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Direct Synthesis of Pyridine Derivatives

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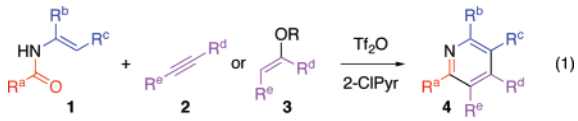
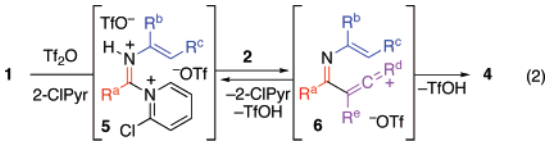
The pyridine substructure is one of the most prevalent heterocycles found in natural products, pharmaceuticals, and functional materials.[1] Many powerful methodologies for the synthesis of these heterocycles rely on condensation of amines and carbonyl compounds or cycloaddition reactions.[2,3] Cross-coupling chemistry also allows introduction of substituents to activated heterocycles.[4] Herein we report a mild, convergent, and single-step procedure for the conversion of readily available *N*-vinyl and *N*-aryl amides[5] to the corresponding substituted pyridines and quinolines, respectively (eq 1).

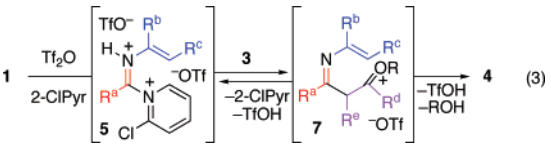
Previously we reported a two-step synthesis of pyridines and a single-step synthesis of pyrimidines from readily available amides.[6] These methodologies were made possible in part because of the recognition of the unique electrophilic activation[6b] of amides with trifluoromethanesulfonic anhydride (Tf_2O)[7] in the presence of 2-chloropyridine (2-ClPyr) as the base additive.[8] A variety of amides were employed in our pyrimidine synthesis using nitriles as σ-nucleophiles.[6b] The current study focuses on the direct condensation of amides **1** with a wide range of π-nucleophiles (**2** or **3**) to provide the corresponding pyridine derivatives **4** (eq 1) in a single step.



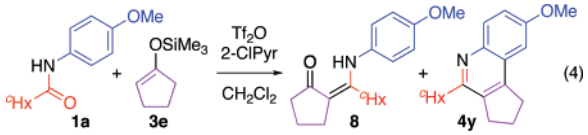
We began our studies by investigating the use of alkoxy and silyloxy acetylenes in direct condensation with amides upon activation with Tf_2O and 2-ClPyr.[6b] Under optimum reaction conditions, these electron-rich π-nucleophiles provided the desired pyridine and quinoline derivatives in one step from the corresponding *N*-vinyl and *N*-aryl amides (Table 1, **4a**−**e**). Similarly, the use of ynamide **2d** and ynamine **2e** readily provided the 4-amino pyridine derivatives in a single step (Table 1, **4f**−**l**). While phenyl acetylene was not sufficiently nucleophilic, the more electron rich derivatives **2f** and **2g** served as π-nucleophiles in this pyridine synthesis (Table 1, **4m**−**o**). Importantly, both electron-rich and electron-deficient *N*-aryl amides can be condensed with π-nucleophiles **2a**−**g** (Table 1, compare **4i** and **4j**).



Based on mechanistic findings in our pyrimidine synthesis,[6b] we propose this single-step pyridine synthesis proceeds by π-nucleophilic addition of acetylenes **2a**−**g** to an activated electrophile **5**[9] followed by expulsion of 2-ClPyr•HOTf and annulation of the highly reactive intermediate **6** (eq 2). The condensation of the terminal alkyne **2f** with an *N*-(4-nitrophenyl) amide gave the desired quinoline **4o** in low yield (Table 1, 42% yield) along with 32% yield of cyclohex-1-yl-3-(4-methoxyphenyl)-propynone, the hydrolysis product of the corresponding alkynyl imine.[10] This observation suggests competitive deprotonation of intermediate **6** (R^e = H) when cyclization to heterocycle **4** is slow.



We next examined the direct condensation of enol ethers with *N*-vinyl and *N*-aryl amides (eq 3). While ethyl vinyl ether (**3a**) could be used as a π-nucleophile when heating is not required (Table 1, **4p** and **4u**), we found triphenylsilyl vinyl ether (**3b**) to provide superior results in more challenging cases (Table 1, **4v**−**x**). The use of excess nucleophile can be beneficial and provides an improved yield of the product (Table 1, **4u**). Importantly, the use of silyl ether **3b** in place of ethyl vinyl ether **3a** eliminates the competitive addition of EtOH, generated in conversion of **7** to **4** (eq 3), to the activated intermediate **5**. Both acyclic and cyclic trimethylsilyl enol ethers can be used in direct condensation with amides (Table 1, **4q**−**t**). However, when desilylation competes with cyclization of oxonium ion **7** (eq 3), the use of more robust silyl enol ether derivatives is preferred. Condensation of amide **1a** with enol ether **3e** at 23 °C predominantly gave the vinylogous amide **8** (eq 4, 78%, **8**/**4y**, >99:1) while heating the reaction mixture at 140 °C for 2 h[11] provided the desired quinoline (eq 4, 53%, **4y**/**8**, >99:1).



Consistent with cyclization of intermediate **7** (eq 3), exposure of amide **8** to the standard reaction conditions provided <10% yield of **4y**. Whereas the use of triisopropylsilyl ether derivatives was not optimal due to slow cyclization, the use of *tert*-butyldimethylsilyl ethers and microwave irradiation extends this chemistry to less reactive amide substrates (Table 1, **4y**−**cc**). The use of enol ethers as the π-nucleophile in conjunction with electron deficient *N*-aryl amides (Table 1, compare **4y**−**aa**) in this azaheterocycle synthesis is less efficient as compared to the use of acetylenic derivatives as the nucleophile (vide supra). Additionally, it should be noted that formamides do not give the corresponding pyridines with alkynyl or alkenyl π-nucleophiles owing to rapid isocyanide formation.

The example shown in eq 5 highlights the greater efficiency of this chemistry when nucleophilic acetylenes are employed in place of enol derivatives. Activation of amide **1m** under standard conditions and the use of silyl enol ether **3b** provided the intramolecular annulation product **9** rather than the expected quinoline product. However, activation of amide **1m** under identical conditions and the use of nucleophile **2d** provided the desired quinoline derivative **4dd** without detectable formation of phenanthridine **9** (eq 5). The synthesis of pyridine **4ee** from the corre-

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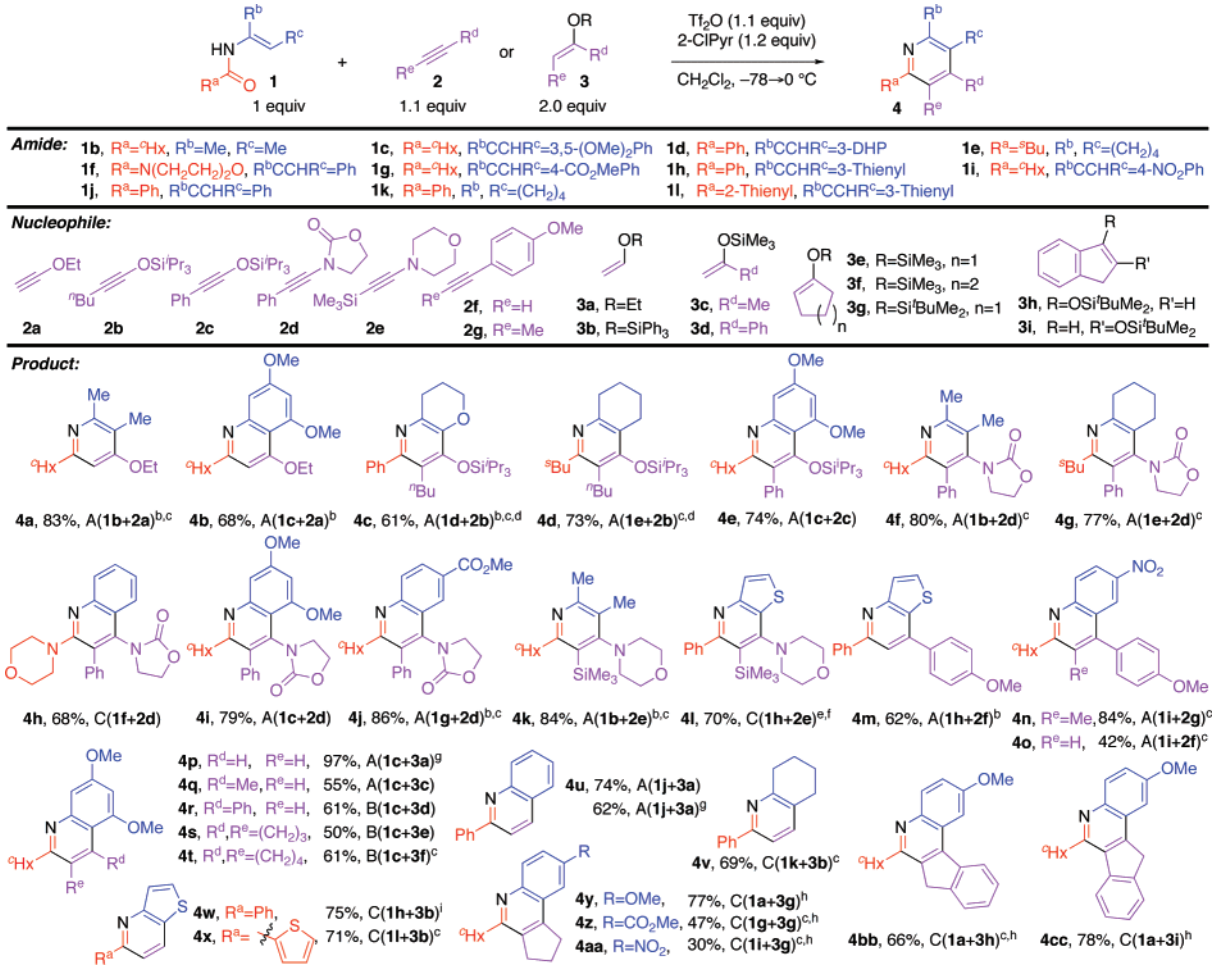
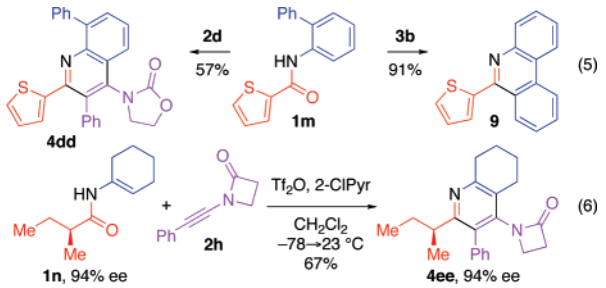
Table 1. Single-Step Synthesis of Pyridine Derivatives by Condensation of π-Nucleophiles with Amides[a]



[a] Average of two experiments. Uniform conditions unless otherwise noted: Tf_2O (1.1 equiv), 2-ClPyr (1.2 equiv), nucleophile (**2** or **3**), CH_2Cl_2, heating: A = 23 °C, 1 h; B = 45 °C, 1 h; C = 140 °C, 20 min. [b] Nucleophile (2.0 equiv). [c] 2-ClPyr (2.0 equiv). [d] Only 10 min at 23 °C. [e] 2-ClPyr (5.0 equiv). [f] Only 1 min heating, nucleophile (3.0 equiv). [g] Nucleophile (1.1 equiv). [h] Heated for 1 h. [i] The yield was 45% using **3a** with condition A.

sponding *N*-vinyl amide **1n** without loss of optical activity (eq 6) is noteworthy and is consistent with our prior observations.[6b]



We describe a single-step and convergent procedure for the synthesis of pyridine derivatives. This chemistry is compatible with a wide range of *N*-vinyl/aryl amides and π-nucleophiles. This methodology alleviates the need for isolation of activated amide derivatives and provides rapid access to highly substituted pyridines with predictable control of substituent introduction. The versatility of this chemistry offers a valuable addendum to methodology for azaheterocycle synthesis.

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Supporting Information Available: Experimental procedures and spectroscopic data for **4a**−**4ee** and X-ray structure of **4j**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) For discussion of the structure and chemistry of **5**, see ref 6b.
(10) See the Supporting Information for details.
(11) Shorter reaction times gave a mixture of amide **8** and product **4y**.

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