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An intramolecular nitro-Mannich route to functionalised tetrahydroquinolines

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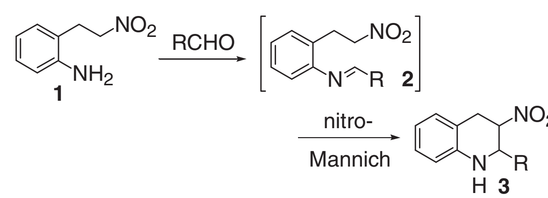
ABSTRACT

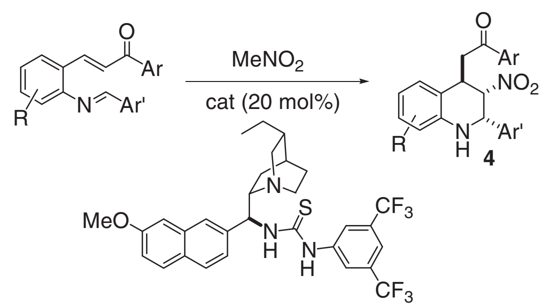
A simple protocol for the diastereoselective synthesis of 3-nitrotetrahydroquinolines has been developed using an intramolecular nitro-Mannich reaction. In situ formation of an imine generated from treatment of 2-(2-nitroethyl)phenylamine with an aldehyde, in EtOH at room temperature, and subsequent addition of NH_4OH, led to the formation of *trans*-products in high yield and diastereoselectivity for 15 representative examples.

Synthetic routes to structurally diverse fused nitrogen heterocycles are of interest due to their importance in medicinal chemistry and abundance in biologically active natural products. The tetrahydroquinoline ring system is a common motif in many natural and unnatural biologically active compounds.[1] Although many methods exist for the synthesis of this ring system, the development of new reactions and protocols to deliver stereochemically pure products is continually needed to enable the synthesis of more refined structures.[2,3] We report here a concise and diastereoselective synthesis of 2-substituted-3-nitro-tetrahydroquinolines that uses an intramolecular nitro-Mannich reaction as the key stereodetermining step. The nitro-Mannich reaction is particularly efficient for the formation of β-nitroamines with two contiguous stereocentres, often with high levels of enantio- and diastereoselectivities.[4–6] It has also been shown to be a useful reaction to synthesise a range of heterocyclic structures.[7] These useful building blocks provide access to other valuable moieties through manipulation of the nitro function, for example by the Nef reaction and nitro reduction.[8]

We recently reported a reductive nitro-Mannich route to 2-substituted-3-amino-tetrahydroisoquinolines that involved an intramolecular palladium-catalysed amination reaction from a diastereomerically pure 1,2-diamine with a pendant aryl bromide.[9] We have also explored an alternative route that involves a base-mediated intramolecular nitro-Mannich reaction. We postulated that treatment of nitroalkane **1** with an aldehyde would give imine **2** which could then undergo an intramolecular nitro-Mannich reaction forming 3-nitrotetrahydroquinoline **3** (Scheme 1).



Scheme 1.



Scheme 2.

At the outset of this work there had been no reports of intramolecular nitro-Mannich reactions of this type. However, during our investigations the group of Xu reported an asymmetric organocatalysed Michael/nitro-Mannich tandem reaction sequence that gave products **4** in excellent yield and enantioselectivity, and moderate to good diastereoselectivity for a range of different imine substituents (Scheme 2).[10] This reaction was only applicable to

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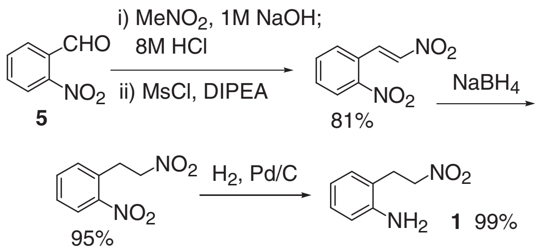


Scheme 3.

aromatic imines and the reactions took 4–7 days to reach completion. In contrast, the protocol we report here is applicable to aromatic- and alkyl-imines, delivers a different diastereoisomer and is complete in 36 h at room temperature.

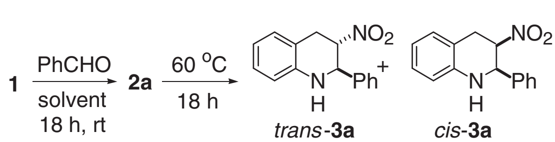
To investigate the reaction we developed a synthesis of nitro amine **1**. Conceptually the most attractive route would have been to subject 2-aminobenzaldehyde to a Henry condensation reaction with nitromethane, followed by reduction. However, due to the propensity of 2-aminobenzaldehyde to undergo polymerisation, 2-nitrobenzaldehyde (**5**) was used as the starting material. Henry condensation and subsequent reduction to the nitroalkane with $NaBH_4$ proceeded in high yield (Scheme 3). Selective hydrogenation of the aromatic nitro group with H_2 over Pd/C could be achieved by careful monitoring of the progress of the reaction by thin-layer chromatography. The reaction reached completion in 1 h and gave a quantitative yield of **1**. The faster rate of reduction of the aromatic nitro group over the aliphatic nitro group is in agreement with previous observations using a variety of different reduction methods.[11]

Formation of imine **2a** (R = Ph) was achieved simply by stirring **1** and benzaldehyde together in various solvents without a dessicant (Table 1). After 18 h ^{1}H NMR analysis showed >90% conversion in all cases, but only trace amounts of tetrahydroquinolines **3a** and only in protic alcohol solvents (entries 1 and 2). The reactions were then heated to 60 °C for 18 h leading to high conversions in EtOH or MeOH, but only trace amounts in aprotic solvents. Unfortunately the conversions of the reactions did not reflect the diastereomeric ratios. Those performed in EtOH or MeOH (entries 1 and 2) were unselective, while those in aprotic solvents gave good selectivities (Table 1). The assignment of diastereoisomers was based upon inspection of ^3J coupling constants between the vicinal protons adjacent to the pendant phenyl ring and the nitro function, $^3J_{trans}$ ~8 Hz versus $^3J_{cis}$ ~4 Hz.

The promising results in alcoholic solvents allowed us to investigate the effect of various additives on the selectivity of the reaction. Initial formation of the imine in EtOH over 18 h was followed by the introduction of a number of additives. Activation of the imine nitrogen with various Lewis acids was attempted, but these proved unsuccessful as no improvement to either the yield or selectivity was observed (Table 2, entries 1–4). The addition of Brønsted bases to activate the methylene adjacent to the aliphatic nitro group proved to be more successful (entries 5–7). Triethylamine gave complete conversion into tetrahydroquinoline **3a** with a slightly improved diastereomeric ratio (60:40, *trans*:*cis*). It was found that the addition of aqueous NH_3 (3.0 equiv) gave **3a** in excellent conversion and diastereoselectivity (90:10, *trans*:*cis*).

Work-up of the NH_4OH reaction after only 3 h revealed 50% conversion into **3a** with a 1:1 ratio of diastereoisomers. Complete conversion and a >90:10 (*trans*:*cis*) diastereoselectivity was realised after 18 h. This suggests the reaction proceeds via an initial unselective and comparatively rapid ring-closure, followed by slower epimerisation into the thermodynamically favourable *trans*-**3a** over approximately 18 h. This contrasts with the work of Xu et al. (Scheme 2) who found that the major product from their intramolecular nitro-Mannich reactions possessed a *cis*-relationship between the NO_2 group and the susbtituent derived from the imine (R^1, Fig. 1). Presumably the stability of this kinetic diastereoisomer is due to the presence of the R^2 substituent destabilising the all *trans*-diastereoisomer due to a potential 1,3-diaxial interaction between R^1 and R^2. In our system where R^2 = H, epimerisation occurs to give the thermodynamically more stable all equatorial *trans*-**3**. The epimerisation process could occur either by a retro-nitro-Mannich process or by deprotonation/reprotonation adjacent to the nitro group, both of which are likely to be facilitated

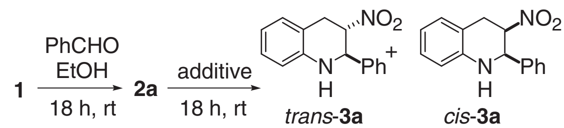
Table 1
Effect of solvent on the intramolecular nitro-Mannich reaction



Entry	Solvent	% Conv. 18 h, rt[a]		% Conv. 18 h, 60 °C[a]	
		2a	**3a** (*trans*:*cis*)	**2a**	**3a** (*trans*:*cis*)
1	EtOH	95	3 (50:50)	12	88 (50:50)
2	MeOH	90	7 (50:50)	4	96 (50:50)
3	CH_2Cl_2	>95	0	97	3 (85:15)
4	PhMe	>95	0	97	3 (90:10)
5	THF	>95	0	98	2 (95:5)
6	Et_2O	>95	0	98	2 (90:10)
7	DME	>95	0	97	3 (90:10)

[a] Determined by ^{1}H NMR spectroscopy.

Table 2
Effects of additives on the formation of **3a**



Entry	Additive	Conversion[a] (%)	dr (*trans*:*cis*)[a]
1	$AlCl_3$	<10[b]	–
2	CAN	<10[b]	–
3	$TiCl_4$	<10[b]	–
4	$Zn(OTf)_4$	<10[b]	–
5	DIPEA	<10[c]	–
6	Et_3N	>95	60:40
7	NH_4OH	>95	90:10

[a] Determined by ^{1}H NMR spectroscopy.
[b] Imine recovered.
[c] Degradation of the imine occurred.

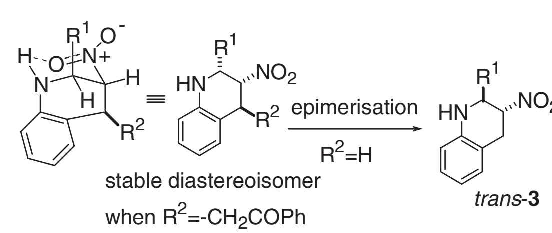
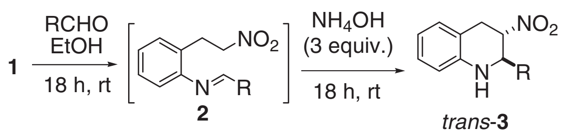


Figure 1. Explanation for the contrasting diastereoselectivity.

Table 3
Scope of the intramolecular nitro-Mannich rection with respect to the aldehyde



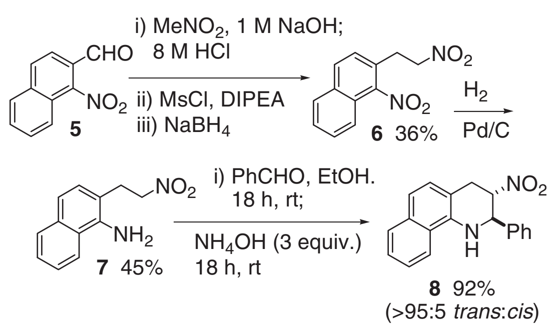
Entry	R	Product	Yield[a] (%)	dr (*trans*:*cis*)[b]
1	Ph	**3a**	82	90:10
2	4-CF_3-C_6H_4	**3b**	94	90:10
3	4-Br-C_6H_4	**3c**	70	90:10
4	4-NO_2-C_6H_4	**3d**	72	85:15
5	4-Me-C_6H_4	**3e**	80	85:15
6	4-MeO-C_6H_4	**3f**	86	90:10
7	3-Cl-C_6H_4	**3g**	84	90:10
8	3-MeO-C_6H_4	**3h**	83	90:10
9	3,5-Cl_2-C_6H_3	**3i**	89	90:10
10	2-Me-C_6H_4	**3j**	92	>95:5
11	2-CF_3-C_6H_4	**3k**	93	95:5
12	2-Cl-C_6H_4	**3l**	92	>95:5
13	2-Br-C_6H_4	**3m**	90	>95:5
14	Cyclohexyl	**3n**	65	90:10
15	CO_2Et	**3o**	0 (70)[c]	60:40

[a] Isolated yield.
[b] Determined by ^{1}H NMR spectroscopy.
[c] Conversion determined by ^{1}H NMR spectroscopy.

by the presence of excess base. The stability of the kinetic *cis*–*trans*-products generated by Xu et al. would be favoured by their catalytic, rather than stoichiometric, use of base in their reaction conditions, which are likely to slow any epimerisation process.

With the formation of 3-nitrotetrahydroquinoline **3a** in excellent yield and diastereoselectivity, the scope of the intramolecular nitro-Mannich reaction was investigated with respect to the aldehyde reaction partner (Table 3). The products 3-nitrotetrahydroquinolines **3a–o** were formed in good to excellent yields and with excellent diastereoselectivites for all electron-rich, electron-poor and *ortho*-substituted aldehydes. The reaction proved less tolerant of alkyl aldehydes, with cyclohexyl carboxaldehyde giving product **3n** in a lower yield of 65%, but still with good diastereoselectivity (entry 14). A lower conversion (70%) was observed with the ethyl glyoxylate and **3o** was formed with a significantly lower *trans*:*cis* ratio of 60:40 (entry 15). The lower decreased conversion into **3o** was attributed to the decreased stability of this product which underwent complete degradation during purification by column chromatography.

The use of more functionalised nitroalkanes was limited by the commercial availability of the substituted 2-nitrobenzaldehydes. More complex products would necessarily involve the synthesis of the required 2-nitroaldehyde. Naphthalene analogue **6** could be converted into nitroalkane **7** in a modest 16% overall yield from



Scheme 4.

5 (Scheme 4). Subsequent intramolecular nitro-Mannich reaction using benzaldehyde under our standard conditions gave 3-nitro-tetrahydroquinoline **8** in 92% isolated yield. This example illustrates the tolerance of additional *ortho*-substitution adjacent to the amine function of **1**.

In conclusion the intramolecular nitro-Mannich methodology presented here provides a convenient method for the synthesis of 3-nitrotetrahydroquinolines in high yield and high selectivity for the *trans*-diastereoisomer. Limitations do exist to the availability of 2-aminonitroalkenes from the corresponding 2-nitroaldehydes. The reaction should be amenable to control of absolute stereochemistry, through one of the many strategies that currently exist for asymmetric nitro-Mannich reactions.[4–6] These products should serve as useful chiral building blocks for further functionalisation towards biologically active targets.

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Supplementary data

Supplementary data (experimental procedures for all compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.08.062.

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