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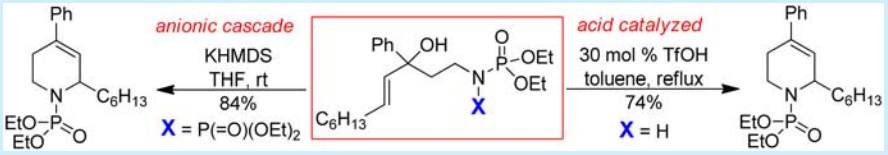
Synthesis of 1,2,3,6-Tetrahydropyridines via Aminophosphate Enabled Anionic Cascade and Acid Catalyzed Cyclization Approaches

Pradipta Das and Jon T. Njardarson*

Department of Chemistry and Biochemistry, University of Arizona, 1306 East University Boulevard, Tucson, Arizona 85721, United States

Supporting Information



ABSTRACT: Two new approaches for forming 1,2,3,6-tetrahydropyridines are reported. Both reactions employ a strategic phosphate substituent on the nitrogen atom. In the presence of an additional phosphate substituent (X = P = $O(OEt)_2$) an anionic cascade can by triggered upon treatment with base. Alternatively, when X = H the same 1,2,3,6-tetrahydropyridine product can be accessed via an acid catalyzed cyclization.

Nitrogen heterocycles are critically important structural components of pharmaceuticals. Our recent comprehensive analysis of US FDA approved small molecules revealed that 59% contain at least one nitrogen heterocycle,[1] which is quite remarkable when compared to the percentage of drugs containing sulfur (26%) or fluorine (13%).[2] Not surprisingly, the vast majority of these ring motifs are five- or six-membered rings, with six-membered nitrogen heterocycles being found in 129 more drugs than five-membered ones. Shown in Figure 1

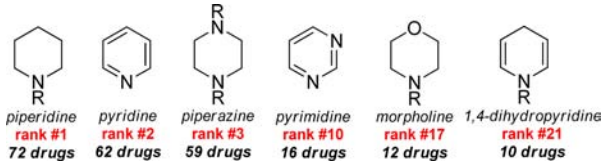
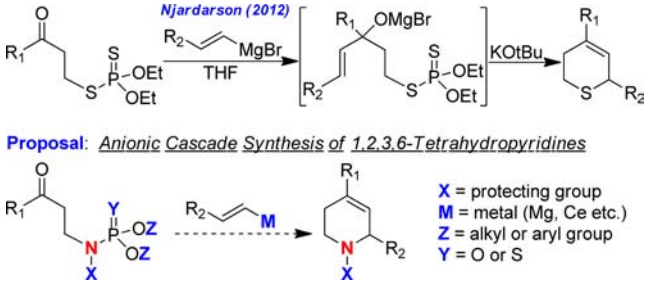


Figure 1. Important six-membered nitrogen heterocycles.

are the most common monocyclic six-membered nitrogen heterocycles found in US FDA drugs ranked in order of their frequency in approved drugs. Impressively, members of this category of nitrogen heterocycles occupy the top three spots of the most commonly employed nitrogen heterocyclic motifs according to our analysis.[1] Given this significance, any new useful method for assembling these nitrogen heterocycles would be of interest.

Our group has focused extensively on the development of new methods for assembling heterocycles.[3] Recently, we reported a new convergent anionic cascade approach for constructing thiopyran products (Scheme 1).[4] This approach relies on the use of a strategic anionic hopping group[5] on the heteroatom (sulfur), which following addition of a carbon nucleophile to either a ketone or an ester affords an alkoxide that participates in a phosphate migration step. The last step in the cascade is a 6-*endo*-*trig* displacement of the phosphate

Scheme 1. Nitrogen Heterocycle Anionic Cascade Proposal



leaving group. We postulated that this anionic cascade strategy could also be used to access the nitrogen heterocyclic variation (1,2,3,6-tetrahydropyridine). Encouraging literature examples describing formation of aziridines[6] and azetidines[7] suggested that such a proposal should be feasible. Our first goal was to identify a synthetically useful nitrogen protecting group (**X**) capable of surviving the conditions of both the addition step and the anionic cascade. In our quest for the optimal reaction conditions other relevant structural parameters would be evaluated (**Y**, **Z**, and **M**).

We soon learned that the nature of the nitrogen protecting group is an important parameter in controlling the outcome of the proposed anionic cascade (Scheme 2). In this underexplored area of investigation, aryl groups have been primarily employed.[5,6] Treatment of the allylic alcohols (**1a**–**c**) with potassium *bis*(trimethylsilyl) amide did indeed result in formation of the expected 1,2,3,6-tetrahydropyridine product, but the protecting group had a significant impact on the anionic cascade. When the nitrogen atom was protected with a toluyl

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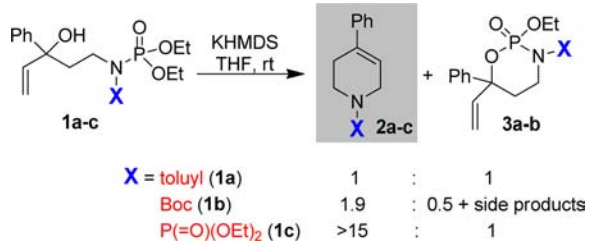
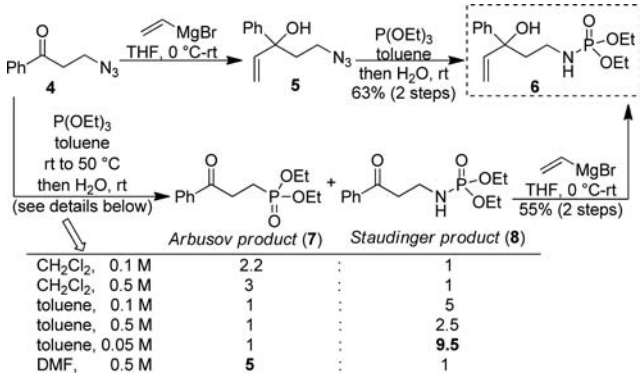
Scheme 2. Choice of Nitrogen Protecting Group is Critical



group the desired product was the minor component. The major product was a phosphorus containing heterocycle, resulting from an incomplete transfer of the phosphate group to the alkoxide.[8] This undesired competing pathway was suppressed slightly when Boc was used as a protecting group, but it was still a side product along with unreacted and deprotected starting material. This undesired pathway could be suppressed using a second phosphate group on the nitrogen atom.

With the ideal protecting group identified we turned our attention to optimizing the synthetic route to the anionic cascade precursor. For synthesis of our thiopyran cascade starting materials we were able to rely on a conjugate addition of a dialkyl dithiophosphoric acid to a Michael acceptor. The equivalent nitrogen nucleophiles (dialkyl phosphoramidate and tetraalkyl imidodiphosphate) did not undergo the Michael reaction. We therefore decided to use an azide,[9] which can be converted into an amino-phosphate using the Staudinger reaction (Scheme 3).[10] Grignard addition to **4** proceeded

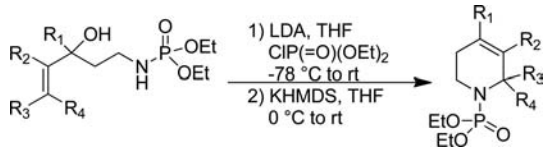
Scheme 3. Aminophosphate Synthesis Challenges

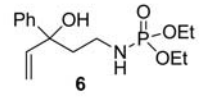
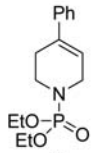
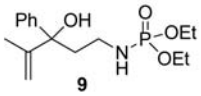
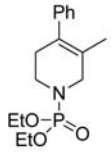
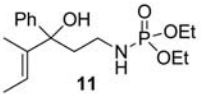
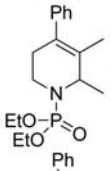
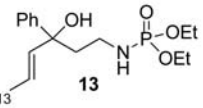
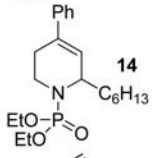
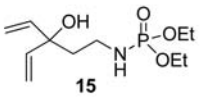
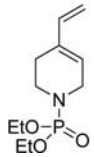


uneventfully to afford **5**, which underwent a smooth Staudinger reaction to form target product **6**. Interestingly, when the order of addition was reversed we encountered unexpected obstacles. In our attempts to convert azido ketone **4** into aminophosphate **8** we observed that the reaction outcome was highly influenced by the choice of solvent and concentration. For example, in methylene chloride or dimethylformamide an Arbusov product **7** was formed as the major product.[11] Use of a less polar solvent such as toluene under dilute reaction conditions allowed suppression of the Arbusov pathway.[12] This was not the only problem, as we soon learned that Grignard addition to **8** was lower yielding and required more equivalents to form **6** than when the alternate route was used.

With a reliable route developed to substrates such as **6** we were now in a position to evaluate the scope of the anionic cascade approach to 1,2,3,6-tetrahydropyridines (Table 1). We

Table 1. Phosphate Mediated Anionic Cascade Results[a]



entry	substrate	product	yield (2 steps)
1		 **2c**	76%
2		 **10**	40%*
3		 **12**	40%*
4		 **14**	25%*
5		 **16**	70%

[a]Yields shown are of isolated product. * = remainder was unreacted starting material.

soon realized that the addition of a second phosphate group to the amine was the more challenging of the two steps. Conditions developed by Hammerschimdt[13] where shown to be most suitable for adding the second phosphate group. Separation of the desired *bis*-phosphates from starting material and side products was challenging, which is why we finally opted for subjecting the crude reaction mixture to the anionic cascade conditions (KHMDS, THF). Yields reported in Table 1 are therefore over two steps. Less substituted substrates (entries 1 and 5) perform remarkably well, affording the products in high yield (76% for **6**, which is 87% per step). Additional substitution on the vinyl group (entries 2−4) results in significantly lower yields. This lower yield is primarily the result of the difficulty in forming the *bis*-phosphate precursor as evident from the reisolation of unreacted starting material.

The challenges associated with the addition of a second phosphate group motivated us to consider alternative applications of the aminophosphate precursors. We postulated that the exact same 1,2,3,6-tetrahydropyridine products could be accessed directly from these same starting materials using an acid catalyzed dehydrative cyclization approach (Scheme 4).[14] This strategy would circumvent the difficulties associated with the anionic cascade. This approach took inspiration from our recently disclosed acid catalyzed oxetane ring expansion reaction,[15] which presumably proceeds via a similar allyl cation intermediate. For this catalytic cascade to be realized, cation

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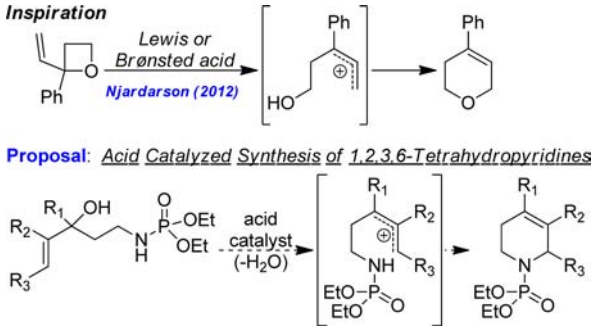
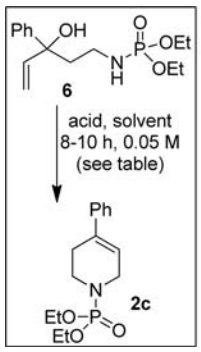
Scheme 4. Redesign: Acid Catalyzed Cyclization Proposal



formation would need to be efficient, the aminophosphate group cyclization would need to be favored over eliminations (diene formation), and the phosphate group would need to survive the reaction conditions.

For our investigation we chose to focus on organic acids (Table 2). We soon learned that this acid catalyzed cyclization

Table 2. Optimization of Acid Catalyzed Cyclization



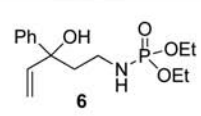
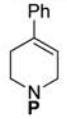
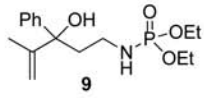
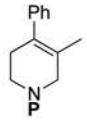
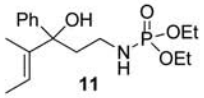
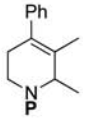
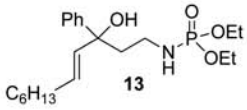
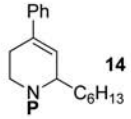
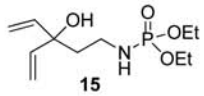
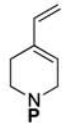
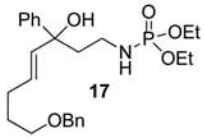
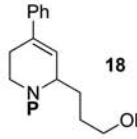
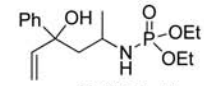
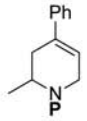
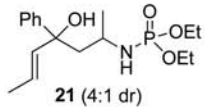
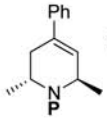
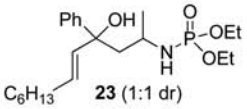
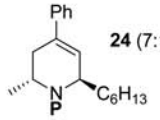
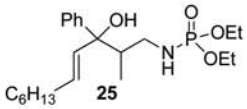
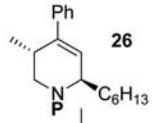
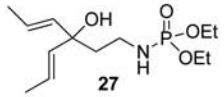
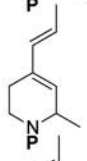
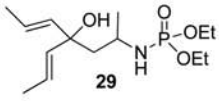
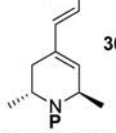
acid	solvent	temp	acid mol %	yield
p-TsOH	THF	rt	30%	0%
p-TsOH	THF	reflux	30%	0%
p-TsOH	toluene	rt	30%	0%
p-TsOH	toluene	reflux	30%	80%
p-TsOH	toluene	reflux	60%	50%
p-TsOH	toluene	reflux	100%	30%
p-TsOH	toluene	reflux	10%	10%
MsOH	toluene	reflux	30%	78%
TfOH	toluene	reflux	30%	82%
TfOH	toluene	rt	30%	10%
TFA	toluene	reflux	30%	0%
AcOH	toluene	reflux	30%	0%
CSA	toluene	reflux	30%	10%

proposal could be realized with sulfonic acids (*p*-TsOH, MsOH, and TfOH) in a nonpolar solvent (toluene). The amount of acid and temperature are critical, with lower molar percentages and refluxing temperatures being preferred. The phosphate group is remarkably stable under these reactions conditions, which afford 1,2,3,6-tetrahydropyridine **2c** in excellent yield.

Using this new acid catalyzed cyclization approach we first revisited the substrates from Table 1 using triflic acid, which we found resulted in simpler purification conditions (entries 1−5, Table 3). In all cases the cyclizations proceeded smoothly and 1,2,3,6-tetrahydropyridine yields were high. In the case of entries 2 and 3 we isolated minor 1,3-diene dehydration pathway products. A benzyl ether tether potentially capable of competing for the allyl cation was shown to be compatible (entry 6). A secondary amino-phosphate group was shown to participate in the cyclization (entry 7).

We next wondered how diastereoselective this new reaction would be if substrates with a secondary phosphate group and terminally substituted olefins were employed. Toward that end we synthesized substrates **21** and **23** as mixtures of diastereomers. Both substrate mixtures cyclized in very good yields to **22** and **24** respectively with the *trans*-diastereomer (shown in Table 3) being the favored stereoisomer in both cases. We consider this is a significant result, which suggests that the size and nature of the phosphate group could be tuned to favor formation of a single diastereomer and potentially a single enantiomer for substrates such as **11**, **13**, **17**, and **27** if a

Table 3. Acid Catalyzed Cyclization Results

entry	substrate	product	yield
1	 **6**	 **2c**	82%
2	 **9**	 **10**	59%
3	 **11**	 **12**	56%
4	 **13**	 **14**	74%
5	 **15**	 **16**	80%
6	 **17**	 **18**	72%
7	 **19** (3.5:1 dr)	 **20**	60%
8	 **21** (4:1 dr)	 **22** (6:1 dr)	65%
9	 **23** (1:1 dr)	 **24** (7:1 dr)	62%
10	 **25**	 **26**	18%
11	 **27**	 **28**	63%
12	 **29**	 **30** (5:1 dr)	56%

conditions: 30% TfOH, toluene, reflux (**P** = P(=O)(OEt)$_2$)

chiral phosphate group could be employed. Interestingly, our calculations and NoE measurements indicated that the alkyl groups prefer to be in a pseudoaxial position to avoid unfavorable interactions with the dialkyl phosphate group. In the case of substrate **25** (entry 10), which could be converted in low yield to **26** as a single diastereomer, we encountered our

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first significant dehydration problem. Divinyl carbinols **27** and **29** also participated successfully, affording useful 1,3-diene containing products (entries 11 and 12) in good yields.

In summary, we report two new approaches for forming 1,2,3,6-tetrahydropyridines, both of which rely on a strategic dialkyl phosphate protecting group for the nitrogen atom. A novel anionic hopping cascade is realized with the aid of a second nitrogen atom phosphate group. Although the initially proposed anionic hopping−cyclization strategy works well, this approach suffers from challenges associated with installing the second phosphate group. This problem can be solved, with the added benefit of one less step, by subjecting the same amino phosphate precursor to an acid catalyzed cyclization. This useful second approach promises to open intriguing new approaches to form chiral 1,2,3,6-tetrahydropyridines.[16]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01937.

Experimental procedures, compound characterization data, and NMR spectra (^{1}H and ^{13}C) (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: njardars@email.arizona.edu.

Notes

The authors declare no competing financial interest.

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(16) The N-phosphate group can be deprotected using acidic or reductive conditions (see Supporting Information for details).

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