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Ruthenium-Catalyzed Straightforward Synthesis of 1,2,3,4-Tetrahydronaphthyridines via Selective Transfer Hydrogenation of Pyridyl Ring with Alcohols

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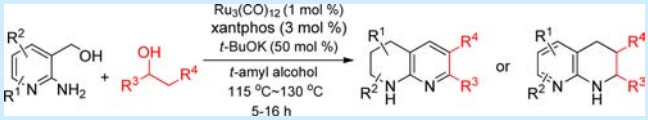
Supporting Information

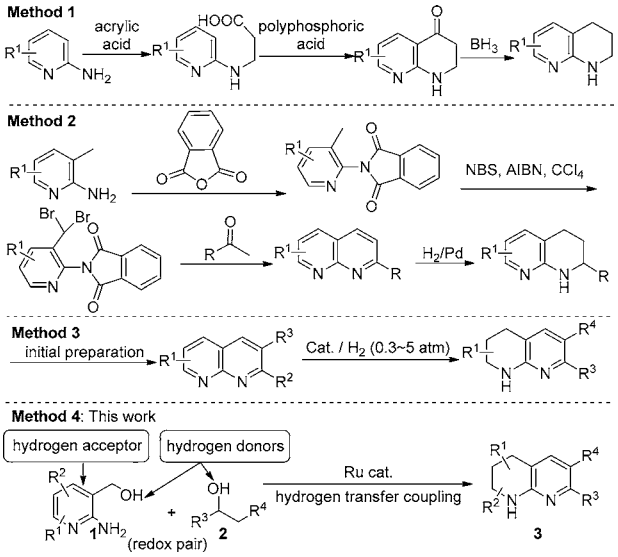
ABSTRACT: Through a ruthenium-catalyzed selective hydrogen transfer coupling reaction, a novel straightforward synthesis of 1,2,3,4-tetrahydronaphthyridines from *o*-aminopyridyl methanols and alcohols has been developed. The synthetic protocol proceeds in an atom- and step-economic fashion together with the advantages of operational simplicity, broad substrate scope, production of water as the only byproduct, and no need for external reducing reagents such as high pressure H_2 gas, offering a highly practical approach for accessing this type of structurally unique products.



The selective hydrogenation of aromatic hydrocarbons is an attractive but challenging task in organic chemistry. Its significance lies in the applications in both organic synthesis and hydrogen energy storage. Pioneered by Birch[1] and Benkeser[2] reduction, the conventional hydrogenation with high-pressure H_2 gas[3,4] and the transfer hydrogenation with specific reducing agents[5] are the common approaches. In comparison, the transfer-hydrogenation reactions at atmospheric pressure do not neefor special equipment such as autoclaves, offering more convenient and safer operations. However, such processes typically produce stoichiometric amounts of waste. To utilize the feedstock atoms to a maximum extent, the hydrogen-borrowing strategy using abundant and sustainable alcohols as both hydrogen sources and coupling partners represent an interesting tool in synthetic chemistry,[6] in which the in situ formed C−C or C−N double bond serve as the hydrogen abstractors. Despite these advances, the development of hydrogen-transfer coupling reactions[7] with alcohols by exploring aromatic systems as both hydrogen absorbers and coupling components remains a new challenging, but highly desirable subject, which would not only enrich the hydrogenation of aromatic system but also pave new pathways to access functional products.

1,2,3,4-Tetrahydronaphthyridines (THNADs) constitute an important class of structurally unique compounds, exhibiting diversely interesting biological and therapeutic activities.[8−13] Moreover, THNADs serve as versatile building blocks for various synthetic purposes including the preparation of functionalized materials.[14] Generally, THNADs were prepared starting from 2-aminopyridine derivatives via step-by-step operations including nucleophilic addition to acrylic acid, intramolecular dehydrative cyclization, and reduction with boron hydrides (Scheme 1, method 1)[14b,d] or amino protection, benzylic bromination, deprotection/intermolecular cyclization with ketones, and reduction (method 2).[10,15] Despite these valuable contributions, the multistep synthesis using either waste-producing or less environmentally benign halogenated reagents could constantly limit their synthetic utility and cause environmental issues. Alternatively, an initial step leading to naphthyridines, followed by hydrogenation with H_2 gas, has offered interesting new access to the related end (method 3).[10,12] Nevertheless, the development of versatile shortcuts to access THNADs from easily available feedstocks still remains a highly demanding goal.

Scheme 1. Conventional Methods and This Work



Through a ruthenium-catalyzed selective hydrogen transfer coupling reaction, we herein report a novel straightforward synthesis of THNADs **3** from *o*-aminopyridyl methanols **1** and

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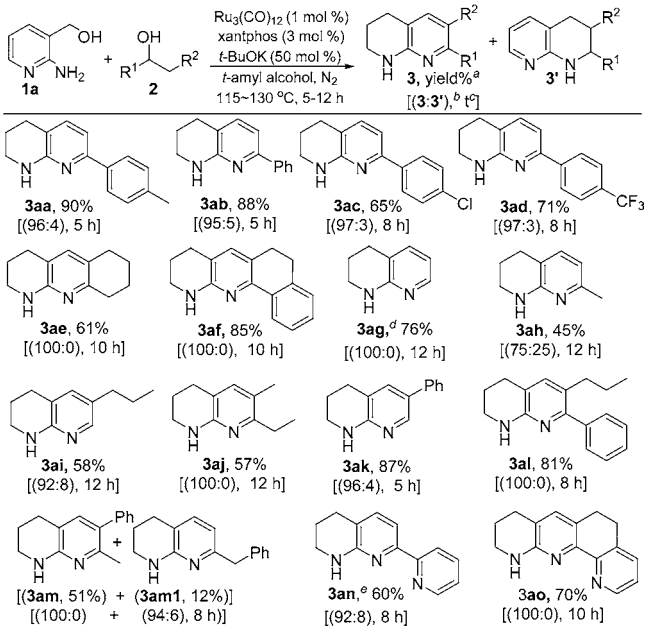
alcohols **2**. In the redox pair, the pyridyl ring and two alcohol units serve as the hydrogen acceptor (oxidant) and hydrogen donors (reductants), respectively. Hence, there is no need for using any external reductants, offering a facile synthesis of THNADs in an atom- and step-economic fashion (method 4).

We initiated our investigation to determine an efficient reaction system.[16] The synthesis of 7-*p*-tolyl-1,2,3,4-tetrahydro-1,8-naphthyridine **3aa** from (2-aminopyridin-3-yl)methanol **1a** and 1-*p*-tolylethanol **2a** was chosen as a model reaction to evaluate the effect of representative precatalysts, ligands, different reaction time, temperatures, and solvents. An optimal yield and selectivity of **3aa** were obtained at 130 °C by using $Ru_3(CO)_{12}$/xanthphos/*t*-BuOK as a catalyst system and *tert*-amyl alcohol as solvent (see the Supporting Information, Table S1).

With the optimized reaction conditions established, we then examined the generality and the limitations of this ruthenium-catalyzed protocol. First, the reactions of **1a** in combination with a wide range of alcohols (see the Supporting Information Scheme S2, for the structures of substrates) were examined. As shown in Scheme 2, all of the reactions proceeded efficiently and

Scheme 2. Synthesis of THNADs from 1a and Alcohols



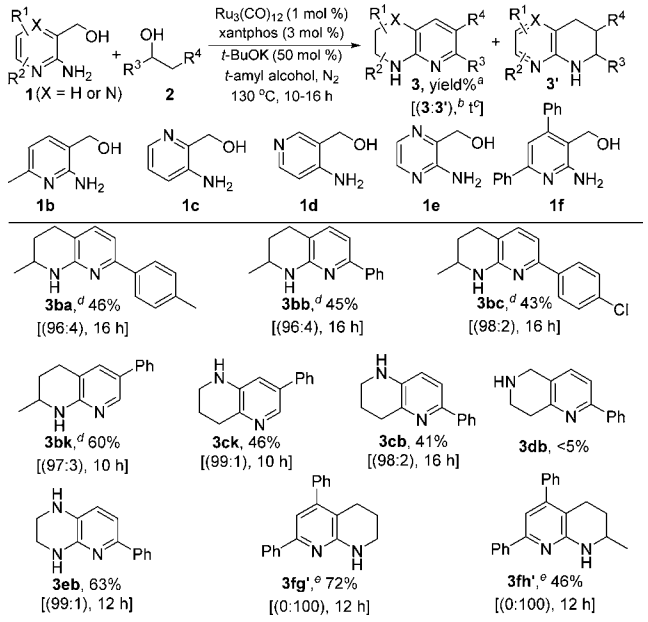
Reaction conditions: Unless otherwise stated, all reactions were carried out under nitrogen atmosphere by using **1a** (0.5 mmol), **2** (0.5 mmol), catalyst (1 mol %), ligand (3 mol %), *t*-BuOK (50 mol %), *tert*-amyl alcohol (1.2 mL), temperature (130 °C). [a]Isolated yield. [b]GC ratio of **3** and **3′**. [c]Reaction time. [d]**2g** (1.5 mmol). [e]Reaction temperature: 115 °C.

the transfer hydrogenation mainly occurred at the sterically less-hindered pyridyl ring, affording the desired products exclusively (**3ae**−**ag**,**aj**,**al**,**ao**) or with excellent regioselectivity (**3aa**−**ad**,**ah**−**ai**,**ak**). Except for the steric influence, the conjugated effect might be another crucial factor in controlling the hydrogenation selectivity, because a stable conjugated system disfavors the pyridyl reduction in the case of pyridyl skeleton bearing a aryl substituent (see **3aa**−**ad**,**af**,**ak**−**ao**). Specifically, 1-aryl ethanols (**2a**−**d**) afforded the 7-aryl THNADs in good to excellent yields in 8 h (**3aa**−**ad**). Owing to possessing a 2-arylpyridine structural unit, these products have the potential for further elaboration of complex molecules via direct C−H bond functionalization.[17]

The reactions of cyclic alcohols (**2e**,**f**) gave the corresponding tri- and tetracyclic products in good yields in 10 h (**3ae**−**af**). These examples demonstrate the potential of the synthetic protocol for the construction of various annulated heterocycles. Further investigations showed that alkyl alcohols (**2g**−**j**) were also effective coupling partners to afford the non-, mono-, and dialkylated products in moderate to high yields (**3ag**−**aj**). 2-Phenylethan-1-ol **2k** demonstrated remarkable reactivity to couple with **1a** at 115 °C, resulting in a 6-phenyl product **3ak** in 5 h with excellent yield, and its structure was confirmed by X-ray diffraction (see the Supporting Information, Figure 1). Further, both alkyl and aryl groups could be flexibly introduced into the newly formed pyridyl skeleton by tuning the alcohols (**3al**,**am**). Notably, 1-phenylpropan-2-ol **2m** led to three regioisomers, and the C−C coupling mainly took place at the more active benzylic position (see **3am**,**am1**). Interestingly, the pyridyl unit containing alcohols **2n** and **2o** also underwent efficient hydrogen-transfer coupling reactions to afford bipyridyl products (**3an**,**ao**), which are important ligands that could be applied in transition-metal catalysis and the preparation of functional organometallic materials.[18]

In addition to the alcohols **2**, we subsequently turned our attention to the utilization of *o*-aminopyridyl methanols **1** with different substitution patterns (Scheme 3). Similar to the results

Scheme 3. Synthesis of THNADs from Various *o*-Aminopyridyl Methanols and Alcohols



Reaction conditions: Unless otherwise stated, all reactions were carried out under nitrogen atmosphere by using **1** (0.5 mmol), **2** (0.5 mmol), catalyst (1 mol %), ligand (3 mol %), *t*-BuOK (50 mol %), *t*-amyl alcohol (1.2 mL), temperature (130 °C). [a]Isolated yield. [b]GC ratio of **3** and **3′**. [c]Reaction time. [d]*t*-BuOK: 0.5 mmol. [e]**2g**, **2h**: 1.5 mmol.

described in Scheme 2, all of the reactions proceeded with high or exclusive transfer hydrogenation selectivity, affording the desired products in moderate to good yields upon isolation. As compared to substrate **1a**, (2-amino-6-methylpyridin-3-yl)methanol **1b** reacting with several representative alcohols afforded the corresponding products in relatively lower yields (**3ba**−**bc**,**bk**), presumably due to the influence of steric effect. Gratifyingly, (3-aminopyridin-2-yl)methanol **1c** also could be transformed into

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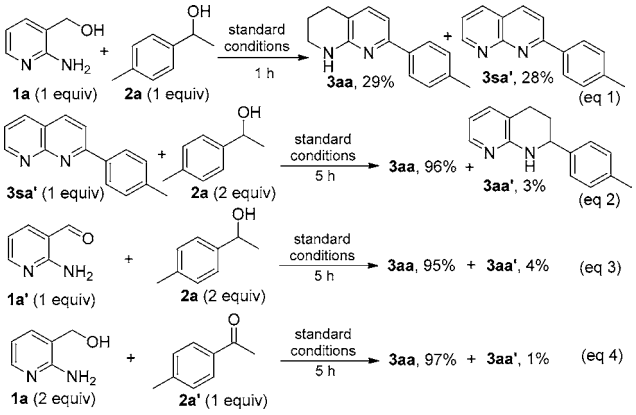
the 1,2,3,4-tetrahydro-1,5-naphthyridines in reasonable yields (**3ck**,**cb**). However, the reaction of (4-aminopyridin-3-yl)-methanol **1d** with **2b** only yielded a trace of product **3db**, indicating the nitrogen atom in the pyridyl ring of substrate **1** *ortho* to the amino or the hydroxymethyl group is essential to obtaining a satisfactory yield. As expected, (3-aminopyrazin-2-yl)methanol **1e** could react with **1b** to afford product **3eb** in 63% yield. Noteworthy, the transfer hydrogenation occurred exclusively on the newly formed pyridiyl ring while using more bulky substrate **1f** with less substituted ethanol **2g** or 2-propanol **2h** (**3fg**′,**fh**′).

To gain insight into the possible mechanism, the model reaction was interrupted after 1 h to analyze the reaction intermediates. By means of GC analyses, both products **3aa** and **3sa**′ were observed in 29% and 28% yields, respectively (Scheme 4, eq 1), indicating the forming rate of **3sa**′ is much faster than

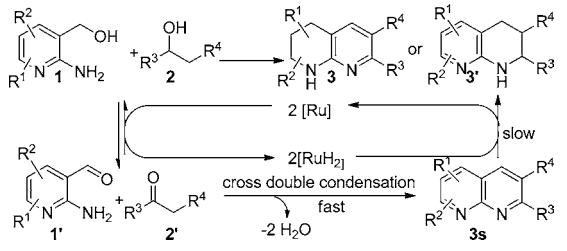
Scheme 4. Control Experiments



that of the reduction process. Hence, the transfer hydrogenation step is believed to be a rate-determining step in the whole reaction. Furthermore, **3sa**′ was separated to react with 2 equiv of **2a**, and product **3aa** was detected in almost quantitative GC yield along with small portion of **3aa**′ (eq 2), showing **3sa**′ is a key reaction intermediate and the annulation step should occur prior to the reduction of the pyridyl unit. However, that **3sa**′ failed to yield even a trace of **3aa** in the absence of **2a** indicates the alcohol serves as a hydrogen supplier during the transfer hydrogenation process (not listed). Moreover, both reactions of 2-amino-nicotinaldehyde **1a**′ with 2 equiv of **2a** or 2 equiv of **1a** with ketone **2a**′ gave product **3aa** in excellent yields (eqs 3 and 4), implying that **1a**′ and **2a**′ are the reaction intermediates.

On the basis of the above-observed findings, a plausible reaction pathway is proposed in Scheme 5. The reaction initiates via ruthenium-catalyzed dehydrogenation of alcohol units of **1** and **2** to form the corresponding carbonyl intermediates **1**′ and **2**′. Through a deuterium-labeling experiment, the partial

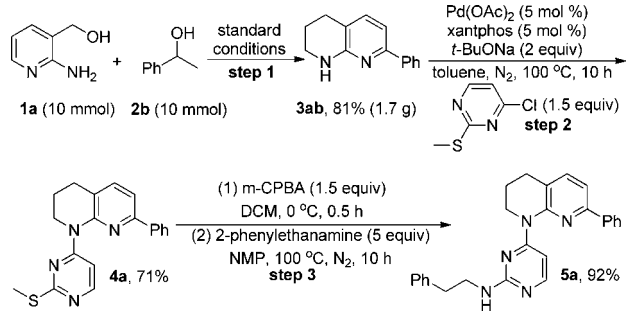
Scheme 5. Possible Pathway for the Formation of 3



deuteration at position 5 of product **3ah** supports that a reversible hydrogenation process takes place in this step (see the Supporting Information, Scheme S3). Then, the consumption of **1**′ and **2**′ via cross double condensations would switch the equilibrium toward the dehydrogenation direction, affording 1,8-naphthyridine **3s**′ along with liberation of water. Finally, the ruthenium-catalyzed transfer hydrogenation of the pyridyl ring gives product **3** or **3**′. Through theoretical calculation for contrastive energy of the regio-isomers, it clearly reveals that the product selectivity correlates with their thermodynamic stability (see the Supporting Information, Tables S10 and S11).

Finally, we were interested in exploring the utility of the synthetic method. We applied it to the rapid synthesis of product **5a**, a therapeutic composition used for the treatment of TNF-α-, IL-1β-, IL-6-, and/or IL-8-mediated diseases such as inflammation, pain, and diabetes (Scheme 6).[6] Initially, the synthesis of

Scheme 6. Utility of the Synthetic Method



3ab was scaled up by using 10 mmol of substrates, which still afforded a good product yield upon isolation (step 1:81%, 1.7 g). Then, the palladium-catalyzed C−N coupling product **4a** from **3ab** and 4-chloro-2-(methylthio)pyrimidine was obtained in 71% yield under the optimized reaction conditions (see the Supporting Information, Table S2). Ultimately, the substitution of the methylthio group in **4a** using excess 2-phenylethanamine afforded the desired product in 92% yield (see the Supporting Information for the synthesis of **5a**).

In summary, we have developed a novel straightforward synthesis of 1,2,3,4-tetrahydronaphthyridines (THNADs). By employing a commercially available catalyst system, a series of *o*-aminopyridyl methanols were efficiently converted in combination with different types of alcohols into various desired products in moderate to excellent isolated yields. Moreover, the utility of the method is demonstrated through a rapid synthesis of a therapeutic product. The synthetic protocol proceeds in an atom- and step-economic fashion together with the advantages of operational simplicity, broad substrate scope, water as the only byproduct, and no need for external reducing reagents, offering a tunable and practicable approach for the construction of this type of structurally unique product. Further investigation utilizing the hydrogen-transfer coupling strategy in other heterocyclic systems as well as the asymmetric synthesis is ongoing in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01976.

Experimental procedures and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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