Chloroazirines: Bifunctional Electrophiles and Precursors for 5*H*-1,4-Benzodiazepines

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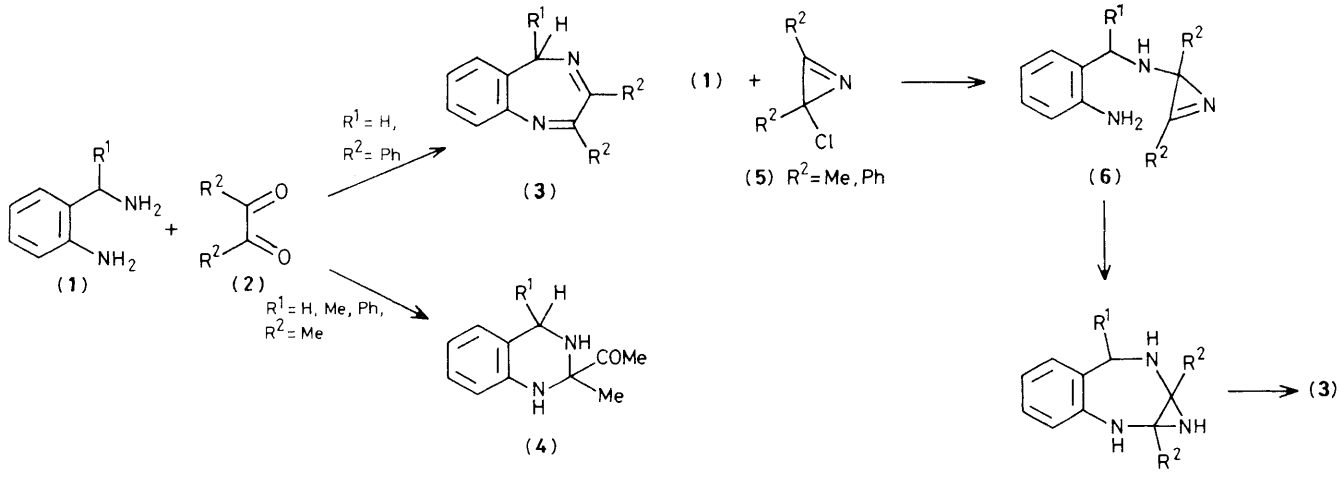
2-Aminobenzylamines can be converted into 5*H*-1,4-benzodiazepines with diphenyl- and dimethyl-chloroazirines; formation of the benzodiazepines from the diamines and 1,2-diketones is less general.

In view of the considerable interest in benzodiazepines[1] it is surprising that there is only one passing reference to a 5*H*-1,4-benzodiazepine in the literature.[2]

An obvious approach to this system is the reaction of the 2-aminobenzylamines (**1**) with the 1,2-diketones (**2**). This is successful in the case of the diamine (**1**; R^1 = H) and benzil which on heating in refluxing acetic acid for 24 h gave the diazepine (**3**; R^1 = H; R^2 = Ph)† (47%) as bright yellow cubes, m.p. 136—138 °C. Under similar conditions the

† ν(C=N) 1610 cm^{-1}. All new compounds were fully characterised and had satisfactory analytical, spectral, and mass spectral data.



Scheme 1

substituted benzylamines (**1**; R^1 = Me and Ph), were recovered unchanged.

In contrast, with biacetyl (**2**; R^2 = Me) all the diamines (**1**; R^1 = H, Me, and Ph) gave the aminals (**4**) as the only products. The structure for (**4**; R^1 = H), (45% yield, m.p. 126—128 °C), follows from its ^{1}H n.m.r. spectrum in $CDCl_3$ which shows an AB pair of doublets, *J* 17 Hz, at δ 3.82 and 3.96, methyl singlets at δ 1.4 and 2.3, and N–H absorptions at δ 1.9 and 4.65 in addition to the aromatic proton signals. The crude aminals (**4**; R^1 = Me and Ph) were mixtures of diastereoisomers from which the major isomer could be separated by chromatography on silica gel in yields of 67% (m.p. 96—98 °C) and 80% (m.p. 126—128 °C), respectively. On the assumption that these aminals (**4**) might be the kinetically controlled products attempts were made to convert them into the diazepines under conditions of thermodynamic control. However, the aminals (**4**) were recovered after heating under reflux in benzene with toluene-*p*-sulphonic acid whereas extensive decomposition occurred in refluxing acetic acid.

The chloroazirines (**5**)[3,4] offer an alternative approach to the diazepines (**3**) since displacement of the reactive chlorine by one nucleophilic centre should give a product (**6**) in which intramolecular attack by the second nucleophilic centre on the azirine function would be highly favoured and lead ultimately to the desired ring system as shown in Scheme 1. Indeed, addition of chlorodiphenylazirine (**5**; R^2 = Ph) to the diamine (**1**; R^1 = H) in pyridine at room temperature gave the diazepine (**3**; R^1 = H, R^2 = Ph) in 30% yield. Moreover, the substituted diamines (**1**; R^1 = Me and Ph) also gave the substituted diazepines (**3**; R^1 = Me and Ph; R^2 = Ph) in 49 and 58% yields, respectively on treatment with chlorodiphenylazirine whereas the reaction failed with the corresponding diketone. With chlorodimethylazirine, the dimethyldiazepine (**3**; R^1 = H, R^2 = Me) was obtained in 21% yield although in this case some of the aminal (**4**; R^1 = H, R^2 = Me) (42%) was also formed.

The diazepine (**3**; R^1 = H, R^2 = Ph) shows an AX pair of doublets (δ $CDCl_3$ 4.85 and 3.95, *J* 12 Hz) in the ^{1}H n.m.r. spectrum indicating that slow inversion of the seven-membered ring renders the methylene protons non-equivalent. These signals coalesced reversibly on heating the sample to 150 °C, from which the energy barrier to ring inversion is calculated to be 84 ± 2 kJ mol^{-1}. For the 5-methyl- and 5-phenyl-diazepines (**3**; R^1 = Me and Ph; R^2 = Ph) only one invertomer, presumably that with the 5-substituent pseudo equatorial, was observed. The AX pair of doublets of the methylene group of the dimethyldiazepine (**3**; R^1 = H, R^2 = Me) is close to coalescence at ambient temperature but becomes sharp on cooling to −40 °C. In this case the barrier to ring inversion is calculated to be 58 ± 2 kJ mol^{-1}. No evidence for conversion into 1*H*- or 3*H*-tautomers was observed for any of these benzodiazepines.

Chloroazirines clearly have advantages as 1,2-diketone equivalents in the synthesis of 5*H*-1,4-benzodiazepines and their use as bifunctional electrophiles is worthy of wider consideration.

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