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Highly selective partial dehydrogenation of tetrahydroisoquinolines using modified Pd/C

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ABSTRACT

A highly selective procedure has been developed for the partial dehydrogenation of 1-substituted-1,2,3,4-tetrahydroisoquinolines over $K_3PO_4·3H_2O$-modified Pd/C catalyst. This new method provides facile, atom-economical and environmentally friendly access to 1-substituted-3,4-dihydroisoquinolines without the need for stoichiometric amounts of harmful oxidants. The use of standard Pd/C as a catalyst for this process gave poor chemoselectivity. Pleasingly, the use of a $K_3PO_4·3H_2O$-modified Pd/C catalyst promoted the partial dehydrogenation of 1-substituted-1,2,3,4-tetrahydroisoquinolines with excellent chemoselectivity by suppressing further dehydroaromatization. Furthermore, conducting the reaction under an atmosphere of oxygen led to further improvements in the chemoselectivity of the dehydrogenation, with the ratio of imine to isoquinoline reaching up to 32/1. The heterogenous Pd/C catalyst could also be recycled and reused at least three times with excellent conversion and chemoselectivity, demonstrating the significantly practical potential of this methodology.

1. Introduction

Imines are one of the most frequently used substrates in synthetic chemistry where they feature strongly in a variety of organic transformations, including cyclization reactions and reactions involving the addition of nucleophiles to the carbon atom of the imine bond. The oxidation of cyclic amines to the corresponding cyclic imines is an important synthetic methodology, which generally requires the addition of a stoichiometric oxidant [1–11], such as iodine, sulfur, *tert*-butylhydroperoxide or 3,3-dimethyl-1-butene, which can lead to the formation of harmful waste products. Furthermore, reactions involving the oxidation of amines with trichloroisocyanuric acid [12] or *tert*-butyl hypochlorite [13] always proceed *via* a two-step process of *N*-chlorination and dehydrochlorination to give the corresponding imines (Scheme 1) The transition-metal catalyzed dehydrogenation of organic compounds represents a powerful, atom-economical and environmentally benign approach for the introduction of unsaturated double bonds, such as C=C [14–19], C=N [20–25] and C=O [26–31] bonds, whilst avoiding the use of stoichiometric amounts of harmful oxidants. The dehydrogenation of *N*-heterocycles has attracted considerable interest from both academic and industrial research groups during the course of the past two decades. This method is generally used to prepare *N*-heteroaromatic compounds, which are common structural motifs in pharmaceutical and material chemistry [32–47], because it provides rapid access to stable dehydroaromatization products.

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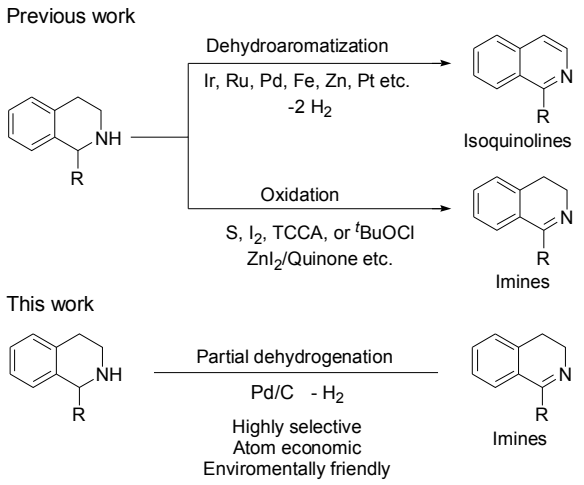

Scheme 1. Metal-catalyzed dehydrogenation of tetrahydroisoquinolines.

Mechanistic studies have shown that the dehydrogenation of *N*-heterocyclic compounds occurs *via* a reactive cyclic imine intermediate, followed by further dehydroaromatization [48,49]. In theory, cyclic imines could be formed by the controllable dehydrogenation of *N*-heterocyclic compounds. However, reports pertaining to the development of partial dehydrogenative processes with cyclic imines as products are scarce [50–52]. Stahl's group [50] recently described a Zn/quinone complex catalyzed reaction for the aerobic oxidation of amines to imines with good to excellent yields. Turner's group [51] creatively applied the monoamine oxidase MAO-N D11C as a catalyst for the enantioselective oxidation of amines. It is easy to understand why the dehydrogenation of *N*-heterocycles is prone to the formation of the final dehydroaromatization products because the resulting aromatic products are much more stable than the corresponding partially oxidized imine intermediates, which are formed as transient species during the dehydrogenative process. The development of new processes capable of achieving high levels of selectivity for the partial dehydrogenation of *N*-heterocyclic compounds remains a challenging subject in this field of research. A critical issue that needs to be addressed by any new methodology is the suppression of further aromatization, which would lead to significant improvements in the chemoselectivity of dehydrogenation. Given that the different dehydrogenative products of *N*-heterocyclic compounds, including aromatic compounds and imines, are valuable organic building blocks, the development of an efficient and controllable process for the dehydrogenation of *N*-heterocyclic compounds is highly desirable. Herein, we report a new Pd/C-promoted process for the partial dehydrogenation of 1,2,3,4-tetrahydroisoquinolines to 3,4-dihydroisoquinolines exclusively with high levels of activity and chemoselectivity.

2. Experimental

2.1. General methods

Commercially available reagents and solvents were used without further purification. The Pd/C (5% Pd on carbon) catalyst used in the current study was purchased from J&K. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded at room temperature in $CDCl_3$ on a 400 MHz instrument (Brucker) with tetramethylsilane (TMS) as an internal standard. Flash column chromatography was performed on silica gel (200–300 mesh). All of the reactions were monitored by TLC analysis. The 1-substituted-1,2,3,4-tetrahydroisoquinolines were prepared according to the literature methods [53].

2.2. General procedure for synthesis of imines (*2a–l*)

Pd/C (254 mg, 0.12 mmol) and $K_3PO_4{\cdot}3H_2O$ (16 mg, 0.06 mmol) were placed in a Schlenk tube followed by acetonitrile (1 mL), and the resulting mixture was stirred at room temperature for 10 min. A solution of 1-substituted-1,2,3,4-tetrahydroisoquinoline (0.30 mmol) in acetonitrile (4 mL) was then added to the reaction mixture, and the Schlenk tube was carefully and quickly vacuum purged before being filled with oxygen using an oxygen balloon. The reaction mixture was then stirred at 60 °C until the 1-substituted-1,2,3,4-tetrahydroisoquinoline had been completely consumed (as determined by TLC analysis). Upon completion of the reaction, the mixture was slowly cooled to room temperature and filtered through diatomite to remove the Pd/C catalyst. The filtrate was then concentrated in vacuo to give the crude product as a residue, which was purified by flash chromatography over silica gel eluting with petroleum ether and ethyl acetate to give the imine product **2**.

1-Phenyl-3,4-dihydroisoquinoline (**2a**): 86% yield, known compound [54], yellow oil, R_f = 0.75 (ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.60–7.56 (m, 2H), 7.44–7.35 (m, 4H), 7.26–7.21 (m, 3H), 3.85–3.82 (m, 2H), 2.80–2.77 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.3, 139.0, 138.9, 130.7, 129.3, 128.9, 128.8, 128.1, 127.9, 127.4, 126.6, 47.7, 26.3.

1-Phenylisoquinoline (**3a**): known compound [55], white solid, R_f = 0.93 (ethyl acetate), mp = 73–74 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.61 (d, J = 5.7 Hz, 1H), 8.10 (d, J = 8.5 Hz, 1H), 7.87 (d, J = 8.2 Hz, 1H), 7.71–7.63 (m, 4H), 7.55–7.47 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.9, 142.4, 139.8, 137.0, 130.2, 130.1, 128.8, 128.5, 127.8, 127.3, 127.2, 126.9, 120.1.

1-(4-Chlorophenyl)-3,4-dihydroisoquinoline (**2b**): 84% yield, known compound [54], colorless oil, R_f = 0.50 (ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.56–7.40 (m, 2H), 7.48–7.37 (m, 3H), 7.27–7.21 (m, 3H), 3.85–3.82 (m, 2H), 2.81–2.77 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.2, 138.9, 137.5, 135.4, 130.9, 130.2, 128.5, 128.4, 127.6, 127.5, 126.7, 47.7, 26.3.

1-(4-Methoxyphenyl)-3,4-dihydroisoquinoline (**2c**): 89% yield, known compound [54], colorless oil, R_f = 0.60 (ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.57–7.55 (m, 2H), 7.36–7.23 (m, 4H), 6.95–6.93 (m, 2H), 3.84 (s, 3H), 3.81–3.78 (m, 2H), 2.78–2.75 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.6, 160.6, 139.1, 131.5, 130.5, 130.3, 128.9, 127.9, 127.4, 126.5, 113.5, 55.3, 47.5, 26.4.

1-*m*-Tolyl-3,4-dihydroisoquinoline (**2d**): 82% yield, known compound [54], colorless oil, R_f = 0.40 (petroleum ether/ethyl