A New Metal-catalysed Route to 4,5-Dihydro-3*H*-1-Benzazepines

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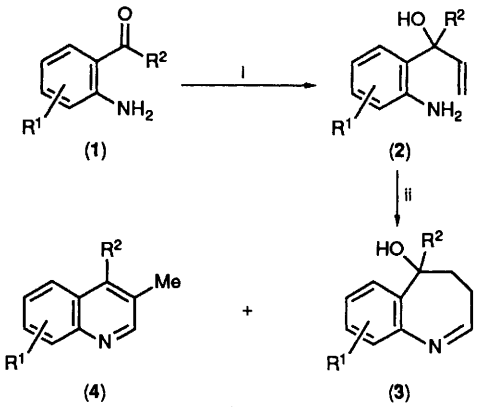
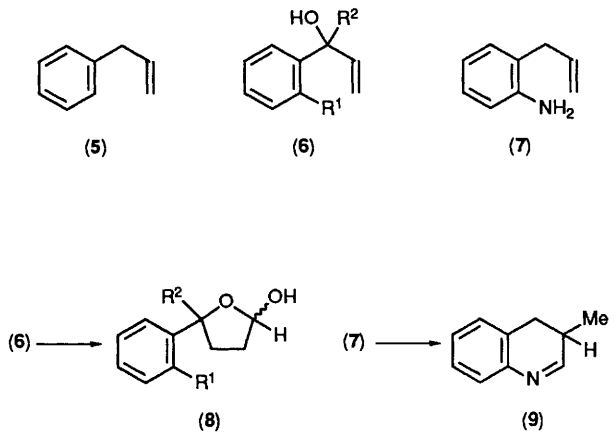
A new, short, high-yielding route to 4,5-dihydro-3*H*-1-benzazepines has been developed based on the rhodium-catalysed hydroformylation of readily available *ortho*-propenylbenzeneamines; a comparison with the hydroformylation of the corresponding *ortho*-propenylphenols is made.

The benzazepines are a class of compound of widespread interest to the pharmaceutical industry.[1] 4,5-Dihydro-3*H*-1-benzazepines, however, have not been widely investigated. A multistep route to 4,5-dihydro-3*H*-1-benzazepin-5-ol has been described,[2] but no facile route to these compounds is available.

We now describe a general preparation of this class of compound based on the rhodium-catalysed hydroformylation of *ortho*-propenylbenzeneamines (**2**) which are readily available in high yield (≥88%) from the reaction of *ortho*-acylbenzeneamines (**1**) with an excess of vinyl magnesium bromide.[3] (Scheme 1). The minor products from these



Scheme 1. Synthesis of dihydrobenzazepines (**3**): i: $CH_2CHMgBr$; ii: H_2/CO, $[Rh(OAc)_2]_2$, PPh_3.



Scheme 2

Table 1. Yields of products from the hydroformylation of *ortho*-propenylbenzeneamines (**2**).[a]

Reactant (**2**)		Products	
		Ratio[b]	Isolated yield of
R^1	R^2	(**3**) : (**4**)	dihydrobenzazepine (**3**) (%)[c]
H	H	75 : 25	69
H	Me	88 : 12	85
H	Ph	91 : 9	79
5-Cl	Ph	91 : 9	86
4-Me	Ph	87 : 13	70
H	4-MeC_6H_4	83 : 17	80

[a] Reactions were carried out in a Parr autoclave using ethyl acetate solutions of the unsaturated amine (**2**), $[Rh(OAc)_2]_2$, and PPh_3 in a ratio of 200 : 1 : 4 and H_2/CO (1 : 1) at an initial pressure of 2760 kPa for 20 h at 60 °C; [b] Ratios were determined from the ^1H NMR spectra (200 or 300 MHz) of the crude product. [c] Satisfactory spectroscopic and analytical data were obtained for all new compounds.

reactions are the 3-methylquinolines (**4**) which are readily separated from the dihydrobenzazepines (**3**) either by acid–base extraction or by chromatography. Yields from reactions of a representative range of substituted *ortho*-propenylbenzeneamines (**2**) are given in Table 1.

The dihydrobenzazepines (**3**) were all obtained in good isolated yields (≥69%). The amount of 3-methylquinolines (**4**) formed was relatively insensitive to the substituents on the aromatic ring but was sensitive to steric effects from the substituents at C-1 in the parent unsaturated benzeneamine (**2**). When R^2 = H, the ratio of (3) : (4) was significantly lower (75 : 25) than for all other reactions in which R^2 = Me or aryl.

The importance of these steric effects was demonstrated in the products obtained from the hydroformylations of 3-phenylprop-1-ene (**5**), 1,1-diphenylprop-2-en-1-ol [(**6**); R^1 = H, R^2 = Ph], 2-(1-hydroxy-2-propen-1-yl)phenols [(**6**); R^1 = OH, R^2 = H, Me, Ph], and 2-(prop-2-enyl)benzeneamine (**7**)[4] under similar conditions.

Hydroformylation of (**5**) gave the terminal and branched chain aldehydes in a ratio of 70 : 30, in the same range as values quoted for reactions carried out with related rhodium catalysts but under more severe conditions.[5] Hydroformylation of the substituted alkene [(**6**); R^1 = H, R^2 = Ph] gave the hemiacetals (**8**) as the only isolated products (84%). Similarly, hydroformylation of the unsaturated phenols [(**6**); R^1 = OH, R^2 = H, Me, Ph] gave mixtures of diastereoisomeric hemiacetals [(**8**); R^1 = OH, R^2 = H, Me, Ph], in good yield. Again, the products resulted from exclusive hydroformylation at the terminal carbon of the alkene. (Scheme 2.)

In contrast, hydroformylation of (**7**) gave no evidence for the formation of any products from hydroformylation at the terminal alkenyl carbon atom and only the dihydroquinoline (**9**) was isolated (albeit in modest yield) and characterized by conversion to the well known 3-methylquinoline. It appears, therefore, that the rhodium-catalysed hydroformylations of 2-(2-propen-1-yl)benzeneamines are susceptible to interaction of the amino nitrogen atom with the metal catalyst and such interactions could become dominant in the absence of steric effects from C-1.

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