3), 310 (3.1 × 10^3); δ_H(CDCl$_3$, 250 MHz): 8.44 (1 H, 5, dt, J 7. 1, 1.1 Hz), 7.62—7.42 (5 H, ArH, m), 7.20 (1 H, 7, dt, J 6.7, 1.1 Hz), 7.18 (1 H, 2, s), and 6.89 (1 H, 6, dt, J 7.0, 1.3 Hz); δ_C(CD$_3$COCD$_3$) 82.94 (1), 114.3 (5), 116.9 (2), 118.4 (7), 123.8, 125.1, 127.9, 129.3, 129.5 (2 H), 129.7, 130.1 (2 H), 131.1, and 139.1.

3-(4-pyridyl)-3-chlorodiazirine (5), provides a potentially interesting extension for the formation of indolizine. Upon LFP, a solution of (5) in iso-octane, without any added pyridine, gives a transient species which is assigned to the ylide (6) for the following reasons: (i) its absorption spectrum ($\lambda_{max.}$ 500 nm) is very similar to that of the ylide (3c); (ii) the plot of the observed pseudo-first-order rate constant for its growth $vs.$ (5) is linear and yields the rate constant $k_6 = 2.88 \pm 0.40 \times 10^9 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ for the addition of (5) to the 4-pyridinylchlorocarbene; (iii) ClACN quenches this species, with $k_q = 8.3 \pm 0.4 \times 10^4 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$, probably in the same way as it adds to the ylides (3a—d), producing the indolizine.

Both the ylide (6) and the corresponding indolizine contain a diazirine ring but, in the LFP conditions, they are not further photolysed because their formation requires several tens of ns whereas the duration of the excitation laser pulse is only 200 ps. However, under continuous irradiation, a photopolymerization process can be initiated by successive photolysis of the diazirine moiety. This is currently under investigation.

References

1 T. Uchida and K. Matsuomoto, *Synthesis*, 1976, 209.
2 W. H. Graham, *J. Am. Chem. Soc.*, 1965, **87**, 4396.
3 N. J. Turro, J. A. Butcher, Jr., R. A. Moss, W. Guo, R. C. Munjal, and M. Fedorynski, *J. Am. Chem. Soc.*, 1980, **102**, 7578.
4 R. Bonneau and M. T. H. Liu, *J. Chem. Soc., Chem. Commun.*, 1989, 510.
5 I. Carmichael and G. L. Hug, *J. Phys. Chem.*, 1986, Ref. Data, **15**, 1.
6 R. Bensasson and E. J. Land, *Trans. Faraday Soc.*, 1971, **67**, 1904.
7 M. T. H. Liu and I. D. R. Stevens, 'Chemistry of Diazirine,' ed. M. T. H. Liu, CRC Press, Boca Raton, Fl., 1987, ch 5.
8 N. Soundarajan, J. E. Jackson, M. S. Platz, and M. T. H. Liu, *Tetrahedron Lett.*, 1988, 3419.
9 M. T. H. Liu, N. Soundarajan, S. M. Anand, and T. Ibata, *Tetrahedron Lett.*, 1987, 1011.
10 R. J. Pugmire, M. J. Robins, D. M. Grant, and R. K. Robins, *J. Am. Chem. Soc.*, 1971, **98**, 1887.