

Selective dehydrogenation of tetrahydroisoquinolines in the presence of sulfoxides

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Dedicated to the memory of Charles Rees and Alan Katritzky, two giants of heterocyclic chemistry

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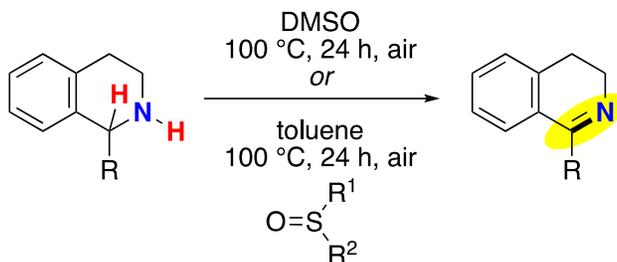
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Abstract

1,2,3,4-Tetrahydroisoquinolines undergo selective dehydrogenation in the presence of compounds with a highly polar X=O bond, particularly sulfoxides, under aerobic conditions to give the corresponding 3,4-dihydroisoquinolines. The reaction can be carried out in DMSO as solvent, or in toluene in the presence of other sulfoxides, including aryl alkyl sulfoxides. The reaction can also be carried out in toluene in the presence of trimethylphosphine oxide in place of DMSO. NMR spectroscopic studies strongly suggest that the sulfoxide is not consumed during the dehydrogenation reaction. The methodology benefits from simplicity of operation, and the lack of harmful reagents or expensive metal catalysts.

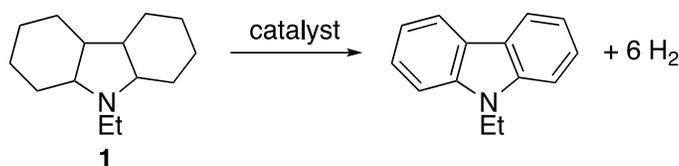


Keywords: Dehydrogenation, 1,2,3,4-tetrahydroisoquinoline, 3,4-dihydroisoquinoline, sulfoxides

Introduction

The dehydrogenation of organic compounds is of pivotal importance for both industry and academia. This is particularly relevant in the case of nitrogen heterocycles where the resulting heteroaromatic compounds are widely employed as pharmaceuticals, agrochemicals and reprographic materials. More recently, the dehydrogenation of *N*-heterocycles has attracted attention for its potential application as liquid organic hydrogen carriers (LOHCs).¹⁻⁷

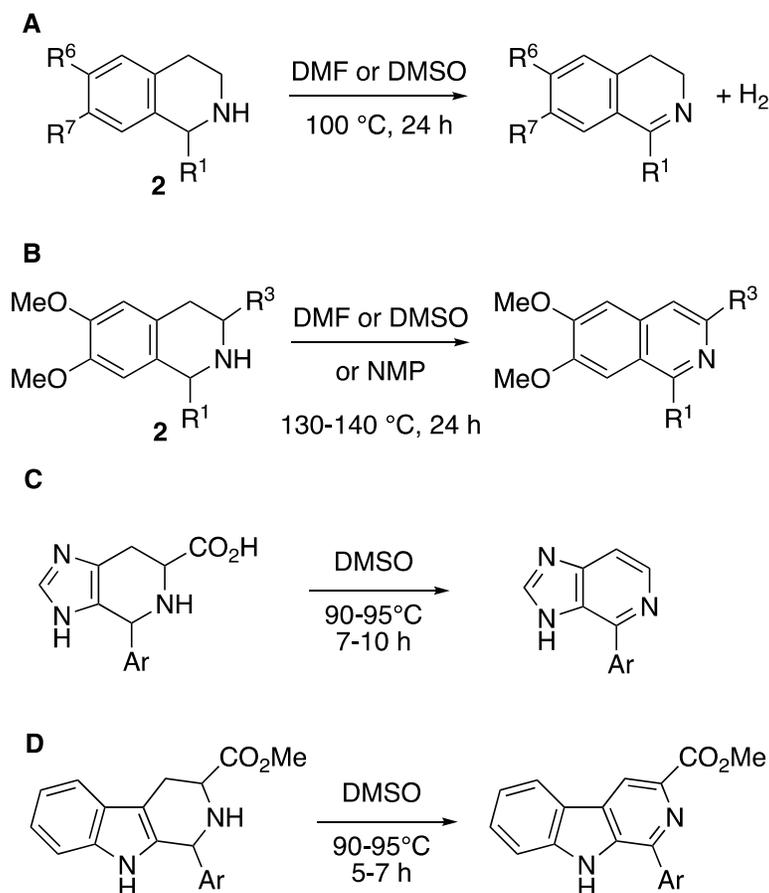
Although such dehydrogenation reactions are energetically unfavorable, the introduction of a *N*-heteroatom into the ring can reduce the enthalpy, making the reaction less thermodynamically unfavorable.^{8,9} Additionally, the release of hydrogen contributes positively to the entropic factor. For example, *N*-ethyl-dodecahydrocarbazole **1** has been proposed as a hydrogen carrier that can release hydrogen for use as fuel upon appropriate catalytic activation (Scheme 1).¹⁰⁻¹²



Scheme 1. Use of *N*-ethyl-dodecahydrocarbazole as a liquid organic hydrogen carrier.

However, dehydrogenation reactions are typically carried out over precious metal catalysts often at very high temperatures. While these conditions might be appropriate in the LOHC arena, they are not more widely applicable due to poor functional group tolerance. In addition, the pharmaceutical industry strives to avoid reactions involving heavy metals due to increased restrictions on trace-metal impurities in active pharmaceutical intermediates. For these reasons, a metal-free variant would be valuable. In this context, in 2016 Feng *et al.* reported a rare dehydrogenation reaction of tetrahydroisoquinolines **2** simply performed by stirring the substrates in DMF at 100 °C for 24 h under air to give the corresponding 3,4-dihydroisoquinolines in high yield and with high chemoselectivity (Scheme 2A).¹³ Although DMF appeared to be the solvent of choice, it was also reported that the reaction proceeded in DMSO, and in DMF in the absence of air. The gas composition of the reaction system was analyzed by Temperature Programmed Desorption-Mass Spectrometry (TPD-MS), and a signal ($m/z = 2$) was detected, suggesting a thermal dehydrogenation with formation of molecular hydrogen. However, the mechanism remained unclear.

In a related, more recent study, Ramu and Baskar reported a similar metal-free dehydrogenation of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines carried out in *N*-methylpyrrolidine (NMP) (or DMF or DMSO) at 130-140 °C (Scheme 2B).¹⁴ However, in their case the reaction proceeded through to the fully dehydrogenated isoquinoline, but only under an oxygen atmosphere. The reaction did not proceed under argon and oxygen was presumed to be the terminal oxidant.



Scheme 2. Thermal dehydrogenations in DMSO: A,¹³ B,¹⁴ C,¹⁵ and D.¹⁶

Similar dehydrogenation reactions upon heating in DMSO had been reported earlier. Thus Lomov and co-workers reported the dehydrogenation and decarboxylation products of spinacine derivatives on heating in DMSO at 90 – 95 °C (Scheme 2C),¹⁵ and the dehydrogenation of tetrahydro- β -carboline derivatives under similar conditions (Scheme 2D).¹⁶ No mechanistic explanation was advanced, although the authors noted that the reaction did not involve atmospheric oxygen with the implication that DMSO was the dehydrogenating agent/oxidant. Related dehydrogenations of tetrahydro- β -carbolines was also reported during a domino Pictet-Spengler reaction and aromatisation in DMSO at 140 °C, although in these cases, the reaction did not proceed upon exclusion of atmospheric oxygen.¹⁷ Dehydrogenations of tetrahydro-quinolines and -isoquinolines in DMSO at 60 °C in the presence of sodium *tert*-butoxide under oxygen have also been described,¹⁸ although the use of DMSO as solvent or an oxygen atmosphere are not essential at higher temperatures since the reaction is reported to proceed under nitrogen in *o*-xylene at 140 °C in the presence of potassium *tert*-butoxide.¹⁹

Intrigued by the possibility of a simple, thermal, catalyst-free dehydrogenation reaction of amines, we elected to investigate the aforementioned DMSO reactions in detail with a view to a greater understanding of the mechanism of the reaction and the nature of the oxidant (if any), and now report the results of this study.

Results and Discussion

We began our investigation with the thermal dehydrogenation of 1,2,3,4-tetrahydroisoquinolines **2** as described by Feng *et al.*¹³ A range of tetrahydroisoquinolines is commercially available, although initial experiments were conducted on the 1-phenyl derivative **2a**. The compound (100 mg, 0.48 mmol) was dissolved in the elected solvent (3 mL) and the reaction mixture was heated to 100 °C for 24 h under air, followed by analysis by GC-MS. In low boiling solvents, the reaction was conducted at reflux. Conducting the reaction in DMF gave 1-phenyl-3,4-dihydroisoquinoline **3a** with little of the “over-oxidation product” isoquinoline **4a** (Table 1, entry 1), as previously described.¹³ In further agreement with the literature, use of acetonitrile and toluene as solvents resulted in no dehydrogenation (Table 1, entries 2 and 3), while in our hands DMSO proved superior to DMF (entry 4). While methanol was unsuccessful, use of ethylene glycol gave the partially dehydrogenated product **3a** in very low yield (10%) (Table 1, entry 6), but better results were achieved with NMP (57%), and acetamide (60%) (Table 1, entries 7, 8). Although limited, this survey of various solvents does indicate the need for a solvent that contains a polar X=O bond as in amides or a sulfoxide, and hence we elected to use DMSO in further studies.

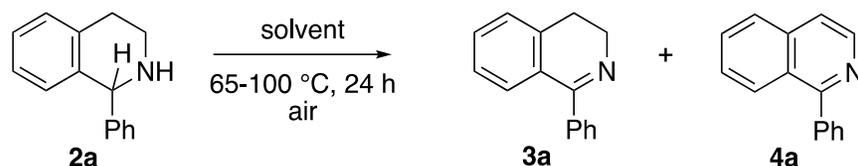


Table 1. Solvent survey. Dehydrogenation of 1-phenyl-1,2,3,4-tetrahydroisoquinoline **2a** (100 mg, 0.48 mmol) in solvent (3 mL), 65-100 °C, 24 h, under air.

Entry	Solvent	Temperature (°C)	2a:3a:4a GC-MS Ratio (%)
1	DMF	100	28 : 68 : 1
2	CH ₃ CN	80	100 : 0 : 0
3	toluene	100	93 : 7 : 0
4	DMSO	100	0 : 97 : 3
5	MeOH	65	100 : 0 : 0
6	ethylene glycol	100	89 : 10 : 0
7	NMP	100	43 : 57 : 0
8	acetamide	100	34 : 60 : 3

Next, we studied the effect of reaction time and temperature (Tables S1 and S2, Supplementary Information). After 6 h, the reaction yielded the partially dehydrogenated product **3a** in low yield (18%) (Table S1, entry 1). After 12 h, the amount of dehydrogenated product **3a** had increased to 52% yield, with no traces of the total dehydrogenated by-product **4a** (Table S1, entry 2). After 18 h, the partially dehydrogenated product **3a** was present in high yield (88%) (Table S1, entry 3), and after 24 h, the partially dehydrogenated product **3a** was the only product present (97%) (Table S1, entry 4). Therefore, 24 h was selected as the standard reaction time. Secondly, the reaction mixture was heated for the same amount of time at different temperatures (Table S2). At room temperature and up to 70 °C, the reaction does not proceed (Table S2, entries 1 and 2). At 80 °C, the reaction gives a good yield of partially dehydrogenated product **3a**, however

there is still some starting material (Table S2, entry 3). At 100 °C, all of the starting material is consumed (Table S2, entry 4).

With a set of standard conditions established (DMSO, 100 °C, under air, 24 h) we were able to study the substrate scope for tetrahydroisoquinolines. 1-Aryl-1,2,3,4-tetrahydroisoquinolines **2a-2c** were readily dehydrogenated, as was the 1-(2-thienyl) derivative **2e** (Table 2, entries 1-3 and 5). The more electron rich 1-(4-methoxyphenyl) compound **2d** failed to undergo dehydrogenation. Mixed success was also observed with 1-alkyl derivatives **2f-2h** (Table 2, entries 6-8). In view of role of reduced carbazoles in LOHCs, tetrahydrocarbazole **5** was also investigated, and readily gave the fully dehydrogenated product **6** in reasonable yield (66% by GC-MS, 38% isolated) (Table 2, entry 9).

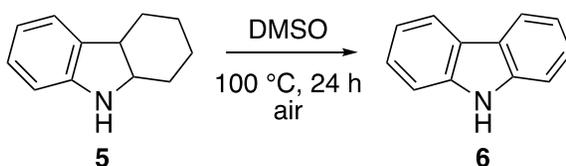
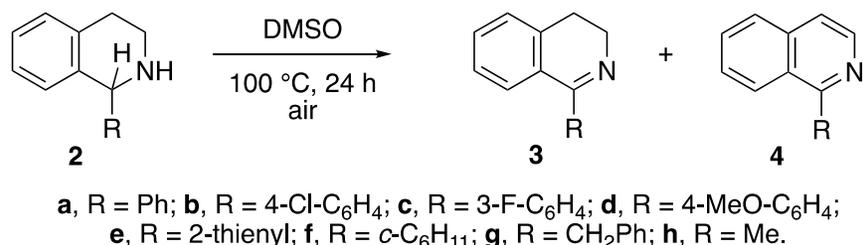


Table 2. Dehydrogenation of 1,2,3,4-tetrahydroisoquinolines **2** and 1,2,3,4-tetrahydrocarbazole **5**.

Entry	Substrate	R	2 : 3 : 4 GC-MS Ratio (%)	Isolated yields 3 (%)
1	2a	Ph	0 : > 97 : < 3	95
2	2b	4-Cl-C ₆ H ₄	0 : > 97 : 0	97
3	2c	3-F-C ₆ H ₄	22 : 77 : 0	
4	2d	4-MeO-C ₆ H ₄	99 : 0 : 0	
5	2e	2-thienyl	< 3 : > 97 : 0	97
6	2f	<i>c</i> -C ₆ H ₁₁	< 2 : 80 : 18	
7	2g	CH ₂ Ph	84 : 16 : 0	
8	2h	Me	< 1 : > 99 : 0	
9	5	-	-	6 66 (GC-MS) 38 (isolated)

Rather than carry out the reaction in DMSO as solvent, it was decided to study the amount of DMSO required for the reaction to proceed. Again, 1-phenyl-1,2,3,4-tetrahydroisoquinoline **2a** was used as the standard substrate, and reactions were performed in dry toluene, chosen because very little dehydrogenation occurred in this solvent alone (Table 1). DMSO was added in varying amounts, and the reaction carried out at 100 °C for 24 h under air. With only 0.5 equiv. of DMSO, the reaction hardly proceeded (Table 3, entry 1). When DMSO was added in only 1 equiv. compared to the substrate, the product **3a** was present in 46% (Table

3, entry 2). With increasing quantities of DMSO the reaction proceeded further (Table 3, entries 3-6), although with 10 equiv. DMSO, the fully dehydrogenated isoquinoline **4a** started to appear (Table 3, entry 6). From these results, it was evident that the reaction is dependent upon the quantity of DMSO with at least 5 equiv. required for good conversion into product. When the reaction was performed under argon in toluene with DMSO (2 equiv.), only starting material **2a** was observed.

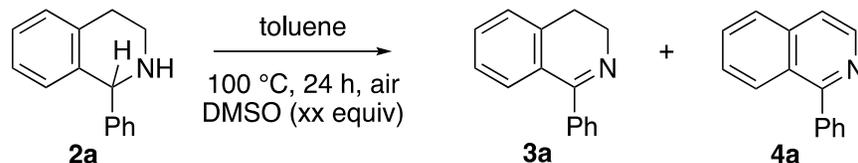


Table 3. Dehydrogenation of 1-phenyl-1,2,3,4-tetrahydroisoquinoline **2a** in toluene, 100 °C, 24 h under air with varying amounts of DMSO.

Entry	DMSO (equiv.)	2a:3a:4a GC-MS Ratio (%)
1	0.5	96 : 4 : 0
2	1	53 : 46 : 0
3	2	40 : 59 : 0
4	2 ^a	100 : 0 : 0
5	5	14 : 86 : 0
6	10	6 : 90 : 3

^aReaction carried out under argon

At this point, it was interesting to see if the dehydrogenation depended not only on the quantity of sulfoxide, but also on its structural type. Therefore, DMSO was replaced with a range of different sulfoxides. Tetrahydrothiophene-1-oxide was chosen as a dialkyl sulfoxide, and a range of aryl methyl sulfoxides with varying substituents were competent in effecting the dehydrogenation of 1-phenyl-1,2,3,4-tetrahydroisoquinoline **2a**. Diphenyl sulfoxide failed to effect any dehydrogenation.

The dialkyl sulfoxide, tetrahydrothiophene-1-oxide was able to effect the reaction in a broadly similar manner to DMSO (Table 4, entries 1 and 2). Likewise, when methyl phenyl sulfoxide was used, the outcome of the reaction was also quite similar to DMSO, although no reaction was observed with only 1 equivalent of the sulfoxide (Table 4, entry 3). With 2 equivalents, the reaction gave the product **3a** in modest yield. Increasing the equivalents of sulfoxide increased the yield of dehydrogenated product **3a**. However, methyl 4-methylphenyl sulfoxide performed less well, and as with DMSO (Table 4, entry 4), no dehydrogenation occurred when the reaction was carried out under argon. The more electron rich methyl 4-methoxyphenyl sulfoxide did not give any dehydrogenation products (Table 4, entry 5), and the fluoro- and trifluoromethyl-substituted sulfoxides showed no improvement in dehydrogenation of the tetrahydroisoquinoline **2a** over and above methyl phenyl sulfoxide itself (Table 4, entries 6 and 7).

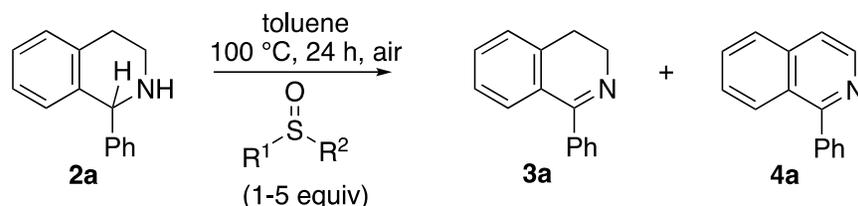


Table 4. Different sulfoxides with different stoichiometries. Dry toluene, 100 °C, 24 h, under air. Ratio of products determined by GC–MS.

Entry	Sulfoxide	1 equiv.	2 equiv.	5 equiv.
1		2a 53% 3a 46%	2a 40% 3a 59%	2a 14% 3a 86%
2			2a 74% 3a 25%	2a 27% 3a 73%
3		2a 95% 3a 5%	2a 45% 3a 55%	2a 24% 3a 76%
4		2a 94% 3a 5%	2a 72% 3a 28% argon 2a 99%	2a 65% 3a 34%
5		2a >99%	2a >99%	2a >99%
6		2a >99%	2a >95% 3a <5 %	2a 68% 3a 32%
7		2a 71% 3a 29%	2a 62% 3a 36% 4a trace	2a 51% 3a 47% 4a trace

Therefore, the reaction is both sensitive to the stoichiometry and to the type of sulfoxide employed. Increasing the amount of sulfoxide in the reaction mixture with the standard substrate 1,2,3,4-tetrahydroisoquinoline **2a**, the amount of product 3,4-dihydroisoquinoline **3a** increases accordingly, although DMSO remains the most convenient sulfoxide for use in such dehydrogenations. Dimethyl sulfone failed to give any dehydrogenation products under similar conditions.

In the original survey of solvents (Table 1), dipolar aprotic solvents generally gave higher yields of dehydrogenation. Therefore, we investigated another compound with a highly polar double bond to oxygen, namely trimethylphosphine oxide. The reactions were performed under the standard conditions, and compared with results previously obtained using DMSO (Table 3). The results are described in Table 5 and show that replacing DMSO with trimethylphosphine oxide results in similar levels of dehydrogenation, suggesting that compounds of high polarity ($\text{Me}_2\text{S}=\text{O}$, $\mu = 3.9$ D; $\text{Me}_3\text{P}=\text{O}$, $\mu = 4.4$ D) are most effective in these dehydrogenation reactions.

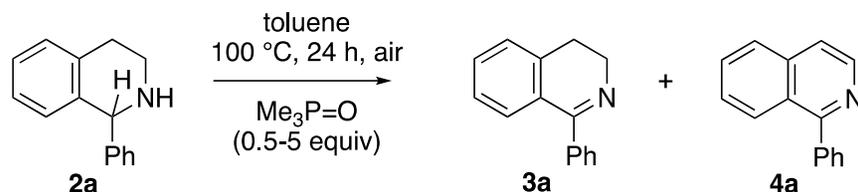


Table 5. Dehydrogenation in presence of trimethylphosphine oxide. Dry toluene, 100 °C, 24 h, under air.

Entry	Oxide (equiv.)	2a:3a:4a	2a:3a:4a
		GC-MS Ratio (%)	GC-MS Ratio (%)
		Me ₃ P=O	Me ₂ S=O
1	0.5	2a 48% 3a 52%	2a 96% 3a 4%
2	1	2a 44% 3a 56%	2a 53% 3a 46%
3	2	2a 37% 3a 63%	2a 40% 3a 59%
4	5	2a 19% 3a 81%	2a 14% 3a 86%

Our goal at this stage was to attempt a mechanistic explanation for the dehydrogenation of tetrahydroisoquinolines in the presence of sulfoxides under aerobic conditions. Therefore, experiments were carried out to confirm or exclude certain reaction pathways, specifically addressing three questions: is the cleavage of the benzylic C-H bond rate determining, is the sulfoxide reduced during the reaction, is there evidence for production of hydrogen gas?

First, we performed an isotopic labeling study using 1-deuterio-1-phenyl-1,2,3,4-tetrahydroisoquinoline **2a-D** and 1-deuterio-1-(4-chlorophenyl)-1,2,3,4-tetrahydroisoquinoline **2b-D**. These were synthesized by reduction of the corresponding dihydroisoquinolines **3** with sodium borodeuteride in methanol, and subjected to our standard dehydrogenation reactions in DMSO under air at 100 °C. The disappearance of starting material was monitored by taking 50 μ L samples followed by analysis with LC-MS, and the rates of protonated and deuterated compounds compared. When the reactions of **2a** and **2a-D** were followed at 15 minute intervals over a 4 hour period (Figures S1 and S2, Supplementary Information), a kinetic isotope effect (KIE), $k_{H/D}$ of 1.2 was observed. The corresponding reactions of **2b** and **2b-D** were followed at hourly intervals over a 10-hour period, and again a small KIE of 1.2 was observed. Although the interpretation of primary kinetic isotope effects is not always straightforward,²⁰ we interpret the observed $k_{H/D}$ of 1.2 is indicative of a mechanism involving cleavage of the C-H in the RDS (see below).

Although DMSO was chosen as a polar solvent for our thermal dehydrogenation reactions, its oxidising properties are well known, with the sulfoxide being reduced to the malodorous dimethyl sulfide. However, in our specific case, no trace of dimethyl sulfide was detected by smell, despite its extremely low threshold of

perception of 0.001 ppm,²¹ although such experiments are not definitive given the volatility of dimethyl sulfide (bp 37 °C) and its likely evaporation from reactions carried out at 100 °C. Therefore, to confirm (or exclude) the role of the sulfoxide as oxidant, we chose to work with the less volatile methyl 4-tolyl sulfoxide since we had already shown (Table 4) that the dehydrogenation of 1-phenyltetrahydroisoquinoline **2a** proceeded readily in the presence of this sulfoxide. Careful analysis of this dehydrogenation reaction mixture by GC-MS showed no trace of a peak corresponding to methyl 4-tolyl sulfide, strongly arguing against its formation as a reaction by product.

The fact that the sulfoxide was not reduced to the sulfide in the dehydrogenation reactions was confirmed using a different analytical technique, namely fluorine NMR spectroscopy. Thus, a solution of 1-phenyl-1,2,3,4-tetrahydroisoquinoline **2a** in toluene was heated to 100 °C for 24 h under air in the presence and 2 equiv. of methyl 4-fluorophenyl sulfoxide. Subsequently, the reaction mixture was analyzed by ¹⁹F NMR spectroscopy. The result clearly shows that, after the reaction, the spectrum of the mixture indicates the presence of the sulfoxide at -110.2 ppm as the only peak, with no evidence for the corresponding sulfide that would be well separated at -60.7 ppm, while the product **3a** was still formed in high yield. A similar result was obtained when methyl 4-trifluoromethylphenyl sulfoxide was used, with no evidence for the formation of the corresponding sulfide by ¹⁹F NMR spectroscopy.

These results strongly suggest that the dehydrogenation of tetrahydroisoquinolines in DMSO, or in toluene in the presence of DMSO (or other sulfoxides) under aerobic conditions does not involve the sulfoxide as oxidant, and that DMSO or any other sulfoxide were not reduced during the reaction.

Evidence for the evolution of hydrogen gas was also sought, notwithstanding the fact that, due to rapid diffusion, hydrogen is notoriously difficult to capture and detect. Therefore, several experiments were undertaken. First of all, the reaction mixture was analyzed by Thermal Gravimetric Analysis/Mass Spectrometry (TGA-MS). The method consisted of heating a sample of tetrahydroisoquinoline **2a** dissolved in DMSO from room temperature to 100 °C with an increase rate of 5 °C/min under an air flow, followed by isothermal conditions for 24 h. The loss of weight recorded is due to the evaporation of DMSO, and the sample was dry at the end of the experiment. Analysis of the dry sample by GC-MS, revealed the presence of only the product **3a**. When the TGA-MS experiment was repeated under argon rather than air, the final sample analyzed by GC-MS showed only the presence of starting material tetrahydroisoquinoline **2a**. Unfortunately, the mass spectrometer provided no convincing evidence for a peak for molecular hydrogen ($m/z = 2$).

Further evidence for the formation of hydrogen was sought using ¹H NMR spectroscopy, based on the fact that the hydrogen molecule has a NMR peak at 4.6 ppm in DMSO.²² An NMR experiment was designed in which a solution of the substrate 1-phenyl-1,2,3,4-tetrahydroisoquinoline **2a** in DMSO-*d*₆ was heated to 80 °C for 4 h in a NMR tube directly in the instrument. Spectra were recorded every 30 min as shown in Figure S3 (Supplementary Information). The spectra show the disappearance of signals due to H-1 (~δ 5.1) and H-4 (~δ 3.2) in the starting material **2a** with the appearance of H-4 (~δ 3.8) in product **3a**. Unfortunately, no signal was observed in the NMR spectrum between 4.5-4.7 and hence no peak directly attributable to H₂ is present.

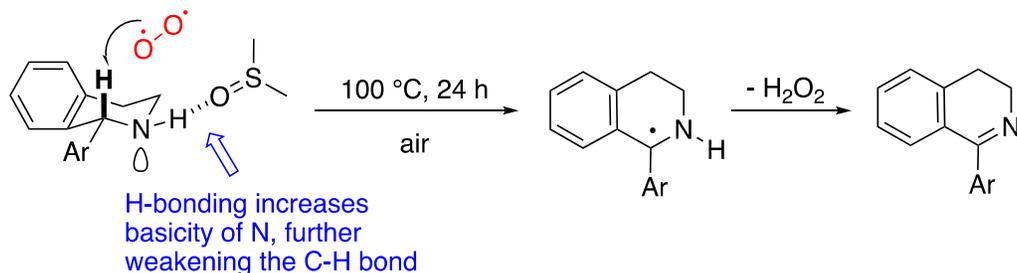
Finally, we adopted a technique used by others to detect the formation of hydrogen in dehydrogenation reactions by “capturing” the hydrogen in a separate alkene hydrogenation reaction.^{23,24} Therefore the gas(es) evolved upon heating the tetrahydroisoquinoline **2a** in DMSO at 100 °C under air was led directly into a second flask containing a solution of 1-decene and Wilkinson’s catalyst in THF. Although the dehydrogenation proceeded to give dihydroisoquinoline **3a**, there was no evidence from GC-MS for the formation of decane by hydrogenation.

Thus, in summary we have shown that in our dehydrogenation of 1,2,3,4-tetrahydroisoquinolines to the corresponding 3,4-dihydro compounds:

- a solvent with a highly polar X=O bond such as the carbonyl bond in DMF or NMP, or the sulfinyl bond in DMSO is required, or in a solvent such as toluene, the presence of a highly polar X=O bond in a sulfoxide or phosphine oxide,
- in the case of sulfoxides, the sulfoxide is not consumed by reduction to the sulfide
- the reaction does not proceed under argon; air is required
- a small, but measurable kinetic isotope effect ($k_{H/D}$ of 1.2) is indicative of a mechanism involving cleavage of the benzylic C-H bond in the RDS
- there is no convincing evidence for the formation of hydrogen gas.

Considering all the above factors, we favor a mechanism (Scheme 3) involving abstraction of the benzylic hydrogen at C-1, with air as the oxidant as suggested by others.¹⁴ Hydrogen abstraction from the α -C-H of amines and amides under radical conditions has been widely studied.²⁵⁻²⁹ Kinetic studies on H- (or D-) abstraction from alkyl amines report values for the KIE $k_{H/D}$ in the range 1.2-1.5,^{25,27} in line with our observed value of 1.2. Further kinetic studies have shown that H-abstraction from the C-1 position of 2-acetyl-1,2,3,4-tetrahydroisoquinoline is significantly faster (20-40 fold) than from acyclic analogues, ArCH_2NHAc .²⁹ The authors suggest a stereoelectronic effect in which the breaking benzylic C-H bond is co-linear with the nitrogen lone pair,²⁹ based on earlier reports that the nitrogen lone pair both weakens the adjacent C-H but also stabilizes the resulting radical, an effect that is greater when the C-H bond and the N lone pair are co-linear.^{25,26} In the case of 1-aryl-1,2,3,4-tetrahydroisoquinolines, X-ray crystallographic studies show that in the solid state at least, the aryl substituent is equatorial and the benzylic C-H bond is co-linear with the nitrogen lone pair as required to facilitate H-abstraction.³⁰⁻³²

The role of the required polar X=O bond is less clear. In their work, Feng *et al.* proposed that hydrogen-bond “interactions” between the polar S=O bond in DMSO (or the C=O bond in DMF) and substrates may result in weakened N-H and C-H bonds although there was no evidence presented for this.¹³ However, the hydrogen bonding of the DMSO oxygen to the N-H of secondary amines has been characterized, and results in an increase in the basicity of the nitrogen.^{33,34} As a result we believe that this increase in basicity could enhance the effect of the nitrogen lone pair in both weakening the adjacent C-H and also stabilizing the resulting radical as discussed above (Scheme 3).



Scheme 3. Possible mechanism for DMSO-promoted dehydrogenation of 1,2,3,4-tetrahydroisoquinolines.

Conclusions

In conclusion, a simple protocol for selective dehydrogenation of 1,2,3,4-tetrahydroisoquinolines to their 3,4-dihydro analogues without significant aromatization to quinolines has been explored. The simplicity of operation, the lack of harmful reagents or expensive metal catalysts, and the environmental benignity of the process are all advantages that make the reaction particularly attractive for industrial purposes. Given the relatively low temperature of dehydrogenation, further work will establish the true utility of such processes, particularly in the arena of LOHCs as fuels of the future.

Experimental Section

General. Commercially available reagents were used without further purification, unless otherwise stated. All anhydrous solvents were used as supplied. Reactions that required anhydrous conditions were conducted under an inert atmosphere of dry argon in flame-dried apparatus. Light petroleum refers to the fractions with bp 40–60 °C. Ether refers to diethyl ether.

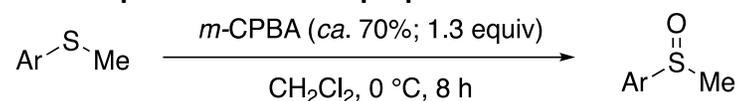
Thin Layer Chromatography (TLC) was performed using Merck aluminum foil-backed plates, pre-coated with silica gel 60 F₂₅₄. Visualization was carried out under UV light and/or staining with potassium permanganate and heating. Flash chromatography was carried out using Davisil silica 60 Å using the specified eluent.

NMR spectroscopy was performed on Bruker DPX400 or Bruker AV400 spectrometers at 400 MHz for ¹H NMR, corresponding ¹³C frequency 100 MHz, at room temperature. Proton magnetic resonance shifts (δ_{H}), recorded in parts per million (ppm), are referenced to residual H in the deuterated solvent. Coupling constants (*J*) are quoted in Hertz (Hz). The multiplicity of each signal is designated by a combination of the following abbreviations; s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). Proton-decoupled carbon chemical shifts (δ_{C}), recorded in ppm, are recorded to one decimal place. In the ¹³C spectra, signals corresponding to CH, CH₂, CH₃ groups are assigned from DEPT; all others are quaternary C. Infrared spectra were obtained on a Bruker Avatar 320 FTIR spectrometer. ATR solid phase IR spectra were recorded using a Bruker Alpha series FT-IR spectrometer over the range 4000 to 600 cm⁻¹. Absorption maxima (ν_{max}) of major peaks are reported in wavenumbers, quoted to the nearest integral wavenumber. Mass spectra were recorded on a Bruker MicroTOF II (ESI) mass spectrometer using electrospray ionization (ESI).

TGA was performed on an Agilent Q500 instrument. Temperature programme: from 30 °C to 100 °C with a ramp of 5 °C/min up to 100 °C, then isotherm for 24 h. LC–MS was performed using an Agilent HPLC Infinity 1260, MS Quadrupole 6120. The HPLC contains a C18 PR HPLC column with a DAD detector at a flow rate of 208 $\mu\text{L}/\text{min}$. GC–MS was performed on a Thermo Single Quadrupole TraceGold TG SQC instrument with a column of 15 m \times 0.25 mm \times 25 μm with He at a flow rate of 1.5 mL/min. The temperature of the injector was 200 °C. Programme of temperature for the oven: 50 °C (5 min) to 350 °C (20 min) at a heating rate of 10 °C/min.

Materials

1,2,3,4-Tetrahydroisoquinolines **2** were used as supplied commercially. Sulfoxides were used as supplied commercially, or prepared by oxidation of the corresponding sulfide.

General procedure for the preparation of sulfoxides from sulfides

A solution of sulfide (1.6 mmol) in dichloromethane (20 mL) was cooled to 0 °C. After addition of *m*-CPBA (ca. 70%; 1.3 equiv.) the solution was stirred for 8 h. The reaction mixture was washed with deionized water (2 × 15 mL), and dried over Na₂SO₄. The solvent was removed under reduced pressure. Further purification was achieved by column chromatography (light petroleum : EtOAc 1:1).

1-Methoxy-4-(methylsulfinyl)benzene

Colorless solid (1.16 g, 48%), mp 44-45 °C; ν_{max} (ATR) 2988, 1246, 1032 cm⁻¹; δ_{H} (400 MHz; CDCl₃) 7.60 (2 H, d, *J* 8.8, ArH), 7.04 (2 H, d, *J* 8.8, ArH), 3.86 (3 H, s, CH₃), 2.71 (3 H, s, CH₃); δ_{C} (100 MHz; CDCl₃) 161.9 (C), 136.6 (C), 125.4 (CH₂), 114.8 (CH₂), 55.5 (OCH₃), 44.0 (CH₃); *m/z* (ESI) C₈H₁₀O₂S (M⁺) *calc.* (M+H) 171.0474, (M+Na) 193.0294, *found* (M+H) 171.0494, (M+Na) 193.0303. This is a known compound, and the spectroscopic data correspond with those reported in literature.³⁵

1-(Methylsulfinyl)-4-(trifluoromethyl)benzene

Colorless solid (1.60 g, 67%), mp 41-42 °C; ν_{max} (ATR) 3001, 2992, 2925, 2911, 1318, 1129, 1058, 1044 cm⁻¹; δ_{H} (400 MHz; CDCl₃) 7.87-7.76 (4 H, m, ArH), 2.78 (3 H, s, CH₃); δ_{C} (100 MHz; CDCl₃) 150.1 (C), 133.1 (q, *J* 32.7, C), 126.3 (q, *J* 3.7, CH), 124.0 (CH), 123.5 (q, *J* 271, CF₃), 43.9 (CH₃); δ_{F} (376 MHz; CDCl₃) -62.9 (s); *m/z* (ESI) C₈H₇OF₃S (M⁺) *calc.* (M+H) 209.0242, (M+Na) 231.0062, *found* (M+H) 209.0246, (M+Na) 231.0064. This is a known compound, and the spectroscopic data correspond with to those reported in literature.³⁵

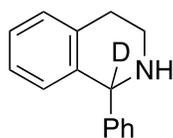
Dehydrogenation of 1,2,3,4-Tetrahydroisoquinolines 2

a. In neat solvent. The tetrahydroisoquinoline (ca. 0.5 mmol) was heated in the solvent (3 mL) at 100 °C for 24 h under air. After cooling to room temperature, the mixture was directly analysed by GC-MS.

b. In toluene in presence of sulfoxides. The tetrahydroisoquinoline (ca. 0.5 mmol) was heated in toluene (3 mL) in the presence of the sulfoxide (0.5 – 10 equiv.) at 100 °C for 24 h under air. After cooling to room temperature, the mixture was directly analysed by GC-MS.

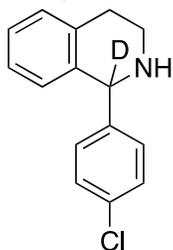
Dehydrogenation of 1,2,3,4-tetrahydrocarbazole 5

1,2,3,4-Tetrahydrocarbazole (100 mg, 0.6 mmol) was placed in a flask with anhydrous DMSO (1 mL). The mixture was stirred at 100 °C for 24 h. Subsequently, the mixture was cooled to room temperature over a period of 30 min. The solvent was removed under reduced pressure to give 9*H*-carbazole **6** as a colorless solid (40 mg, 38%), mp 241-243 °C (lit.,³⁶ mp 246 °C); ν_{max} (ATR) 3417, 3048, 2934, 2872, 1599, 1449, 1324, 1235 cm⁻¹; δ_{H} (400 MHz; CDCl₃) 8.11 (2 H, d, *J* 7.8, ArH), 7.45 (4 H, d, *J* 6.5, ArH), 7.26 (2 H, d, *J* 7.0, ArH) (NH not observed); δ_{C} (100 MHz; CDCl₃) 139.5 (C), 125.8 (CH), 123.9 (C), 120.3 (CH), 119.4 (CH), 110.5 (CH); *m/z* (ESI) C₁₂H₉N (M⁺) *calc.* (M+H) 168.0808, *found* (M+H) 168.0806.

1-D-Phenyl-1,2,3,4-tetrahydroisoquinoline 2a-D

1-Phenyl-3,4-dihydroisoquinoline (0.73 mg, 3.5 mmol) was dissolved in MeOH (10 mL). NaBD₄ (0.22 g, 5.3 mmol) was added to the resulting solution. The reaction mixture was stirred at room temperature for 3 h. After that, the solvent was concentrated under reduced pressure, and the product was purified by column chromatography (light petroleum : EtOAc 1:1) to yield a colorless solid (0.58 g, 79%), mp 92-94 °C (lit.,³⁷ mp 79-80 °C for (*R*)-enantiomer); ν_{\max} (ATR) 3255, 2960, 2819, 2783, 1117 cm⁻¹; δ_{H} (400 MHz; DMSO-*d*₆) 7.35-7.23 (5 H, m, ArH), 7.17-7.06 (2 H, m, ArH), 7.00 (1 H, ddd, *J* 7.6, 6.6, 2.1, ArH), 6.63 (1 H, dd *J* 7.5, 1.2, ArH), 3.14-3.03 (1 H, m), 2.97-2.85 (2 H, m), 2.74 (1 H, dd *J* 5.2, 2.7), 2.73-2.86 (1 H, m); δ_{C} (100 MHz; DMSO-*d*₆) 145.8 (C), 139.2 (C), 135.9 (C), 129.3 (CH), 129.3 (CH), 128.4 (CH), 128.0 (CH), 127.3 (CH), 126.3 (CH), 125.7 (CH), 61.3 (CD, t, *J* 35.0), 42.0 (CH₂), 29.7 (CH₂); *m/z* (ESI) C₁₅H₁₄ND *calc.* (M+H) 211.1340, *found* (M+H) 211.1341.

1-D-(4-Chlorophenyl)-1,2,3,4-tetrahydroisoquinoline 2b-D



1-4-Chlorophenyl-3,4-dihydroisoquinoline (2.90 g, 12.0 mmol) was dissolved in MeOH (30 mL). NaBD₄ (0.76 g, 18.0 mmol) was added to the resulting solution. The reaction mixture was stirred at room temperature for 3 h. After that, the solvent was concentrated under reduced pressure, and the product was purified by column chromatography (petroleum : EtOAc 1:1) to yield a colorless solid (1.63 g, 56%), mp 78-79 °C (lit.,³⁷ mp 100-101 °C for (*R*)-enantiomer); ν_{\max} (ATR) 3245, 1085, 736 cm⁻¹; δ_{H} (400 MHz; CDCl₃) 7.31 (2 H, t, *J* 8.8 ArH), 7.26-7.21 (2 H, m, ArH), 7.20-7.16 (2 H, m, ArH), 7.07 (1 H, t, *J* 8.5, 4.4, ArH), 6.78-6.72 (1 H, m, ArH), 3.28 (1 H, dt, *J* 10.7, 4.7, CH₂-NH), 3.17-3.00 (2 H, m, CH₂), 2.85 (1 H, dt, *J* 16.1, 4.0), 1.89 (1 H, s, NH); δ_{C} (100 MHz; CDCl₃) 143.3 (C), 137.6 (C), 135.4 (C), 133.1 (C), 130.3 (CH), 129.1 (CH), 128.5 (CH), 127.9 (CH), 126.4 (CH), 125.7 (CH), 61.1 (CD t, *J* 21.0) 42.1 (CH₂), 29.6 (CH₂); *m/z* (ESI) C₁₅H₁₃N³⁵ClD *calc.* (M+H) 245.0950, (M+Na) 267.0770, *found* (M+H) 208.0950, (M+Na) 267.0766.

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Supplementary Material

Additional details of experiments performed and NMR spectra pertaining to conversion of **2a** into **3a**.

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