Journal of Laboratory Chemical Education 2023, 11(1): 11-14
DOI: 10.5923/j.jlce.20231101.03

# Studies of Tethering Atom Effect in Cobalt-catalyzed Alkyne/Nitrile Cyclization Reactions towards the Synthesis of Tetrahydronaphthyridines with Shown Significant Activities against *Mycobacterium Tuberculosis*

**Ya Zhou*, Daniel Encarnacion, Connor Sullivan, Vivian Tam**

Department of Chemistry and Physics, Salem State University, Salem, MA, United States of America

**Abstract** Nitrogen-containing small heterocyclic molecules have drawn great attention in the design of biologically active molecules in pharmaceutical industry. We have been interested in the synthesis of nitrogen- containing 5,6,7,8-tetrahydro-1,6-naphthyridines. Recently, several molecular libraries of this 6,6-membered bicyclic tetrahydronaphthyridines have been synthesized and have shown significant activities against *Mycobacterium Tuberculosis.* We noticed that these reported microwave-promoted cobalt-catalyzed intermolecular alkyne/nitrile [2+2+2] cyclization reactions gave only poor to modest yields. These modest reaction yields are suspected to be caused by a probable unfavorable chelation of the nitrogen atom of the cyclization precursor with the cobalt catalyst. This chelation may retard the formation of the key cobaltacycle reaction intermediate. In this study, we investigate the effect of different tethering atoms such as nitrogen, carbon and oxygen in this cyclization reaction using a 5,6-membered bicyclic model study system. We observe that lower cyclization reaction yields are obtained from the nitrogen-tethered precursors compared to the other precursors. Our next step is to elucidate the reason for low-yielding using the real 6,6-membered bicyclic system. We plan to protect the nitrogen atom in cyclization precursor with different protecting groups to see if the protected nitrogen-tethered precursors can provide higher alkyne/nitrile [2+2+2] cyclization reaction yields.

**Keywords** Tetrahydronaphthyridine, *Mycobacterium Tuberculosis*, High atom economic synthesis, Cobalt-catalyzed, Alkyne/Nitrile, [2+2+2] Cyclization, Tethering atom effect

## 1. Introduction

Small polyfunctionalized heterocyclic molecules have attracted great attention in the design of biologically active compounds in the drug discovery process as well as in the isolation and structural identification of biological macromolecules [1-4]. Many natural and unnatural heterocyclic molecules inhibit the progression of the cell cycle through binding to the proteins required for cell division. In this way, heterocyclic small molecules can also be employed as tools to understand cell cycle events. Among these heterocycles, nitrogen-containing heterocycles have received increasing attention in the past two decades. The nitrogen-containing heterocycle is not only able to readily accept or donate a proton, but it can also easily establish a diverse weak interactions with a variety of enzymes and receptors in biological targets through hydrogen bindings, dipole-dipole interactions, hydrophobic effects, van der Waals forces and π-stacking interactions. FDA databases reveals nearly 75% small-molecule drugs contain a nitrogen heterocycle [5].

Fully aromatized naphthyridines are nitrogen-containing heterocyclic molecules defined as a group of six isomeric heterocyclic systems with two fused pyridine rings having different relative positioning of the nitrogen atoms (**Figure 1**). This general class of compounds has received great interest from organic chemists because of the exceptionally broad range of biological activities displayed by some of its members [6-7].

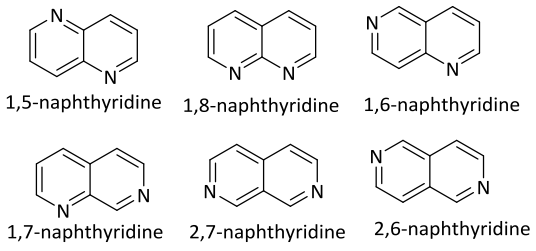



**Figure 1.** Naphthyridine isomers

* Corresponding author:
yzhou2@salemstate.edu (Ya Zhou)
Received: May 31, 2023; Accepted: Aug. 2, 2023; Published: Aug. 12, 2023
Published online at http://journal.sapub.org/jlce

In contrast to the fully aromatized naphthyridines, their tetrahydronaphthyridines derivatives (**Figure 2**) have been relatively unexplored, in terms of both synthetic approaches and bioactivities. Contributing to this lack of studies is the limited approaches for their preparations.

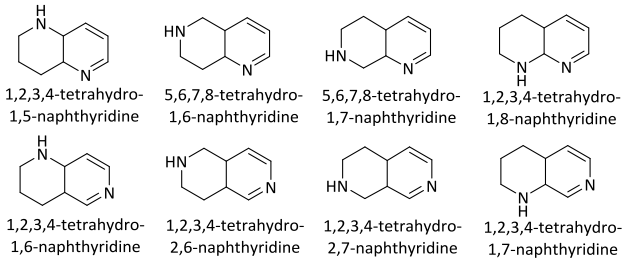



**Figure 2.** Tetrahydronaphthyridine isomers

Until recently, a synthetic methodology was developed for the synthesis of 5,6,7,8-tetrahydro-1,6-naphthyridines and related heterocyclic molecules through cobalt-catalyzed microwave-promoted alkyne/nitrile [2+2+2] cyclization reaction (**Figure 3**) [8].

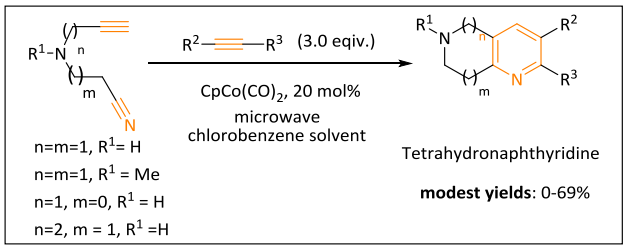



**Figure 3.** Modest yields observed in the reported intermolecular [2+ 2+ 2] alkyne/nitrile cyclization reactions

More recently, several molecular libraries of 5,6,7,8-tetrahydro-1,6-naphthyridines were synthesized using this efficient cyclization reactions. Three of the tetrahydro-naphthyridines (**Figure 4**) have shown significant activities against *Mycobacterium Tuberculosis* [9].

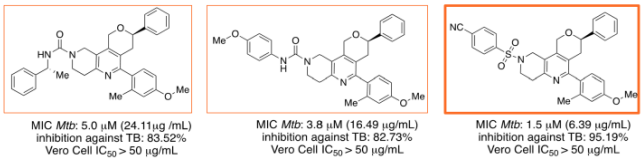



**Figure 4.** Three 5,6,7,8-tetrahydro-1,6-naphthyridines with inhibition against *Mycobacterium Tuberculosis*

Atom economy is one important common measure of how "green" a reaction is. This cobalt-catalyzed microwave-promoted alkyne/nitrile cyclization reaction is a 100% atom economic reaction and it is considered as a high atom economic synthesis. However, this interesting reaction only provided poor to modest yields (0-69%) as shown in **Figure 3**. Given the obvious advantages of this synthesis and the interesting biological activities of 5,6,7,8-tetrahydro-1,6-naphthyridines, we become interested in investigating the possible cause of these low yields and providing more insight into this reaction.

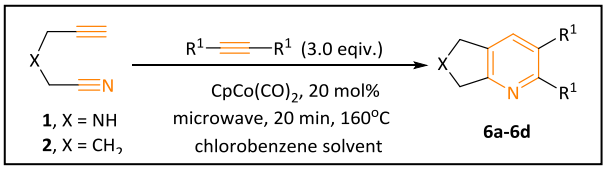
# 2. Experimental

The reported modest yields of the [2+2+2] cyclization reactions are suspected to be caused by a probable unfavorable chelation of the nitrogen tethering atom of the cyclization precursor alkynyl nitrile with the cobalt catalyst, which may retard the formation of the key cobaltacycle reaction intermediate. To test our hypothesis, we synthesized a series of cyclization precursors with different tethering atoms as a model study to investigate the effects of different tethering atoms in this type of cyclization reactions. Even though these model reactions only provided the 5,6-membered bicyclic products **6a-6d** and **7a-7f** as shown in **Scheme 1** and **Scheme 2**, not the 6,6-membered bicyclic products 5,6,7,8-tetrahydro-1,6-naphthyridines, these studies still helped us to understand the tethering atom effect in this type of cobalt-catalyzed [2+2+2] cyclization reactions.

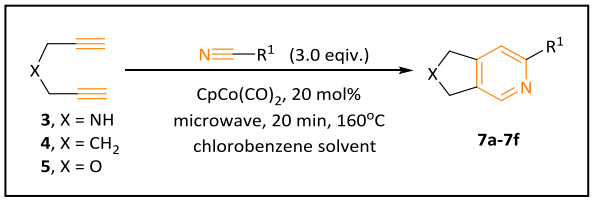
Our future plan is to synthesize the nitrogen tethered precursor of the 5,6,7,8-tetrahydro-1,6-naphthyridine and protect the precursor with different nitrogen protecting groups. Using the real system, we can exam if the protected precursors can provide tetrahydronaphthyridine products in better yields.

## 2.1. Experimental Design

The alkynyl nitrile precursor **1** with nitrogen tether and the percussor **2** with carbon tether were prepared according to the literature procedures [8]. The cyclization reactions of these precursors with another alkyne partner were tested (**Scheme 1**). These two precursors **1** and **2** were reacted with the same set of alkyne partners respectively. One alkyne partner has an electron donating group, while the other one has an electron withdrawing group. These reaction results are discussed in Result and Discussion section.




**Scheme 1**




**Scheme 2**

To further probe the tethering atom effect, the carbon, the oxygen and the nitrogen linked diynes **3**, **4** and **5** were also prepared according to the literature procedures [10]. Under the same reaction conditions as **Scheme 1**, these three precursors were reacted with the same set of nitrile partners respectively as shown in **Scheme 2**. One of the nitrile

partners contains an electron donating group, while the other one contains an electron withdrawing group. These reaction results are discussed in Result and Discussion section.

### 2.2. Procedure

General procedure of the intermolecular microwave-promoted cobalt-catalyzed alkyne/nitrile [2+2+2] cyclization reaction: all reactions were run in sealed 10 mL thick-walled microwave pressure tubes (CEM Corporation) purged with nitrogen in a CEM Discover SP microwave synthesizer (**Figure 5**). For the cyclization reactions in **Scheme 1**, a chlorobenzene solution of alkynyl nitriles **1** or **2** (1.0 eq) and alkynes (3.0 eq) were added into the microwave tube, then the catalyst $CpCo(CO)_2$ (0.2 eq, 20 mol%) was added into the mixture. For the cyclization reactions in **Scheme 2**, a chlorobenzene solution of diynes **3**, **4** or **5** (1.0 eq) and benzonitriles (3.0 eq) were added into the microwave tube. The resulting solution was subjected to microwave irradiation at 300 W, 160℃ for 20 min with stirring.

After microwave irradiation, the reaction crude mixture was gravitationally filtered through celite plug, the celite plug was then washed with additional ethyl acetate (EtOAc). The volatile components were removed in vacuo and the crude residue was purified by flash chromatography to yield the cyclization product.

**Figure 5.** CEM Discovery SP microwave synthesizer, microwave pressure tube, celite plug and flash chromatography

## 3. Results and Discussion

The results of the cyclization reactions in **Scheme 1** were summarized in **Table 1**. As we expected, the intermolecular cyclization reactions of the carbon-tethered alkynyl nitrile **2** with alkyne partners provided products **6a** and **6c** in much better yields (90% in entry **1** and 95% in entry **3**) compared to the nitrogen-tethered alkynyl nitrile **1** (**6b**, 24% in entry **2**; **6d,** 65% in entry **4**). Furthermore, we observed the similar trends in both the electron donating alkyne substate (entries **1** and **2**) and the electron withdrawing alkyne substrate (entries **3** and **4**).

The results of reactions in **Scheme 2** were summarized in **Table 2**. The intermolecular cyclization reactions of carbon and oxygen-tethered diynes **4** and **5** were compared to the nitrogen-tethered diyne **3.** In entries **1**-**3**, diyne precursors reacted with benzonitrile partner containing electron donating group. Again, as we expected, the carbon and oxygen-tethered diynes **4** and **5** provided much better yields (**7b**, 92% in entry **2** and **7c**, 69% in entry **3**) compared to the nitrogen-tethered diyne (**7a**, 33% in entry **1**).

In entries **4**-**6**, diyne precursors reacted with benzonitrile partner containing electron withdrawing group. The carbon-tethered diyne **4** provided better yields (**7e**, 91% in entry **5**) compared to the nitrogen-tethered diyne (**7d**, 75% in entry **4**). Unfortunately, we were not able to isolate the product **7f** through flash chromatography.

**Table 1.** Comparison of Cyclizations of Carbon-tethered Alkynyl Nitrile with Nitrogen-tethered Alkynyl Nitrile

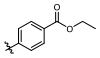
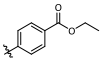
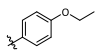
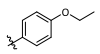
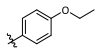
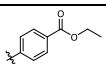
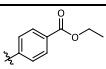
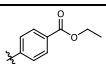
| Entry | Alkynyl Nitrile | Alkyne $R^1$ group | Product & Yield (%) |
|---|---|---|---|
| 1 | carbon tethered **2** |  | **6a**, 90 |
| 2 | nitrogen tethered **1** |  | **6b**, 24 |
| 3 | carbon tethered **2** |  | **6c**, 95 |
| 4 | nitrogen tethered **1** |  | **6d**, 65 |

**Table 2.** Comparison of Cyclizations of Carbon and Oxygen-tethered Diynes to Nitrogen-tethered Diyne

| Entry | Diyne | Nitrile $R^1$ group | Product & Yield (%) |
|---|---|---|---|
| 1 | nitrogen tethered **3** |  | **7a**, 33 |
| 2 | carbon tethered **4** |  | **7b**, 92 |
| 3 | oxygen tethered **5** |  | **7c**, 69 |
| 4 | nitrogen tethered **3** |  | **7d**, 75 |
| 5 | carbon tethered **4** |  | **7e**, 91 |
| 6 | oxygen tethered **5** |  | **7f** * |

* **7f** was unable to be separated by flash chromatography.

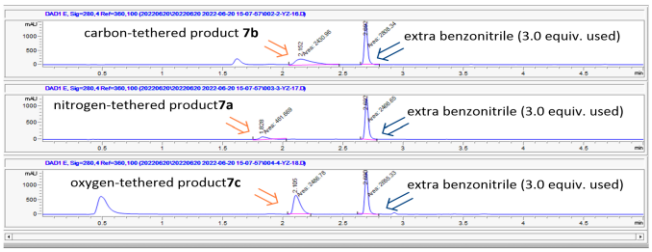



**Figure 6.** Crude LC-MS data for entries **1**-**3** in Table **2**

As illustrated in **Figure 6**, the crude LC-MS data of entries **1**-**3** in **Table 2** also demonstrated that the nitrogen tethering precursor gave the lowest yield of product **7a** compared to the carbon and oxygen-tethered precursor products **7b** and **7c**.

## 4. Conclusions

This alkyne/nitrile intermolecular [2+2+2] cyclization reaction is a high atom economic reaction. It provides us an efficient way to synthesize this rarely addressed biologically active 5,6,7,8-tetrahydro-1,6-naphthyridines. The results obtained from these studies supported our hypothesis that the previously reported modest yields of the cyclization reactions were related with the existence of the nitrogen tethering atom. After replacing the nitrogen tethering atom of the reaction precursor with carbon or oxygen tethering atoms, our model cyclization reactions proceeded in higher yields.

Our continuing effort will be focusing on synthesizing the nitrogen-tethered processor of 5,6,7,8-tetrahydro-1,6-naphthyridine and further improving the cyclization reaction yield in real system by protecting the nitrogen atom with different protecting groups.

## ACKNOWLEDGEMENTS

We thank Salem State University for funds and consumables associate with this work. Special thanks to Jessica Christel for ordering, providing us with the materials and equipment.

## REFERENCES

[1] Bemis, G. W.; Murcko, M. A. *J. Med. Chem.* 1996, *39*, 2887.

[2] Hinterding, K.; Alons-Diaz, D.; Walddmann, H. *Angew. Chem. Int. Ed. Engl.* 1998, *37*, 688.

[3] Hung, D. T.; Jamison, T. F.; Schreiber, S. L. *Chem. Biol.* 1996, *3*, 623.

[4] Schreiber, S. L. *Bioorg. Med. Chem.* 1998, *6*, 1127.

[5] Kerru, N.; Gummidi, L. Maddila, S; Gangu, K. K; Jonnalagadda, S.B. *Mol.* 2020, *25*, 1909.

[6] Gordon, C. P.; Griffith, R.; Keller, P. A. *Med. Chem.* 2007, *3*, 199.

[7] Appelbaum, P. C.; Jacobs, M. R. *Curr. Opin. Microbiol*. 2005, *8*, 510.

[8] Zhou, Y; Porco, J.A.; Snyder, J. K. *Org. Lett.* 2007, *9*, 393.

[9] Zhou, Y.; Beeler, A. B.; Snyder, J. K. *J. Comb. Chem.* 2008, *10*, 534.

[10] Rees, M. S.; Van Kuijik, F. J. G. M.; Siakotos, A. N.; Mundy, B. P. *Synth. Commun.* 1995, *25*, 3225.