Metal-free [2+2+2] cycloaddition of alkynes and nitriles for the construction of pyridine cores

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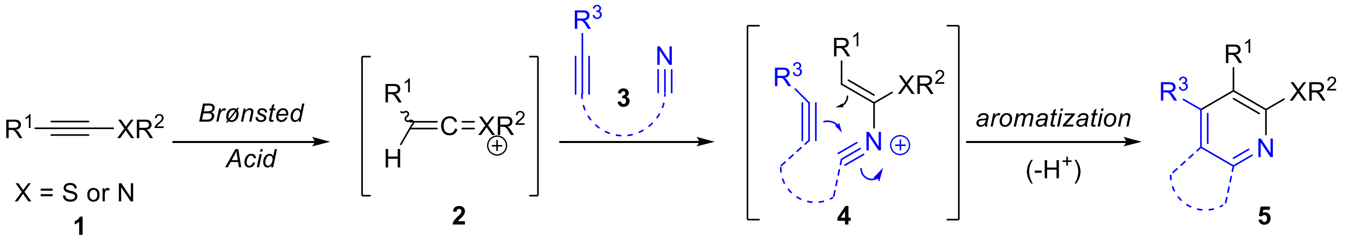
Among the heteroaromatic structures, pyridine plays a central role in the pharmaceutical industry.[1] Over the past decade, a number of synthetic strategies have been documented along with investigations focusing on transition metal- and organocatalysts.[2] Comparing with these strategies, [2+2+2] cycloaddition of simple alkynes and a nitrile offers an efficient, highly atom-economical, straightforward tool to access complex pyridine building blocks.[3] Nevertheless, strategies for pyridine construction by metal-free [2+2+2] cycloaddition are scarce.[4] We envisioned that an alkynyl-nitrile **3** might intercept a stabilized vinyl cation **2**, generated in situ by the addition of TfOH to an electron-rich alkyne **1**.This should form a tethered intermediate **4** in situ, which would be prone to cycloaddition leading to the corresponding pyridine product **5**. This protocol would offer us a metal-free, formal intermolecular [2+2+2] cycloaddition to form substituted pyridine cores.[5]



Scheme 1. Proposed metal free [2+2+2] cycloaddition to generate pyridines.

Herein, we present our results on this novel methodology. The modularity and simplicity of the reagents, combined with the mild reaction conditions and low temperatures conspire to make this an appealing method for the rapid assembly of substituted pyridine structures.[5]

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