Organic LETTERS

Letter

pubs.acs.org/OrgLett

Dehydrogenative [2 + 2 + 2] Cycloaddition of Cyano-yne-allene Substrates: Convenient Access to 2,6-Naphthyridine Scaffolds

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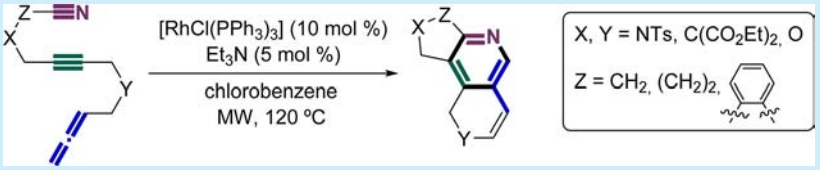
Supporting Information



ABSTRACT: A rhodium-catalyzed [2 + 2 + 2] cycloaddition of cyano-yne-allene scaffolds followed by a dehydrogenative process enabling the direct synthesis of unsaturated pyridine-containing compounds that can be conveniently converted to 2,6-naphthyridine derivatives is reported.

Naphthyridine[1] derivatives have received significant attention due to their broad spectrum of biological activity. Among the six isomeric naphthyridines, 2,6-naphthyridine, the last to be synthesized in the series, has been found to have promising medicinal properties and is currently under investigation in HIV[2] and cancer[3] research (Figure 1).

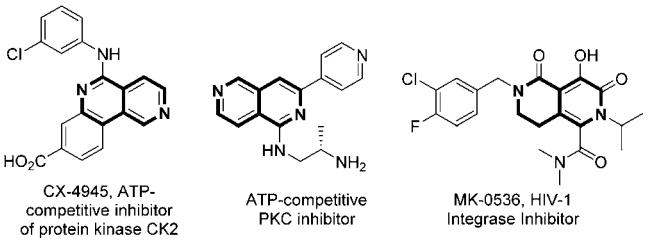
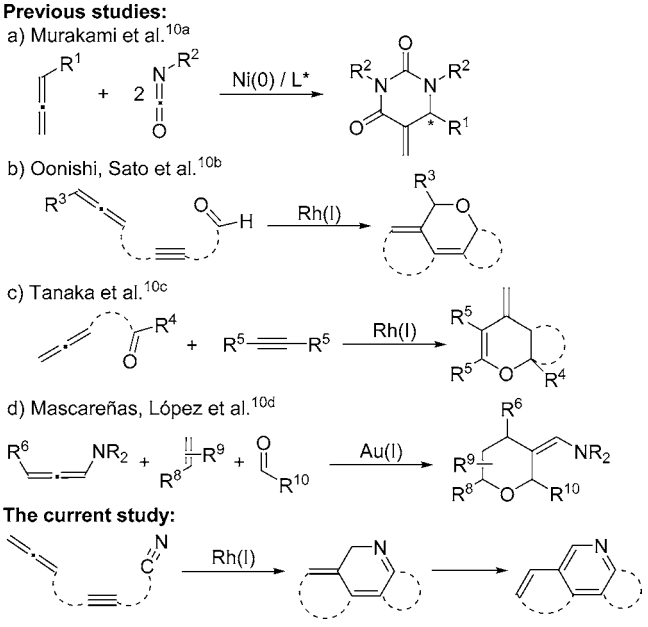


Figure 1. Biologically active 2,6-naphthyridine scaffolds.

The development of sustainable transformations permitting readily available precursors to be converted to relevant products is an interesting goal in organic synthesis. The [2 + 2 + 2] cycloaddition reaction involving two alkynes and one nitrile is an excellent option for the synthesis of pyridines.[4] This atom economic strategy has been efficiently used for the synthesis of mono- and polycyclic pyridine-containing molecules.[5] More recently, the [2 + 2 + 2] cycloaddition reaction in which two nitriles have been involved to yield pyridazine[6] and pyrimidine[7] cores has also been reported. Allenes, which are recognized as very attractive unsaturated partners in metal-catalyzed cycloaddition reactions,[8] can also be involved in [2 + 2 + 2] cycloaddition reactions.[9] Among the studies in this field, allenes have only been reacted with heterounsaturated partners in a few examples (Scheme 1).[10] The first, by Murakami et al., describes the nickel-catalyzed [2 + 2 + 2] cycloaddition of two molecules of isocyanate and one molecule of allene to enantioselectively afford

Scheme 1. [2 + 2 + 2] Cycloaddition Reactions of Allenes and Heterounsaturation Partners



dihydropyrimidine-2,4-diones.[10a] Three other papers have described [2 + 2 + 2] cycloadditions involving allene and aldehyde moieties to afford pyran derivatives that are completely intramolecular,[10b] partially intramolecular,[10c] or fully intermolecular.[10d]

A [2 + 2 + 2] cycloaddition reaction involving both allenes and nitriles is unprecedented, and to the best of our knowledge, only

Received: March 27, 2015
Published: June 11, 2015

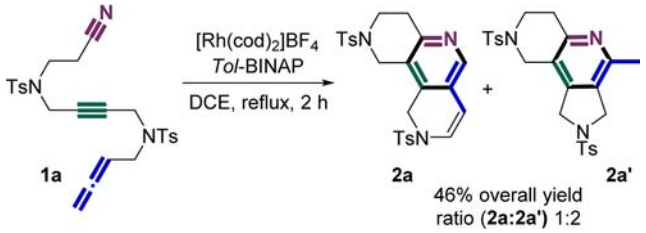
DOI: 10.1021/acs.orglett.5b01554
Org. Lett. 2015, 17, 2882–2885

two examples of cycloadditions involving both an allene and a cyano group have been reported. In the first, Danheiser et al. described a formal, metal-free [2 + 2 + 2] cycloaddition to form pyridines that takes place by a propargylic ene reaction, furnishing a vinylallene that subsequently participates in a Diels–Alder reaction with a tethered cyano group.[11] In the other, Mukai et al. describe a rhodium(I)-catalyzed intramolecular carbonylative [2 + 2 + 1] cycloaddition (aza-Pauson–Khand type reaction) of allenenitrile substrates.[12] It should be noted that the authors postulate a mechanism in which the nitrile does not directly participate in the reaction but rather isomerizes to a ketenimine, which enters the catalytic cycle.

The present study describes an intramolecular rhodium(I)-catalyzed [2 + 2 + 2] cycloaddition of cyano-yne-allene substrates leading to the construction of dihydronaphthyridine and pyranopyridine scaffolds after a dehydrogenative process.

The feasibility of the cycloaddition was assessed with *N*-tosyl (NTs)-tethered cyano-yne-allene substrate **1a**, which was synthesized from readily available starting materials (see the Supporting Information for details on the synthesis). First, the reaction was tested using $[Rh(cod)_2]BF_4$ as a cationic rhodium source in combination with Tol-BINAP in dichloroethane. Two products were formed, which could be isolated by column chromatography. One was assigned to product **2a**′ (Scheme 2),

Scheme 2. Preliminary Tests



which arises from a cycloaddition involving the internal double bond of the allene, and is followed by an isomerization to furnish the pyridine derivative. Although the same product can be obtained by reacting a cyanodyine scaffold,[5b] the result showed that the allene moiety can effectively be involved in such a cycloaddition. In the case of the second product, a mass loss of two units as compared with the starting material was detected by ESI-MS analysis. After a detailed spectroscopic analysis, the product was identified to be tricyclic adduct **2a** (Scheme 2) in which there was a central pyridine as indicated by the proton signal at 8.00 ppm surrounded by two 6-membered nitrogenated rings, one of which had a double bond, giving characteristic signals at 5.79 and 6.83 ppm. The external double bond of the allene reacts to achieve cycloadduct **2a**. Overall, the results showed that the allene participates in the cycloaddition but that the reaction is not regioselective. The regioselectivity of the reaction could not be improved by changing the reaction conditions (reaction temperature or use of microwave heating) nor by the use of other biphosphines, such as (*R*)-H_8-BINAP, BINAP, or SegPhos. The reaction was also tested in the presence of a stoichiometric amount of η^5-cyclopentadienyl-dicarbonyl cobalt(I) $[CpCo(CO)_2]$ in boiling xylenes under irradiation, but no reaction took place under these conditions.

The cationic rhodium catalytic system was then replaced by the neutral Wilkinson's catalyst $[RhCl(PPh_3)_3]$. When **1a** was added to a hot solution of the Wilkinson's catalyst in toluene, cycloadduct **2a** could be isolated with 48% yield after column chromatography (entry 1, Table 1) in a regioselective reaction (pyridine derivative **2a**′ could not be detected in the reaction

Table 1. Optimization of the Intramolecular Cycloaddition[a]

entry	solvent[b]	temp (°C)	additive (equiv)	rt (min)	yield of **2a**
1[c]	toluene	110		240	48
2	toluene	90		45	30
3	MCB	120		30	50
4[d]	MCB	120		30	40
5	*o*-DCB	140		30	40
6	1:1 DMF/H_2O	90		30	nr
7	MCB	120	TFA (1)	30	30
8	MCB	120	Et_3N (1)	10	54
9	MCB	80	Et_3N (1)	10	46
10	MCB	120	Et_3N (0.1)	10	64
11	MCB	120	Et_3N (0.05)	10	66
12	MCB	120	quinuclidine (0.05)	30	41
13	MCB	120	DIPEA (0.05)	10	49
14	MCB	120	Cy_2NH (0.1)	20	40
15	MCB	120	2,6-di-*tert*-butylpyridine (0.05)	40	33

[a]A solution of **1a** (0.05 M) and Wilkinson's catalyst (10 mol %) in the noted solvent was heated at the indicated temperature under microwave irradiation. [b]MCB = Chlorobenzene; *o*-DCB = 1,2-dichlorobenzene. [c]Reaction carried out under conventional heating. [d]Reaction carried out at 0.025 M concentration of **1a**.

mixture). For the decomposition observed in this first test to be minimized, the reaction was run under microwave irradiation. A first trial using toluene as the solvent at 90 °C for 45 min achieved the formation of 30% yield of the dehydrogenative cycloadduct in a process that had only a 30% conversion (entry 2, Table 1). For this conversion to be improved, the solvent was switched to chlorobenzene, and the temperature was increased to 120 °C. The resulting reaction led to a 50% yield in a process with full conversion (entry 3, Table 1). The reaction was not improved by diluting the reaction mixture, increasing the temperature, or changing the solvent system (entries 4–6, Table 1).

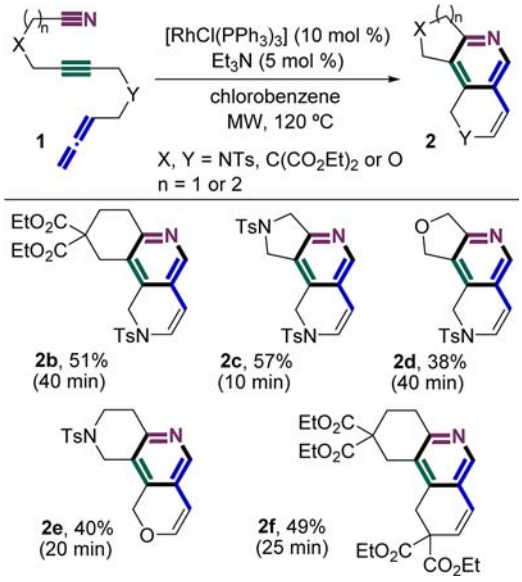
We then decided to test the effect of additives on the reaction mixture. Whereas the addition of trifluoroacetic acid was detrimental to the reaction (entry 7, Table 1), the addition of triethylamine[13] allowed the cyloadduct to be obtained in an increased yield and with a shorter reaction time (entry 8, Table 1). The reaction was then evaluated with different amounts of triethylamine and temperature, and optimal results were obtained with 5 mol % (entries 9–11, Table 1). Finally, the use of alternative tertiary amines, such as quinuclidine or *N*,*N*-diisopropylethylamine (DIPEA), secondary amines, such as dicyclohexylamine, or a hindered pyridine base, such as 2,6-di-*tert*-butylpyridine, was tested. However, none proved to have a beneficial effect, and the reactions gave cycloadduct **2a** in lower yields than the reaction carried out without Et_3N (compare entry 3 with entries 12–15, Table 1). In summary, the base is not acting as an acid scavenger because Et_3N gives better results in substoichiometric quantities, and this is not general with other bases. To check if new species were forming when mixing the Wilkinson's catalyst and Et_3N, we analyzed a mixture of these two compounds in chlorobenzene in a 2:1 ratio at the concentration of the optimized reaction conditions by ^{31}P NMR. Several spectra were recorded from room temperature to 120 °C, but no new species were observed. Although we have not found clear evidence for the role of triethylamine, based on precedents in the

DOI: 10.1021/acs.orglett.5b01554
Org. Lett. 2015, 17, 2882–2885

literature,[13b,e] we propose that triethylamine functions as a labile ligand for intermediate rhodium species.

We next proceeded to evaluate the scope of the process. A series of cyano-yne-allene scaffolds (**1**) with different tethers and numbers of methylenic units between the tether and the cyano group were reacted under the optimized conditions (Scheme 3). Both 6,6,6- and 5,6,6-tricyclic scaffolds were obtained in fairly good yields and with fast reactions.

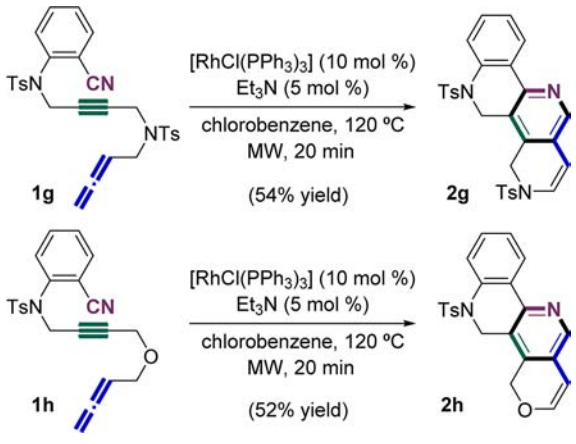
Scheme 3. Scope of the Intramolecular Cycloaddition Reaction



To assess the generality of the dihydrogenative cycloaddition, we designed new substrates that have a more rigid linker between the tether and the cyano group using 2-aminobenzonitrile as a building block. Substrates **1g** and **1h**, which differ in the tether between the alkyne and the allene, were synthesized (see the Supporting Information for details of the synthesis). Their subsequent reaction under the optimized conditions efficiently furnished cycloadducts **2g** and **2h** (Scheme 4).

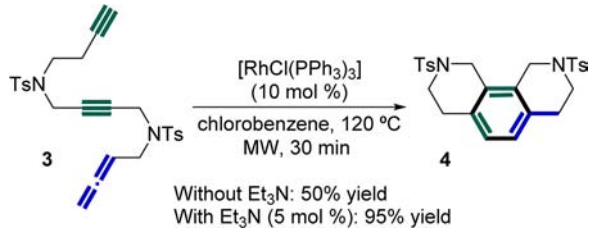
We then investigated whether dehydrogenative cyclization also takes place when other unsaturations are used. Diyneallene substrate **3** was synthesized, and its reactivity was tested under the optimized conditions. A [2 + 2 + 2] cycloaddition reaction

Scheme 4. Synthesis of Tetracyclic Frameworks



took place followed by an isomerization to furnish tricyclic benzene scaffold **4** (Scheme 5). Interestingly, the addition of

Scheme 5. [2 + 2 + 2] Cycloaddition of a Diyneallene Substrate



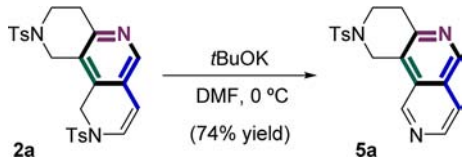
triethylamine almost doubles the yield, and the allene regioselectively reacts with its outer double bond, as opposed to what is typically found when terminal allenes are used. When a cyanodiyne substrate analogous to **1a** but with the allene isomerized to the corresponding terminal alkyne was reacted under optimized conditions, the reaction did not afford a pyridine-containing cycloadduct but rather a benzenic compound, which resulted from the homodimerization of the substrate (see the Supporting Information). Therefore, the dehydrogenation step seems to be effective only when the substrate features both an allene and a nitrile.

Although the details of the mechanism have yet to be established, a conventional [2 + 2 + 2] cycloaddition reaction that is followed by dehydrogenation to deliver final product **2** is postulated to take place. In trying to favor the dehydrogenation step, we carried out a couple of experiments. The first consisted of the addition of MnO_2 to favor hydrogen elimination following an observation by Saito et al.,[14] who had found this to be efficient in the intramolecular [2 + 2 + 2] cycloaddition of bis-(propargylphenyl)carbodiimides in the only example in which a [2 + 2 + 2] cycloaddition is followed by dehydrogenation. However, adding the oxidant did not improve the yield.[15] The reaction was also run in nondegassed solvent, but this also failed to favor dehydrogenation.

The cleavage of a tosyl group to release a free amine requires harsh conditions unless an oxidative elimination, usually leading to an aromatic compound, is possible.[16] Because the removal of the tosyl group in our compound should furnish the aromatic 2,6-naphthyridine core, we decided to try the dehydrosulfonylation/aromatization in our compounds. Therefore, cycloadduct **2a** was treated with 1 equiv of potassium *tert*-butoxide in dried DMF at 0 °C to deliver the corresponding deprotected product in 74% yield (Scheme 6), thus demonstrating that this is an efficient entry to the 2,6-naphthyridine nucleus, which is otherwise difficult to obtain.[1]

In summary, a novel type of rhodium-catalyzed [2 + 2 + 2] cycloaddition involving allenes and nitriles has been developed. Starting from linear substrates, the use of Wilkinson's catalyst allows the regioselective reaction of allenes through their external double bond to afford unsaturated pyridine-containing scaffolds

Scheme 6. Dehydrosulfonylation/Aromatization of 2a



DOI: 10.1021/acs.orglett.5b01554
Org. Lett. 2015, 17, 2882−2885

after a dehydrogenative step, opening the door to the synthesis of 2,6-naphthyridine-containing molecules.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and characterization data for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01554.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the Spanish Ministry of Education and Science (MINECO) (Project No. CTQ2011-23121, CTQ2014-54306-P, and a RyC contract to A.L.) and the DIUE of the Generalitat de Catalunya (Project No. 2014SGR931) are acknowledged. Thanks are due to the Universitat de Girona for a predoctoral grant to E.H.

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(15) Reactions were carried out on substrate **1c** under conventional heating either with or without Et_3N with 3 equiv of MnO_2 added at the end of the reaction, giving 30 and 24% yield of **2c**, respectively.

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DOI: 10.1021/acs.orglett.5b01554
Org. Lett. 2015, 17, 2882−2885