Unexpected Stereoselective Access to 2-Aminooxazolines from Propargyl Ureas by Silver Salts under Mild Conditions

DOI: 10.1002/adsc.202((will be filled in by the editorial staff))

# Unexpected Stereoselective Access to 2-Aminooxazolines from Propargyl Ureas by Silver Salts under Mild Conditions

Aleksandr Voronov,[a,†] Alessandra Casnati,[a,†] Paolo P. Mazzeo,[a,b] Paolo Pelagatti,[a] Alessia Bacchi,[a,b] Raffaella Mancuso,[c] Bartolo Gabriele,[c] Elena Motti,[a,d] Giovanni Maestri,[a] Péter Pál Fehér,[e] András Stirling,[e,f] and Nicola Della Ca',[a,d,*]

[a] Department of Chemistry, Life Sciences and Environmental Sustainability (SCVSA) University of Parma, Parco Area delle Scienze, 17/A, 43124 Parma (Italy)
Tel.: +39 0521 905676
Fax: +39 0521 905472
E-mail: nicola.dellaca@unipr.it
[b] Biopharmanet-tec, Parco delle Scienze, 27/A, 43124 Parma (Italy)
[c] Laboratory of Industrial and Synthetic Organic Chemistry (LISOC), Department of Chemistry and Chemical Technologies, University of Calabria, Via P. Bucci 12/C, 87036 Arcavacata di Rende, Cosenza (Italy)
[d] CIRCC (Interuniversity Consortium Chemical Reactivity and Catalysis), via Celso Ulpiani 27, 70126 Bari (Italy)
[e] Institute of Organic Chemistry, Research Centre for Natural Sciences, Magyar Tudósok krt. 2, 1117, Budapest (Hungary)
[f] Institute of Chemistry, Department of Chemistry, Eszterházy Károly University, Leányka utca 6, 3300 Eger (Hungary)
[†] These authors contributed equally to this work.

Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

**Abstract.** Propargyl ureas can lead to a range of possible heterocyclic compounds, mainly depending on the employed catalyst. Silver salts are known to promote the *N*-5-*exo-dig* cyclization mode to imidazolidinone derivatives. Conversely, a versatile and stereoselective *O*-5-*exo-dig* cyclization of propargyl ureas to 2-aminooxazolines by Ag(I) catalysis is here disclosed. Good to excellent yields and complete stereoselectivity of the external double bond have been achieved under milder reaction conditions (50-60 °C). A one-pot protocol starting from the corresponding propargylic amines and isocyanates has been developed as well. *N*,*N*'-Dipropargyl ureas underwent a singular *O*-5-*exo-dig*/*N*-5-*endo-dig* double cyclization sequence. Finally, insights into the tautomeric equilibrium of 2-aminooxazoles and on their relative reactivity are provided.

**Keywords:** Propargyl ureas; Oxazol-2-amines; Silver catalysis; *O*-5-*exo-dig* Cyclization; *N*-5-*endo-dig* cyclization

In recent years, 2-aminooxazoline-based compounds have seen a remarkable upsurge of applications in medicinal chemistry (Figure 1).[1] For instance, *Tucatinib*, containing the 2-aminooxazoline unit, has been recently approved for the treatment of patients with advanced metastatic HER2-positive breast cancer,[1a] aminooxazoline xanthenes are potent and selective human β-secretase inhibitors and are highly active in the treatment of Alzheimer,[1b] and quinuclidine-containing spirooxazolidines have been found to act as α7 nicotinic acetylcholine receptor partial agonists.[1c] In addition, 2-aminooxazoline derivatives have also revealed a high activity as TAAR1 agonists,[1d] as selective adrenergic receptor ligands[1e] and antitubercular agents[1f]. Furthermore, 2-aminooxazolines are invoked as intermediates in the

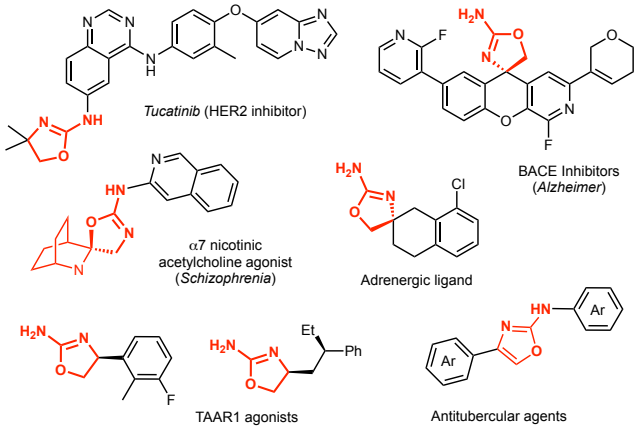



**Figure 1.** Bioactive 2-aminooxazoline-containing compounds.

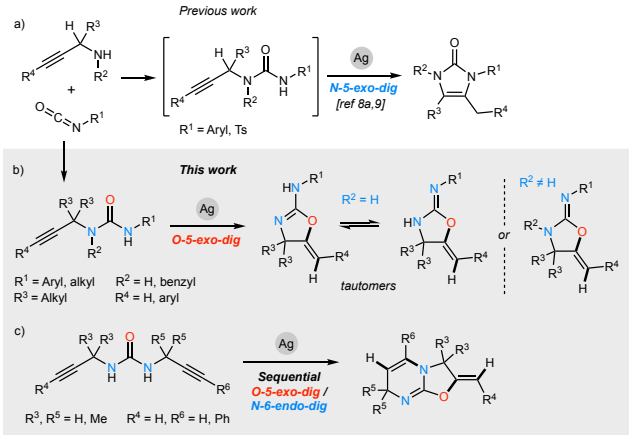
prebiotic synthesis of RNA[2] and represent relevant building blocks in organic synthesis[3].

Despite their relevance, a limited number of syntheses have been reported. The aminooxazoline nucleus can be obtained by reacting aminoalcohols with BrCN[1d,e] or by a two-step synthesis with thiourea and DIC[1c] (diisopropylcarbodiimide). Biaryl

aminooxazolines can be prepared through a multistep procedure that involves the use of a large excess of AgOCN and $I_2$.[4] Another method for obtaining amino-2-oxazoles involves the condensation of α-bromoacetophenones with ureas, leading to the formation of final products in limited yields.[1f] The use of properly functionalized ureas is one of the most efficient strategies for the preparation of 2-aminooxazolines.[5] For example, halogenated oxazolidin-2-imines can be prepared from propargylic ureas in the presence of stoichiometric amounts of a halide source and, in one case, with catalytic copper salts[6]. Catalytic methods if compared to uncatalyzed ones, usually feature often milder reaction conditions, wider functional group tolerance and improved atom and step economy. To the best of our knowledge, the catalytic access to 2-aminooxazolines is feasible under palladium-catalyzed oxidative carbonylation conditions[7] with limited chemoselectivity or in the presence of expensive cationic gold species activated by silver salts[8]. Silver alone is specifically competent in promoting the *N-exo-dig* cyclization of properly functionalized propargyl ureas to 2-imidazolones (Scheme 1a)[8a,9]. Here we present the unexpected *O-exo-dig* route to 2-aminooxazolines promoted by silver salts (Scheme 1b, *this work*), that complements the N-*exo-dig* one reported by Van der Eycken and co-workers. We demonstrate that the promotion of *O-exo-dig* pathway followed by propargylic ureas is not a prerogative of Pd and Au, but the more convenient Ag can also efficiently catalyze the nucleophilic attack of O on the triple bond (Scheme 1b). In particular, we anticipate that the different substitution pattern of the starting urea is at the origin of this complementary reactivity. Moreover, compared to catalyst-free routes to 2-aminooxazolines[5b] this protocol leads exclusively to *Z* isomer, and secondly, the final products display an equilibrium between two tautomeric forms, whose reactivity has been briefly explored. In addition, more complex bicyclic structures can be accessed through a sequential *O*-5-*exo-dig* / *N*-6-*endo-dig* reaction performed in a regioselective one-pot fashion (Scheme 1c). Far as we know, this is the first report on a silver-catalyzed cycloisomerization of propargylic ureas to oxazoline derivatives.

We have recently reported the synthesis of imidazolidinones starting from a series of propargylic ureas under superbase catalysis (TBD or BEMP superbases).[10] The reaction is highly efficient, very fast (less than 1 min of reaction times) and agrees with the previous observations on the base-promoted cyclizations of propargylic ureas that mainly follow the *N*-5-*exo-dig* cyclization mode.[5b] However, it fails to cyclize *N*-alkyl-substituted ureas, as many other reported protocols.[6,8,9] So, we were very pleased when we caused to react one of these starting ureas (1-butyl-3-(2-methylbut-3-yn-2-yl)urea, **1a**) under silver catalysis (AgOTf) and saw complete conversion of the substrate after 24 h at 50 °C in acetonitrile.

On the basis of the previous reports on pure silver-catalyzed cycloisomerization of propargylic ureas,[8a,9] we expected to isolate an imidazolidinone derivative. Unpredictably, we observed the exclusive formation of the oxazoline isomer.




**Scheme 1.** Ag-catalyzed cycloisomerizations of propargylic ureas: *previous work* on a) the *N*-5-*exo-dig* cyclization mode, *this work* on b) the *O*-5-*exo-dig* and c) the *O*-5-*exo-dig* / *N*-6-*endo-dig* reaction sequence.

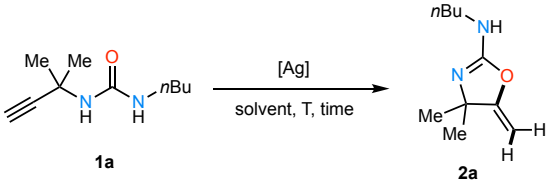
This was further confirmed by a number of X-ray structures that swept away any doubt on this preliminary result (*vide infra*).

We then started the optimization study on the same substrate **1a** that was converted to the corresponding 2-aminooxazoline **2a** in 90% NMR yield at the first attempt (Table 1, entry 1). Silver nitrate proved to be even more effective, ensuring 94% of yield (Table 1, entry 2). $Ag_2CO_3$ and $Ag_2O$ were found ineffective to promote the formation of the 5-membered cyclic oxazoline (Table 1, entries 3 and 4). Contrarily, silver salts possessing a bulky anion, such as $AgPF_6$, $AgBF_4$ and $AgSbF_6$ resulted in good yields of the expected products that were obtained in 68%, 79% and 57% yield, respectively (Table 1, entries 5-7). Once silver nitrate was confirmed as the most active silver precursor, we turned our attention to other reaction parameters. When the temperature was raised to 60 °C, a quantitative yield of **2a** was observed after 18 h (Table 1, entry 8). Other polar aprotic solvents, such as DMF and THF afforded quantitative yields in 36 and 16 h, respectively (Table 1, entries 9 and 12). Chlorinated solvents, such as DCE (1,2-dichloroethane) and $CHCl_3$, were also suitable, providing **2a** in 99 and 83%, respectively after 18 and 24 h (Table 1, entries 10 and 11). To our delight, protic solvents dramatically reduced the reaction time. Compound **2a** was quantitatively obtained in methanol after 4 h of reaction time (Table 1, entry 13), while ethanol and isopropyl alcohol were found to be less efficient solvents (Table 1, entries 14 and 15). In the end, a control experiment in the absence of catalyst was performed, resulting in the recovery of the unconverted starting material **1a** (Table 1, entry 16).

Having established the optimized reaction conditions (Table 1, entry 13), we investigated the

reaction scope by introducing different substituents on the propargylic urea scaffold (Table 2). Ureas bearing

**Table 1.** Optimization study.[a]




1a 2a

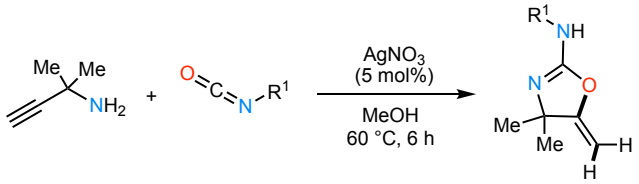
| Entry | [Ag] | Solvent | T (°C) | Time (h) | Yield (%)[b] **2a** |
|---|---|---|---|---|---|
| 1 | AgOTf | MeCN | 50 | 24 | 90 |
| 2 | $AgNO_3$ | MeCN | 50 | 24 | 94 |
| 3 | $Ag_2CO_3$ | MeCN | 50 | 24 | traces |
| 4 | $Ag_2O$ | MeCN | 50 | 24 | traces |
| 5 | $AgPF_6$ | MeCN | 50 | 24 | 68 |
| 6 | $AgBF_4$ | MeCN | 50 | 24 | 79 |
| 7 | $AgSbF_6$ | MeCN | 50 | 24 | 57 |
| 8 | $AgNO_3$ | MeCN | 60 | 18 | 99 |
| 9 | $AgNO_3$ | DMF | 60 | 36 | 99 |
| 10 | $AgNO_3$ | DCE | 60 | 18 | 99 |
| 11 | $AgNO_3$ | $CHCl_3$ | 60 | 24 | 83 |
| 12 | $AgNO_3$ | THF | 60 | 16 | 99 |
| **13** | **$AgNO_3$** | **MeOH** | **60** | **4** | **99** |
| 14 | $AgNO_3$ | EtOH | 60 | 4 | 74 |
| 15 | $AgNO_3$ | *i*PrOH | 60 | 4 | 66 |
| 16 | - | MeOH | 60 | 16 | - |

[a] *Reaction conditions*: **1a** (0.2 mmol), silver salt (0.01 mmol, 5 mol%), solvent (0.1 M). [b] NMR yield.

alkylic fragments ($R^1$) on the nitrogen, such as *n*-propyl, *tert*-butyl and cyclohexyl, gave **2c**, **2d** and **2e**, respectively, in excellent yields and short reaction times, regardless of the steric hindrance of the group.

Due to the relatively low boiling point of the expected product, the cyclization of urea **1b** bearing an ethyl substituent ($R^1$ = Et) was performed in an NMR tube using $CD_3OD$ as solvent. A high NMR yield of the deuterated product *d*-**2b** was in this way ensured (94%). Deuteration of the starting acetylenic C(sp)-H bond took place without silver source[11] and, it is worth to note that no other acidic protons in the product *d*-**2b**, such as NH, underwent hydrogen-deuterium exchange. While the benzyl moiety was perfectly tolerated (**2g**, 94%), an allyl group was less compatible with the transformation (**2f**, 67%). Substrate **1h**, bearing the ethyl ester function, afforded in satisfactory yield (62%) compound **2h**, featuring the $CO_2Me$ group, which was likely obtained through a transesterification process. An aryl moiety in $R^1$ was also tolerated, and quantitative yields of the corresponding oxazolines **2i-m** with electron donating and electron withdrawing groups in different positions (4-Me, 2-OMe, 4-F, 2,4-F) were obtained. The $NO_2$ group was less compatible with the reaction conditions, but the regioselectivity was maintained, as confirmed by the X-ray analysis (**2n**). We were pleased to find that the useful naphthyl moiety can be successfully incorporated in the final product with excellent yield (**2o**, 90%). The increased steric hindrance of the *alpha* substituents at the propargylic function, such as in **1p** ($R^3$ = Et) and **1q** (Cy), was well tolerated. However, if a substituent was missing, such as in **1r** and **1s**, the desired cyclization did not occur, even at higher reaction temperatures. Evidently, the *gem* dialkyl effect[12] is here essential to render the cyclization energy barrier low enough for the transformation to occur. Propargylic ureas featuring an internal triple bond were converted into products (**2t-v**) with *Z* configuration of the alkene fragment, as confirmed by the X-ray structure of (*Z*)-**2t**. The presence of functional groups of different nature (2-$CO_2Me$, 3-OMe) at the phenylacetylene moiety of the substrate extended the reaction time and diminished the yields of the corresponding aminooxazolines (*Z*)-**2u** and (*Z*)-**2v**.[13] Interestingly, substitution on the N bearing the propargyl unit was compatible and led to the desired oxazoline product. Indeed, ureas with benzyl (**1w**) and 4-fluorobenzyl group (**1x**) were readily converted into the corresponding oxazolines in 73% and 68% yield, respectively. Finally, the degree of substitution of the N, in competition with the O for the nucleophilic attack on the triple bond, was studied. Gladly, the expected compounds bearing a secondary pyrrolidine motif (**2y**) in one case and a primary amino group $NH_2$ (**2z**) in the other, were both obtained in excellent yield.

To further expand the applicability of the developed silver-catalyzed protocol, we performed one-pot experiments starting from 2-methyl-3-butyn-2-amine and corresponding isocyanates (Scheme 2). To our delight, products **2a** and **2c** were both recovered in quantitative yield after 6 h of reaction time.



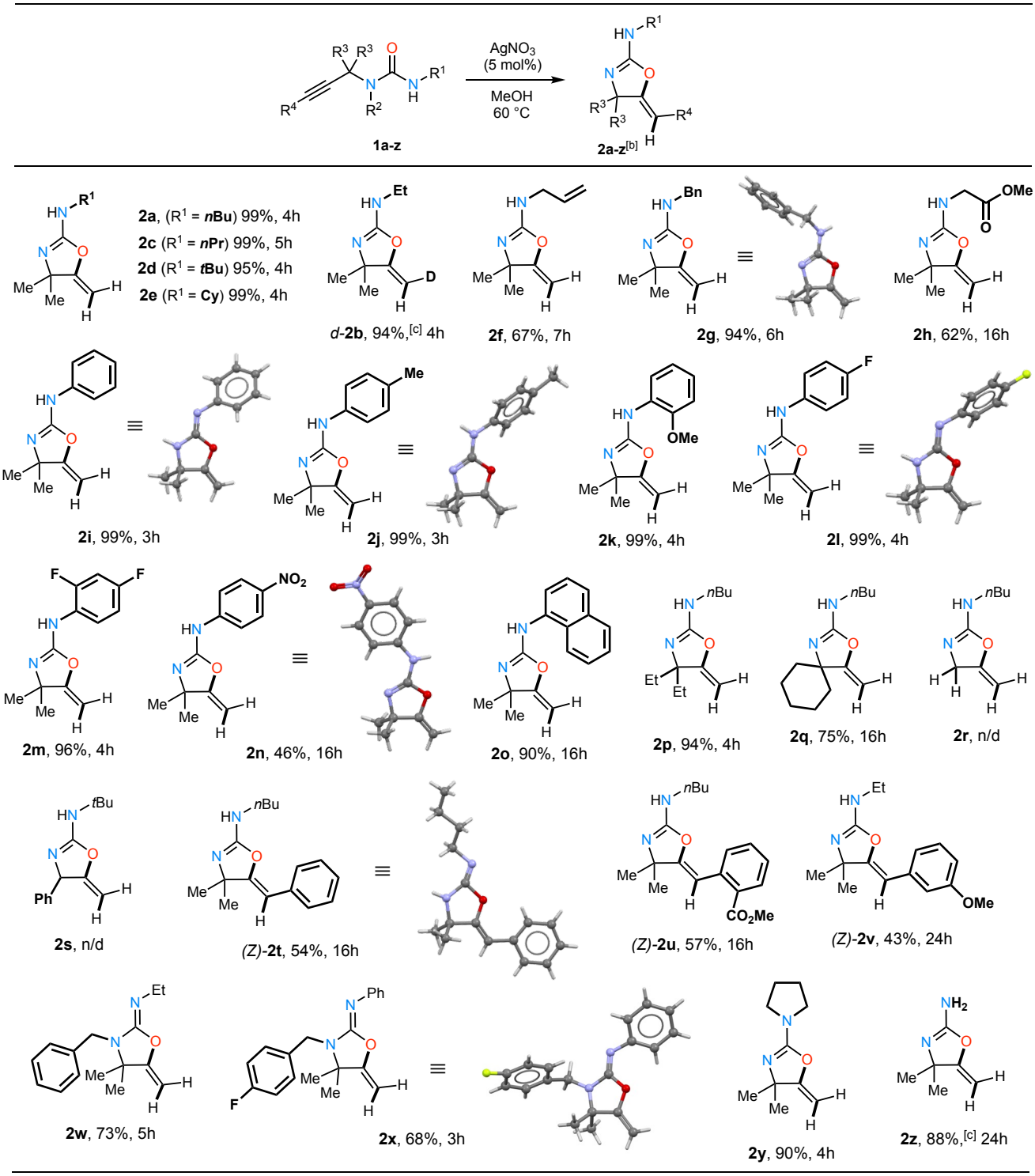

$R^1$ = *n*Bu, **2a**, 99%
$R^1$ = *n*Pr, **2c**, 99%

**Scheme 2.** One-pot silver-catalyzed synthesis of 2-aminooxazoline **2a** and **2c** from amine and isocyanate.

We were then intrigued by the possible behavior of the ureas with two propargyl "arms" as substituents (**3**, Table 3). Pleasingly, the useful class of oxazolo[3,2-a]pyrimidines,[14] previously prepared only by multistep procedures, was here approached in a one-pot manner. The symmetrical propargyl urea **3a** afforded the bicyclic compound **4a** in 71% isolated yield (Table 3).[15] The X-ray diffraction on single crystal was essential for the determination of the relative structure. It is worth to mention that this kind of product is likely obtained through a sequential *O*-5-*exo-dig* cyclization followed by a *N*-6-*endo-dig* annulation proceeding in a highly regioselective fashion. Non-symmetrical urea **3b** gave the corresponding compound **4b** in synthetically useful yield. Remarkably, the *O*-5-*exo-dig* cyclization occur at the disubstituted propargylic arm, while the *N*-6-

*endo-dig* ring closure takes place on an unsubstituted ($R^5$ = H) one. Urea **3c**, not possessing geminal substituents at both propargylic positions, did not react and was fully

**Table 2.** Reaction scope of the Ag-catalyzed synthesis of 2-aminooxazolines.[a]



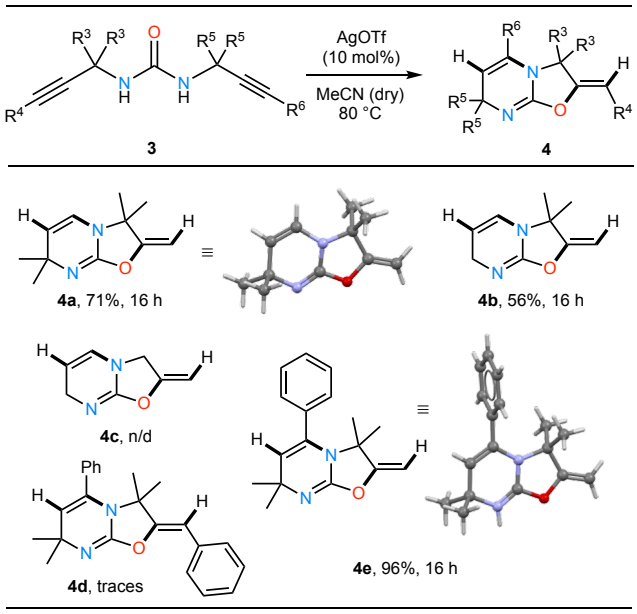

[a] *Reaction conditions*: **1** (0.2 mmol), $AgNO_3$ (0.01 mmol, 5 mol%), MeOH (0.1 M), 60 °C. [b] Isolated yield. [c] Reaction carried out in a NMR tube using $CD_3OD$ as solvent and the reported yield is based on $^1H$ NMR spectrum.

recovered after 24 h of reaction time. The presence of phenyl rings at the terminal position of the triple bonds, such as in the urea **3d**, was also detrimental for the reaction, the corresponding product **4d** being formed only in traces. On the other hand, when only one phenyl was present, the *O*-5-*exo-dig* cyclization proceeded selectively on the unsubstituted triple bond, while the internal alkyne moiety underwent *N*-6-*endo-dig* one, leading to **4e** (96% yield).

Except for substances containing trisubstituted nitrogens (as **2w-y**), the structures here reported exist in an equilibrium between two tautomeric forms. A

great part of these compounds has been crystallized, and the relative X-ray structures have been solved. It

**Table 3.** Ag-catalyzed synthesis of oxazolo[3,2-a]pyrimidine derivatives **4** from dipropargylic ureas **3**.[a,b]




[a] *Reaction conditions*: **3** (0.2 mmol), AgOTf (0.02 mmol, 10 mol%), MeCN (0.1 M), 80 °C. [b] Isolated yield.

is clear that the preferred conformation in the solid state does not reflect what we can encounter in the liquid phase. To have an insight of what can be expected in solution and explore a plausible isomerization mechanism, computational tool has been exploited. It was found that the tautomer **2** with endocyclic C=N bond is slightly more stable than **2'** for most of the modelled structures (See Table S2 in the SI). Even when $R^1$ is an aryl, that could stabilize the exocyclic C=N by resonance, **2** generally results to be more stable. The tautomeric form **2'** prevails in solution only in case of compound **2n** with a *para*-nitrophenyl substituent. Moreover, the calculation, as well as experiments in deuterated methanol, suggest that the tautomerization proceeds through the formation of a dimer featuring two hydrogen bonds (see Figure S11).

At this point we were intrigued by the idea of performing a series of common *N*-functionalization reactions, to evaluate the reactivity of the two tautomers under different conditions. To this end, oxazoline **2g** ($R^1$ = Bn) was employed as a model substrate.

Moderate to excellent selectivity has been achieve in the reported experiments (Figure 2). In particular, *acetylation* carried out using acetyl chloride (AcCl) as acetylating agent and DMA as solvent, allowed quantitative formation of products **5** and **6** in 92/8 ratio based on $^1$H NMR integration (Figure 2a). On the contrary, the ratio can be reversed (27/73 = **5**/**6**) using $Et_3N$ as reaction medium (see SI for details). Under basic conditions, *methylation*, performed with MeI in DMF, led to a mixture of **5** and **6** in 61/39 molar ratio (Figure 2b). Gratifyingly, *formylation* carried out in acidic medium ($HCO_2H$ and $Ac_2O$) was completely selective toward isomer **5** (Figure 2c). Although we cannot take these results as an indication of the relative stability of the two tautomers in solution, we have preliminarily demonstrated that their reactivity can be conveniently controlled using the proper transformation in a suitable solvent.

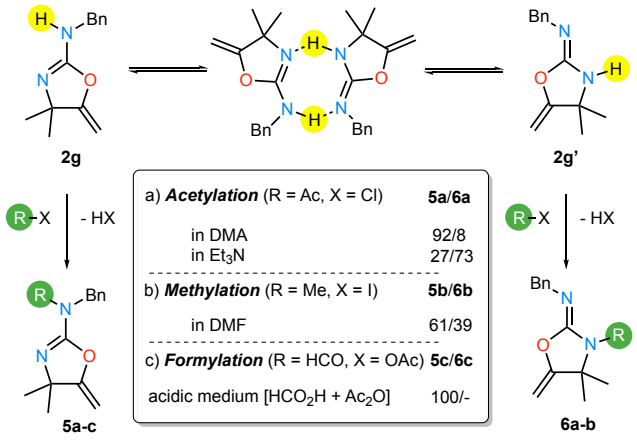
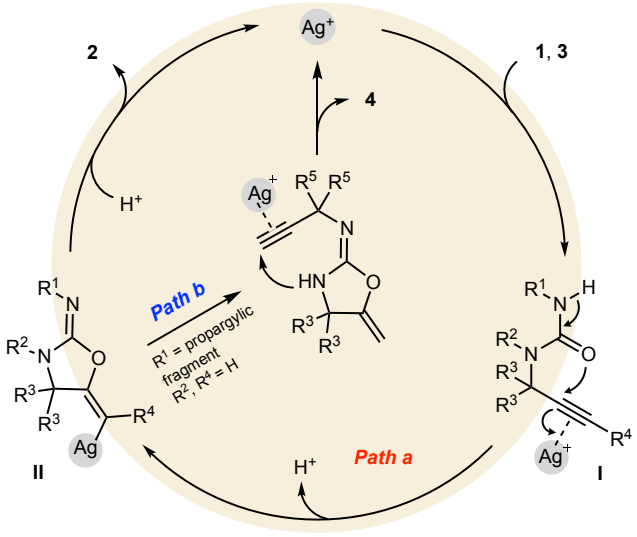



**Figure 2.** Tautomerization pathway and reactivity of compound **2g** under different reaction media (selected results).

Based on previous research[6,8a,9,16] and the present study, a plausible pathway of the silver-catalyzed transformation is here described (Scheme 3). Thanks to the Lewis acid character of Ag(I) along with its "carbophilicity", the coordination of the triple bond leads to the formation of complex **I**, which consequently undergoes *anti* 5-*exo*-*dig* nucleophilic




**Scheme 3.** Proposed mechanism for the one-pot silver-catalyzed synthesis of **2** (Path a) and **4** (Path b).

attack by the oxygen of the ureidic moiety to give the *E* vinylsilver intermediate **II** (Scheme 3, path a). Then, stereospecific protonolysis on **II** delivers the desired product **2**, and silver(I) is ready to restart a new

catalytic cycle. The stereoselective formation of the *Z* isomer can be explained through the Ag(I)-assisted nucleophilic *trans* addition of the O of the urea moiety to the activated triple bond, generating intermediate **II** exclusively. If another propargylic function is present at the other N ($R^1$ = propargyl fragment) and $R^2$ and $R^4$ are hydrogens, a second annulation process takes place in a regioselective 6-*endo-dig*[16], providing the final oxazolopyrimidine product **4** (Scheme 3, path b). Remarkably, compared to our previous base-catalyzed protocol,[10] the exclusive formation of *Z* configuration on the exocyclic C-C double bond is observed, and moreover, ureas bearing alkyl substituents on the N ($R^1$) can be competent substrates, widening the scope of previously reported methods.[6,8,9]

What seems clear is that the different substitution pattern of the starting urea dictates the regioselectivity of the reaction. The Hard Soft Acids Bases theory (HSAB) used to explain the complementary reactivity of Au and Ag systems with propargyl urea derivatives,[8a] cannot be employed here, since a change in the substitution pattern of the starting reagent leads to the opposite outcome,[17] and, in general, silver can duplicitously promote both the *O*- and the *N*-cyclization, depending mainly on the substitution setup of the 3-position of propargyl fragment. The possible existence of two distinct reaction mechanisms could in principle justify the experimental observations: one is the above-reported mechanism of the cyclization of ureas **1** and **3** (Scheme 3), and the other, which can only be applied to the mono- or unsubstituted at 3-position ($R^3$) propargylic ureas,[8a,9] might involve the formation of an allene intermediate which would eventually bear a nucleophilic attack of N.

In summary, we have disclosed a novel facile and efficient method for the synthesis of 2-aminooxazolines and oxazolo[3,2-a]pyrimidines from readily available propargylic ureas under the catalysis of Ag(I). Quite unexpectedly, silver salts in the absence of ligands led to the regio- and stereoselective formation of *O*-5-*exo-dig* products in high yields under mild conditions. Benign alcoholic medium accelerated the process reducing the reaction time to 4 hours. The one-pot process (from propargyl amines and isocyanates) was demonstrated as well. Studies aimed to overcome the limitations of the reported methodology and get insights into the reaction mechanism are currently in progress.

# Experimental Section

**General procedure for the Ag-catalyzed cyclization of propargylic ureas 1 to oxazoline-2-amines 2**

A 10 mL tube equipped with a magnetic stirrer was charged with propargylic urea (0.2 mmol) and MeOH (2 mL). Then $AgNO_3$ (1.7 mg, 0.01 mmol) was added. The reaction mixture was stirred at 60 °C and monitored by TLC. After completion of the reaction, the mixture was filtered through Celite® and concentrated in vacuo. If required, the residue was purified by silica gel column chromatography using a mixture of hexane and ethyl acetate as eluent.

**General procedure for the Ag-catalyzed cyclization of propargylic ureas 3 to oxazolo[3,2-a]pyrimidine 4**

A 10 mL tube equipped with a magnetic stirrer was charged with urea **3** (0.2 mmol) and MeCN dry (2 mL). Then AgOTf (5.1 mg, 0.02 mmol) was added. The reaction mixture was stirred at 80 °C and monitored by TLC. After 16-24 h, the mixture was filtered through Celite® and concentrated in vacuo. The residue was purified by silica gel column chromatography using hexane/EtOAc (1:1) as eluent.

**Single Crystal X-ray Diffraction**

SCXRD analysis was performed on single crystal samples on a Bruker D8 Venture diffractometer equipped with a kappa goniometer and an Oxford cryostream. Low temperature data collections were performed under nitrogen flux. Microfocused MoKα radiation (λ = 0.71073 Å) was used for sample **2g**, **2i**, **2j**, **2l**, **2n**, **4a** and **4d** while Microfocused CuKα radiation (λ = 1.5418 Å) was used for sample **2t**, **PUM168@2x** and **8**. Additional details are included in ESI. CCDC 2190425-2190434 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

# Acknowledgements

*We wish to thank MIUR (Progetto Competitivo 2020 CMPT200224), UniPR for the financial support and CIM (Interdepartmental Measurements Centre) for NMR facilities. This work has benefited from the equipment and framework of the COMP-HUB Initiative, funded by the "Departments of Excellence" program of the Italian Ministry for Education, University and Research (MIUR, 2018-2022). The "Laboratorio di Strutturistica - M. Nardelli" of the University of Parma and Chiesi Farmaceutici SpA are thanked for the X-ray diffraction data collection. P.P.F. and A.S. acknowledge support from Grant K132236 of the NRDI Office, Hungary and the computational resources of KIFÜ.*

# References

[1] a) C. Corti, G. Antonarelli, C. Criscitiello, N. U. Lin, L. A. Carey, J. Cortés, P. Poortmans, G. Curigliano, *Cancer Treatment Reviews* **2022**, *103*, 102324; b) J. D. Low, M. D. Bartberger, K. Chen, Y. Cheng, M. R. Fielden, V. Gore, D. Hickman, Q. Liu, E. Allen Sickmier, H. M. Vargas, J. Werner, R. D. White, D. A. Whittington, S. Wood, A. E. Minatti, *Med. Chem. Commun.* **2017**, *8*, 1196–1206; c) J. Cook, F. C. Zusi, I. M. McDonald, D. King, M. D. Hill, C. Iwuagwu, R. A. Mate, H. Fang, R. Zhao, B. Wang, J. Cutrone, B. Ma, Q. Gao, R. J. Knox, M. Matchett, L. Gallagher, M. Ferrante, D. Post-Munson, T. Molski, A. Easton, R. Miller, K. Jones, S. Digavalli, F. Healy, K. Lentz, Y. Benitex, W. Clarke, J. Natale, J. A. Siuciak, N. Lodge, R. Zaczek, R. Denton, D. Morgan, L. J. Bristow, J. E. Macor, R. E. Olson, *J. Med. Chem.* **2016**, *59*, 11171–11181; d) G. Galley, A. Beurier, G. Décoret, A. Goergler, R. Hutter, S. Mohr, A. Pähler, P. Schmid, D. Türck, R. Unger, K. G. Zbinden, M. C. Hoener, R. D. Norcross, *ACS Med. Chem. Lett.* **2016**, *7*, 192–197; e) E. Jnoff, B. Christophe, P. Collart, F. Coloretti, A. Debeuckelaere, M. De Ryck, B. Fuks, C. Genicot, M. Gillard, M. Guyaux, N. Price, M.-C. Vandergeten, C. Vermeiren, *ChemMedChem* **2012**, *7*,

385–390; f) E. Azzali, M. Girardini, G. Annunziato, M. Pavone, F. Vacondio, G. Mori, M. R. Pasca, G. Costantino, M. Pieroni, *ACS Med. Chem. Lett.* **2020**, *11*, 1435−1441.

[2] a) M. W. Powner, B. Gerland, J. D. Sutherland, *Nature* **2009**, *459*, 239–242; b) A. C. Fahrenbach, C. Giurgiu, C. P. Tam, L. Li, Y. Hongo, M. Aono, J. W. Szostak, *J. Am. Chem. Soc.* **2017**, *139*, 8780–8783.

[3] a) R. P. Singh, J. Das, M. Yousufuddin, D. Gout, C. J. Lovely, *Org. Lett.* **2017**, *19*, 4110–4113; b) D. V. Gribkov, S. J. Pastine, M. Schnürch, D. Sames, *J. Am. Chem. Soc.* **2007**, *129*, 11750–11755; B. M. Cochran, F. E. Michael, *Org. Lett.* **2008**, *10*, 5039–5042.

[4] H. Huang, D. S. La, A. C. Cheng, D. A. Whittington, V. F. Patel, K. Chen, T. A. Dineen, O. Epstein, R. Graceffa, D. Hickman, Y.-H. Kiang, S. Louie, Y. Luo, R. C. Wahl, P. H. Wen, S. Wood, R. T. Fremeau, *J. Med. Chem.* **2012**, *55*, 9156–9169.

[5]a) Y. J. Park, N. S. Sickerman, J. W. Ziller, A. S. Borovik, *Chem. Commun.* **2010**, *46*, 2584–2586; b) N. R. Easton, D. R. Cassady, R. D. Dillard, *J. Org. Chem.* **1964**, *29*, 1851–1855.

[6] S. Gazzola, E. M. Beccalli, T. Borelli, C. Castellano, M. A. Chiacchio, D. Diamante, G. Broggini, *J. Org. Chem.* **2015**, *80*, 7226–7234.

[7]A. Bacchi, G. P. Chiusoli, M. Costa, C. Sani, B. Gabriele, G. Salerno, *J. Organomet. Chem.* **1998**, *562*, 35–43.

[8] a) O. P. Pereshivko, V. A. Peshkov, J. Jacobs, L. V. Meervelt, E. V. Van der Eycken, *Adv. Synth. Catal.* **2013**, *355*, 781–789; b) M. J. Campbell, F. D. Toste, *Chem. Sci.* **2011**, *2*, 1369–1378.

[9] a) V. A. Peshkov, O. P. Pereshivko, S. Sharma, T. Megana- than, V. S. Parmar, D. S. Ermolat'ev, E. V. Van der Eycken, *J. Org. Chem.* **2011**, *76*, 5867–5872; b) V. A. Peshkov, O. P. Pereshivko, A. A. Nechaev, A. A. Peshkov, E. V. Van der Eycken, *Chem. Soc. Rev.* **2018**, *47*, 3861–3898.

[10] A. Casnati, A. Perrone, P. P. Mazzeo, A. Bacchi, R. Mancuso, B. Gabriele, R. Maggi, G. Maestri, E. Motti, A. Stirling, N. Della Ca', *J. Org. Chem.* **2019**, *84*, 3477−3490.

[11] Deuterated **1b** (*d*-**1b**) was obtained simply dissolving **1b** in $CD_3OD$ (see 1H NMR spectrum of **1b** and *d*-**1b** in the SI).

[12] a) M.E. Jung, G. Piizzi, *Chem. Rev.* **2005**, *105*, 1735−1766; b) P.G. Sammes, D.J. Weller, *Synthesis* **1995**, *10*, 1205−1222.

[13] Reactions performed starting from ureas bearing an internal alkyne fragment (**1t-v**) led to the corresponding products **2t-v** in limited yields (43-57%): in these experiments, the major part of the catalyst precipitates within the first 2-3 hours, and the final reaction mixture consists of the desired product, the starting urea, and a couple of minor unidentified by-products.

[14] E. V. Babaev, V. L. Alifanov, A. V. Efimov, *Russ Chem Bull* **2008**, *57*, 845–862.

[15] The best reaction conditions for the double sequential cyclization of ureas **3** to compounds **4** feature an increased temperature (80 °C), MeCN, that was find the most compatible solvent, and AgOTf in place of $AgNO_3$.

[16] R. Lok, R. E. Leone, A. J. Williams, *J. Org. Chem.* **1996**, *61*, 3289–3297.

[17] An example of this opposed reactivity has been performed by us (from urea **7** to imidazolidinone **8**) and the structure of product **8** has been determined by X-ray diffraction analysis (see ESI, Figure S10)

Unexpected Stereoselective Access to 2-Aminooxazolines from Propargyl Ureas by Silver Salts under Mild Conditions

*Adv. Synth. Catal.* **Year**, *Volume*, Page – Page

Aleksandr Voronov, Alessandra Casnati, Paolo P. Mazzeo, Paolo Pelagatti, Alessia Bacchi, Raffaella Mancuso, Bartolo Gabriele, Elena Motti, Giovanni Maestri, Péter Pál Fehér, András Stirling, and Nicola Della Ca'*