# 1-Azidoisochromenes. A New Route to 3,1-Benzoxazepines



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Nucleophilic attack of sodium azide on isochromylium salts leads to the preparation of 1-azidoisochromenes which when heated lose molecular nitrogen and give 3-1-benzoxazepines.

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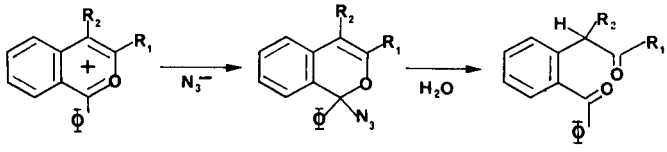
Thermolysis and photolysis of alkyl and aryl azides have been extensively studied in the last twenty years (1) but little attention has been paid to rearrangements of heterocyclic azides. We have shown that azidopyrans and azidochromenes offer a remarkable access to 1,3-oxazepines and to 1,3-benzoxazepines (2). The purpose of the studies described in the paper was to test the rearrangements of 1-azidoisochromenes II as a possible route to 3,1-benzoxazepines (3).

These heterocyclic azides were unknown. They were prepared according to our usual procedure by nucleophilic attack of sodium azide on isochromylium salts I (4). Azides II were obtained quantitatively; attempts to crystallise them results in hydrolysis to pseudo-bases III which are the main impurity (5). Azides II were characterized by their ir and nmr spectra and used without further purification.

Figure 1



I II III

a) $R_1 = R_2 = H$ b) $R_1 = \Phi = C_6H_5$ $R_2 = H$

c) $R_1 = R_2 = \Phi$ d) $R_1, R_2 =$ o-phenylene

Thermal rearrangements of azides II were achieved at 130° in xylene. The course of the reaction was monitored by measuring the volume of nitrogen evolved. Preparative tlc allowed isolation of 3-1-benzoxazepines IV, anils V, and hydrolysis derivatives III, VI, VII.

More accurate determination of the yields was made by hplc analysis comparing reaction mixtures with standard solution of pure compounds (Table I).

The structure of the anils was established by considering spectral data and by hydrolysis to corresponding isochromones VII. In the case of anils VIb and VIc an independant synthesis was made according to the procedure (6).

Figure 2

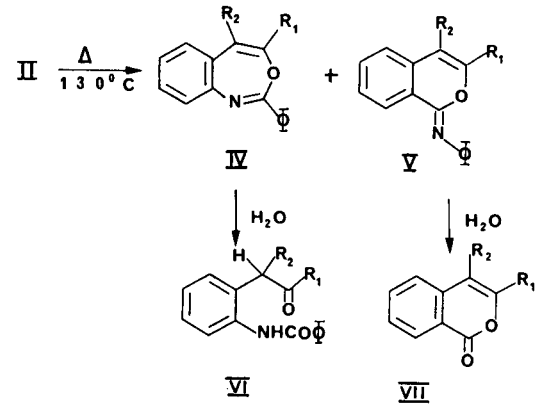


Table I

| II $\xrightarrow{\Delta}$ | IV | + | V | + | III | Migratory ratio (a) |
|---|---|---|---|---|---|---|
| a | 50 (25) (b) | | 20(8) | | (6) | 2.5 |
| b | 55 (35) | | 30(15) | | (10) | 1.9 |
| c | 30 (20) | | 45(20) | | (10) | 0.7 |
| d | 40 (25) | | 20(10) | | — | 2 |

(a) Migratory ratio: $\frac{\%\text{ oxazepine IV}}{\%\text{ anil V}}$

(b) Fifty = hplc analysis yield, (25) = tlc isolated product yield. Compounds III were insoluble in the hplc eluant.

Structure of benzoxazepines agrees with spectral and analytical data and hydrolysis to keto amides VI. Benzoxazepine IVa had been previously obtained and comparison was made with an authentic sample prepared according to the method reported (3).

The generally admitted mechanism for thermal rearrangements of aliphatic azides to imines involves an intermediate electrophilic nitrene, in agreement with the statistical migration of an alkyl or an aryl substituent $R_1$ to nitrogen (7).

Figure 3

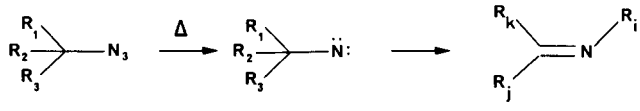


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Table II

| IV | a | b | c | d |
|---|---|---|---|---|
| M.p. | 68 | 55-57 | 144-145 | 86 |
| Ir | 1655 | 1645 | 1630 | 1642 |
| $\nu$ cm$^{-1}$ | 1625 | 1630 | 1600 | 1695 |
| | 1595 | 1595 | | |
| Uv (ether) | 317 (3.75) | 330 (3.58) | 320 (s) (3.86) | 306 (3.84) |
| $\lambda$ max nm | | 267 (4.32) | 268 (4.45) | 273 (3.93) |
| (log $\epsilon$ max) | | | | |
| RMN$^1$H | | | | |
| $\delta$ $H_3$ ppm | 6.3 (d) J = 5.8 Hz | — | — | — |
| $\delta$ $H_4$ ppm | 5.9 (d) J = 6.8 Hz | 6.6 (s, broad) | — | — |
| Analyses | | Calcd. Found | Calcd. Found | Calcd. Found |
| C | | 84.82 84.59 | 86.84 86.51 | 84.11 84.10 |
| H | | 5.09 5.11 | 5.13 5.28 | 4.83 4.85 |
| N | | 4.71 4.89 | 3.75 4.10 | 5.16 5.24 |

Table III

| V | a | b | c | d |
|---|---|---|---|---|
| M.p. | oil | 125 (6) | 175 (6) | 78-80 |
| Ir | 1650 | 1660 | 1660 | 1640 |
| | | 1625 | 1650 | 1610 |
| $\nu$ cm$^{-1}$ | 1595 | 1595 | 1595 | 1595 |
| $^1$H nmr | 7.0 (d) J = 6 Hz | 6.7 (s) | | |
| $\delta$ $H_3$ | 6.3 (d) J = 6 Hz | large | | |
| High | $C_{15}H_{11}NO$ | | | $C_{19}H_{13}NO$ |
| Resolution | Calcd. Found | | | Calcd. Found |
| Mass Spectra | | | | |
| $M^{\cdot+}$ | 221.0841 | | | 271.0997 |
| | 221.0843 | | | 271.0999 |

Thermolysis of azidoisochromenes II seems to fit this mechanism because no migration of electronegative oxygen is observed and migratory aptitudes of the two aromatic substituants at $C_1$ are of comparable value (see Table I). From a synthetic point of view, the yields of formation of benzoxazepines IV is quite acceptable due to the simplicity of the reaction procedure.

## EXPERIMENTAL

$^1$H Nmr spectra were obtained in deuteriochloroform on a Varian EM 360 spectrometer. Ir spectra (potassium bromide) were obtained on a Perkin-Elmer 357 spectrometer, uv spectra on a Varian Techtron spectrometer and mass spectra on AEI MS30 and MS50.

Tlc analyses were performed on Merck PF 254 silica and elutions were carried out with dry solvents under dry nitrogen. Hplc analyses were performed on a waters chromatograph using a waters $\mu$ porasil column, uv detection at 254 nm and calibration curves with titrated solutions of pure samples.

Whenever satisfactory elemental analysis could not be obtained for new compounds, a high resolution mass spectrum was carried out.

A typical experimental procedure follows.

Azidoisochromenes II.

Sodium azide (0.5 g) was added to a solution of 0.550 g of isochromylium perchlorate I in dry acetonitrile (20 ml) at 0° under a dry nitrogen atmosphere. The resulting suspension was stirred until decolorization occured. Solvent was eliminated at 0° under reduced pressure. The resulting oily resdiue was extracted with dry ether. After filtration and evaporation of the ether at 0°, azides II were obtained as colourless oils in quantitative yields. Characteristic ir spectra (potassiumm bromide) were performed; $\nu$ $N_3$ = 2100 cm$^{-1}$ and when necessary $^1$H nmr spectra.

Thermolysis of Azidoisochromenes.

Azide II (0.15 g) was heated in 10 ml of xylene at 130°. When the theoretical volume of nitrogen had evolved, the solvent was removed under reduced pressure. Analysis of the resulting residue was performed by tlc or hplc.

Preparative tlc afforded benzoxazepine IV and anil V but also various amounts of the hydrolysis compounds III, VI and VII. Pure IV and V were used to prepare standard solutions in order to calibrate the hplc analysis conditions of which were as follows: injection volume, 100 $\mu$l; initial eluant:isopropyl ether-isooctane (10-90); final eluant:isopropyl ether-isooctane (20-80); 7 minutes after injection an eluant gradiant was started for 15 minutes the flow rate being 2 ml/minute. Integration of signals and comparison with titration curves allowed determination of concentrations in IV and V (Table I).

3,1-Benzoxazepines IV.

Oxazepine IVa was the only known compound in our series. It was identified with an authentic sample prepared according to the method reported (3). Physical properties are detailed in Table II. Mass spectra are not reported, they are in agreement with proposed structures and fit the mechanism proposed by Djerassi (8).

Anils V.

Anils Vb and Vc were identified with samples prepared according to the procedure reported (6). Because of their extreme sensitivity to hydrolysis anils Va and Vd do not give satisfactory elemental analyses despite numerous attempts. Assignment of structures was based on spectral data and high resolution mass spectra.

Anils V are quantitatively hydrolysed into the corresponding isochromones VII by extended contact with silica.

Table IV

| VII | b | | c | | d | |
|---|---|---|---|---|---|---|
| M.p. | 230 | | 120 | | 235 | |
| Ir | 3280-3320 | | 3230-3240 | | 3400-3310 | |
| $\nu$ cm$^{-1}$ | 1680 | | 1685 | | 3150 | |
| | 1650 | | 1650 | | 1640 | |
| $^1$H nmr | (2H) 4.3 (s) | | (1H) 6.25 (s) | | (13H) (6.8-7.8) (m) | |
| | (14H) (7.1-8.1) (m) | | (19H) (7.1-8.2) (m) | | (1H)(a) 9.25 (s) | |
| | (1H)(a) 8.2 (s) | | (1H)(a) 8.6 (s) | | (1H)(a) 10.2 (s) | |
| Analyses | $C_{21}H_{17}NO_2$ | | $C_{27}H_{21}NO_2$ | | $C_{19}H_15NO_2$ | |
| | Calcd. | Found | Calcd. | Found | Calcd. | Found |
| C | 79.98 | 80.08 | 82.84 | 82.80 | 78.87 | 78.59 |
| H | 5.34 | 5.43 | 5.41 | 5.50 | 5.22 | 5.26 |
| N | 4.44 | 4.57 | 3.58 | 3.64 | 4.89 | 4.73 |

(a) Can exchange with deuterium oxide.

Pseudo Bases III.

Diketones IIIa-c had been previously obtained by photooxydation of the corresponding indenes (5). They were better prepared (yield >95%) by alkaline hydrolysis (sodium carbonate) of isochromylium salts I.

When heated with perchloric acid, diketones III gave back isochromylium perchlorate I.

Hydrolysis of Benzoxazepines IV.

Benzoxazepines IV were hydrolysed by contact with silica or by hot hydroalcoholic solutions (50-50). Amidoketones VIIb-c and amidophenol VIId were quantitatively obtained.

## REFERENCES AND NOTES

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