

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 [ $E_a = 132.6 \pm 1.7 \text{ kJmol}^{-1}$ ,  $\Delta S_{443}^\ddagger = -12.1 \pm 4.2 \text{ JK}^{-1}\text{mol}^{-1}$ ] 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-azidoacetophenone under the similar conditions afforded a moderate yield of 5-acetyl-3H-azepine. For comparison, photolyses of 4- and 2-azidoacetophenones were also studied.

Thermolysis and photolysis of arylazides have been reported by many workers,<sup>1</sup> but they do not appear to lend themselves well to the synthesis of 3H-azepines. In particular, the thermolysis, regardless of the conditions employed,<sup>2,3</sup> is in no ways a preparatively useful reaction. The only exception is the photolysis of *o*-carbonylphenylazides which affords 3H-azepines in a moderate yield.<sup>4</sup> Despite these discouraging observations, we dared to study the thermolysis of azidoacetophenones 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%)<sup>5</sup> and 4-acetyl-2-methoxy-3H-azepines (6) (25%),<sup>6</sup> whose structural proofs rest on the <sup>1</sup>H n.m.r. spectra of the azepinones (4) and (7), each prepared by hydrolysis of the corresponding methoxy-

azepines by  $\text{SiO}_2$ .<sup>7</sup> The 7-H of 4 observed at  $\delta$  7.30 as a broad doublet collapsed to a sharp singlet upon addition of  $\text{D}_2\text{O}$ , and a broad doublet ( $\delta$  6.50) of the 7-H of 2 to a sharp doublet. The disappearance rates of 1 were determined at  $160^\circ\text{C}$ ,  $170^\circ\text{C}$ , and  $180^\circ\text{C}$  by means of HPLC,<sup>8</sup> from which the following kinetic parameters were obtained:  $E_a = 132.7 \pm 1.7 \text{ kJmol}^{-1}$ ,  $\Delta S_{443}^\ddagger = -12.1 \pm 4.2 \text{ JK}^{-1}\text{mol}^{-1}$ ,  $\Delta H_{443}^\ddagger = 128.9 \pm 1.7 \text{ kJmol}^{-1}$ , and  $\Delta G_{443}^\ddagger = 134.3 \pm 3.6 \text{ kJmol}^{-1}$ .

A MeOH solution of the azide (1) was irradiated with a Ushio high pressure Hg lamp through a pyrex filter. The  $^1\text{H}$  n.m.r. spectral and HPLC analyses of the photolysate revealed the formation of a number of products, among which only the azepines (3) and (6) and 3-aminoacetophenone were isolated in less than 6% yield each. Thermolysis of 4-azidoacetophenone (8) in MeOH in a sealed glass ampoule gave 5-acetyl-2-methoxy-3H-azepine (9) in 60% yield, itself being converted to the azepinone (10) by  $\text{SiO}_2$ , whereas photolysis of a MeOH solution of 8 yielded the azepine (9) in 8% yield. The azide (8) appears to be less reactive than 1 because a substantial quantity of the starting azide was recovered from the thermolysate as well as the photolysate.

Likewise, 2-azidoacetophenone (11), when irradiated in MeOH, furnished 3-acetyl-2-methoxy-3H-azepine (12) (11% yield), 3-methylantranil (13) (18%), and 7-acetyl-

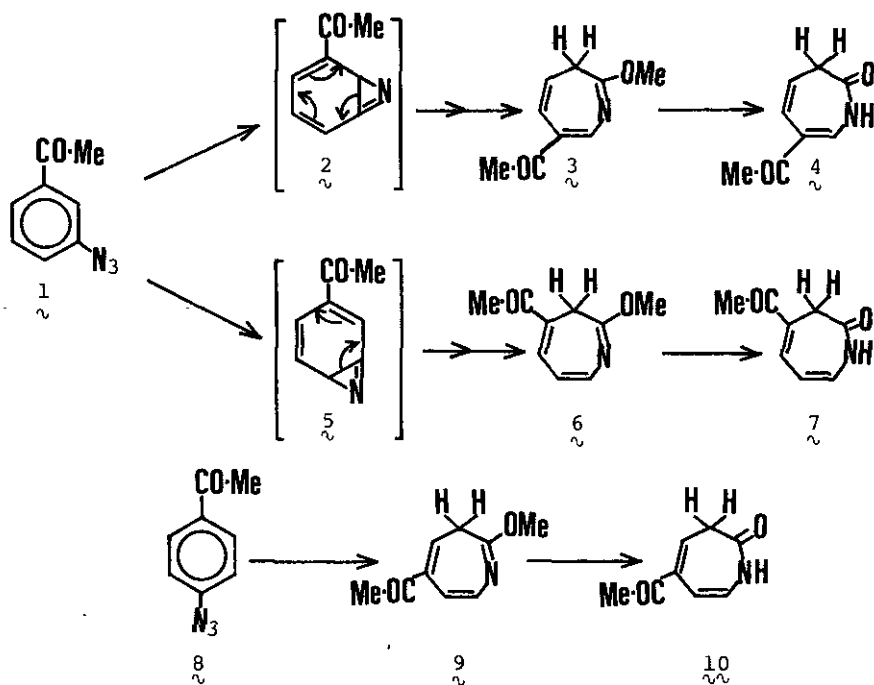


Table.  $^1\text{H}$  N.m.r. spectra of the 3H-azepine derivatives in  $\text{CDCl}_3$  ( $\delta$  values)

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)	$J_{3,4} 6.7$ ; $J_{4,5} 9.6$ ; $J_{\text{NH},7} 5.0$
(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)	$J_{5,6} 6.0$ ; $J_{6,7} 9.0$ ; $J_{\text{NH},7} 5.0$
(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)	$J_{3,4} 7.2$ ; $J_{\text{NH},7} 5.0$
(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,<sup>9</sup> 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 intermediate 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 trivalent phosphorus compound.<sup>10</sup> 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  $22.6 \text{ kJmol}^{-1}$  and  $\Delta S^\ddagger$  value by about  $43.5 \text{ JK}^{-1}\text{mol}^{-1}$  as compared to those observed for phenylazide,<sup>11</sup> 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 way 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  $\text{cm}^{-1}$ ;  $\lambda_{\max}$  (EtOH) 217 ( $\epsilon$  18,300) and 288.5 nm (13,900).
6. 6; pale yellow oil;  $\nu_{\max}$  (oil) 2940, 2840, and 1658  $\text{cm}^{-1}$ ;  $\lambda_{\max}$  (EtOH) 221 ( $\epsilon$  12,800) and 313 nm (6,300).
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8. Column conditions: Dupont Zorbax ODX, 15.0 cm x 4.6 mm; solvent, MeOH/H<sub>2</sub>O=1:1.
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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;  $E_a=155.2 \pm 8.0 \text{ kJmol}^{-1}$ ,  $\Delta S_{443}^\ddagger=31.4 \pm 8.0 \text{ JK}^{-1} \text{mol}^{-1}$ ,  $\Delta H_{443}^\ddagger=151.5 \pm 8.0 \text{ kJmol}^{-1}$ , and  $\Delta G_{443}^\ddagger=137.2 \pm 11.6 \text{ kJmol}^{-1}$ .

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