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Facile synthesis of vicinal diamines via oxidation of *N*-phenyltetrahydroisoquinolines with DDQ

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Dedicated to Professor Max Crossley on the occasion of his 60th birthday

ABSTRACT

The oxidation of *N*-phenyltetrahydroisoquinolines occurs rapidly with DDQ. Under ambient conditions and in the presence of nitromethane, the corresponding β-nitroamine derivatives are isolated in good to excellent yields. Variation in the electronic nature of the isoquinoline and the *N*-phenyl substituent showed that a broad range of substituents are tolerated, with electronic communication between the isoquinoline aromatic ring and the C1 carbon being stronger than with the *N*-aryl ring. Reduction of the β-nitroamines to the corresponding novel chiral vicinal diamines are straightforward. Examination of the reaction by ^{1}H NMR spectroscopy suggested that the reaction proceeds via an iminium ion, which then reacts with nitromethane upon work-up. This information was used to shorten the required reaction time.

There has been a great deal of recent interest in direct C–H bond activation at sp^3 centres adjacent to heteroatoms, frequently catalysed by metal complexes.[1] Li has developed a powerful 'Cross-Dehydrogenative Coupling' in which unfunctionalised sp^3 centres can be coupled via copper(I) catalysis.[2] The method gives high yields, and is catalytic, using a copper catalyst in addition to the stoichiometric oxidant. Fu has reported a similar procedure that is capable of amidation of sp^3 C–H bonds adjacent to nitrogen.[3] We wondered whether mild reaction conditions could be found for this important bond formation, which do not require the presence of a metal catalyst. DDQ[4] was an attractive candidate reagent since it is an inexpensive, stable crystalline solid that is easy to handle, and has been used in the oxidative formation of C–C bonds.[5]

To the best of our knowledge, such a DDQ-effected transformation has never been attempted with nitromethane as the (pro)nucleophile. In the course of our studies towards an enantioselective synthesis of the important pharmaceutical praziquantel,[6] we were interested in the efficient synthesis of the key diamine **1** (Scheme 1). An oxidative coupling, of the kind demonstrated by Li, would permit the generation of the key β-nitroamine precursor **2** from tetrahydroisoquinoline **3** and nitromethane. The C–C bond forming step would in effect be an aza-Henry reaction without pre-formation of either nitronate or iminium ion. Oxidation of **4** to the iminium ion **5** would be followed by nucleophilic attack by the azinic acid tautomer of nitromethane **6**. Such a scheme would access diverse β-nitroamines, which could be reduced to valuable chiral vicinal diamines, molecules of wide use in chemistry and biology.[7] Since 1-nitromethyl-1,2,3,4-tetrahydroisoquinoline (**2**, R = H) is unstable with respect to starting materials,[8] we chose to employ N-phenylated tetrahydroisoquinolines for this study, with a view to a later deprotection that would allow us to liberate the diamine **1**.

A screen of several available reagents confirmed that DDQ is able to oxidise *N*-phenyltetrahydroisoquinoline (**4a**, R = Ph)[9] in good yield in a range of solvents (e.g., EtOAc, EtOH and MeOH). The conversion was particularly efficient when nitromethane itself was used as solvent. The reaction conditions initially identified were mild (ca. 1 equiv DDQ, non-dried solvent, open to air, room temperature, 3 h). The procedure involved a very simple aqueous work-up followed by filtration through a plug of silica to yield the product, **2a** (R = Ph), in ca. 50% yield, pure by ^{1}H NMR spectroscopy.

Variation in the number of equivalents of DDQ was then assayed. Starting material was reclaimed when less than 1 equiv of DDQ was used, and use of more than 1.2 equiv of DDQ gave rise to other products according to monitoring by TLC (presumably through over-oxidation to the corresponding isoquinolinium ions). While one equivalent of DDQ gave good results, it was found that the use of 1.1 equiv gave a significantly faster conversion. When the concentration of the reaction mixture was varied (between 0.48 and 0.024 M starting material) it was found that the best combination of rate and ease of handling (low viscosity and low dilution) was at a concentration of approximately 0.15 M (e.g., 100 mg starting material in 5 mL $MeNO_2$).

We then turned to variation of the substrate. If the mechanism of this oxidation is hydride abstraction by DDQ, then the reaction should be sensitive to electronic variation of the substrate. *N*-Aryltetrahydroisoquinolines **4a**–**c**,**e** were synthesised via

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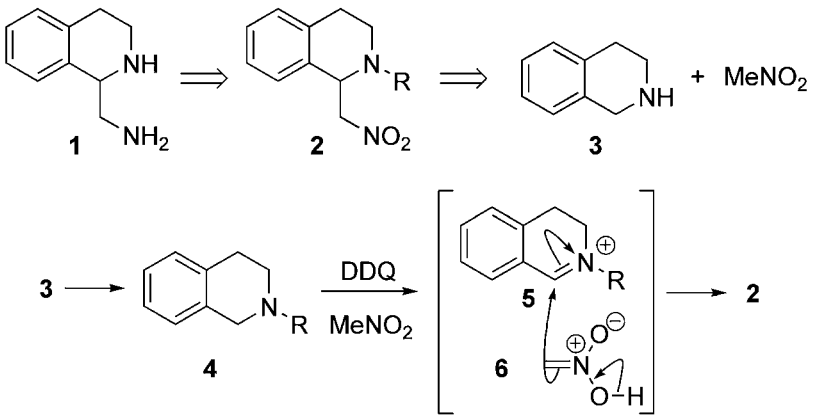
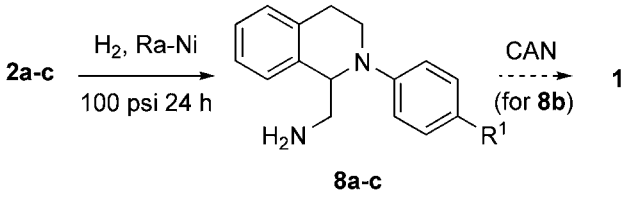


Scheme 1. Proposed synthesis of chiral vicinal diamine **1** using an oxidative coupling of tetrahydroisoquinolines and nitromethane, via iminium ion **5**.



Scheme 2. Reduction of *N*-phenyl-β-nitroamines, and attempted cleavage of the *N*-*p*-methoxyphenyl protecting group in **8b**.

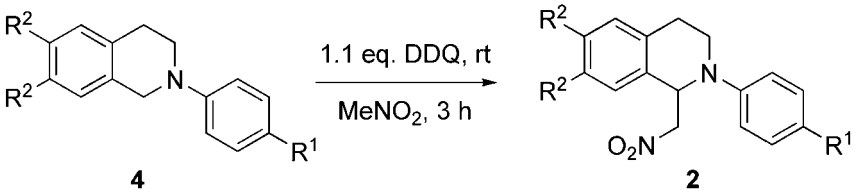
copper(I)-catalysed coupling of aryl iodides and the relevant tetrahydroisoquinoline.[9] The NO_2-substituted derivatives, **4d** and **4h**, were more troublesome and attempted synthesis using the same procedure was unsuccessful. We found that N-phenylation could be achieved in these cases by a copper(II)-catalysed coupling reaction[10] with the *p*-nitrophenylboronic ester,[11] furnishing **4d** and **4h** in 10% and 13% yields, respectively. The low yields are due, in part, to formation of the dinitrobiphenyl byproduct, during the coupling reaction. Compounds **4f** and **4g** were synthesised through a similar coupling reaction, but with the relevant boronic acids.[12]

Subjecting these substrates to the standard reaction conditions gave most products in good to excellent yield (Table 1). It was found that correct work-up of the reactions was very important: the optimised procedure involved extraction with several portions of CH_2Cl_2, and washing with saturated sodium bicarbonate solution, followed by loading the residual nitromethane solution (after removal of the volatiles) directly onto a short silica gel flash column.[13]

It can be seen from these data that the reaction is more influenced by changes in R^2 than R^1: yields are generally lower when R^2 = OMe, whereas there are no clear trends for variation in yield with variation in R^1. We were able to obtain a crystal structure of one of the precursor compounds (**4e**, Fig. 1),[14] which clearly showed the C-1 carbon (the site of reaction) to be coplanar with the isoquinoline aromatic ring, but non-coplanar with the *N*-phenyl ring. These results suggest electronic communication between the C-1 position and the isoquinoline aromatic ring is more efficient (and influential) than with the *N*-phenyl ring.

We examined the reaction between *N*-phenyltetrahydroisoquinoline (**4a**) and DDQ in deuterated nitromethane over time by ^{1}H NMR spectroscopy. The product of this reaction was isolated in 66% yield on a preparative scale. When the reaction was run in the NMR tube, a simple conversion of starting material to product was not seen, and instead a number of broad signals were observed that were neither starting material nor product. The reaction appeared to halt after approximately 20 min, giving a spectrum containing only small signals corresponding to the ex-

Table 1
Yields for oxidative coupling of substituted *N*-phenyltetrahydroisoquinolines and nitromethane with DDQ



Product **2**	R^1	R^2	Yield (%)
a	H	H	95
b	OMe	H	80
c	Me	H	69
d	NO_2	H	58
e	H	OMe	71
f	OMe	OMe	52
g	Me	OMe	30
h	NO_2	OMe	68

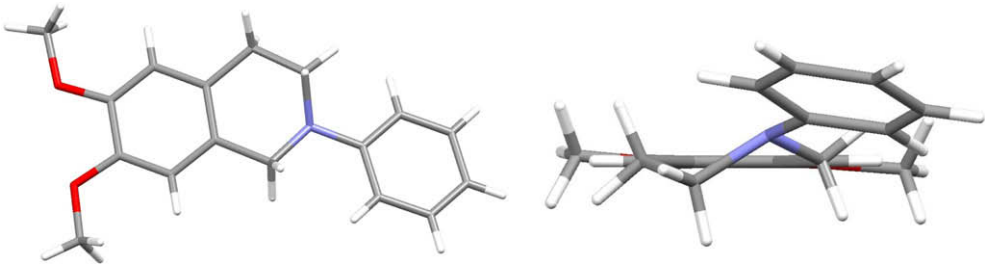
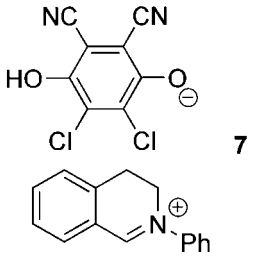


Figure 1. X-Ray crystal structure of **4e**. Regular view (left) and view showing lack of coplanarity of the *N*-phenyl aromatic ring with position C-1 (right).

pected reaction product. By comparison with an internal standard (1,1,2,2-tetrachloroethane), the yield of product was seen to be approximately 10%, despite giving a far higher yield after work-up. A large resonance could clearly be observed downfield at 9 ppm. We postulate that this downfield signal, and others observed in the ^{1}H NMR spectrum, arise from the iminium ion **5**, possibly trapped as an ion pair with the phenolate **7** derived from DDQ.[15] Support for this was obtained from monitoring the reaction by ^{13}C NMR spectroscopy, where a broad signal appeared at approximately 170 ppm, presumably arising from the C-1 carbon of the iminium ion **5** in **7**. The reaction between **4a** and nitromethane with DDQ was not inhibited by the initial presence of 2.2 equiv of TEMPO suggesting that the reaction does not proceed via a radical mechanism. By allowing the reaction to stand, following reaction with DDQ, and adding no external nucleophile, a yellow precipitate was formed. Isolation and dissolution in acetone-d_6 gave a ^{1}H NMR spectrum identical to that observed at the end of the reaction. Further characterisation of this solid, presumed to be the salt **7**, is ongoing.



7

These NMR studies suggested that the reaction was essentially complete after 20–30 min, and that the attachment of the nitromethane was presumably occurring during the work-up with aqueous base. When the reaction was re-run using a shorter reaction time of 30 min with substrate **4a**, we were delighted to be able to isolate the expected product in 95% yield. The role of the base is under study; one could envisage roles in dissociation of the ions in **7** or deprotonation of nitromethane (i.e., the attacking species is a nitronate, not an azinic acid tautomer). It is notable that this procedure does not require slow addition of DDQ to give high yields of products, unlike some related DDQ-based reactions.[5f]

Reduction of these β-nitroamines has never been reported.[16] We found that reduction of **2a** to the novel corresponding diamine **8a** (Scheme 2) could not be achieved with Pd/C (starting material reclaimed) or $LiAlH_4$ (complex mixture) but could be achieved with Raney nickel in an unoptimised 42% yield. The product was purified by column chromatography using 90:9:1 CH_2Cl_2/MeOH/aq NH_3 as eluent.[17] These conditions were also found to be very effective for the reduction of **2b** (66%) and **2c** (86%) to the corresponding novel diamines. Dephenylation of the diamines involves oxidative removal of the phenyl group. Cleavage of the bond between a nitrogen atom and its *p*-methoxyphenyl substituent is known to be possible using ceric ammonium nitrate.[18] When this was attempted, disappearance of starting material was observed by TLC, but adequate purification of this key diamine (which would constitute a new formal synthesis of praziquantel) has not so far been possible.

In summary, we have described a novel, operationally simple method for the synthesis of chiral vicinal diamines based on a DDQ-mediated coupling between tetrahydroisoquinolines and nitromethane. NMR monitoring of this reaction suggests that the DDQ oxidation is fast, and gives an intermediate iminium ion, probably as a salt, that may be isolated. Reaction with nitromethane appears to occur during basic work-up. We used this information to reduce the reaction time of the process to 30 min, providing rapid access to these potentially useful structures.

Acknowledgement

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13. *Representative procedure*: To 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.120 g, 0.53 mmol, 1.1 equiv) in nitromethane (5 mL) was added 2-phenyl-

1,2,3,4-tetrahydroisoquinoline (0.100 g, 0.48 mmol, 1.0 equiv). The reaction mixture was stirred at room temperature for 30 min, diluted with saturated $NaHCO_3$ solution (50 mL) and extracted with dichloromethane (3 × 50 mL). The organic phases were combined, washed with saturated $NaHCO_3$ solution (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give a red liquid. The residue was purified by flash column chromatography (5:1 hexane/ethyl acetate) to give the tetrahydroisoquinoline **2a** as a pale yellow, crystalline solid (0.121 g, 95%). mp 87–88 °C. ^{1}H NMR ($CDCl_3$ 300 MHz): δ 2.79 (1H, ddd, *J* 16.3, 10.1, 4.9, H-4), 3.09 (1H, ddd, *J* 16.3, 14.3, 7.1, H-4), 3.65 (2H, m, H-3), 4.56 (1H, dd, *J* 12.0, 8.0, C*H*HNO$_2$), 4.87 (1H, dd, *J* 12.0, 8.0, CH*H*NO$_2$), 5.55 (1H, dd, *J* 8.0, 8.0, H-1), 6.85 (1H, dd, *J* 7.2, 7.2, H-4′), 6.97 (2H, d, *J* 8.1), 7.06–7.31 (6H, m). IR ($CHCl_3$) ν_{max}/cm^{-1} 1596, 1550, 1380, 1496. *m/z* (ESI) 208.3 ([M−CH_2NO_2]$^+$, 100%). Spectral data matched those reported, see Refs.[2a,b].

14. CCDC number 707604.
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16. For a recent solution to the difficulties that may be encountered in the reduction of related β-nitroamines see: Anderson, J. C.; Chapman, H. A. *Synthesis* **2006**, 3309–3315.
17. (a) *Representative procedure*: To 1-(nitromethyl)-2-(*p*-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (0.519 g, 1.71 mmol) in methanol (100 mL) were added 25% of aqueous ammonia (20 mL) and Raney Nickel (10 mL). The reaction mixture was stirred at room temperature under H_2 (100 psi) for 24 h. The reaction mixture was filtered, concentrated under reduced pressure and extracted into ethyl acetate (100 mL). The organic phase was dried ($MgSO_4$) and purified by flash column chromatography (1:9:90 aq ammonia/methanol/dichloromethane) to give the diamine **8b** as a brown oil (0.272 g, 66%). ^{1}H NMR (MeOD 300 MHz): δ 2.53 (1H, ddd, *J* 16.5, 7.5, 3.6, H-4), 2.75–2.97 (3H, m, H-4, H-3), 3.47 (2H, dd, *J* 7.9, 3.9, CH_2NH$_2$), 3.66 (3H, s, Me), 4.46 (1H, dd, *J* 8.7, 5.1, CHN), 6.76 (2H, d, *J* 9.0, Ar), 6.92 (2H, d, *J* 9.0, Ar), 7.02-7.18 (4H, m, Ar). ^{13}C NMR (MeOD 75 MHz): δ 26.4, 44.6, 47.0, 55.9, 62.8, 115.5, 120.5, 127.1, 127.2, 128.2, 130.0, 136.7, 137.4, 146.1, 155.1. IR ($CHCl_3$) ν_{max}/cm^{-1} 2401, 1506, 1261, 1095. *m/z* (ESI) 269.0 (MH$^+$, 90%), 252.1 ([M−NH_2]$^+$, 63%), 238.1 ([M−CH_2NH_2]$^+$, 100%). HRMS (ESI) 269.16464 (MH$^+$); calcd for $C_{17}H_{21}N_2O$ (MH$^+$) 269.16484. 2-(*p*-Methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline was also obtained (0.052 g, 10%); (b) Lázár, L.; Kivelä, H.; Pihlaja, K.; Fülöp, F. *Tetrahedron Lett.* **2004**, *45*, 6199–6201.
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