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Synthesis of Tetrahydropyridine Derivatives through a Modular Assembly Reaction Using 3,4-Dihydropyran as Dual Substrate and Template

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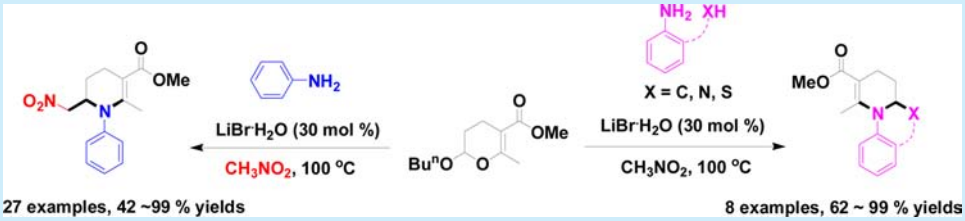
Supporting Information



ABSTRACT: A concise method to synthesize 1,2,3,4-tetrahydropyridines is described that involves the use of 2-alkoxy-3,4-dihydropyran as a modular precursor to react with aniline and a nucleophile. In this method, the heteroatom of the dihydropyran ring was replaced by nitrogen of aniline while the nucleophile attached to its adjacent position. Various druglike polyheterocycles were prepared with this method by using NH_2-containing 1,5- or 1,4-bisnucleophiles.

1,2,3,4-Tetrahydropyridines (THPs), which are an important class of endocyclic enamines, have recently attracted a lot of attention because of their widespread occurrence and their utility as research tools in both pharmacology and food chemistry.[1−5] Some representative examples are aphyllidine,[2] multiflorine,[3] vulgaxanthin ,I[4] and 2,3- or 5,6-dehydrosparteine.[5] Therefore, these THPs are very attractive synthetic targets in the search for an efficient and selective synthesis.[6] The methods so far reported for their synthesis can be categorized into two major strategies: (i) derivatization of ready-made six-membered N-heterocycles, such as hydrogenations of pyridines or dihydropyridines,[7] dehydrogenation of piperidines,[8] and tandem reduction and dehydration of lactam,[9] and (ii) cyclizations of acyclic or cyclic precursors, such as Diels−Alder reactions of 1-azadienes,[10] aza-[3 + 3] cycloaddition of a Büchi Grignard reagent to aziridines,[11] ring-closing metathesis of functionalized olefins,[12] intramolecular amidocarbonylation of *N*-homoallylamides or carbomates,[13] and intermolecular or intramolecular condensations of aldehyde with enamides or amines.[14] An intramolecular C−H activation approach to access THPs has also been developed by Yoon recently.[15] However, most of these methods often involve the use of expensive reagents or catalysts and suffer from lack of simplicity; the yields and selectivities reported are not always satisfactory as well. In view of the increasing importance of the title THPs, a simple, convenient, and environmentally friendly approach is desirable.

This work focuses on the synthesis of THPs with a peg-and-socket strategy. In this method, an oxygen-containing congeneric heterocyle of THP is first preconstructed, which acts as "socket-like substrate". Replacement of the heteroatom with nitrogen of a primary amine, which acts as "peg-like substrate", results in formation of THPs through a modular assembly reaction. Advantages of this approach, if established, will include the following: (i) the use of a six-membered oxygen-containing heterocycle as preconstructed unit endowed a simple reaction system, thus ensuring a concise and selective synthesis of THPs; (ii) water is the byproduct of the heteroatom replacement, which conferred this method a green credential; (iii) all the substituent groups in the preconstructed oxygen-containing congeneric heterocyles can be delivered into the THPs. In order to demonstrate the feasibility, we used a 2-substituted 3,4-dihydropyran as the "socket-like substrate", as they have recently emerged as useful building blocks in organic synthesis.[16]

Our expectations came to reality by subjecting 2-butoxy-3,4-dihydropyran (**1a**) to the conditions of Scheme 1. Nitromethane works here as both solvent and substrate. $LiBr{\cdot}H_2O$ was found to be the best catalyst for this reaction. In the absence of $LiBr{\cdot}H_2O$ catalyst, no reaction occurred (Table S1, Supporting Information). When other Lewis or Brønsted acids were used, the yield of **3a** was decreased dramatically. The present approach for THP synthesis turned out to be quite general (Scheme 1). Anilines with electron-donating groups, such as methyl, methoxy, fluoro, and trifluoromethoxy, participated readily in the condensation reactions, providing the corresponding THPs in good to excellent yields (**3a−g,k,n**). Due perhaps to steric hindrance, *o*-anisidine participated in the reaction reluctantly, and only 65% of

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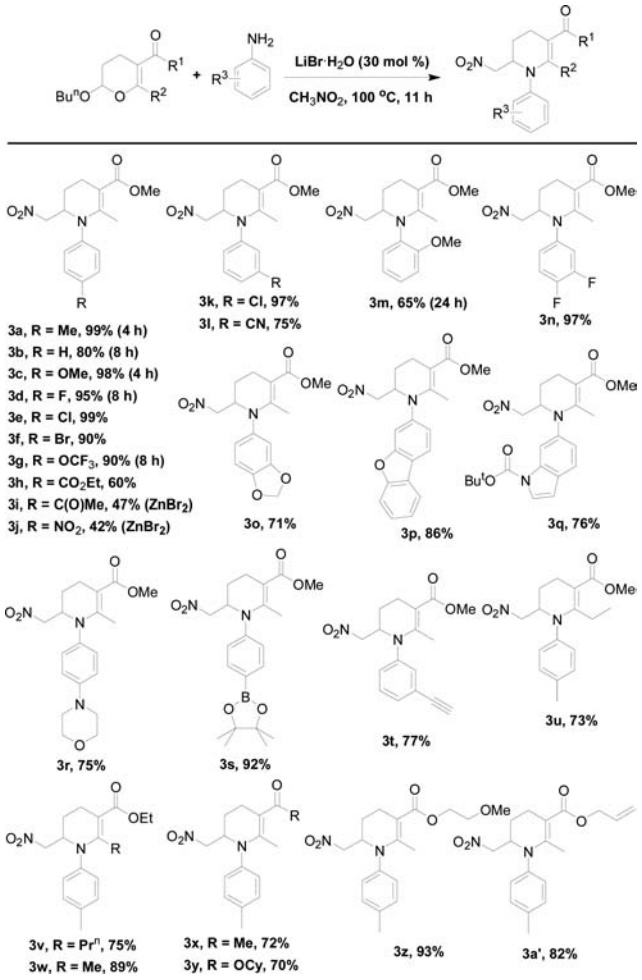
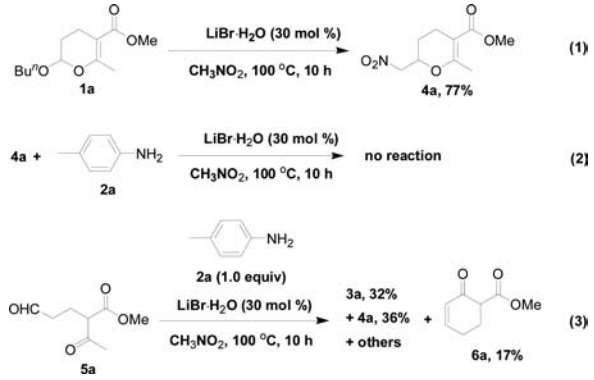
Scheme 1. Synthesis of the Title THPs from 2-Butoxy-3,4-dihydropyrans



yield was obtained after 24 h of reaction (**3m**). Anilines with electron-withdrawing groups, such as ethoxycarbonyl, acetyl, cyano, and nitro, can also be used in the reaction. However, in these cases, LiBr·H_2O catalyst has to be replaced by $ZnBr_2$, even though, the yields obtained are slightly inferior (**3h**−**j**,**l**). Heterocycle-containing anilines, such as 3,4-(methylenedioxy)-aniline, 3-dibenzofuranamine, *N*-Boc-6-aminoindole, and 4-morpholinoaniline can also be smoothly converted without affecting the stability of these moieties (**3o**−**r**). It should be noted that although an electrophilic ring-opening of dihydropyran **1a** with indole has been reported,[16c] the reaction of *N*-(Boc)-6-aminoindole selectively occurred in the aromatic NH_2 group under the present conditions as **3q** was obtained exclusively. 4-Aminophenylboronic acid pinacol ester reacted readily also with **1a** and nitromethane, producing the corresponding product **3s** in 92% of yield. Reaction with 3-ethynylaniline also proceeded very well, and the desired product **3t** was obtained in 77% of yield. Aliphatic amines, such as cyclohexylamine and benzylamine, have also been examined; however, no desired products were obtained. A wide range of 2-butoxy-3,4-dihydropyrans could be successfully used in this reaction (**3u**−**y**). Double bonds and ether groups in the dihydropyran can be uneventfully delivered into the final products without damage to these fragments (**3z** and **3a**′). It is worth noting that the reaction can be effectively scaled up with similar efficiency. For a 20 mmol scale reaction of dihydropyran **1a**, *p*-toluidine, and nitromethane, **3a** was obtained in 94% yield (5.7 g, Scheme S1, Supporting Information).

To gain insights into this reaction, several control experiments were carried out to elucidate the mechanism. First, **1a** was treated in nitromethane in the presence of a catalytic amount of LiBr·H_2O. Compound **4a** was obtained unexpectedly (Scheme 2, eq

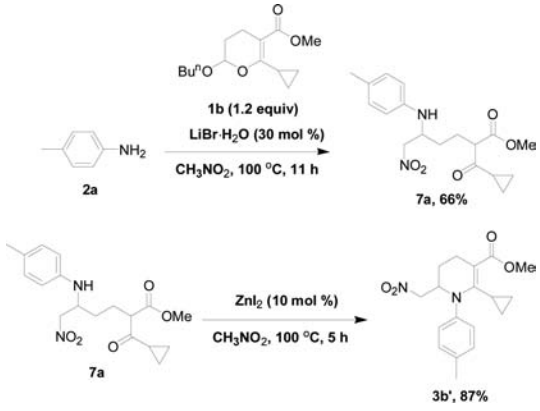
Scheme 2. Control Experiments



1). However, no reaction occurred when **4a** was treated with *p*-toluidine over LiBr·H_2O catalyst (eq 2). It is known that **1a** can be converted into **5a** in the presence of weak Lewis acid.[16b] In nitromethane, **5a** can indeed be converted into **3a** in the presence of *p*-toluidine (eq 3). However, the reaction is not selective as **4a** and an unexpected compound **6a** was obtained along with the formation of some other inseparable products. Under the reaction conditions, **6a** cannot be converted into **3a**.

We have also obtained an unexpected product **7a** when dihydropyran **1b** was used (Scheme 3). Interestingly, **7a** can be readily converted into a THP **3b**′ in the presence of ZnI_2.

Scheme 3. Synthesis of THP 3b′ from Dihydropyran 1b



A DFT calculation about the optimal structure of **1a** revealed that the length of the endocyclic C(2)−O bond is 1.45 Å, which is longer than that of the exocyclic C(2)−O bond, 1.40 Å (see the Supporting Information). This implies that the former C−O bond is more labile. On the basis of all these results, we speculated that the initial event of the reaction was cleavage of the endocyclic C(2)−O bond of **1a** with the aid of LiBr catalyst, which resulted in the formation of a linear oxonium intermediate (**I**). The generated intermediate (**I**) was then trapped by *p*-toluidine, forming another intermediate (**II**). As an indirect proof for this step, a similar compound, **II-a**, was obtained when *p*-toluidine was replaced by *p*-toluenethiol (Scheme S2, Supporting

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Information). The intermediate (**II**) underwent a nucleophilic attack of nitromethane to generate an intermediate (**III**) through an aza-Henry reaction. Finally, **3a** was formed through an intramolecular enamination reaction (Figure 1).

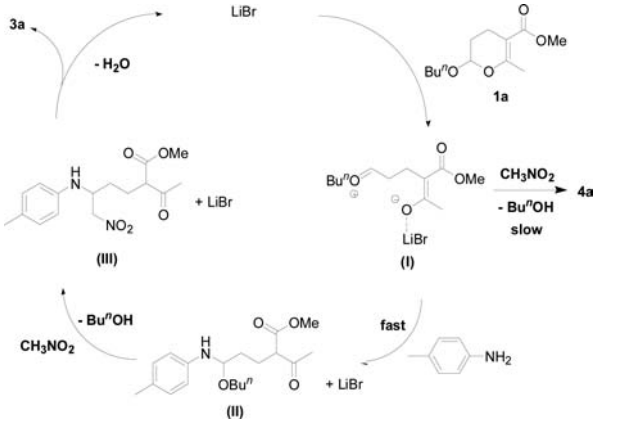


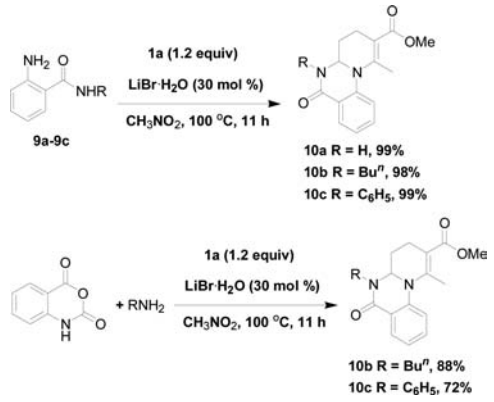
Figure 1. Proposed mechanism.

The results in Scheme 2 also manifested that **5a** is too active under the present conditions, so that synthesizing THP **3a** from **5a** is virtually unpractical.[17] The success of applying dihydropyran **1a** as a precursor for the synthesis of **3a** can be ascribed partially to an adequate rate for generating the intermediate (**I**) that ensures a smooth downstream trapping. If the proposed mechanism in Figure 1 is operative, the present nucleophile, nitromethane, may not be irreplaceable. As we anticipated, a commonly used nucleophile, cyanotrimethylsilane, reacted with **1a** and *p*-anisidine readily in the presence of ZnI_2. With this reaction, a new THP derivative, **8a**, was obtained in 74% of yield (Scheme 4).

Scheme 4. Reaction of 1a, 2b, and TMSCN

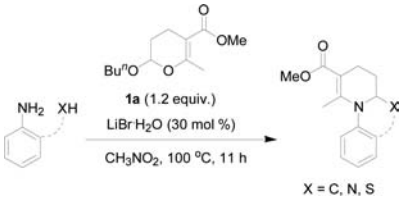
The mechanism also permitted the use of NH_2-containing 1,5-bisnucleophiles, which were amenable to a double cyclization with dihydropyran **1a**. As shown in Scheme 5, anthranilamides **9a−c**, reacted readily with **1a** over LiBr·H_2O catalyst to afford heterocyclic compounds **10a−c**, in excellent yields. The molecules with this skeleton has been identified to have promising TNF-α (tumor necrosis factor-α) and PARP-1 (poly(ADP-ribose)polymerase-1) inhibitory properties.[18] A known method to construct this skeleton involved the use of expensive 2-(1-alkyn-1-yl)benzaldehydes, which were synthesized through palladium-catalyzed C−C coupling reactions.[18a] Our method thus offers a cost-effective route to access this kind of polyheterocycle. In addition, the same compounds can also be synthesized through a three-component reaction of isatoic anhydride **1a** and a primary amine under identical conditions (Scheme 5). This method not only allowed an easy construction of this skeleton starting from simple substrates but also enabled us to use both aliphatic and aromatic amines, thus increasing the potential value of this approach.

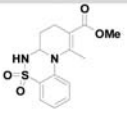
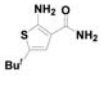
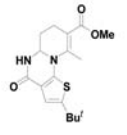
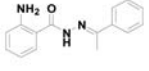
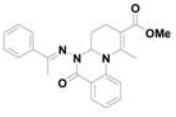
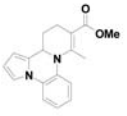
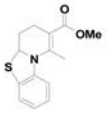
Scheme 5. Reaction of 1a and Anthranilamide or Isatoic Anhydride



Many NH_2-containing bisnucleophiles were then used to react with **1a**, and the results are listed in Table 1. *o*-Aminobenzenesulfonamide **9d** reacted readily with dihydropyran **1a** to afford a double cyclization product **10d** in moderate yield (entry 1). Gewald's amide **9e** can also be converted smoothly under the identical conditions, providing **10e** in good yield (entry 2). Incidentally, a **10e**-like polyheterocycle has been used as a

Table 1. Reaction of Dihydropyran 1a with Different Bisnucleophiles[a]



entry	bisnucleophile		product		yield (%)
1		**9d**		**10d**	65
2		**9e**		**10e**	83
3		**9f**		**10f**	62
4		**9g**		**10g**	87
5		**9h**		**10h**	95

[a]Key: bisnucleophile, 0.30 mmol; **1a**, 0.36 mmol; LiBr·H_2O, 0.09 mmol; nitromethane, 1.0 mL; 100 °C, 11 h.

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precursor for the synthesis of some thiadiazasteroid analogues.[19] Cyclization in a previous method was accomplished by using an expensive 1,5-dicarbonyl compound as precursor. The synthesis with our method displayed evident advantages in terms of both eco-efficiency and structural flexibility. Acetophenone anthraniloylhydrazone **9f** was also proven to be tolerable in this system, with which a hitherto unreported polyheterocycle **10f** was obtained (entry 3). Condensations of **1a** with 1-(2-aminophenyl)pyrrole **9g** proceeded also very well over LiBr·H_2O catalyst (entry 4). It should be noted that skeleton of the generated product **10g** was proved to possess an excellent activity against *Mycobacterium smegmatis*.[20] A reported method to construct this skeleton has to use expensive reagents, such as 5-hexyn-1-ol and $PtCl_4$.[21] A 1,4-bisnucleophile, 2-aminobenzenethiol, was successfully used in this type of double cyclization as well (entry 5). All these examples demonstrated that **1a**-type dihydropyran was indeed an invaluable modular precursor to construct polyheterocycles.

In summary, a method with a modular assembly strategy to synthesize 1,2,3,4-tetrahydropyridines was described that involved the use of 2-alkoxy-3,4-dihydropyran as dual precursor and template. In the presence of catalyst and a suitable nucleophile, the heteroatom of the dihydropyran can be replaced concisely by nitrogen while the nucleophile is attached to its adjacent position. The mechanism of the modular assembly reaction is also discussed. The dihydropyran acted as an aldo-acid bifunctional building block. Various polyheterocycles have also been prepared by using 2-alkoxy-3,4-dihydropyran as a modular substrate to react with NH_2-containing 1,5- or 1,4-bisnucleophiles. This strategy to access nitrogen-containing heterocycles may be applicable in the synthesis of many other molecules, which we are actively pursuing.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure, spectroscopic data of the obtained products, and ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(17) We have also examined many other conditions for synthesizing **3a** from **5a**; however, because of the lack of selectivity, the yields obtained are rather low.

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