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Solvent-promoted highly selective dehydrogenation of tetrahydroisoquinolines without catalyst and hydrogen acceptor

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ABSTRACT

An unusual solvent DMF-promoted dehydrogenation of 1-substituted 1,2,3,4-tetrahydroisoquinolines to synthesize cyclic imines is described. This environmentally friendly reaction features no requirement of any metal catalysts, oxidants, or hydrogen acceptors. A wide range of structurally varied 3,4-dihydroisoquinolines can be obtained with good yields and excellent chemoselectivities.

Transition-metal catalyzed dehydrogenation of organic compounds is one of the powerful, atom-economic and environmentally benign synthetic methodologies to introduce unsaturated double bonds, such as C=C, C=N and C=O, because this process avoids the utility of stoichiometric amounts of oxidants which will also produce the undesired waste. Dehydrogenation of *N*-heterocycles is a fundamental and important process in organic synthesis. The corresponding dehydroaromatization products are prevalent in pharmaceuticals, agrochemicals, and functional organic materials.[1] Dehydrogenative transformation is considered to be a thermodynamically uphill process,[2] therefore, the harsh reflux condition or sacrificial hydrogen acceptor may sometimes be needed. So far, catalytic dehydrogenation reactions of *N*-heterocycles usually employed conventional heterogeneous metal catalysts, which usually show poor functionality tolerance and require harsh reaction conditions.[3] Recently, homogenous iridium,[4] ruthenium,[5] palladium,[6] iron,[7] zinc,[8], nickel,[9] and platinum,[10] complexes have been found to be competent for the catalytic dehydrogenation of tetrahydroquinolines, tetrahydroisoquinolines, indolines, tetrahydroquinoxalines, Hantzsch esters and saturated bicyclic ondecahydro-1,5-naphthyridine with good to excellent results.

From the point of view of synthetic chemistry, imine bears the reactive C=N bond and is capable of undergoing various types of transformations, including cyclization reactions and the reactions with nucleophiles. Generation of imine in situ by dehydrogenating amine has been regarded as a new and substrate-activating strategy for the direct transformation of amines.[11] Although many trials have been devoted to dehydrogenation of *N*-heterocyclic compounds, the partial dehydrogenative processes to obtain cyclic imines are still rare.[12] It is easy to understand that hydroaromatic compounds containing nitrogen atoms are prone to form the final dehydroaromatization products for the aromatic stability and the intermediates are normally short-living species during dehydrogenating process. How to realize the high selectivity of partial dehydrogenation of *N*-heterocyclics is a challenging subject in this research field. A critical issue to resolve is the suppression of aromatization which in turn improves the chemoselectivity of dehydrogenation. Given that the different dehydrogenation products of *N*-heterocyclics, including aromatic compounds and imines, both are valuable organic building blocks, developing an efficient and well controllable dehydrogenation process of *N*-heterocyclic compounds is of great significance. Herein, we report an unusual solvent-promoted partial dehydrogenation of tetrahydroisoquinolines to exclusively generate 3,4-dihydroisoquinolines as products with high chemoselectivity, providing greener and more practical approach for the preparation of useful cyclic imines (Fig. 1).

In the beginning of our research, we performed the dehydrogenative oxidation reaction of 1-phenyl-1,2,3,4-tetrahydroisoquinoline (**1a**). Firstly, a survey of solvents was conducted to examine the reaction. No product was obtained in most solvents (Table 1, entries 1–3). To our surprise, when the DMF or DMSO was used as the solvent, the imine product **2a** was obtained with excellent conversion and perfect chemoselectivity (Table 1, entries 4 and 5). Further investigation of temperature revealed that the reaction temperature is a very important effect factor and 100 °C is the best choice for a satisfied conversion and chemoselectivity

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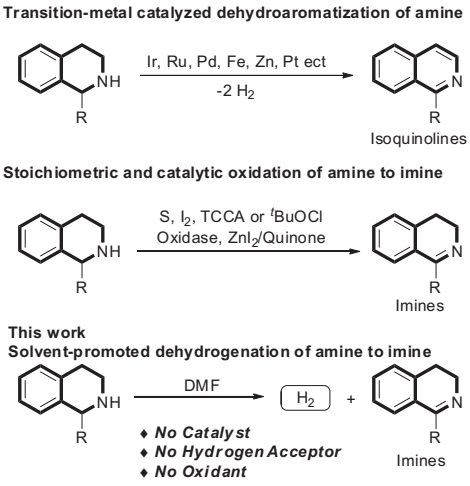
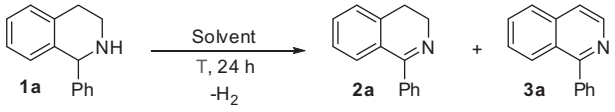


Figure 1. Selective dehydrogenation of amines.

Table 1
Examination of reaction parameters[a]



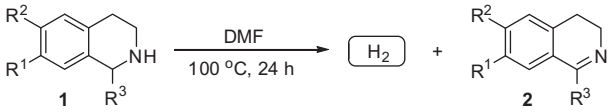
Entry	Solvent	*T* (°C)	Conv.[b] (%)	**2a**:**3a**[b]
1	Toluene	111	<5	ND
2	CH_3CN	82	<5	ND
3	Cyclohexane	81	<5	ND
4	DMF	100	>95	>20:1
5	DMSO	100	>95	>20:1
6	DMF	80	90	>20:1
7	DMF	60	33	>20:1
8[c]	DMF	100	92	>20:1

[a] Reaction conditions: **1a** (0.2 mmol), solvent (1.0 mL).
[b] Determined by ^{1}H NMR.
[c] Degassed DMF and N_2 atmosphere were used.

(Table 1, entries 5–7). Even if air was carefully excluded from reaction system, the imine **2a** was still obtained in excellent yield (Table 1, entry 8). Moreover, the gas composition of the reaction system was examined by TPD-MS (Temperature Programmed Desorption-Mass Spectrometer), and the signal of hydrogen ($m/z = 2$) released from substrates was detected (see the SI for details). On the basis of the above two facts, we considered that this reaction might be a solvent-promoted thermal-dehydrogenation process. But it is still unclear how DMF promotes this process. We assume that the N—H and C1—H bond are both weakened via the hydrogen-bond interactions between DMF/DMSO and substrates, which may result in a low dehydrogenation energy barrier.

With the optimal reaction condition in hand, we explored the scope of the solvent-promoted partial dehydrogenation of tetrahydroisoquinoline. As shown in Table 2, to our delight, almost all the aryl substituted substrates performed dehydrogenation very well under the standard conditions. The reaction was found not significantly affected by the substituents on the aromatic ring of either the tetrahydroisoquinoline structure or the 1-aryl group, providing the desired products with good to excellent yields (Table 2, entries 1, 3–7, 9–17). It was noteworthy that some key synthetic intermediates for manufacturing some drug molecules or nature products containing tetrahydroisoquinoline skeleton[13] were also suitable candidates for this reaction, and they underwent the partial dehydrogenation reaction smoothly to afford the corresponding imine

Table 2
Scope for the 1-substituted tetrahydroisoquinoline[a]



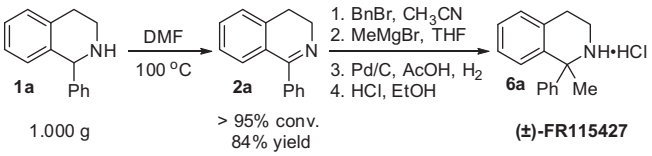
Entry	R^1/R^2	R^3	Yield[b] **2** (%)
1	H/H	Ph	83 (**2a**)
2[c]	H/H	Ph	87 (**2a**)
3	H/H	4-ClC_6H_4	88 (**2b**)
4	H/H	4-$MeOC_6H_4$	82 (**2c**)
5	H/H	3-MeC_6H_4	85 (**2d**)
6	H/H	4-MeC_6H_4	90 (**2e**)
7	H/H	4-$CF_3C_6H_4$	77 (**2f**)
8[c]	H/H	4-$CF_3C_6H_4$	76 (**2f**)
9	Me/H	Ph	75 (**2g**)
10	Cl/H	Ph	75 (**2h**)
11	MeO/H	Ph	75 (**2i**)
12	MeO/MeO	Ph	72 (**2j**)
13	MeO/MeO	3,4-$(MeO)_2C_6H_3$	85 (**2k**)
14	H/H	2-ClC_6H_4	79 (**2l**)
15	H/H	4-FC_6H_4	82 (**2m**)
16	H/H	4-BrC_6H_4	87 (**2n**)
17	MeO/MeO	4-ClC_6H_4	91 (**2o**)
18[d]	H/H	Cy	64 (**2p**)

[a] Reaction conditions: **1** (0.3 mmol), DMF (2.0 mL), 100 °C.
[b] Isolated yields.
[c] In DMSO.
[d] 80 °C.

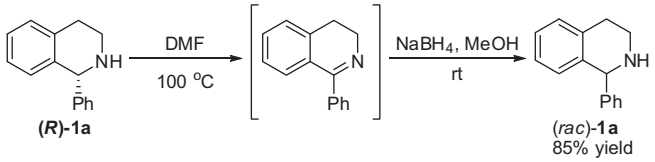
products with good yields (Table 2, entries 1, 12, 13 and 17). In addition, the bromo or chloro groups on the aromatic ring of substrates could survive well through this process, thus provided a handle for further potential functionalization (Table 2, entries 3, 14 and 16). The substrate scope exploration may offer the potential application for some chiral pharmaceutical synthesis and resolution in the industry. On the other hand, we also investigated the 1-alkyl substituted tetrahydroisoquinoline on the reactivity and chemoselectivity (Table 2, entry 18). The desired imine product was also obtained with 64% yield when the reaction was carried out at 80 °C for 24 h, which maintained an excellent chemoselectivity. Extension of this reaction to other amines such as 2-methyl-1,2,3,4-tetrahydroquinoline and 4-methoxy-*N*-(1-phenylethyl)aniline, however, met with failure and no desired products were obtained.

To further highlight the practical utility of the current method, the selective partial dehydrogenation of 1-phenyl-1,2,3,4-tetrahydroisoquinoline **1a** was performed under the optimal condition on a gram scale. As illustrated in Scheme 1, the desired product cyclic imine **2a** was obtained in gram scale with 84% isolated yield. Prolongation of reaction time ensured that a complete conversion and good chemoselectivity was maintained. Furthermore, the (±)-FR115427 was rapidly synthesized from the resulting cyclic imine **2a** in four steps (Scheme 1, for the detailed procedure, see SI).[14]

Racemization of enantiomerically enriched compound is very useful in industry because it can recycle the undesired isomer in resolution operation of a racemate, thus increasing the overall yield.[15] One-pot racemization of enantiomerically pure amine **1a**



Scheme 1. Gram scale experiment and synthesis of (±)-FR115427.



Scheme 2. Racemization of (*R*)-1-phenyl-1,2,3,4-tetrahydroisoquinoline **1a**.

could be easily realized via a dehydrogenation/reduction one-pot process by using this catalyst-free dehydrogention methodology. (*R*)-1-Phenyl-1,2,3,4-tetrahydro-isoquinoline **1a** with 97% ee was subjected to the optimized reaction conditions to access the cyclic imine after removing DMF under *vacuum*, and then reduction with sodium borohydride in methanol afforded the racemic product with 85% isolated yield (Scheme 2). Clean condition, brief operation and easy scalability of this racemization process may lead to a further industrial application in the near future.

In summary, we have successfully developed a green protocol for accessing cyclic imine in good yields with excellent chemoselectivities by an solvent-promoted highly selective dehydrogenation of tetrahydroisoquinolines without catalyst and dehydrogen acceptor. Moreover, efficient and practical racemization of enantiomerically pure 1-substituted tetrahydroisoquinoline can be realized via one-pot dehydrogenation/reduction treatment. This metal-free and oxidant-free dehydrogenation process may apply in industrial syntheses owing to some advantages such as simplicity, easy operation, free of expensive mutagenic reagents, no harsh reaction conditions, and so on. Our ongoing experiments are focused on this solvent-promoted dehydrogenation reaction of other substrates and further application in cascade process.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.01.008.

References and notes

1. For recent reviews on metal-catalyzed dehydrogenation see: (a) Dobereiner, G. E.; Crabtree, R. H. *Chem. Rev.* **2010**, *110*, 681; (b) Choi, J.; MacArthur, A. H. R.; Brookhart, M.; Goldman, A. S. *Chem. Rev.* **2011**, *111*, 1761.
2. (a) Li, H.; Jiang, J.; Lu, G.; Huang, F.; Wang, Z.-X. *Organometallics* **2011**, *30*, 3131; (b) Zhang, X.-B.; Xi, Z. *Phys. Chem. Chem. Phys.* **2011**, *13*, 3997.
3. (a) Adkins, H.; Lundsted, L. G. *J. Am. Chem. Soc.* **1949**, *71*, 2964; (b) Hara, T.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Tetrahedron Lett.* **2003**, *44*, 6207; (c) Wang, Z.; Tonks, I.; Belli, J.; Jensen, C. M. *J. Organomet. Chem.* **2009**, *694*, 2854; (d) Dean, D.; Davis, B.; Jessop, P. G. *New J. Chem.* **2011**, *35*, 417; (e) Luca, O.; Huang, D.-L.; Takase, M. K.; Crabtree, R. H. *New J. Chem.* **2013**, *37*, 3402; (f) Jin, X.; Liu, Y.; Lu, Q.; Yang, D.; Sun, J.; Qin, S.; Zhang, J.; Shen, J.; Chu, C.; Liu, R. *Org. Biomol. Chem.* **2013**, *11*, 3776.
4. (a) Gu, X.; Chen, W.; Morales-Morales, D.; Jensen, C. M. *J. Mol. Catal. A: Chem* **2002**, *189*, 119; (b) Lu, S.-M.; Wang, Y.-Q.; Han, X.-W.; Zhou, Y.-G. *Chin. J. Catal.* **2005**, *26*, 287; (c) Wang, D.-W.; Wang, X.-B.; Wang, D.-S.; Lu, S.-M.; Zhou, Y.-G.; Li, Y.-X. *J. Org. Chem.* **2009**, *74*, 2780; (d) Yamaguchi, R.; Ikeda, C.; Takahashi, Y.; Fujita, K. *J. Am. Chem. Soc.* **2009**, *131*, 8410; (e) Wu, J. J.; Talwar, D.; Johnston, S.; Yan, M.; Xiao, J.-L. *Angew. Chem., Int. Ed.* **2013**, *52*, 6983; (f) Fujita, K.; Tanaka, Y.; Kobayashi, M.; Yamaguchi, R. *J. Am. Chem. Soc.* **2014**, *136*, 4829; (g) Manas, M. G.; Sharninghausen, L. S.; Lin, E.; Crabtree, R. H. *J. Organomet. Chem.* **2015**, *792*, 184.
5. (a) Tsuji, Y.; Kotachi, S.; Huh, K. T.; Watanabe, Y. *J. Org. Chem.* **1990**, *55*, 580; (b) Yi, C. S.; Lee, D. W. *Organometallics* **2009**, *28*, 947; (c) Wendlandt, A. E.; Stahl, S. S. *J. Am. Chem. Soc.* **2014**, *136*, 11910.
6. (a) Ji, Y.; Chen, M.-W.; Shi, L.; Zhou, Y.-G. *Chin. J. Catal.* **2015**, *36*, 33.
7. Chakraborty, S.; Brennessel, W. W.; Jones, W. D. *J. Am. Chem. Soc.* **2014**, *136*, 8564.
8. Wendlandt, A. E.; Stahl, S. S. *J. Am. Chem. Soc.* **2014**, *136*, 506.
9. For some representative examples on heterogenous transition-metal catalyzed dehydroaromatization of *N*-heterocycles, see: (a) Adkins, B. H.; Lundsted, L. G. *J. Am. Chem. Soc.* **1949**, *71*, 2964; (b) Angelici, R. J. *J. Organomet. Chem.* **2008**, *693*, 847.
10. Zhang, D.; Wu, L.-Z.; Zhou, L.; Han, X.; Yang, Q.-Z.; Zhang, L.-P.; Tung, C.-H. *J. Am. Chem. Soc.* **2004**, *126*, 3440.
11. Kruger, K.; Tillack, A.; Beller, M. *ChemSusChem* **2009**, *2*, 715.
12. (a) Ghislieri, D.; Green, A. P.; Pontini, M.; Willies, S. C.; Rowles, I.; Frank, A.; Grogan, G.; Turner, N. J. *J. Am. Chem. Soc.* **2013**, *135*, 10863; (b) Köhler, V.; Wilson, Y. M.; Dürrenberger, M.; Ghislieri, D.; Churakova, E.; Quinto, T.; Knörr, L.; Häussinger, D.; Hollmann, F.; Turner, N. J.; Ward, T. R. *Nat. Chem.* **2013**, *5*, 93.
13. For selected examples of some drug molecules containing tetrahydroisoquinoline skeleton, see: (a) Naito, R.; Yonetoku, Y.; Okamoto, Y.; Toyoshima, A.; Ikeda, K.; Takeuchi, M. J. *J. Med. Chem.* **2005**, *48*, 6597; (b) Ohkubo, M.; Kuno, A.; Katsuta, K.; Ueda, Y.; Shirakawa, K.; Nakanishi, H.; Nakanishi, I.; Kinoshita, T.; Takasugi, H. *Chem. Pharm. Bull.* **1996**, *44*, 95; (c) Ludwig, M.; Hoesl, C. E.; Höfner, G.; Wanner, K. T. *Eur. J. Med. Chem.* **2006**, *41*, 1003.
14. (a) Li, X.; Coldham, I. *J. Am. Chem. Soc.* **2014**, *136*, 5551.
15. (a) Bolchi, C.; Pallavicini, M.; Fumagalli, L.; Straniero, V.; Valoti, E. *Org. Process Res. Dev.* **2013**, *17*, 432; (b) Zhu, R.; Xu, Z.; Ding, W.; Liu, S.; Shi, X.; Lu, X. *Chin. J. Catal.* **2014**, *32*, 1039.