The first aza Diels–Alder reaction involving an α,β-unsaturated hydrazone as the dienophile: stereoselective synthesis of C-4 functionalized 1,2,3,4-tetrahydroquinolines containing a quaternary stereocenter†

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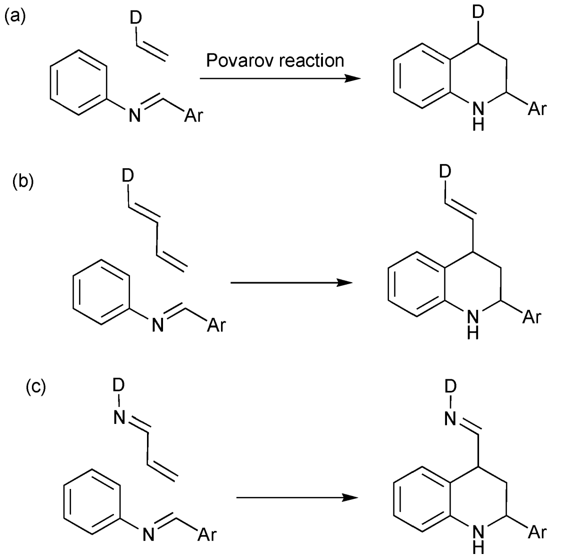
Received 28th February 2007, Accepted 26th March 2007
First published as an Advance Article on the web 4th April 2007
DOI: 10.1039/b703083e

The reaction between aromatic imines and methacrolein dimethylhydrazone in the presence of 10% indium trichloride affords in good to excellent yields biologically and synthetically relevant 1,2,3,4-tetrahydroquinolines bearing a hydrazone function at C-4 in a one-pot process that involves the formation of two C–C bonds and the stereoselective generation of two stereocenters, one of them quaternary, and this constitutes the first example of an α,β-unsaturated dimethylhydrazone behaving as a dienophile in a hetero Diels–Alder reaction and the first vinylogous aza-Povarov reaction.

The 1,2,3,4-tetrahydroquinoline moiety is a structural fragment of several natural products, including the well-known enedyine antitumour drug dynemycin, alkaloids of the benzastatin-virantmycin family, some of which possess potent antiviral activity,[1] and the marine alkaloids discorhabdin[2] and martinelline.[3] Furthermore, many unnatural tetrahydroquinoline derivatives exhibit a broad range of biological activities,[4] which has prompted the selection of tetrahydroquinoline-derived targets in programs aimed at the solid-phase library generation of natural product-like scaffolds with privileged substructures.[5] Tetrahydroquinolines are also important as synthetic intermediates, especially in the preparation of quinoline derivatives.[6] The interest in these compounds has stimulated the development of a large number of synthetic methods,[7] among which one of the most efficient is the so-called imino Diels–Alder reaction, *i.e.* the reaction between imines derived from aromatic aldehydes and electron-rich alkenes [Scheme 1(a)], which was discovered by Povarov in the 1960s[8] and has experienced a resurgence in the last 10 years following the discovery that lanthanide triflates were efficient catalysts for this transformation.[9] In spite of its interest, many aspects of the Povarov reaction have received little attention; for example, the range of dienophiles so far employed is relatively small, since most attention has been directed to enol ethers, particularly cyclic ones like dihydrofuran and dihydropyran.[10] Vinylogous versions of the Povarov reaction, *i.e.* cycloadditions of arylimines where one of the double bonds of an open-chain diene-type structure acts as the dienophile, would be synthetically very useful, but are almost unknown in the literature. The use of 1,3-butadienes as dienophiles would provide access to tetrahydroquinoline derivatives bearing a two-carbon substituent at C-4 [Scheme 1(b)]. A similar reaction involving an aza derivative of an electron-rich diene [Scheme 1(c)] would also be very interesting in that it would yield tetrahydroquinolines with a carbon functional group directly attached to C-4, which is the substitution pattern found in many relevant tetrahydroquinolines, including some natural products. In spite of the synthetic potential of these transformations, only two cases of the Scheme 1(b) situation have been reported[11] and the strategy summarized in Scheme 1(c) is unknown, to our knowledge. We present here the first implementation of the formal cycloaddition between aromatic imines and 1-azadienes where the imine acts as the diene and the C=C portion of the azadiene behaves as the dienophile. This transformation involves a vinylogous aza-Povarov reaction according to Scheme 1(c).



Scheme 1 The imino Diels–Alder (Povarov) reaction and two proposed vinylogous versions thereof.

α,β-Unsaturated hydrazones have long been known to behave as the diene component in hetero Diels–Alder reactions leading to pyridine and fused pyridine derivatives.[12] Due to the electron-withdrawing effect of the nitrogen atom, the C=C double bond of these 1-azadienes can be considered as an electron-poor alkene and therefore unsuitable as a partner for the imino Diels–Alder reaction. However, the introduction of electron-releasing groups on nitrogen such as dimethylamino,[13] acetylamino[14] or 1-*tert*-butyldimethylsilyloxy[15] substituents reverses this situation and

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† Electronic supplementary information (ESI) available: Analytical and spectral characterization data and representative spectra. See DOI: 10.1039/b703083e

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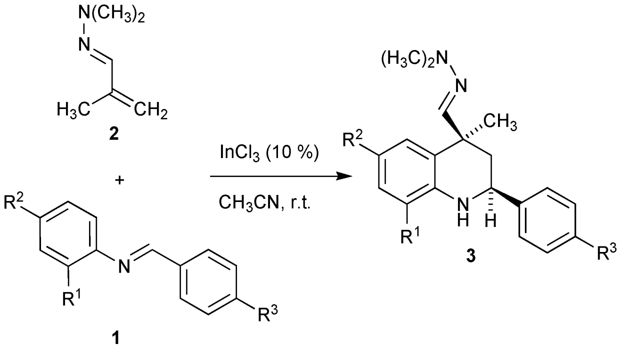
allows the use of α,β-unsaturated hydrazones as dienes in normal electron demand Diels–Alder reactions. With this precedent in mind, we undertook the study of the reaction between aromatic imines **1**, and methacrolein dimethylhydrazone **2**, hoping to be able to use for the first time the latter compound as the dienophile component, rather than the diene, in an imino Diels–Alder reaction. Gratifyingly, we discovered that the use of 10% indium trichloride as a catalyst allowed us to carry out the expected transformation, furnishing the C-4 functionalized 1,2,3,4-tetrahydroquinolines **3** in good to excellent yields (Scheme 2 and Table 1).[16] It is noteworthy that the reaction tolerates well the presence of both electron-withdrawing and electron-releasing groups at both aromatic rings of the starting imine. Small amounts of 4-(R^3-aryl)dimethylhydrazones, arising from a transimination reaction[17] between compounds **1** and **2**, were also observed in the crude reaction mixtures.

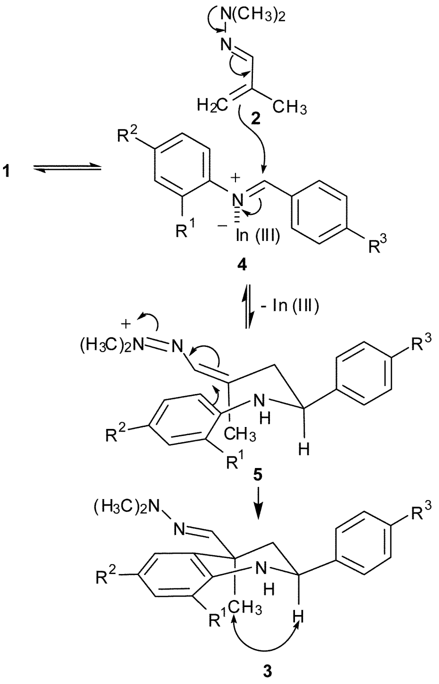


Scheme 2 Three-component reaction between anilines, aromatic aldehydes and an α,β-unsaturated hydrazone.

The vinylogous aza-Povarov reaction thus developed was stereoselective and afforded exclusively compounds **3** with a *cis* relationship between the C-2 hydrogen and the C-4 methyl. This structure was established by NOESY studies, which showed a correlation peak between the H-2 and C_4-CH_3 signals, which is only consistent with a *cis* arrangement for these substituents, both being equatorial. The observed stereoselectivity can be explained by taking into account that the Povarov reaction is known to proceed in a stepwise manner, as proved by the trapping of the intermediate iminium species when the reaction is carried out in the presence of nucleophiles.[18] Therefore, the generation of intermediates **6** from the reaction between dimethylhydrazone **2** and indium–imine complex **5** is expected under our conditions. The final cyclization step should take place through a chair-like transition state, leading to a preference for an equatorial arrangement of the bulky dimethylhydrazono and aryl substituents and hence to the observed stereochemistry for compounds **4** (Scheme 3). The generation with complete control of the stereocenter at the tetrahydroquinoline C-4 position is noteworthy, since the stereoselective installation of quaternary stereocenters is one of the most challenging tasks for synthetic organic chemistry.[19]

Table 1 Results obtained in the indium-catalyzed reaction between anilines, aromatic aldehydes and methacrolein dimethylhydrazone

Entry	Compound	R^1	R^2	R^3	Time/h	Yield (%)
1	**3a**	H	OCH_3	H	2	90
2	**3b**	H	CH_3	H	2	71
3	**3c**	H	CH_3	Cl	2	76
4	**3d**	H	OCH_3	Cl	3	87
5	**3e**	H	OCH_3	CH_3	2	93
6	**3f**	OCH_3	H	Cl	3	70
7	**3g**	H	CH_3	OCH_3	2	72
8	**3h**	H	OCH_3	OCH_3	2	80
9	**3i**	CH_3	CH_3	Cl	3	79
10	**3j**	CH_3	CH_3	OCH_3	3	83
11	**3k**	CH_3	CH_3	CH_3	5	81
12	**3l**	CH_3	CH_3	Br	3	80



Scheme 3 Rationale for the stereoselectivity of the vinylogous imino Diels–Alder reaction.

In conclusion, we have developed a new domino reaction that involves the creation of two C–C bonds and the generation of two stereocenters, one of them quaternary, with complete diastereoselectivity and in a single synthetic operation. Furthermore, this method affords synthetically valuable C-4 functionalized 1,2,3,4-tetrahydroquinolines in good to excellent yields using simple and readily available starting materials and a non-toxic and inexpensive catalyst. This transformation can be considered as a new type of vinylogous aza-Povarov reaction, and constitutes the first example of an α, β-unsaturated hydrazone behaving as the dienophile component in an aza Diels–Alder reaction.

Acknowledgements

The stay of PTP in Madrid was supported by a grant from the Santander-UCM "Programa de Visitantes Distinguidos". Financial support from MEC (grant CTQ2006-10930), UCM–CAM (Grupos de Investigación, grant 920234) is also gratefully acknowledged.

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16 **General procedure**: Imines **1** were prepared by the standard procedure of refluxing equimolecular amounts of the suitable aniline and aldehyde in ethanol for 3 h and filtering the solid that precipitated after cooling. The suitable imine **1** (2 mmol) was dissolved in acetonitrile (15 ml). To this stirred solution was added 1.2 eq. of methacrolein dimethylhydrazone **2** (270 mg, 2.4 mmol) and indium trichloride (45 mg, 10 mol%), and stirring was continued for the time period specified in Table 1. After completion of the reaction, as indicated by TLC, the reaction mixture was diluted with water (10 ml), extracted with CH_2Cl_2 (4 × 10 ml), dried and evaporated. Purification was achieved through silica gel column chromatography, using petroleum ether–ethyl acetate (95 : 5, v/v) as eluent. Characterization data for one representative example (compound **3a**) follow. Data for all other compounds, together with copies of representative spectra, can be found in the Electronic Supporting Information†. **(±)-(2*S**,4*S**)-4-Methyl-6-methoxy-2-phenyl-1,2,3,4-tetrahydro-quinoline-4-carbaldehyde *N*,*N*-dimethylhydrazone** (**3a**): Viscous liquid. IR (neat) 3389.3, 2914.4, 2852.5, 1603.9, 1486.0, 1316.3, 1262.6, 1016.2 cm^{-1}. ^1H-NMR ($CDCl_3$, 250 MHz) δ 1.61 (s, 3H), 1.86 (dd, J = 12.9, 2.3 Hz, 1H), 2.08 (dd, J = 12.9, 12.0 Hz, 1H), 2.15 (s, 3H), 2.25 (s, 3H), 2.78 (s, 6H), 3.89 (bs, 1H), 4.59 (dd, J = 12.0, 2.3 Hz, 1H), 6.70 (s, 1H), 6.81–8.83 (m, 2H), 7.33–7.55 (m, 5H). ^{13}C-NMR ($CDCl_3$, 62.9 MHz) δ 18.0, 21.0, 28.4, 41.4, 44.0, 44.8, 53.7, 122.1, 126.5, 126.6, 127.2, 127.4, 128.2, 129.2, 130.0, 140.4, 145.0, 145.8. Anal. Calcd for $C_{21}H_{27}N_3$: C, 78.46; H, 8.47; N, 13.07. Found: C, 78.23; H, 8.30; N, 12.78%.

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