In the last few years, we have been interested in the synthetic applications of the hetero-Diels–Alder reaction using vinylallenes as dienes. We found that semicyclic vinylallenes can react with aldehydes in the presence of Lewis acids, giving the corresponding cycloadducts with a hexahydrochromone skeleton (Equation 1). The reaction proceeds with complete regio- and facial selectivity, with good endo/exo selectivity and in fair to good yields.

Intramolecular Hetero-Diels–Alder Reaction of Vinylallenes and Imines: Synthesis of 9-Methyl-1,2,3,4,5,6,7,8-octahydroacridine

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Abstract: The intramolecular hetero-Diels–Alder reaction of vinylallenes and imines has been carried out. Depending on the substituents on the allene and the length of the tether linking diene and heterodienophile, the reaction proceeds thermally or with Lewis acid activation. The transformation of one of the adducts into a 9-substituted octahydroacridine is reported.

Key words: vinyl allenes, intramolecular reaction, hetero-Diels–Alder reaction, imines, cycloaddition

The intramolecular Diels–Alder reaction is generally more favorable than the intermolecular process, mainly due to entropic reasons, and although only a few examples of intramolecular Diels–Alder reaction of dienes with a carbonyl group as dienophile have been reported, we decided to test the vinylallene moiety in this reaction with aldehydes as heterodienophiles. The required compounds containing the semicyclic vinylallene and the aldehyde linked by a chain of two or three carbon atoms were prepared, and it was found that the reaction took place yielding only one isomer (trans) in each case due to the restrictions imposed by the length of the tether and the rigidity of the allene (Equation 2). The compounds with the shorter chains were more reactive, as expected, and in fact some of the reactions were spontaneous at room temperature (R = alkyl, n = 1, Equation 2). What was more interesting was the finding that the reaction took place even without any alkyl substituent on the allene carbon bonded to the vinyl group (R = H, n = 1, Equation 2), although in this case heating or Lewis acid activation was needed. With the longer chain compounds (n = 2) only the substituted vinylallenes reacted (R = alkyl) with heating or Lewis acid catalysis.

In these reactions, some limitations were found, the most important one being the need for a substituent on the allene carbon to bond to the vinyl moiety (R in Equation 1). This substituent could act as an activating group facilitating the reaction and also controlling the regiochemistry. It is important to note that for a similar reaction to take place using nonallenic dienes, a strong electron-releasing group, such as alkoxy or silyloxy, needs to be present, whereas with vinylallenes it suffices to have a simple alkyl group as substituent.

Intramolecular Hetero-Diels–Alder of Vinylallenes and -imines

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When these semicyclic vinylallenes were reacted with N-benzylimines, the adducts with an octahydroquinoline skeleton were obtained as a single isomer with cis-stereochemistry in each case (Equation 1). The reaction proceeds with complete regio- and facial selectivity, with good endo/exo selectivity and in fair to good yields.

In this paper we present our results on the synthesis, reactivity and transformation of the imine-vinylallene systems.

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We decided to test the reaction first with the imines with disubstituted allenes 5 and 6 (Scheme 1, R = H), which were prepared from the corresponding vinylallene aldehydes 1 and 2 by treatment with benzylamine and MgSO$_4$ at 0 °C for 30 minutes. The crude reaction product of each reaction was then treated with BF$_3$·Et$_2$O in dichloromethane at –78 °C and the reaction was stirred at room temperature for 8 hours. In the first case, after chromatography, the tricyclic compound 9 was obtained in a 41% yield, indicating that this process is more favorable than the corresponding direct cyclization reaction of aldehyde 1, which gave only 18% yield of the product. However, in the case of the second compound 6, only decomposition products were obtained under all conditions tried; same result was obtained for the cyclization of aldehyde 2.

Scheme 1

When the reaction was repeated using aldehyde 3, the cyclization of the corresponding imine 7, gave the cycloaduct 10 in 54% yield, again slightly better than the yield of the cyclization of aldehyde 3 to the oxygenated tricyclic compound (45%). The best result was obtained with the tert-butyl substituted aldehyde 4, which after imine formation and cyclization gave 11 in an 88% yield, whereas direct cyclization of aldehyde 4 gave the cycloaduct in only 48% yield.

In the case of the synthesis of the compound with a trisubstituted allene and a two-carbon tether (Scheme 2), our previous results indicated that the aldehyde could not be isolated, since it cyclized easily at room temperature without the need for Lewis acid, but it could be observed by $^1$H NMR spectroscopy that it was the main product in the Swern reaction crude. For that reason, we decided to prepare the imine after quenching of the oxidation reaction of alcohol 12 without purification. Thus, the reaction crude was dissolved in dichloromethane and benzylamine was added at 0 °C. The reaction was allowed to stand for 12 hours and, after extraction and chromatography, a 1:1.5 mixture of the desired nitrogenated compound 13 and the oxygenated compound 14 was obtained in good yield (70%). This result indicates that the cyclization of the aldehyde was faster than we had anticipated, and thus the procedure was changed in that the imine was formed directly in the solution resulting from the addition of Et$_3$N to the oxidation reaction. After allowing the reaction to proceed for 12 hours, 13 was isolated as the only compound in a 69% yield.

Scheme 2

The stereochemistry of all compounds obtained, studied using noesy experiments, was shown to be trans as expected.

Once the reactivity of the vinylallene-imine systems was established, we decided to study the transformation of the tricyclic adducts. We started by attempting to deprotect the N-benzyl group of tricyclic compound 10 using catalytic transfer hydrogenation with cyclohexene as the hydrogen donor and 10% Pd/C as the catalyst. Under these conditions and after 2 hours, the major product of the reaction, isolated in a 40% yield, was identified by $^1$H NMR spectroscopy as a compound in which not only has the nitrogen been deprotected, but also double bond migration and aromatization of the central ring have occurred, resulting in 9-methyl-1,2,3,4,5,6,7,8-octahydroacridine 15 (Scheme 3). Octahydroacridines are interesting compounds, which have different applications, and this procedure adds to the arsenal of methods devised for their preparation.
As a minor product of the reaction, a compound with a tetrahydroacridine skeleton 16 was obtained (20% yield), pointing to the possibility that longer reaction times could lead to more aromatic acridine derivatives.

In conclusion, we have found that the intramolecular hetero-Diels–Alder reaction of semicyclic vinylallenes, using imines as the heterodieneophile, is a synthetically useful reaction, and the adducts obtained can be transformed into interesting compounds.

All commercial reagents were used as supplied. NMR Spectra were recorded on a 400 MHz spectrometer. Chemical shifts are reported in ppm with the solvent signal used as internal standard (CDCl3, δ = 7.26). All reactions were conducted in an argon atmosphere. Solvents were distilled from sodium benzenophene ketyl. Column chromatography was performed using silica gel (grade 60, 230–400 mesh). HRMS were obtained on a Fisons Instruments VG Autoscope.

4-Benzyl-3,3a,4,4a,5,6,7,8-octahydro-2H-cyclopenta[b]quinoline (9); Typical Procedure

To a solution of 1 (281 mg, 1.59 mmol) in Et2O (2 mL) under argon at 0 ºC were added benzylamine (0.17 mL, 1.59 mmol) and MgSO4 (800 mg). After stirring for 30 min the reaction was filtered and concentrated. The crude reaction mixture was dissolved in CH2Cl2 (50 mL) and cooled to –78 ºC. Then BF3·Et2O (0.22 mL, 1.75 mmol) was added and the reaction was allowed to warm to r.t. After stirring for 8 h, Et2O (0.2 mL) was added and the reaction mixture was concentrated and purified by flash chromatography (hexane–EtOAc, 90:10) to give 176 mg of 9 (41% yield) as a clear oil.

1H NMR (CDCl3): δ = 7.53–7.51 (m, 2 H), 7.31–7.17 (m, 3 H), 6.13 (s, 1 H), 5.52 (s, 1 H), 3.84–3.78 (m, 2 H), 3.60 (d, J = 7.53 Hz, 1 H), 1.82 (dq, J = 3.5, 12.3 Hz, 1 H), 1.22 (m, 1 H), 0.98 (m, 1 H).

13C NMR (CDCl3): δ = 145.9, 141.9, 140.0, 128.7, 126.7, 120.7, 114.7, 62.0, 60.2, 52.4, 35.9, 31.7, 30.7, 29.8, 26.9, 25.6.

HRMS (FAB): m/z calcd for C23H23N (M⁺): 311.1638; found: 311.1637.

Attempts to Deprotect 10

To a solution of 10 (185 mg, 0.63 mmol) in MeOH (14 mL) under argon, were added cyclohexene (2.5 mL) and 10% Pd/C (18.5 mg). The reaction mixture was refluxed for 2 h and then filtered and concentrated. After flash chromatography (hexane–EtOAc, 1:1), 15 (51 mg, 40%) and 16 (25 mg, 20%) were obtained.

9-Methyl-1,2,3,4,5,6,7,8-octahydroacridine (15)

1H NMR (CDCl3): δ = 2.85 (br s, 2 H), 2.62 (br s, 2 H), 2.06 (s, 3 H), 1.81 (br s, 4 H).

13C NMR (CDCl3): δ = 153.1, 144.5, 128.0, 32.8, 26.2, 23.1, 22.8, 13.8.

9-Methyl-1,2,3,4-tetrahydroacridine (16)

1H NMR (CDCl3): δ = 7.96 (dd, J = 8.8 Hz, 2 H), 7.59 (dd, J = 7.9, 7.6 Hz, 1 H), 7.45 (dd, J = 7.9, 7.6 Hz, 1 H), 3.11 (br s, 2 H), 2.89 (br s, 2 H), 2.54 (s, 3 H), 1.93 (m, 4 H).

13C NMR (CDCl3): δ = 158.5, 145.8, 141.3, 128.9, 128.7, 128.1, 126.9, 125.2, 123.3, 34.4, 27.1, 23.2, 22.7, 13.5.

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References

(1) The term semicyclic refers to a dienic or vinylallenic system in which only one of the double bonds is a part of a cycle.


(8) All compounds described in this paper were prepared in racemic form.
