De Novo Synthesis of 1,4-Dihydropyridines and Pyridines

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S *Supporting Information*

ABSTRACT: An efficient and general method for the synthesis of 1,4-dihydropyridines and pyridines based on a lithiation/isomerization/intramolecular carbolithiation sequence is reported. This procedure provides an efficient, divergent, and straightforward entry to a wide range of polysubstituted dihydropyridines and pyridines starting from readily available *N*-allyl-ynamides.

Nitrogen-containing heterocycles are subunits found in numerous natural products and many biologically active pharmaceuticals. In 2010, 18 of the top 20 small-molecule drugs contained at least one nitrogen heterocycle.[1] Among these, the pyridine[2] and 1,4-dihydropyridine[3] substructures are among the most prevalent, the most famous ones certainly being the proton-pump inhibitor esomeprazole, the tranquilizer bromazepam, vitamin B6, the calcium agonists felodipine and israpidine, and NADPH (Figure 1). In addition to being among
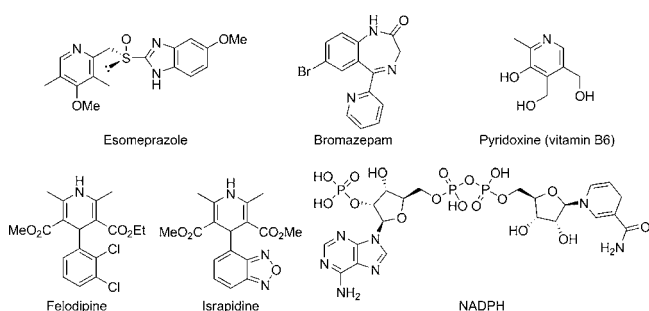

Figure 1. Most representative biologically active pyridines and 1,4-dihydropyridines.

the most prevalent heterocyclic structural units in pharmaceutical and agrochemical targets, they are also especially versatile building blocks, notably for the synthesis of piperidines. As a result, pyridine synthesis has attracted significant efforts for more than 130 years, and while there are many methods for their preparation, mostly based on condensation of amines and carbonyl compounds, cycloaddition reactions, or cross-coupling chemistry, the search for new strategies that offer concise and regiospecific access remains a topic of considerable interest.[4] In

contrast, the synthesis of dihydropyridines has been far less investigated and cannot yet be considered a trivial task. Indeed, besides strategies based on nucleophilic addition to N-activated pyridines, where the chemoselective generation of 1,4-dihydropyridines over their 1,2-isomers is a frequent issue,[5] most methods, including the classical Hantzsch synthesis[6] and related processes,[3] are restricted to the synthesis of dihydropyridines bearing a carbonyl group at the 3-position.[7]

Herein we report a general, efficient, single-step, and divergent synthesis of 1,4-dihydropyridines **6** and pyridines **7** from readily available *N*-allyl-ynamides **1** (Scheme 1).[8,9] On the

Scheme 1. New Approach to 1,4-Dihydropyridines and Pyridines by Deprotonation/Carbolithiation from *N*-Allyl-ynamides
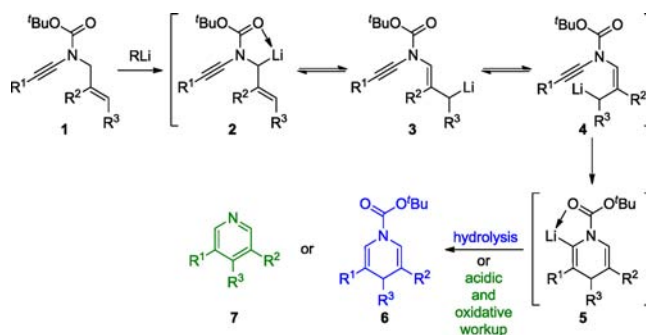

basis of the work of Beak and co-workers on the α-lithiation of Boc-protected amines,[10] we anticipated that the *N*-alkynyl, Boc-protected allylamines **1** would be readily deprotonated with a suitable base, affording a chelation-stabilized allylic organolithium intermediate **2** that might be in equilibrium with the less-stable allyllithium species **3** and **4**.[11] The unique combination of the electronic bias of the triple bond associated with the chelating group of the ynamide moiety would then allow for a highly regioselective 6-endo-dig intramolecular carbolithiation from **4**,[12−14] which would afford the desired 1,4-dihydropyridine **6** or pyridine **7** after simple hydrolysis or oxidative workup, respectively.

To test the feasibility of such a transformation, allylamine **1a**[9b] was treated with 1 equiv of *s*-butyllithium and tetramethylethylenediamine (TMEDA) in tetrahydrofuran (THF) at −78 °C. To our delight, hydrolysis of the reaction mixture after 1 h provided the desired highly sensitive dihydropyridine **6a** as a single product, while treatment with acetic acid and *o*-chloranil[7a] afforded the corresponding pyridine **7a** in 81% isolated yield (Scheme 2).

Scheme 2. Optimized Conditions for the Divergent Synthesis of 1,4-Dihydropyridines and Pyridines
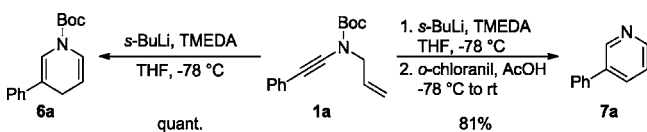
With the appropriate conditions for the lithiation/cyclization sequence and the workup leading to the selective formation of either 1,4-dihydropyridines or pyridines, we next carefully studied the scope of this procedure. The results from these studies are collected in Table 1. A variety of electron-rich and electron-deficient aromatic substituents could be successfully introduced at the C3 position of the dihydropyridine/pyridine ring, the cyclized products being obtained in all cases in good to excellent yields from the corresponding *N*-Boc-*N*-alkynyl-allylamine (Table 1, entries 1−6). Notably, no competitive direct carbolithiation of the ynamide moiety, metalation of the aromatic rings, 5-exo-dig carbolithiation, [1,2]-Boc migration, or isomerization of the 1,4-dihydropyridine could be detected, even in the presence of an additional phenyl substituent at the C4 position (Table 1, entry 14).

The cyclization was also found to proceed smoothly starting from a conjugated enynamine and efficiently produced the corresponding alkenyl-substituted 1,4-dihydropyridine and pyridine (Table 1, entry 7). However, the cyclization of an alkyl-substituted ynamide was found to be more substrate-dependent. Indeed, while a *tert*-butyl group on the starting ynamide was perfectly tolerated (Table 1, entry 8), extensive degradation was observed in the presence of a linear alkyl chain such as an *n*-hexyl substituent (Table 1, entry 9), which is certainly due to competitive lithiation at the propargylic position.

The presence of additional substituents on the starting allylamine had virtually no effect on the outcome of the reaction, allowing for the preparation of various 3,5-disubstituted (Table 1, entries 10−13) and 3,4- disubstituted (Table 1, entries 14 and 15) 1,4-dihydropyridines and pyridines

Table 1. Scope of the Synthesis of 1,4-Dihydropyridines and Pyridines by Lithiation of *N*-Allyl-ynamides[a]


[a]Conditions: *s*-BuLi (1.2 equiv) was added to a solution of **1** (1.0 equiv) and TMEDA (1.1 equiv) in THF (0.5 mol. L⁻¹) at −78 °C. [b]The reaction was quenched with a saturated aqueous solution of ammonium chloride. [c]1,4-Dihydropyridines are especially sensitive to trace acids and oxygen and were obtained in virtually pure form after extraction. [d]The reaction was quenched with acetic acid and *o*-chloranil (3,4,5,6-tetrachloro-1,2-benzoquinone) and stirred at room temperature for 30 min. [e]Yields of the pure, isolated products. [f]Yield on a gram scale. [g]The volatile product was isolated as its hydrochloride salt.

with similar efficiency. Interestingly, the reaction was not limited to the small scale used for the reactions described above (i.e., 1.0 mmol), as illustrated by the gram-scale synthesis of dihydropyridine **6a** and pyridine **7a** (Table 1, entry 1).

This metalation/carbometalation strategy was finally also found to be quite efficient for the synthesis of fused ring systems when started from the corresponding cyclic allylamines, as exemplified by the straightforward synthesis of hexa- and tetrahydroisoquinoline derivatives **9** and **10**, respectively, from **8** (Scheme 3).

Scheme 3. Synthesis of Tetra- and Hexahydroisoquinoline Derivatives
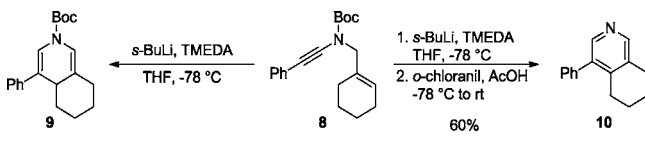
In an effort to introduce an additional substituent at the C2 position of the dihydropyridine/pyridine ring, we next briefly evaluated the possibility of trapping the final stabilized vinyllithium intermediate by an electrophile. With this goal in mind, *N*-allyl-ynamide **1a** was metalated under our standard conditions and treated with deuterated water or methyl iodide. To our delight, the corresponding C2-substituted 1,4-dihydropyridines **11** and **13**, which are especially challenging to prepare using alternative methods, were formed, albeit in modest yields (Scheme 4). The reaction with methyl iodide was

Scheme 4. 2,3-Disubstituted 1,4-Dihydropyridines and Pyridines
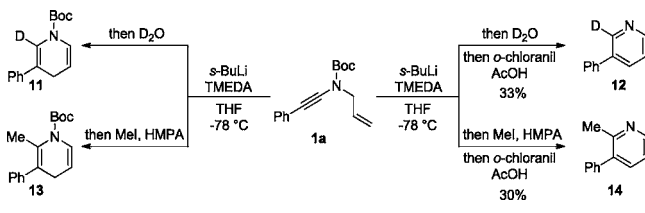
found to be quite sluggish at −78 °C, and the use of additional hexamethylphosphoramide (HMPA) allowed for a cleaner and faster reaction, while a simple increase in the reaction temperature resulted in extensive degradation. In situ aromatization with a combination of *o*-chloranil and acetic acid finally allowed for the synthesis of the corresponding 2,3-disubstituted pyridines **12** and **14**.

In conclusion, we have developed an efficient, general, simple, and modular method to prepare polysubstituted 1,4-dihydropyridines and pyridines. This method employs a high-yielding lithiation/isomerization/carbolithiation reaction from readily available materials and provides, to the best of our knowledge, the first examples of an anionic 6-endo-dig cyclization reaction. The broad availability of the starting ynamides implies that an extensive range of substituents can be selectively incorporated on the (dihydro)pyridine ring. In addition to its use in heterocyclic chemistry, for which we envision great acceptance, this new and simple intramolecular carbometalation extends the chemistry of ynamides and invites additional mechanistic and synthetic studies.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. 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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