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Intermolecular [4π + 2π]-Cycloadditions of Aromatic Methyleneamines

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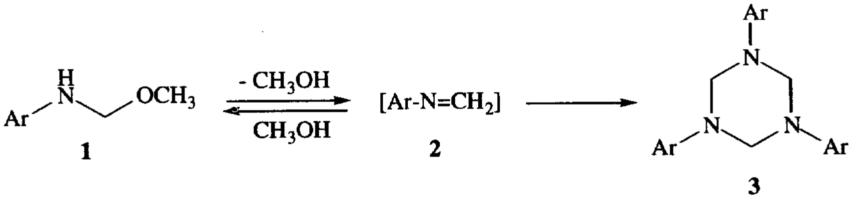
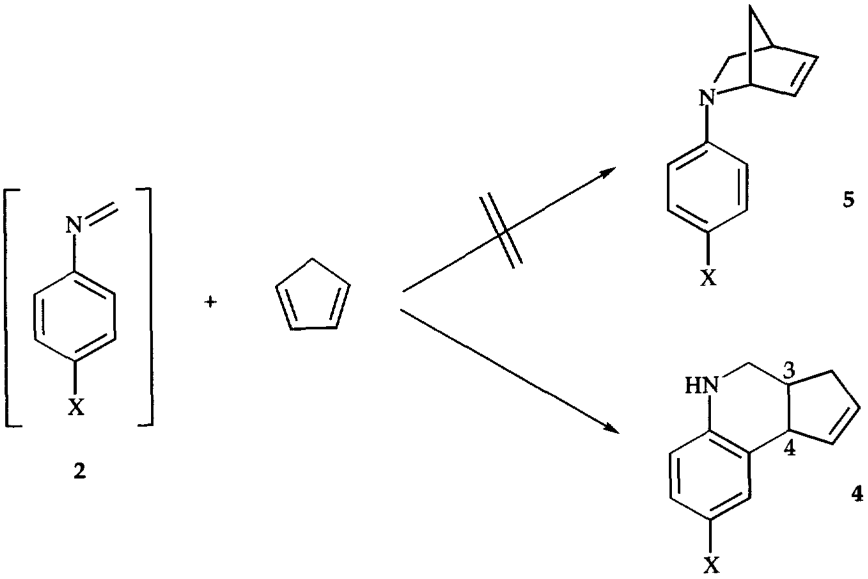
***Abstract*:** Aromatic methyleneamines react with dienes (in a reverse-electron-demand Diels-Alder cycloaddition) and with simple and activated alkenes. The observed regio- and stereochemistry suggests a concerted mechanism for this reaction. © 1997 Elsevier Science Ltd.

In previous papers, we described the reactivity of aromatic methyleneamines **2** towards nucleophiles.[1] The unstable products **2** are easily accesible from their precursors N-(methoxymethyl)arylamines **1** as an equilibrium mixture in methanol[2] or as an isolated imine at low temperature.[3] In fact, the heating of compunds **1** results in the fast β-elimination of an alkoxide to give **2**, which trimerizes quantitatively into the corresponding arylperhydrotriazine **3** in the absence of methanol (Scheme 1). Historically hetero Diels-Alder reactions have played a very important role in the synthesis of heterocycles but there are only few examples of the use of neutral imines derived from aldehydes as dienophiles.[4] The formation of compounds **2** prompted us to study their reactivity toward dienes since this reaction would lead to a general entry to tetrahydropyridine derivatives. Here, we report the preliminary results obtained in the reactions of aromatic methyleneamines **2** with unsaturated systems.



Scheme 1

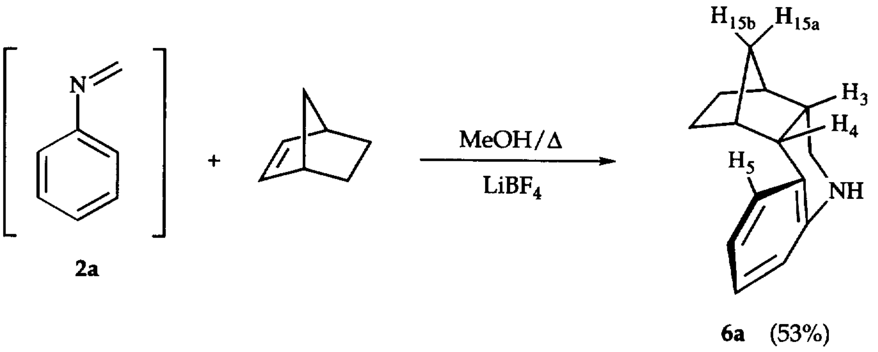
Firstly, we carried out the treatment of phenylmethyleneamine **2a**, prepared *in situ* by heating N-(methoxymethyl)phenylamine **1a** at 40°C, with an excess of cyclopentadiene in methanol for six hours. This reaction gave the tetrahydroquinoline **4a**, together with the cyclopentadiene dimer, instead of the expected tetrahydropyridine **5a**, as indicated by the spectoscopic data (^{1}H and ^{13}C NMR) and mass spectrometry (Scheme 2). The formation of the cycloadduct **4a** signifies an unexpected reverse-electron-demand procedure. This kind of reverse-electron-demand adduct has been detected previously (*i.e.*, when nitroalkenes catalyzed by $SnCl_4$ react with dienes)[5] and some reactions of aromatic imines with activated alkenes have been described.[6] However, the reaction reported here constitutes the first case in which an unactivated 2-azabutadiene undergoes an intermolecular Diels-Alder reaction with a diene (acting as a simple alkene) under very mild conditions and without acid catalysis. The extension of this reaction to *p*-substituted phenylmethyleneamine **2b** and **2c** requires heating at reflux and the presence of $LiBF_4$ as a catalyst.[7] Interestingly, only the regioisomers and the *cis*-fused stereoisomers [$J(H_3\text{-}H_4)$ = 4.5 - 4.8 Hz][8] represented in Scheme 2 were detectable in the crude mixture (^{1}H NMR, 300 MHz).



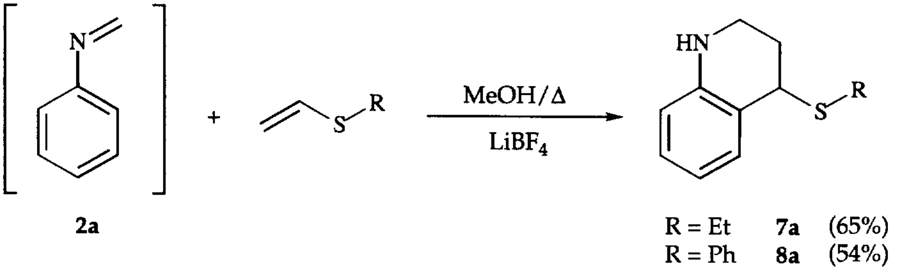
a	X = H	**4a**	(78%)
b	X = OMe	**4b**	(75%)
c	X = CO_2Me	**4c**	(71%)

Scheme 2

In view of the reaction characteristics, we have also proved the reactivity of aromatic methyleneamines towards norbornene (as a single alkene, Scheme 3) and vinylsulphides (as electron-rich dienophiles, Scheme 4). In these cases, the reaction proceed in methanol under reflux and in the presence of $LiBF_4$ to give the *cis*-fused stereoisomer (**6a**)[9] and one single regioisomer (**7a** and **8a**).



Scheme 3



Scheme 4

In conclusion, this work reveals that easily available imines of formaldehyde react with dienes (in a reverse-electron-demand Diels-Alder cycloaddition) and with simple and activated alkenes. The observed regio- and stereochemistry suggests a concerted mechanism for this reaction. In addition, tetrahydroquinoline skeleton is often used in the total synthesis of natural products[10] and in medicinal chemistry.[11]

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12. Typical Experimental Procedure:

    To a solution of the corresponding dienophile (6 mmol) in anhydrous methanol (15 ml) was added a solution of $LiBF_4$ (0.2 mmol, 0.019 g, except for **4a**) in the same solvent under an argon atmosphere. The mixture was heated at reflux (40°C for **4a**) and the aromatic N-(methoxymethyl)arylamine was added and the mixture stirred for 6 hours at the same temperature. The solution was hydrolized and standard work-up and column chromatography (silica gel; hexane-ether) gave pure 1,2,3,4-tetrahydroquinoline.

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