RE-EXPLORATION OF THE THERMOLYSIS OF ARYLAZIDES AS A ROUTE
TO 3H-AZEPINES: CHEMISTRY OF AZIDOACETOPHENONES

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Abstract— Thermolysis of 3-azidoacetophenone in methanol in a sealed
glass ampoule gave 6-acetyl- and 4-acetyl-3H-azepines in moderate yields,
whose kinetic data [$E_a$=132.6 $\pm$ 1.7 kJmol$^{-1}$, $\Delta S_{443}^{\ddagger}$= -12.1 $\pm$ 4.2 JK$^{-1}$mol$^{-1}$]
were obtained by means of HPLC. Photolysis of this azide in methanol gave
the same pair of the 3H-azepines in poor yields. Thermolysis of 4-azido-
acetophenone under the similar conditions afforded a moderate yield of
5-acetyl-3H-azepine. For comparison, photolyses of 4- and 2-azidoaceto-
phenones were also studied.

Thermolysis and photolysis of arylazides have been reported by many workers,[1] but
they do not appear to lend themselves well to the synthesis of 3H-azepines. In
particular, the thermolysis, regardless of the conditions employed,[2,3] is in no
ways a preparatively useful reaction. The only exception is the photolysis of
*o*-carbonylphenylazides wich affords 3H-azepines in a moderate yield.[4] Despite
these discouraging observations, we dared to study the thermolysis of azidoaceto-
phenones in the hope that the directive influence of an acetyl group to the ring
expansion of an intermediate arylnitrene and the transition state of the reaction
would be clarified. An additional object of the study was to find a correlation
between thermolysis and photolysis of the carbonyl-substituted arylazides. It has
been disclosed from the present study that thermolysis of the azides in a sealed
glass ampoule finds a way as a synthesis of 3H-azepines.
Heating of a MeOH (10 ml) solution of 3-azidoacetophenone (1) (1.00 g) in a sealed
glass ampoule at 170°C for 4 h gave 6-acetyl- (3) (58%)[5] and 4-acetyl-2-methoxy-3H-
azepines (6) (25%),[6] whose structural proofs rest on the $^1$H n.m.r. spectra of the
azepinones (4) and (7), each prepared by hydrolysis of the corresponding methoxy-

azepines by $SiO_2$.[7] The 7-H of <u>4</u> observed at δ 7.30 as a broad doublet collpased

to a sharp singlet upon addition of $D_2O$, and a broad doublet (δ 6.50) of the

7-H of <u>7</u> to a sharp doublet. The disappearance rates of <u>1</u> were determined at

160°C, 170°C, and 180°C by means of HPLC,[8] from which the following kinetic para-

meters were obtained: $E_a$=132.7 ± 1.7 kJmol$^{-1}$, $\Delta S^{\ddagger}_{443}$= -12.1 ± 4.2 JK$^{-1}$mol$^{-1}$,

$\Delta H^{\ddagger}_{443}$=128.9 ± 1.7 kJmol$^{-1}$, and $\Delta G^{\ddagger}_{443}$=134.3 ± 3.6 kJmol$^{-1}$.

A MeOH solution of the azide (<u>1</u>) was irradiated with a Ushio high pressure Hg lamp

through a pyrex filter. The $^1$H n.m.r. spectral and HPLC analyses of the photoly-

sate revealed the formation of a number of products, among which only the azepines

(<u>3</u>) and (<u>6</u>) and 3-aminoacetophenone were isolated in less than 6% yield each.

Thermolysis of 4-azidoacetophenone (<u>8</u>) in MeOH in a sealed glass ampoule gave

5-acetyl-2-methoxy-3H-azepine (<u>9</u>) in 60% yield, itself being converted to the

azepinone (<u>10</u>) by $SiO_2$, whereas photolysis of a MeOH solution of <u>8</u> yielded the

azepine (<u>9</u>) in 8% yield. The azide (<u>8</u>) appears to be less reactive than <u>1</u> because

a substantial quantity of the starting azide was recovered from the thermolysate

as well as the photolysate.

Likewise, 2-azidoacetophenone (<u>11</u>), when irradiated in MeOH, furnished 3-acetyl-

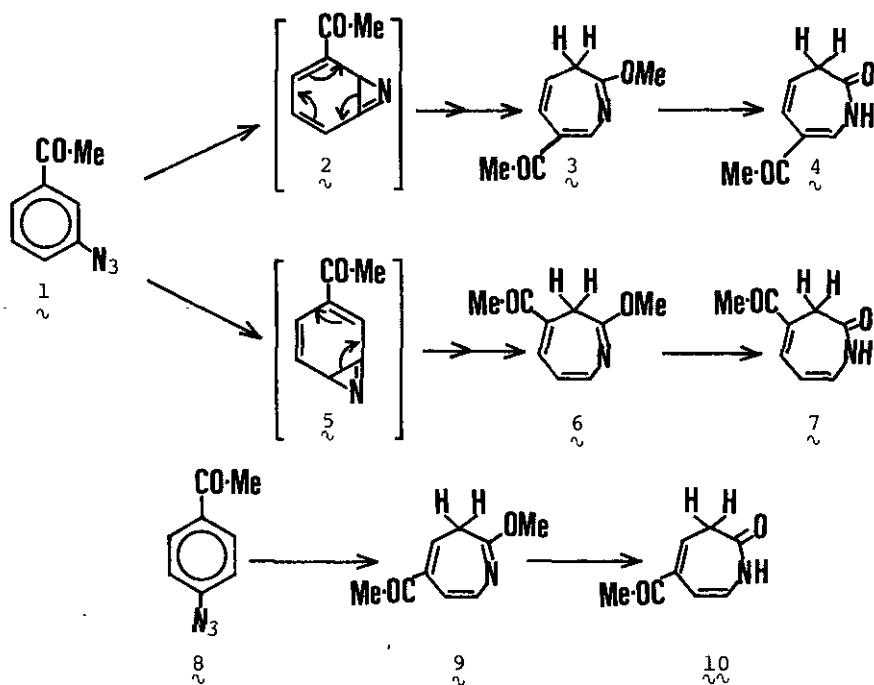2-methoxy-3H-azepine (<u>12</u>) (11% yield), 3-methylanthranil (<u>13</u>) (18%), and 7-acetyl-

Table. $^1$H N.m.r. spectra of the 3H-azepine derivatives in CDCl$_3$ ($\delta$ values)

| Compound | MeCO | MeO | 3-H | 4-H | 5-H | 6-H | 7-H | coupling constant (Hz) |
|---|---|---|---|---|---|---|---|---|
| (3) | 3.73 | 2.43 | 2.66(d) | 5.47(dt) | 6.79(dd) | ——— | 7.94(d) | $J_{3,4}$7.0; $J_{4,5}$9.0; $J_{5,7}$1.0 |
| (4) | —— | 2.34 | 2.92(d) | 5.69(dt) | 6.72(d) | ——— | 7.30(d) | $J_{3,4}$6.7; $J_{4,5}$9.6; $J_{NH,7}$5.0 |
| (6) | 3.70 | 2.37 | 2.98(s) | ——— | 7.14(dd) | 6.09(dd) | 7.22(d) | $J_{5,6}$6.0; $J_{5,7}$1.0; $J_{6,7}$8.0 |
| (7) | —— | 2.37 | 3.20(s) | ——— | 7.14(d) | 5.92(dd) | 6.50(dd) | $J_{5,6}$6.0; $J_{6,7}$9.0; $J_{NH,7}$5.0 |
| (9) | 3.73 | 2.38 | 2.79(d) | 6.22(t) | ——— | 6.52(d) | 7.10(d) | $J_{3,4}$7.5; $J_{6,7}$8.0 |
| (10) | —— | 2.39 | 3.06(d) | 6.61(t) | ——— | 6.35(s) | 6.35(d) | $J_{3,4}$7.2; $J_{NH,7}$5.0 |
| (14) | 3.77 | 2.45 | 2.65(d) | 5.56(dt) | 6.48(dd) | 7.00(d) | ——— | $J_{3,4}$7.0; $J_{4,5}$9.0; $J_{5,6}$6.0 |

2-methoxy-3H-azepine (14) (3%), which could be isolated by means of medium pressure liquid chromatography. The last, though suggested as a possible primary product of 11 by Berwick,[9] could not be isolated by him.

Among the three azidoacetophenones studied, the thermal transformation of the *meta*-isomer (1) to a 3H-azepine is by far the most efficient. In this case, a MeCO group reduces the electron density of both of the carbon atoms which suffer electrophilic attack by a singlet nitrene, thus rendering the formation of inter- mediate 2H-azirines (2) and (5) rather difficult. But if they are once formed, their isomerization to 3H-azepines would be facilitated as shown in the Scheme. The preferred formation of 2-substituted 6-acetyl-3H-azepine over the corresponding 4-acetyl-3H-azepine by the ratio of 2:1 is in keeping with the regiochemistry observed for the deoxygenation of ethyl *m*-nitrobenzoate by a tervalent phosphorus compound.[10]   The nitrene formed from 1 would attack the C(2)-position more readily. Activation parameters observed for the thermal decomposition of 1 indicate that an acetyl group reduces $E_a$ value by about 22.6 kJmol$^{-1}$ and $\Delta S^*$ value by about 43.5 JK$^{-1}$mol$^{-1}$ as compared to those observed for phenylazide,[11] which would imply the degree of freedom of the transition state to be rather small.

Our tentative conclusion is that thermolysis of 3- and 4-azidoacetophenones in a sealed glass ampoule is much more profitable as a synthetic was of 3H-azepines than their photolysis, whose unprofitableness might be associated with the rapid intersystem crossing of a singlet nitrene formed. We are now studying if this synthesis works well with other carbonyl-substituted arylazides and what solvent is most suitable for the reaction.

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5. 3; pale yellow oil; $\nu_{max.}$(oil) 2940, 2840, and 1663 cm$^{-1}$; $\lambda_{max.}$(EtOH) 217 ($\varepsilon$ 18,300) and 288.5 nm (13,900).

6. 6; pale yellow oil; $\nu_{max.}$(oil) 2940, 2840, and 1658 cm$^{-1}$; $\lambda_{max.}$(EtOH) 221 ($\varepsilon$ 12,800) and 313 nm (6,300).

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11. The disappearance rates of phenylazide were determined at 150°C, 160°C, 170°C, and 180°C by means of HPLC; $E_a$=155.2 ± 8.0 kJmol$^{-1}$, $\Delta S_{443}^{\ddagger}$=31.4 ± 8.0 JK$^{-1}$mol$^{-1}$, $\Delta H_{443}^{\ddagger}$=151.5 ± 8.0 kJmol$^{-1}$, and $\Delta G_{443}^{\ddagger}$=137.2 ± 11.6 kJmol$^{-1}$.