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Synthesis Of Tetrahydroquinolines From Aromatic Amines, Formaldehyde And Electron Rich Alkenes: Evidence For Nonconcertedness

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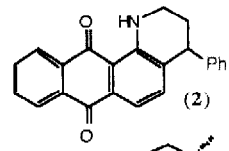
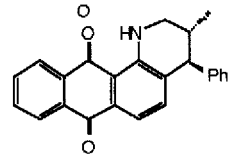
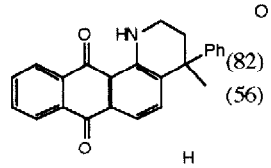
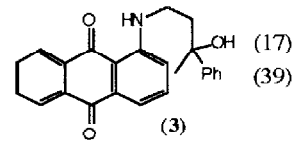
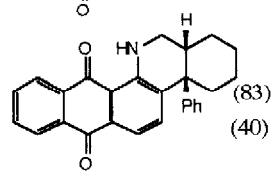
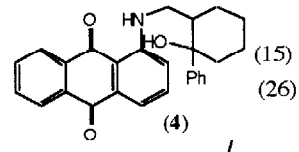
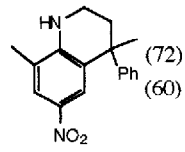
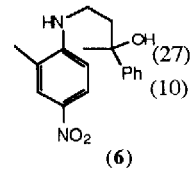
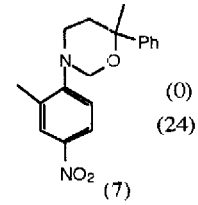
*Abstract. The one pot synthesis of tetrahydroquinolines can be achieved by reaction of aromatic amines and formaldehyde with a variety of electron rich alkenes including styrenes and enol ethers. The cyclisation is multi-step as evidenced by the isolation of intermediates, which can be cyclised to give the tetrahydroquinolines, and by the observation of side-products such as oxazines, and in the case of o-phenylenediamine, the interesting tricycle (**14**)*

Grieco and Bahsas[1] have described the reaction of cyclopentadiene with aldehydes and anilines to afford tetrahydroquinolines. Using this protocol, which does not require the prior formation of a Schiff 's base, we have used cyclopentadiene[2] to construct azasteroids. A number of earlier studies have described related additions to preformed imines and iminium ions. Thus not only cyclopentadiene and related dienes[3,4], but also styrenes[5], acetylenes[6], benzyne[7], enol ethers[8-10], enamines[11] and vinyl sulphides[12] have successfully been reacted with imines and related species. In spite of the considerable potential in these syntheses of diverse tetrahydroquinolines, there is little evidence permitting a discrimination between a possible concerted mechanism, i.e. a Diels Alder reaction characterised by inverse electron demand, and the alternative stepwise mechanism. Although the former concerted process has been favoured in certain reports[8,9], a recent more detailed analysis[4] is unable to assess their relative importance. In this communication we are able not only to establish the direct synthesis of tetrahydroquinolines by reaction of diverse electron rich alkenes with formaldehyde and aromatic amines, but by observation of reaction intermediates in a variety of examples, we are able to establish that under the protic conditions of Grieco and Bahsas[1] reactions are not concerted.

By reaction of aromatic amines with formaldehyde and cyclopentadiene in acetonitrile containing trifluoroacetic acid, tetrahydroquinolines are efficiently synthesized. Under similar conditions styrene reacts with formaldehyde and 1-aminoanthraquinone (**1**) to afford the quinone (**2**) in 86% yield. This and related examples[13] are shown in Table 1. In the additions of *trans*-β-methylstyrene and 1-phenylcyclohexene to 1-aminoanthraquinone a single cycloadduct is obtained in both cases. In the former case the methyl and phenyl substituents are shown to be *trans* from the ^{1}H-^{1}H coupling constant, and in the latter case the *cis* ring fusion is established by nOe analysis. The observed stereospecificity might be interpreted as evidence of a ring closure via a concerted aza-Diels Alder reaction. However high stereoselectivity has been observed in related cyclisations[14],

TABLE 1

Reaction of Styrenes with Formaldehyde and Aromatic Amines

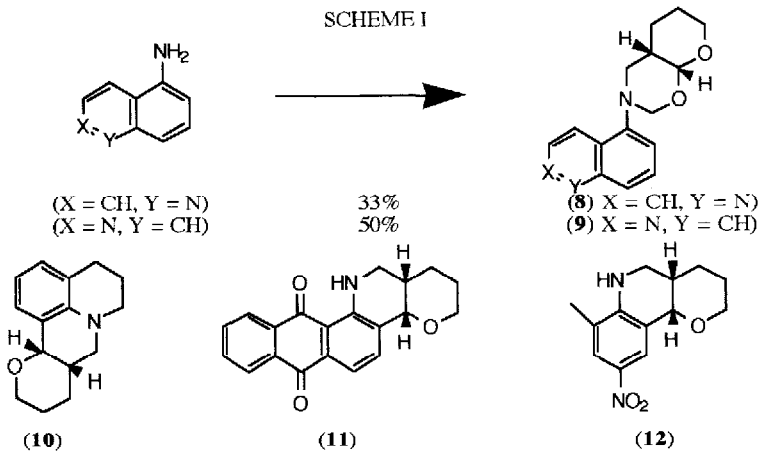
Substrates	Ratio (amine: formaldehyde: alkene)	Products (Yield%)
1-Aminoanthraquinone Styrene	1:4:4	 (86)
1-Aminoanthraquinone *Trans*-β–methylstyrene	1:3:3	 (82)
1-Aminoanthraquinone α–Methylstyrene	1:3:3	 (82)
1-Aminoanthraquinone[a] α–Methylstyrene	1:3:3	(56)
		 (17) (39) (3)
1-Aminoanthraquinone 1-Phenylcyclohexene	1:3:3	 (83)
1-Aminoanthraquinone[a] 1-Phenylcyclohexene	1:3:3	(40)
		 (15) (26) (4)
2-Methyl-4-nitroaniline[a] α–Methylstyrene	1:1.2:1.2	 (72)
2-Methyl-4-nitroaniline[a] α–Methylstyrene	1:3:3	(60)
		 (27) (10) (6)
		 (0) (24) (7)

a Reaction at room temperature

All other reactions at reflux.

which are multi-step. We have been able to conduct the reactions with α–methylstyrene and phenylcyclohexene under the conditions that permit the isolation of additional products. Following work-up the alcohols (**3**) and (**4**) could be isolated in 39 and 26% yield respectively. Under similar reaction conditions in acetonitrile in the presence of trifluoroacetic acid the alcohols were efficiently transformed into the cycloadducts. Therefore the isolation of these alcohols, and their subsequent easy conversion to cycloadducts provides clear evidence of the nonconcerted nature of the processes leading to the observed cycloadducts. The isolation of alcohols (**3**) and (**4**) suggests that formation of tetrahydroquinolines by reaction of styrenes under the conditions of Grieco and Bahsas is not via a concerted aza-Diels Alder reaction.

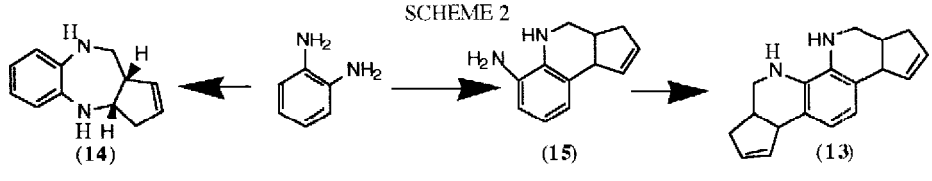
SCHEME 1



Reaction of 2-methyl-4-nitroaniline with formaldehyde and α-methylstyrene gives the adduct (**5**) in 72% yield, and the alcohol (**6**) in 27% yield after work-up.The oxazine (**7**) under similar conditions, but in the presence of excess formaldehyde, is obtained in 24% yield. The alcohol (**6**) can again be efficiently transformed to the adduct (**5**). The isolation of (**6**) and (**7**) strongly suggests that reaction of the amine with formaldehyde and the styrene affords an intermediate, which gives the alcohol (**6**). The intermediate can either react with further formaldehyde to give the oxazine, or by an electrophilic attack on the aromatic ring lead through to the cycloadduct. The possibility that formation of an oxazine might become the dominant pathway is shown in the reaction of dihydropyran with formaldehyde and aminoquinolines, and aminoisoquinolines. As shown in Scheme 1 the pyranooxazines (**8**) and (**9**) are obtained in 33 and 50% yield respectively. The *cis* ring fusion is established by observation of a 2.5Hz. coupling between the ring-junction protons, which is in good agreement with recent results[15]. In neither case are cycloadducts isolated. However under the usual conditions dihydropyran can undergo cycloaddition. Tetrahydroquinoline, 1-aminoanthraquinone and 2-methyl-4-nitroaniline afford the respective adducts (**10**), (**11**) and (**12**) in 45, 36 and 73% yield respectively. In each cycloadduct the observation of the relevant 2.5Hz. coupling establishes the *cis* ring fusion. Again this selectivity for formation of a *cis* adduct accords with the results of related electrophilic cyclisations. These reactions indicate that dihydropyran can afford tetrahydroquinolines and the competitive formation of pyranooxazines is further evidence of electrophilic intermediates.

The observation of intermediates and side-products implying the nonconcerted reaction of styrenes and enol

SCHEME 2



(**14**) (**15**) (**13**)

ethers raises the question whether cyclopentadiene reacts via a concerted mechanism. Neither Grieco andBahsas[1] in their earlier study, nor we in the reactions of cyclopentadiene with diverse monoamines[2] have found evidence for addition via a multi-step process. However we find that cyclopentadiene reacts with o-phenylenediamine to give not only the expected adduct (**13**) but also the tricyclic amine (**14**), an interesting example of a rarely isolated skeleton. Observation of this tricyclic amine indicates that the cycloaddition leading to the adduct (**15**) is probably again nonconcerted.

These results lead to two conclusions. The protic conditions of Grieco and Bahsas permit the efficient synthesis of tetrahydroquinolines by direct reaction not only of cyclopentadiene, but also electron rich alkenes with formaldehyde and aromatic amines. Further these reactions are not [4+2] concerted Diels Alder processes proceeding with inverse electron demand. The isolation of diverse side-products shows the nonconcerted character of these tetrahydroquinoline syntheses. These results raise questions on the earlier reports[9] of the concerted cycloaddition of imines with enol ethers under conditions of Lewis acid catalysis. As the stereoselectivity of such a reaction is catalyst dependent[16] it will be interesting to examine the character of these additions under conditions of Lewis catalysis.

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