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Three component coupling reactions of *N*-acetyl-2-azetine- rapid stereoselective entry to 2,3,4-trisubstituted tetrahydroquinolines

Paul J. Stevenson,* Mark Nieuwenhuyzen and Daire Osborne
School of Chemistry, The Queen's University of Belfast, Belfast, UK. E-mail: p.stevenson@qub.ac.uk; Fax: +12890-382117; Tel: +12890-274426

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_N_-Acetyl-2-azetine undergoes Lewis acid catalysed [4 + 2]-cycloaddition with imines derived from aromatic amines and gave a 1:1 mixture of *exo–endo* diastereoisomeric azetidine cycloadducts which reacted further with aromatic amine, to give 2,3,4-trisubsitituted tetrahydroquinolines in good to excellent yield, predominantly as one diastereoisomer.

The imino Diels–Alder reaction of imines derived from aromatic amines with electron rich alkenes has emerged as a powerful tool for the synthesis of tetrahydroquinolines, and the subject has recently been reviewed.[1] The pioneer of this chemistry, Povarov,[2] originally used boron trifluoride etherate as catalyst and notable recent developments to this chemistry have been the introduction of milder Lewis acid catalysts such as lanthanide triflates,[3] indium trichloride,[4] chiral transition metal reagents[5] and benzotriazole-mediated reactions.[6]

Recently we have been investigating [4 + 2]-imino Diels–Alder reactions of imines derived from aromatic amines with enamides as a method for rapidly assembling the central heterocyclic core of the alkaloid martinelline.[7] As an extension to this study, *N*-acetyl-2-azetine[8] was investigated as an enamide substrate and the unprecedented results of this study are shown in Scheme 1 and Table 1.

Reaction of imine **2b** with *N*-acetyl-2-azetidine **1** in acetonitrile d-3 using 3 mol% of yttrium triflate as catalyst was monitored by proton nmr spectroscopy. The reaction proceeded smoothly at room temperature over four hours and gave a 1:1 mixture of *endo–exo*-cycloadducts **3b** and **4b**. However, on standing overnight complete decomposition was observed indicating that, in general, isolation of compounds **3** and **4** was going to be difficult. When aromatic amine, from which the imine was derived, was added to the reaction mixture this reacted with the azetidines **3b** and **4b** at room temperature over 12 h and gave adducts **6b** and **7b** in quantitative yield by nmr spectroscopy.

For preparative reactions, one molar equivalent of aromatic amine was added at the start of the reaction with no detrimental effect on the catalyst and the results are summarised in Table 1. Again, monitoring the reaction by nmr spectroscopy revealed new signals for adducts **3** and **4**, which were slowly replaced at approximately the same rate for each isomer, with those of ring-opened products **6** and **7**, indicating that consumption of adducts **3** and **4** was the limiting step in the sequence. When an aromatic amine was employed, which was different to the one used for making the imine, complex mixtures of products resulted and this was not pursued further.

Table 1 Yield of tetrahydroquinolines **6** from *N*-acetyl-2-azetine **1**, aromatic imines **2** and aromatic amines

Entry	R^1	R^2	R^3	Ratio **6**:**7**[a]	Yield **6**(%)
a	H	H	H	95:5	91
b	MeO	MeO	H	90:10	89
c	Me	Me	NO_2	99:1	28[b]
d	H	H	OMe	90:10	97
e	CO_2Me	CO_2Me	MeO	72:28	[c]
f	Me	H	NO_2	96:4	90[d]

[a] Isomer ratio determined by ^{1}H nmr spectroscopy on crude mixture. [b] Low yield due to precipitation of azetidine intermediate. [c] Isomers could not be separated due to their insolubility. [d] Reaction of isolated azetidines **3c** and **4c** with aniline.

Fig. 1 shows an X-ray[9] structure of major adduct **6d** clearly depicting the relative stereochemistry and unusual conformation of this diastereoisomer. Of particular note was that the two

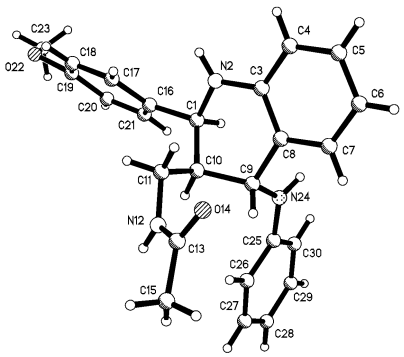
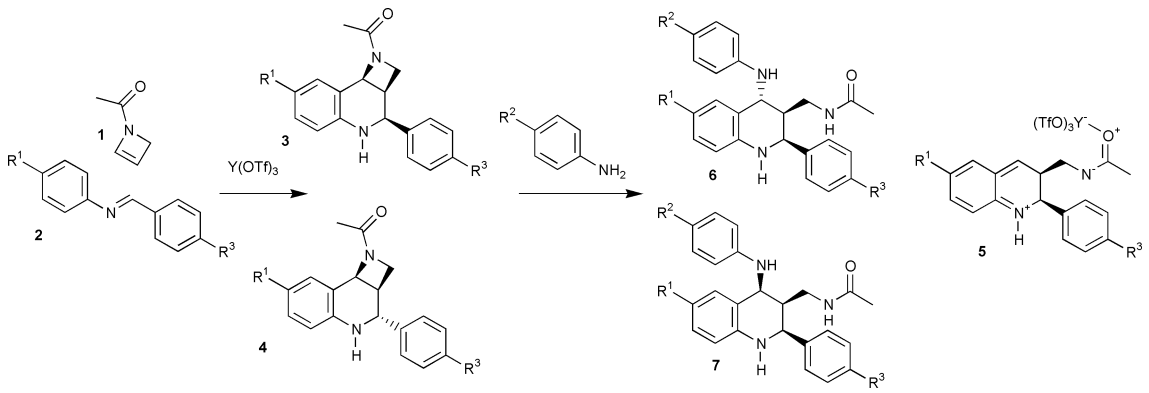


Fig. 1 X-Ray structure of adduct **6d** depicting the relative stereochemistry and unusual conformation in the saturated ring.



Scheme 1 Yttrium triflate catalysed reaction of *N*-acetyl-2-azetine with aromatic imine and aromatic amine.

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groups at positions C-3[10] and C-4 were unexpectedly *trans*-diaxial. This substrate also adopts this conformation in solution giving rise to small di-equatorial coupling constant J_{H34} of 1.4 Hz. Purification of the minor diastereoisomers **7** was impossible as these compounds were configurationally unstable at C-4. However, in one case the minor isomer **7d** was enriched to a 67:33 mixture by flash chromatography in which the silica was neutralised with triethylamine. Saturation of proton H-2 gave a 3.7% and a 4.4% NOE enhancement to protons H-3 and H-4 respectively, confirming that the relative stereochemistry of this isomer was 2*S**,3*R**,4*S** as shown. On standing for one day in deuteriochloroform the isomer ratio **6d**:**7d** changed from 67:33 to 39:71. The configurational instability at C-4 in these compounds goes some way to explaining why the isolated yield of **6d** is higher than the theoretical maximum.

It was intriguing that reaction of an aromatic amine with a 1:1 mixture of *exo–endo* isomeric intermediates **3** and **4** gave products **6** and **7** with the same relative stereochemistry at C-2. A large number of possible mechanisms exist for scrambling the stereochemistry at C-2. However, if it could be proved that the initial [4 + 2] cycloaddition was essentially irreversible under the reaction conditions and that the final adduct **6** was not in equilibrium with imine **2** by a [4 + 2] cyclo-reversion, this would rule out a large number of the possible pathways. Serendipitously, when imine **2c** was used as substrate a solid precipitated from the reaction mixture which was subsequently shown to be a 55:45 mixture of *exo–endo* isomers **4c** and **3c**. When cycloadducts **3c** and **4c** were treated with aniline and yttrium triflate only two products, **6f** and **7f** ratio 96:4 were observed, Table 1 entry f. The absence of a complex mixture, previously observed when an imine and an amine different to that used for making the imine were present at the same time, confirmed that the initial cycloaddition was essentially irreversible and that the final products **6** and **7** were not in equilibrium with starting imine **2** under standard reaction conditions. In the absence of yttrium triflate, azetidines **4c** and **3c** were stable in acetonitrile d-3 containing aniline at room temperature confirming that a Lewis acid was required for the subsequent azetidine ring opening reaction.

These experiments strongly suggest that adducts **6** and **7** are directly produced from azetidines **3** and **4** by a Lewis acid-catalysed, nucleophilic ring opening reaction. Since C-4 is configurationally unstable it is unsafe to infer mechanistic detail on the ring opening reaction from the relative stereochemistry at this centre. However, direct nucleophilic substitution by an aromatic amine does not adequately explain why there is a preference for one diastereoisomer being produced from essentially a 1:1 mixture of *exo–endo*-diastereoisomers. Even though the stereoelectronics are not particularly favourable,[11] it is tempting to postulate a push–pull mechanism, where release of the lone pair of electrons from the tetrahydroquinoline nitrogen is responsible for opening the azetidines **3** and **4** giving rise to intermediate **5**. This mechanism has the added bonus that in intermediate **5** there is enhanced acidity at C-2 allowing the possibility of an epimerisation leading to a preference for formation of one diastereoisomer. Regardless of whether or not adduct **5** was initially produced by a push–pull mechanism, the subsequent configurational instability at C-4 in the products is undoubtedly due to this effect.

In conclusion, multi-component domino reactions offer tremendous opportunity for the synthesis of diverse heterocycles, and this new three-component coupling procedure will add to the ever expanding repertoire of tetrahydroquinoline syntheses.[12]

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