Hydroamination

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Synthesis of Pyridines and Pyrazines Using an Intramolecular Hydroamination-Based Reaction Sequence**

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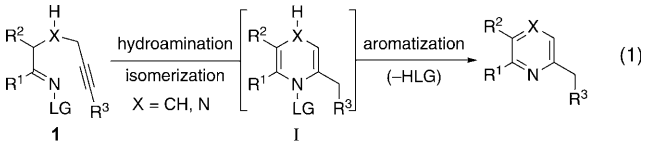
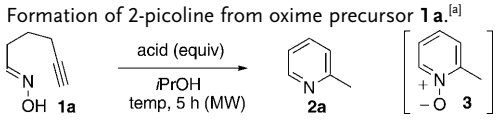
The prevalence and diversity of aromatic nitrogen heterocycles found in natural products and used in medicinal chemistry continues to fuel the development of new methods and strategies for their syntheses.[1] Recently, advances in amination chemistry (e.g., C–H insertions, metal-catalyzed annulations, Buchwald–Hartwig cross-couplings, oxidative aminations, hydroaminations) have enabled routes to diverse aromatic ring systems and offer excellent potential for broad applicability in heterocycle synthesis. Specifically, several hydroamination routes to access unsaturated nitrogen functional groups are emerging.[2] The hydroamination of alkynes using amines (and equivalents thereof) affords enamines or imines reliably, and alkene "hydroiminiumation" reactivity of imines recently reported by Bertrand et al.[3] are representative examples. However, hydroamination routes to aromatic nitrogen heterocycles are rare and have so far been mostly limited to five-membered ring systems.[4] Analogously, metal-catalyzed alkyne annulations have been thoroughly studied,[5] such as indole formation from *o*-alkynylanilines or isoquinoline formation from *o*-alkynylbenzaldimines,[6] but reports of such cyclizations to form pyridines or pyrazines are rare.[7] Herein we report a simple acid-catalyzed hydroamination/isomerization/aromatization sequence leading to pyridines and pyrazines from simple acyclic alkynyl oxime (LG = OH) precursors [Eq. (1)].



1 I (1)

Combining the necessary requirement of using more-oxidized precursors to access aromatic six-membered nitrogen heterocycles, and the prior work showing that intermediates such as **I** aromatize readily to form pyridine rings,[1] we sought to form pyridines and pyrazines by intramolecular hydroamination of substrates such as **1**. Whereas several nitrogen-containing precursors could provide the required oxidation state adjustment (e.g., N–OH, N–SO_2Ar, N–NR_2), oxime precursors were selected since the only by-product of the reaction would be H_2O. Therefore, initial efforts focused on the transformation of precursor **1a** into 2-picoline (**2a**), and selected optimization data is shown in Table 1.

Table 1: Formation of 2-picoline from oxime precursor **1a**.[a]



1a **2a** **3**

Entry	Acid (equiv)	*T* [°C]	Yield of **2** [%][c]
1	none	180	15 (**3**)
2[b]	CH_3CO_2H (1 equiv)	120	0
3[b]	CF_3CO_2H (1 equiv)	120	35
4	CCl_3CO_2H (5 equiv)	120	37
5[b]	CF_3CO_2H (5 equiv)	120	45
6	CF_3CO_2H (5 equiv)	160	80
7	TsOH (1.25 equiv)	160	12
8	TsOH (0.1 equiv)	160	80
9	TsOH (0.02 equiv)	160	99

[a] Reaction conditions: in *i*PrOH (0.1 M), 5 h, in a Biotage Initiator EXP US microwave reactor (MW; 0–400 W). [b] EtOH used as solvent. [c] Determined by NMR analysis. Ts = 4-toluenesulfonyl.

As a continuation of our efforts on Cope-type hydroamination reactivity of hydroxylamines,[8,9] and drawing inspiration from the work of Grigg et al. on intramolecular aza-protio transfer (hydroamination) reactivity of oximes with π bonds,[10] thermolysis of **1a** was attempted (Table 1, entry 1) and resulted in the formation of a modest yield of 2-picoline *N*-oxide (**3**). A variety of approaches were surveyed and control experiments revealed that a stoichiometric amount of TFA (CF_3CO_2H) resulted in the formation of **2a** in modest yield (Table 1, entry 3). Optimization of the reaction conditions using TFA showed that the reaction is more efficient with excess acid (Table 1, entry 5) or at higher temperatures (Table 1, entry 6), which suggests reversible protonation of the oxime precursor and rate-limiting cyclization. In stark contrast, the reaction with TsOH was almost inhibited in the presence of excess acid (Table 1, entry 7), suggesting irreversible protonation of the oxime by TsOH. However, the sequence could be catalyzed efficiently using 2 mol% TsOH at 160°C (Table 1, entry 9). Given that the product **2a** inherently buffers the acidity of the medium, these results illustrate that the nature of the counteranion is crucial for this reactivity.[11]

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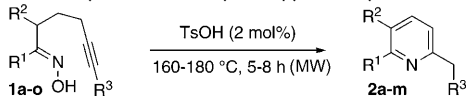
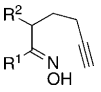
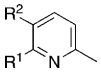
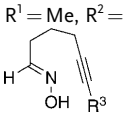
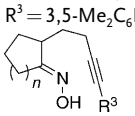
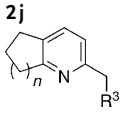
With the optimized reaction conditions in hand, the scope for the formation of pyridines was investigated (Table 2). Gratifyingly, the procedure proved applicable to a variety of aldoximes (Table 2, entries 1 and 8–12) and ketoximes

Table 2: Preliminary substrate scope for pyridine synthesis.[a]



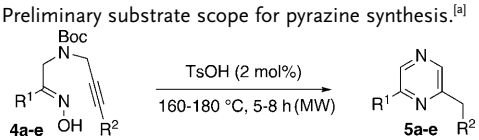
Entry	Substrate	Conditions	Product	Yield [%]
				
1	R^1,R^2 = H (**1a**)	A	**2a**	95
2	R^1 = *n*Bu, R^2 = H (**1b**)	A	**2b**	94
3	R^1 = *i*Pr, R^2 = H (**1c**)	A	**2c**	55
4	R^1 = Ph, R^2 = H (**1d**)	A	**2d**	50
5	R^1 = Ph, R^2 = H (**1d**)	B	**2d**	99
6	R^1 = Me, R^2 = CO_2Me (**1e**)	A	**2e**	72
7	R^1 = Me, R^2 = $CONEt_2$ (**1f**)	A	**2f**	68
				
8	R^3 = Ph (**1g**)	A[b]	**2g**	45
9	R^3 = Ph (**1g**)	B	**2g**	81
10	R^3 = 4-ClC_6H_4 (**1h**)	B	**2h**	83
11	R^3 = 4-$NO_2C_6H_4$ (**1i**)	B	**2i**	91
12	R^3 = 3,5-$Me_2C_6H_3$ (**1j**)	B	**2j**	61
				
13	*n* = 1, R^3 = H (**1k**)	A	**2k**	77
14	*n* = 2, R^3 = H (**1l**)	A	**2l**	90
15	*n* = 3, R^3 = H (**1m**)	A	**2m**	74
16	*n* = 1, R^3 = $SiMe_3$ (**1n**)	A	**2k** (R^3 = H)	92
17	*n* = 3, R^3 = $SiMe_3$ (**1o**)	A	**2m** (R^3 = H)	63

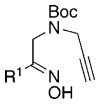
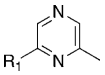
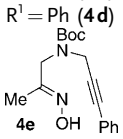
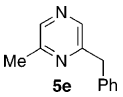
[a] Reaction conditons A: in *i*PrOH (0.1 M) at 160 °C for 5 h (MW). Reaction conditions B: in PhCl (0.1 M) at 180 °C for 8 h (MW). [b] Run at 180 °C.

(Table 2, entries 2–7 and 13–17). The presence of ester and amide functionalities (Table 2, entries 6 and 7) and substitution on the terminal position of the alkyne (Table 2, entries 8–12) are also tolerated. For benzoic oxime **1d** (Table 2, entries 4 and 5) and aryl alkynes **1g–j** (Table 2, entries 8–12), slightly modified reaction conditions proved optimal.[12] Finally, the procedure also allows formation of various bicyclic ring systems (Table 2, entries 13–17), and TMS-substituted alkynes also proved to be efficient cyclization precursors (Table 2, entries 16 and 17) under the reaction conditions.

We then sought to explore if this sequence would allow the synthesis of pyrazine derivatives. Toward this goal, we opted to form the parent cyclization substrate [Eq. (1); X = N] in situ, by acid-catalyzed removal of a *tert*-butoxycarbonyl (Boc) group from the precursor. Remarkably, this strategy resulted in pyrazine formation under similar reaction conditions, as shown in Table 3.

Table 3: Preliminary substrate scope for pyrazine synthesis.[a]



Entry	Substrate	Conditions	Product	Yield [%]
				
1	R^1 = H (**4a**)	A	**5a**	67[b]
2	R^1 = Me (**4b**)	A	**5b**	75
3	R^1 = Et (**4c**)	A	**5c**	81
4	R^1 = Ph (**4d**)	A	**5d**	35[b]
5	R^1 = Ph (**4d**)	B	**5d**	45
6		B		51

[a] Reaction conditons A: in *i*PrOH (0.1 M) at 160 °C for 5 h (MW). Reaction conditions B: in PhCl (0.1 M) at 180 °C for 8 h (MW). [b] Yield determined by NMR analysis.

In summary, we have reported a unified approach for the synthesis of pyridines and pyrazines by an intramolecular hydroamination based sequence. Extensions of this work, including efforts to access other heterocycles, identification of other catalysts and precursors, and the development of milder reaction conditions are in progress and will be reported in due course.

Experimental Section

General procedure for the alkyne cyclizations: An oven-dried 5–20 mL microwave tube was charged with a stir bar, capped with a septum, and purged with argon for 5 min. The alkynyl oxime (1.00 equiv), *p*-toluenesulfonic acid (0.02 equiv), and isopropanol or chlorobenzene (conditions A or B, concentration = 0.1 M) were added to the sealed tube, while keeping it under an argon atmosphere. The septum was removed and the tube was then quickly sealed with a microwave cap and heated at 160 °C for 5 h or at 180 °C for 8 h (conditions A or B). The reaction solution was then cooled to ambient temperature, additionally acidified using trifluoroacetic acid (1.0 equiv), concentrated under reduced pressure, and analyzed by ^{1}H NMR analysis using styrene or 1,4-dimethoxybenzene as an internal standard. The unpurified material was then again concentrated under reduced pressure, cooled to 0 °C, basified using triethylamine (1.5 equiv), and directly purified by silica gel chromatography to give the corresponding products. For details see the Supporting Information.

Complete experimental procedures including preparation of the substrates, solvent scan for the cyclizations of oximes **1a** and **1h**, and spectroscopic characterization of all new products are provided in the Supporting Information.

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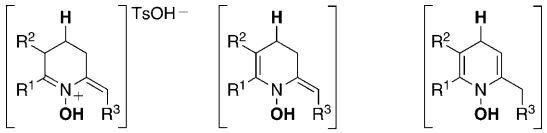
[11] After cyclization, intermediate **II** could be formed after deprotonation (**III**→**IV**) and isomerization (**IV**→**II**). So far, all attempts to observe reaction intermediates by NMR methods have not been fruitful.



III IV II

[12] The use of the milder reaction conditions A is generally optimal for aldoximes (which tend to decompose at higher temperatures) or for cyclization onto terminal alkynes (which are typically more facile). To provide calibration on the usual reaction conditions, substrate **1a** provided the desired pyridine **2a** in 73% yield after 2 h as determined by NMR methods, whereas only a 14% yield was observed after 6 h at 100 °C (NMR methods). By NMR methods, most of the mass balance proved to be unreacted starting material.

