EurJOC European Journal of Organic Chemistry

SHORT COMMUNICATION

DOI: 10.1002/ejoc.201201258

# Silver-Catalyzed Cyclization of *N*-(Prop-2-yn-1-yl)pyridin-2-amines

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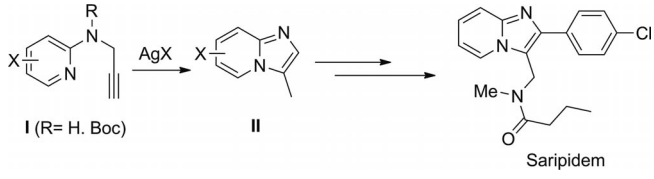
**Keywords:** Amines / Nitrogen heterocycles / Silver / Cyclization / Reaction mechanisms

We report herein the silver-catalyzed cycloisomerization of readily available *N*-(prop-2-yn-1-yl)pyridine-2-amines as a new and practical method for the synthesis of differently substituted 3-methylimidazo[1,2-*a*]pyridines. The isomerization reactions proceeded under mild reactions conditions to give good yields and excellent regioselectivity. A DFT-based mechanistic analysis is also reported.

## Introduction

Compounds containing the imidazo[1,2-*a*]pyridine ring system,[1] for example, saripidem (Scheme 1), necopidem or zolpidem, are of wide medicinal interest.[2] Consequently, a number of synthetic methods have been reported[3] for the synthesis of this heterocyclic system,[4–9] however, these methods are compromised by the numerous steps needed to obtain the required precursors and the narrow substrate scope. Thus, new and more efficient synthetic methods are sought.




Scheme 1. Structure of saripidem and a general approach to the synthesis of diversely functionalized 3-methylimidazo[1,2-*a*]pyridines (**II**) by silver-mediated cyclization of *N*-(prop-2-yn-1-yl)pyridin-2-amines (**I**).

In this communication we report a new method for the preparation of imidazo[1,2-*a*]pyridine derivatives (**II**) based on the unprecedented silver-mediated heterocyclization of *N*-(prop-2-yn-1-yl)pyridin-2-amines (**I**), a DFT-based mechanistic analysis and its application to the total synthesis of saripidem (Scheme 1).

## Results and Discussion

Although silver-mediated coupling and heterocyclization reactions are well documented, there are few precedents for silver-catalyzed cyclizations of substituted aromatic or heterocyclic *N*-propargylamines.[10] A recent communication on the silver-catalyzed 6-*endo-dig* cyclization reactions of *N*-propargylated heterocyclic compounds[11] prompted us to test this reaction on the readily available *N*-(prop-2-yn-1-yl)pyridin-2-amine derivatives.[7,9]

The reaction of *N*-(prop-2-yn-1yl)pyridin-2-amine (**1a**)[7] with cheap $AgNO_3$ (10%) as catalyst in dry acetonitrile at reflux under argon gave a mixture of the easily separable 3-methylimidazo[1,2-*a*]pyridine (**2a**)[7,12] and imidazo[1,2-*a*]-pyridine-3-carbaldehyde (**3a**),[9,13] isolated in yields of 69 and 8%, respectively (entry a, Table 1). $SeO_2$-promoted allylic oxidation of compound **2a** gave aldehyde **3a** in 58% yield (see Scheme 2), which was reduced with sodium borohydride to afford imidazo[1,2-*a*]pyridin-3-ylmethanol (**4a**)[14] in 86% yield. Remarkably, only the 5-*exo-dig* cyclization products **2a** and **3a** were formed,[6] in sharp contrast to the results obtained from the silver-mediated cyclization of 6-(prop-2-yn-1-ylamino)-2*H*-chromen-2-ones,[11] 1-alkyl-6-(prop-2-yn-1-ylamino)quinolin-2(1*H*)-ones,[11] 1,3-dimethyl-5-(prop-2-yn-1-ylamino)pyrimidine-2,4(1*H*,3*H*)-diones,[11] *N*-(prop-2-yn-1-yl)benzo[*d*]oxazol-2-amines[15a] or $N^9$-propargylguanine,[15b] for which only the *6-endo* products were isolated.

On the basis of these results, the reaction was optimized (see Table 1). The use of a base, such as $Et_3N$, resulted in a slower reaction (17 h) giving the imidazo[1,2-*a*]pyridine **2a** in a lower yield (23%) and aldehyde **3a** in a higher yield (19%, entry b, Table 1). With regard the silver catalyst,

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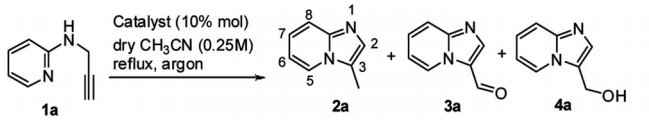
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201201258.

Table 1. Silver-mediated heterocyclization of *N*-(prop-2-yn-1-yl)-pyridin-2-amine (**1a**).



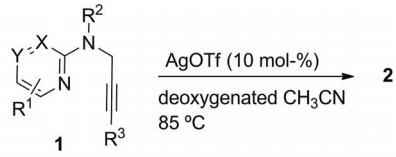

| Entry | Catalyst | Time (h) | Yield (%) | | |
|---|---|---|---|---|---|
| | | | 2a | 3a | 4a |
| a | $AgNO_3$ | 4 | 69 | 8 | 0 |
| b | $AgNO_3$[a] | 17 | 23 | 19 | 0 |
| c | AgF | 3 | 61 | 8 | 0 |
| d | $AgBF_4$ | 2 | 50 | 8 | 0 |
| e | AgOAc | 7 | 77 | 5 | 0 |
| f | AgOTf | 2 | 52 | 9 | 18 |
| g | AgOTf[b] | 4 | 84 | 2 | traces |
| h | $CuCl_2$[b] | 24 | 82 | traces | 0 |
| i | $PtCl_2$[b] | 6 | 39 | 3 | 0 |
| j | $NaAuCl_4$[b] | 8 | 36 | 5 | 0 |

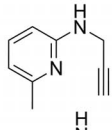
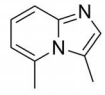
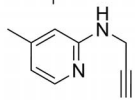
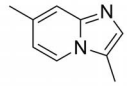
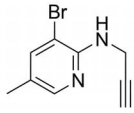
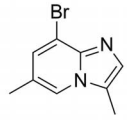
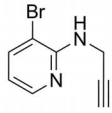
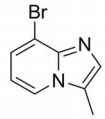
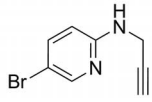
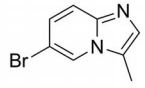
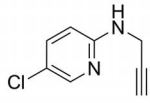
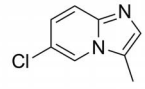
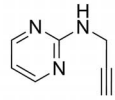
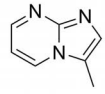
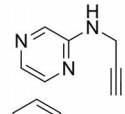
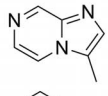
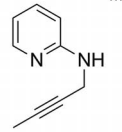
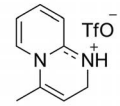
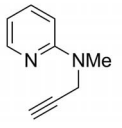
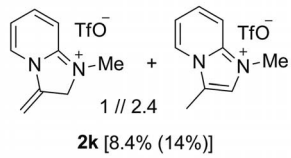
[a] With $Et_3N$ (1 equiv); [b] Deoxygenated $CH_3CN$.

readily available AgF, $AgBF_4$ and AgOAc were investigated and were found to give similar yields of compounds **2a** and **3a** (entries c–e, Table 1). With AgOTf, a mixture of 3-methylimidazo[1,2-*a*]pyridine (**2a**; 52%), aldehyde **3a** (9%) and alcohol **4a** (18%) was obtained (entry f, Table 1). Interestingly, when we carried out the reaction in deoxygenated acetonitrile, not only did the yield of compound **2a** increase to 84%, but the yield of aldehyde **3a** was reduced to 2% and only traces of alcohol **4a** were detected (entry g, Table 1). Overall, the formation of the compounds **3a** and **4a**, although obtained in low chemical yields, was totally unexpected, and to the best of our knowledge these results are the first examples of the intramolecular dehydrogenative aminooxygenation (IDA) of *N*-(prop-2-yn-1-yl)pyridin-2-amines.[16] Finally, other catalysts, for example, $CuCl_2$ (entry h), gave compound **2a** in a clean and high-yielding reaction, whereas with $PtCl_2$ (entry i) and $NaAuCl_4$ (entry j), the yields of compound **2a** were significantly lower than those observed for AgOTf (entry g, Table 1).

Once the optimal experimental conditions had been determined [AgOTf (10%) in dry deoxygenated acetonitrile at reflux under argon], the scope and generality of the reaction was next investigated with *N*-(prop-2-yn-1-yl)pyridin-2-amine derivatives **1b**–**k**[17] (Table 2). Methyl-substituted precursors (entries a–c), even when the Me group was located at C-6 or the substrate also bore a bromine atom at C-3, gave the corresponding imidazopyridines in moderate-to-good yields in short reaction times (2–4 h). The cyclization of the bromo- or chloro-substituted precursors (entries d–f), regardless of the position of the halogen, afforded the expected product, but the reaction was markedly slower (16–24 h). Finally, the cyclization of *N*-propargylamines in other heterocyclic ring systems, such as an imidazole (entry g) or a pyrazine (entry h), under the same experimental conditions, was also possible, providing the expected imidazo-fused heterocycles **2h**[18] and **2i**[19] in variable yields. Very interestingly, internal alkyne analogue **1j** or *N*-Me-substituted precursor **1k** gave the corresponding triflates **2j** and **2k**, respectively, in poor yields after long reaction times (entries j and k, Table 2). However, when precursor **1j** was treated with AgTfO (1 equiv.), compound **2j** was isolated in 92% yield in a quick reaction (30 min). The structure of

Table 2. Silver-mediated heterocyclization of *N*-(prop-2-yn-1-yl)-pyridin-2-amines **1b**–**k**.




| Entry | Precursor | | Time (h) | Product [Yield (%)] |
|---|---|---|---|---|
| a |  | **1b** | 2 |  **2b** (71%) |
| b |  | **1c** | 2 |  **2c** (41%) |
| c |  | **1d** | 4 |  **2d** (76%) |
| d |  | **1e** | 18 |  **2e** (56%) |
| e |  | **1f** | 24 |  **2f** (34%) |
| f |  | **1g** | 16 |  **2g** (74%) |
| g |  | **1h** | 16 |  **2h** (27%) |
| h |  | **1i** | 18 |  **2i** (64%) |
| j |  | **1j** | 48 |  **2j** [9.5% (23%)] |
| k |  | **1k** | 96 |  1 // 2.4 **2k** [8.4% (14%)] |

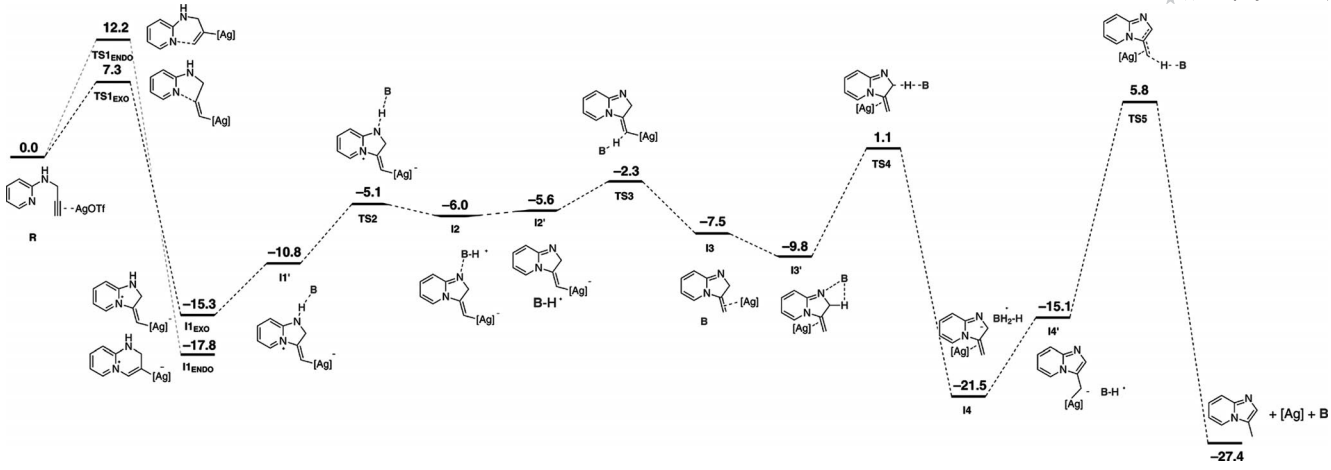



Figure 1. Free-energy profile (in kcal/mol) computed in solution (acetonitrile) for the Ag-catalyzed heterocyclization of **1a**. **B** refers to **1a** acting as a base assisting the proton-shift steps.

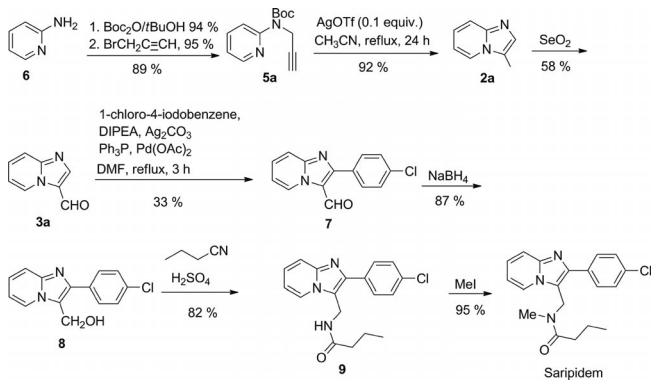
compounds **2j**,**k** were established by NMR spectroscopy, and in the case of the 6-*endo*-*dig* cyclization product **2j**, also by X-ray diffraction analysis (see the Supporting Information). Very interestingly, 2-[methyl(prop-2-yn-1-yl)amino]nicotinonitrile was recovered unreacted, which shows the strong deactivating effect of an electron-withdrawing substituent.

With these results in hand, we proposed and examined several potential mechanisms[20] for the cyclization of *N*-(prop-2-yn-1-yl)pyridin-2-amine (**1a**; Figure 1). For the formation of product **2a** from precursor **1a**, the more favourable mechanism computed in acetonitrile (Figure 1) involves a kinetically favoured *exo*-*dig* rather than an *endo* cyclization proceeding via intermediate $\mathbf{I1_{EXO}}$, followed by successive deprotonation/protonation events assisted by the basic pyridine framework (denoted as **B** in Figure 1). This base-assisted deprotonation/protonation pathway was proposed by Gevorgyan and co-workers for a closely related Ag-mediated cycloisomerization and supported by labelling studies.[21] The sequence involves a formal [1,4] hydrogen shift from the amine group and a formal [1,3] hydrogen shift from the endocyclic methylene to the exocyclic carbon. Our calculations suggest that the former would take place before the latter process.[22]

On the basis of this mechanism, we hypothesized that *N*-Boc-*N*-propargylaminopyridines, as readily available key intermediates for the preparation of precursors **1** (Table 1 and Table 2), could also be substrates for the AgOTf-mediated cyclization reaction leading to imidazopyridines if triflic acid can trigger the elimination of isobutylene and $CO_2$, followed by cyclization of the resulting *N*-pyridyl carbanion to the Ag-activated alkyne. To probe this hypothesis, we investigated the silver-catalyzed cycloisomerization of *N*-Boc-*N*-propargylaminopyridines **5a**–**j** (Table 3). As shown, and with the exception of precursor **5i**, all the carbamates reacted to give the imidazopyridine (or imidazopyrimidine) derivatives in yields ranging form 12 (**2f**, entry f) to 92% (**2a**, entry a). Similarly, the internal alkyne substituted analogue **5j** gave the 6-*endo*-*dig* product **2l** in moderate yield, taking into account the recovered unreacted precursor (entry j; Table 3). Interestingly, when precursor **5j** was treated with AgTfO (1 equiv.), compound **2l** was isolated in 94% yield after 30 min reaction time. In general, it is clear that for the same structural/functional motif, the free propargylamines **1** (Table 1 are Table 2) are better precursors than the corresponding Boc derivatives **5** (Table 3) for the AgOTf-mediated synthesis of the imidazopyridines.

At this point, comparison with the *t*BuOK/THF-promoted cyclization reactions of *N*-propargylaminopyridines[7] seems appropriate. As shown in Table 3, and for the same carbamate, the Ag-catalyzed method compares very favourably with the *t*BuOK-promoted cyclization (entries a and g) taking place under milder conditions. In addition, for the *N*-propargylaminopyridine **1a** (Table 1, entries a–g) or the carbamates **5d**, **5h** and **5j** (entries d, h and j; Table 3), the *t*BuOK-promoted cyclization did not lead to the expected heterocyclic derivatives, whereas the AgOTf-catalyzed reaction afforded the expected products in moderate-to-good yields.

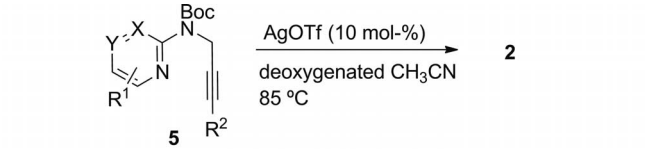
Finally, to test the utility of our method, we carried out the total synthesis of the anxiolytic sarpidem[23] from 2-aminopyridine (**6**) in 11% overall yield with imidazo[1,2-*a*]-pyridine **2a** as the key intermediate (Scheme 2). Heck reac-

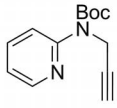
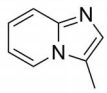
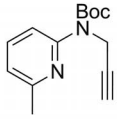
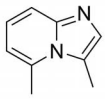
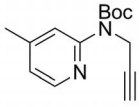
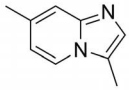
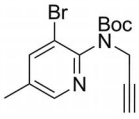
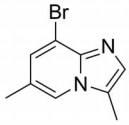
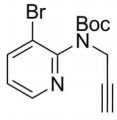
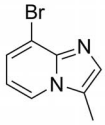
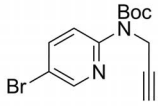
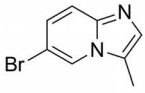
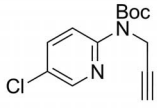
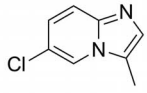
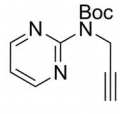
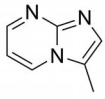
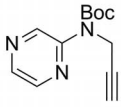
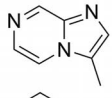
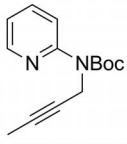
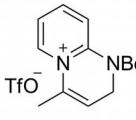



Scheme 2. Total synthesis of saripidem from 2-aminopyridine (**6**).

Table 3. Silver-mediated heterocyclization of *N*-(prop-2-yn-1-yl)-(pyridin-2-yl)carbamates **5a**–**j**.




| Entry | Precursor | | Time (h) | Product [Yield (%)] |
|---|---|---|---|---|
| a |  | **5a** | 24 |  **2a** (92%) **(70%)**[7] |
| b |  | **5b** | 4 |  **2b** (28%) **(58%)**[7] |
| c |  | **5c** | 4 |  **2c** (39%) **(52%)**[7] |
| d |  | **5d** | 96 |  **2d** (46%) **(0%)**[7] |
| e |  | **5e** | 96 |  **2e** (25%) |
| f |  | **5f** | 20 |  **2f** (12%) |
| g |  | **5g** | 19 |  **2g** (54%) **(53%)**[7] |
| h |  | **5h** | 16 |  **2h** (75%) **(0%)**[7] |
| i |  | **5i** | 24 |  **2i** (0%) |
| j |  | **5j** | 16 |  **2l** [5.8% (48%)] **(0%)**[7] |

tion of carbaldehyde **3a** with 1-chloro-4-iodobenzene gave the well-known imidazopyridine **7**[9,14] in 33% yield (not optimized). Reduction of **7** with sodium borohydride to afford alcohol **8**[14] (87%) followed by sequential reaction with propanenitrile/$H_2SO_4$ and *N*-methylation gave saripidem via *N*-{[2-(4-chlorophenyl)imidazo[1,2-*a*]pyridin-3-yl]-methyl}butyramide (**9**; see the Supporting Information).

## Conclusions

We have reported herein for the first time the silver-mediated cycloisomerization of readily available *N*-(prop-2-yn-1-ylamino)pyridines as a new and practical method for the regioselective synthesis of differently substituted 3-methylimidazo[1,2-*a*]pyridines, suitable intermediates for further synthetic transformations and modulation, that proceeds under mild reaction conditions in good-to-high yields and with excellent regioselectivity.

## Experimental Section

**General Method for the Silver-Mediated Cyclization of *N*-(Prop-2-yn-1-yl)pyridin-2-amine Derivatives:** A catalytic amount of AgOTf (10 mol-%) was added to a solution of the corresponding *N*-(prop-2-ynyl)pyridin-2-amines **1a**–**k** (Method A) or *N*-(prop-2-yn-1-yl)-*N*-(pyridin-2-yl)carbamates **5a**–**j** (Method B) (1.0 mmol) in dry acetonitrile. The mixture was deoxygenated with argon for 10 min and then heated at 85 °C for the time indicated for each compound. When the reaction was complete (TLC analysis), the solvent was evaporated under reduced pressure and the residue purified by flash chromatography to give the pure products.

**Supporting Information** (see footnote on the first page of this article): Experimental procedures, NMR spectra, computational results, X-ray analysis, and NMR analysis.

## Acknowledgments

M. C. thanks the Instituto de Salud Carlos III (ISCIII) for a "Sara Borrell" contract and A. S. thanks the Consejo Superior de Investigaciones Científicas (CSIC) for a ".JAE-doc" contract. J. M. C. thanks the Ministerio de Ciencia e Innovación (MICINN) (SAF2009-07271; SAF2012-33304) for financial support. E. S. thanks the Ministerio de Ciencia e Innovación (MICINN) for a grant (CTQ2009-10478). L. I. thanks Comunidad de Madrid (Spain) for financial support (BIPEDD-2: S2010-BMD-2457). The authors thank Prof. J. Elguero (IQM, CSIC) for advice and useful comments.

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Received: September 21, 2012
Published Online: November 19, 2012

  