Angewandte Chemie International Edition

Cycloaddition

International Edition: DOI: 10.1002/anie.201606604
German Edition: DOI: 10.1002/ange.201606604

Metal-Free Synthesis of Highly Substituted Pyridines by Formal [2+2+2] Cycloaddition under Mild Conditions

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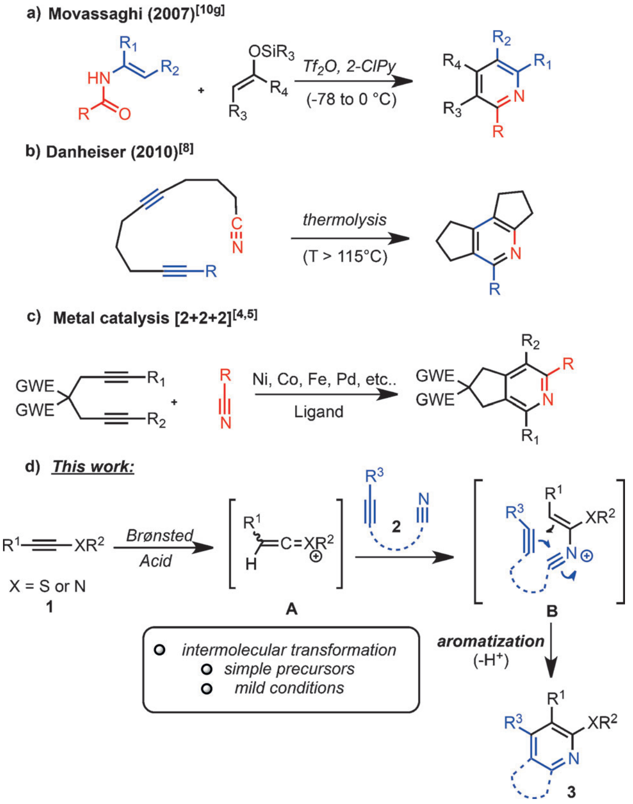
Abstract: *The synthesis of pyridines through direct intermolecular cycloaddition of alkynes and nitriles is a contemporary challenge in organic synthesis. A Brønsted acid mediated formal [2+2+2] cycloaddition of heteroalkynes and nitriles was developed that proceeds under mild conditions. This constitutes a modular approach to highly substituted pyridine cores.*

Among the aromatic heterocycles, the pyridine ring plays a central role in both natural product chemistry and synthetic pharmaceutical chemistry.[1] Consequently, the development of synthetic methods to access these motifs has attracted extensive interest. Condensation reactions, represented by the classical Hantzsch, Chichibabin, and Kröhnke reactions, represent the most widespread approach in the synthetic library.[2] Over the past decade, a number of alternative strategies have also been documented, along with investigations focusing on transition-metal catalysts and organocatalysts.[3]

Nevertheless, when compared to these strategies, the direct [2+2+2] cycloaddition of two readily available alkynes and a nitrile remains perhaps the most atom-economical and straightforward tool to access complex pyridine building blocks.[4,5] The considerable enthalpic and entropic penalty of bringing the three reaction partners together has dictated that most studies on this cross-trimerization reaction have been centered on the development of metal catalysts,[6] whilst chemo- and regioselectivity remains a largely unsolved issue (Scheme 1 c). Among the few metal-free [2+2+2] cycloadditions described,[7] Movassaghi reported an elegant enamide-based strategy employing electron-rich olefins as annulation partners (Scheme 1 a). The uncatalyzed formal cycloaddition of tethered cyanodiynes to fused pyridines by Sakai and Danheiser (Scheme 1 b) probably represents the state of the art. This thermal transformation, based on purely intramolecular cascade reactions, mandates the prior multistep synthesis of the cyanodiyne substrates and requires temperatures higher than 115 °C to proceed.[8a,b]



Scheme 1. Previous milestone by Movassaghi and Danheiser, and a proposed intermolecular [2+2+2] cycloaddition en route to pyridines.

We envisioned that a simple cyanoalkyne (**2**; Scheme 1 d) might reversibly intercept a stabilized keteniminium or ketenethionium (**A**), generated in situ through the protonation of an electron-rich alkyne (**1**),[9–12] to form an active tethered intermediate **B**. Such an intermediate would be poised to undergo a formal cycloaddition, leading to the corresponding pyridine product **3**. Herein, we report a metal-free intermolecular [2+2+2] cycloaddition of simple precursors to access pentasubstituted and highly functionalized pyridine cores that proceeds under mild conditions.

At the onset of our studies, we evaluated the reaction of thioalkyne **1a** with alkynenitrile **2a** (Table 1). Although the mechanistic hypothesis above (Scheme 1) postulates the need for only catalytic amounts of acid, only traces of pyridine product were observed when using 0.2 equiv of TfOH (entry 1). We were pleased to detect product **3a** in 72 % yield when using stoichiometric amounts of acid (entry 2). The amount of thioalkyne and TfOH was lowered to 1.1 equiv, leading to better yields of **3a** (entry 4). Concentration was also shown to play an important role in this process (entry 5).

With suitable conditions in hand, we next examined the scope of this pyridine synthesis by using various thioalkynes

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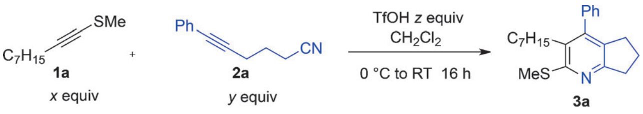
Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201606604.

Table 1: Optimization of the synthesis of **3a**.[a]

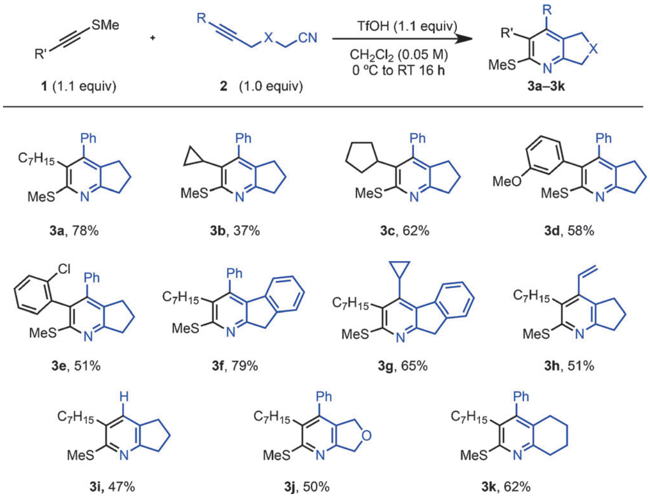


Entry	*x*	*y*	*z*	Concentration	Yield [%][b]
1	1.1	1.0	0.2	0.05 м	Trace
2	1.5	1.0	1.5	0.05 м	72
3	1.1	1.0	1.5	0.05 м	70
4	**1.1**	**1.0**	**1.1**	**0.05M**	**78**
5	1.1	1.0	1.1	0.1 м	62

[a] Reactions were conducted on a 0.2 mmol scale. For details, see the Supporting Information. [b] Yield of isolated product.

1 in conjunction with alkynylnitrile **2** (Scheme 2). Cyclopropyl and cyclopentyl substrates could be incorporated into the pyridine products (**3b** and **3c**) in 37% and 62% yield.

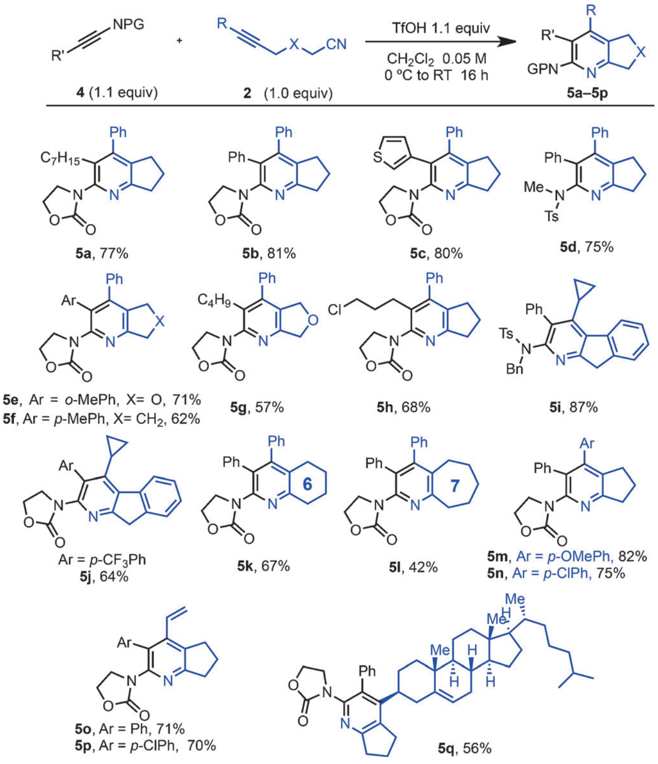
We also tested the reactions of different thioalkynes, in which an aryl appendage carries different substituents in varied positions (**3d**–**3e**).



Scheme 2. Scope of the synthesis of pyridines from thioalkynes.[a] [a] Reactions were conducted on a 0.2 mmol scale. NMR yields with DMAP as internal standard are shown. DCM = dichloromethane.

This method is also well suited for the introduction of an additional arene ring along the tether, as illustrated by the synthesis of tricyclic pyridines **3f**,**g**. A vinyl-substituted alkynylnitrile furnished the corresponding alkenylpyridine **3h** in good yield. A terminal cyanoalkyne can also be employed, and product **3i** was produced in 47% yield. Importantly, the reaction was also applicable to the synthesis of the six-membered-ring-fused pyridine **3k**, as well as ether-linked pyridine **3j**.

Subsequently, a broad range of ynamides **4** were subjected to this formal cycloaddition (Scheme 3) to afford the desired substituted pyridines in good to excellent yields. The reaction proceeds smoothly with alkyl- and (hetero)aryl-substituted ynamides, furnishing the heterocycles **5a**–**c** and **5f**–**h** in good to excellent yields.



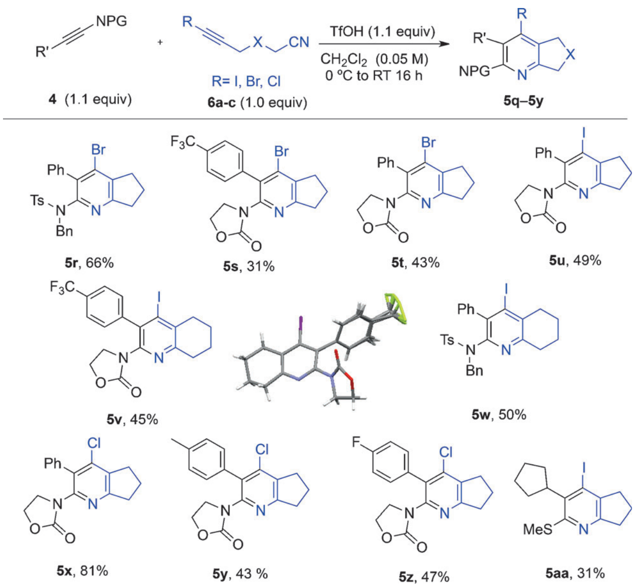
Scheme 3. Scope of the reaction with ynamides.[a] [a] Reactions were conducted on a 0.2 mmol scale. The yield of isolated product is shown. NPG = nitrogen-protecting group.

With a tosyl-protected ynamide, the reaction proceeded smoothly as well (**5d** and **5i**). Heteroatom-tethered cyanoalkynes are also amenable to this transformation, leading to the furopyridines **5e** and **5g**. The 7-membered bicyclopyridine **5l** can also be prepared in moderate yield. Very good yields are observed for cyanoalkynes carrying aryl groups (**5m**,**n**) or vinyl groups (**5o**,**p**), as well as cholesterol derivative **5q**.

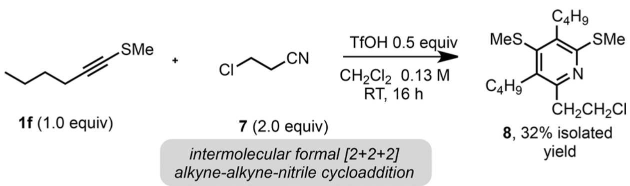
Interestingly, the use of halogen-substituted cyanoalkynes **6** led to halogenated pyridines. As seen in Scheme 4, different halogenated cyanoalkynes carrying I, Br, or Cl reacted productively with different ynamides to furnish pyridine moieties **5r**–**5z** in good to moderate yields. In addition, thioalkynes with the corresponding halogen-substituted cyanoalkynes **6** led to the corresponding pyridine cycle (**5aa**) with a relatively lower yield.

The ultimate challenge in these transformations would be a fully intermolecular [2+2+2] combination of two non-tethered alkynes and a nitrile.[13] Such a transformation is hardly possible in regioselective manner even under transition-metal catalysis.[8c] In the event, we found that product **8** could be synthesized by treating 1.0 equiv of **1f** and 2.0 equiv of nitrile **7** with 0.5 equiv of TfOH at room temperature (Scheme 5).

The products contain reactive handles for further manipulation.[14] In particular, the halopyridines shown in Scheme 4



Scheme 4. Scope of the reaction with halogen-containing cyanoalkynes.[a] [a] Reactions were conducted on a 0.2 mmol scale. The yield of isolated product is shown.

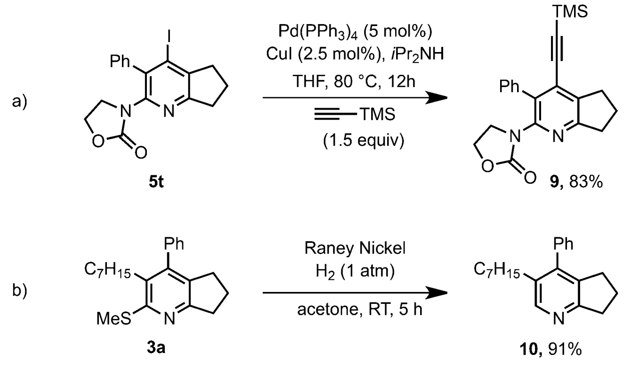


Scheme 5. Intermolecular formal [2+2+2] cycloaddition to form pyridine **8**.

appear to be ideally suited for cross-coupling reactions, as exemplified in Scheme 6a.

Finally, the (methylthio) moiety of pyridines such as **3a** can be readily hydrogenated in the presence of Raney Nickel (Scheme 6b).

In summary, we have developed a Brønsted acid promoted, metal-free formal [2+2+2] intermolecular cycloaddition of heteroalkynes and nitriles that proceeds under mild conditions. The reaction displays generality and a broad substrate scope with respect to both reaction partners. The modularity and simplicity of the reagents, combined with the mild reaction conditions and low temperatures, conspire to make this a powerful and appealing method for the rapid assembly of substituted pyridine structures.



Scheme 6. Derivatization of products: cross-coupling and reduction. THF = tetrahydrofuran, TMS = trimethylsilyl.

Acknowledgements

We are grateful to the University of Vienna, the Deutsche Forschungsgemeinschaft (Grant MA 4861/1-2) and the ERC (StG 278872, FLATOUT) for support of this work. Crystallographic analysis by Ing. A. Roller (U. of Vienna) is acknowledged.

Keywords: alkynes · cycloaddition · heteroalkynes · nitriles · pyridines

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[14] Attempts to effect direct cross-coupling of the sulfur substituent on 2-thiomethylpyridine derivatives were not successful.

Received: July 7, 2016
Revised: July 22, 2016

Communications

Cycloaddition

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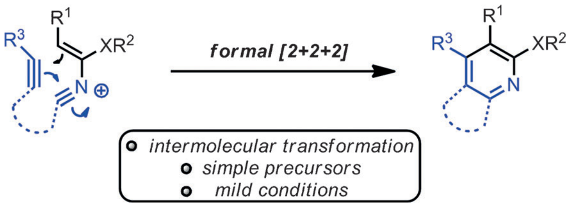

When 2 + 2 + 2 = π: The synthesis of pyridines through direct intermolecular cycloaddition of alkynes and nitriles is a contemporary challenge in organic synthesis. A Brønsted acid mediated formal [2+2+2] cycloaddition of heteroalkynes and nitriles was developed that proceeds under mild conditions. This constitutes a modular approach to highly substituted, densely functionalized pyridine cores.