Propargylic ureas as powerful and versatile building blocks in the synthesis of various key medicinal heterocyclic compounds

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This review article is an attempt to highlight the most important contributions toward the synthesis of various nitrogen-containing heterocyclic compounds from corresponding propargylic ureas through regio- and chemoselective 5-exo-dig and 6-endo-dig modes of N- and O-cyclization reactions. The review is divided into three major sections. In the first section we only focus on 5-exo-dig N-cyclization fashion. In the second section 5-exo-dig O-cyclization is described. The third section is devoted to 6-endo-dig N- and O-cyclizations.

Keywords:
propargylic ureas
5-exo-dig cyclization
6-endo-dig cyclization
heterocyclic compounds

1. Introduction

Heterocyclic compounds are the special class of organic compounds that contain a ring structure containing atoms in addition to carbon, such as nitrogen, oxygen or sulfur, as part of the ring [1]. These compounds constitute a common structural unit of most of the currently marketed drugs [2]. Over 90% of new drugs contain at least one heterocyclic (especially nitrogen-containing ring) fragment in their structures [3]. Interestingly, of the top five US small molecule drug retail sales in 2014, four are or contain N-heterocycle fragments in their overall structure (Figure 1) [4]. Although many synthetic approaches are reported to make this special class of organic compounds [5], still there is a demand for new methods.

![Chemical structures](image)

**Fig. 1** N-heterocycle molecule drugs present in the US top five prescription drugs and respective retail sales in 2014 (in billions of U.S. $)

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The intramolecular cyclization of heteroatom-containing acetylenic compounds has emerged as an effective and general synthetic route to the construction of various heterocyclic systems in an atom- and step-economic manner. This methodology is one of the most useful tools to create new carbon–heteroatom bonds both in the academic laboratory and in industry [6]. Propargyl urea derivatives are one of the most specific classes of heteroatom containing alkynes having diverse reaction patterns. These compounds not only can undergo regio- and chemoselective 5-exo-dig and 6-endo-dig N-cyclization reactions to provide synthetically and biologically important 1H-imidazol-2(3H)-one and 2,4-dihydropyrimidin-2(1H)-one derivatives, respectively, but also can undergo regioselective 5-exo and 6-endo modes of O-cyclization reactions to produce corresponding oxazolidin-2-imine and 3,4-dihydro-1,3-oxazin-2-imines, respectively (Figure 2). To the best of our knowledge, the significance of propargylic ureas as useful building blocks in organic syntheses has not been reviewed. In continuation of our reviews in the synthesis of N-heterocycles compounds [7-18], in this mini review, we will highlight the most important developments on the regio- and chemoselective cyclization of titled compounds which will be helpful in the development of improved methods for the synthesis of various biologically important nitrogen-based heterocycles. The review is divided into three major sections. In the first section we only focus on 5-exo-dig N-cyclization fashion. In the second section 5-exo-dig O-cyclization is described. The third section is devoted to 6-endo-dig N- and O-cyclizations.

![Fig. 2 Synthesis of heterocyclic compounds from propargyl ureas through regio- and chemoselective 5-exo-dig and 6-endo-dig modes of N- and O-cyclization reactions.](image)

### 2. 2-Imidazolones

Imidazole is a planar five-membered ring heterocyclic compound with two nitrogen atoms at the 1,3-positions. Many imidazole derivatives are known to have a wide range of biological properties such as antibacterial, anti-tubercular, anti-parasitic, anti-cancer, anti-neuropathic, anti-convulsant, anti-histaminic, anti-inflammatory, and anti-obesity activity [19]. Among those known are several 1H-2-imidazolone derivatives, such as citronamide A and B [20], domperidone [21], and IACS-9571 [22]. Regio- and chemoselective cyclization reactions of propargyl ureas provide an interesting and practical route for the preparation of 2-imidazolone core structures.

The first mention of the synthesis of imidazolidinone derivatives 4 through a base catalyzed intramolecular cyclization of propargyl ureas 3 (generated in situ by the reaction of corresponding propargylamines 1 with isocyanates 2) can be found in a 1963 paper by Shachat and Bagnell, [23] although only three low-yielding examples were described (Scheme 1). After a half-century, Proulx and Lubel successfully applied this synthetic procedure in the construction of N-amino-imidazolin-2-one peptide mimic 6 (Scheme 2) [24].

In 2011, Ermolat’ev and Eycken along with their co-workers studied the possibility of synthesizing highly substituted 2-imidazolones 10 from secondary propargylamines 7 and isocyanates 8 via a one-pot acylation, Ag(I)-catalyzed 5-exo-dig cyclization procedure. Thus, the careful analysis of the optimized
reactions revealed that the optimum condition for this reaction was the addition of 20 mol% of commercially available AgOTf to a solution of propargylic ureas 9, derived from propargylamines 7 and isocyanates 8, in refluxing toluene (Scheme 3). It is noted that other silver catalysts also promoted the reaction (e.g., AgSbF6, AgNO3, AgOCCF3); however, in lower yields. Under the optimized conditions, an array of tetrasubstituted 2-imidazolones was successfully produced. It was suggested that the reaction proceeds through the coordination of Ag+ to the triple bond of propargylic urea 9, derived from the corresponding propargylamine and isocyanate, to form intermediate A; which after a regioselective 5-exo-dig cyclization step affords cationic intermediate B. Subsequent proton transfer in intermediate B provides the 2-imidazolone C bearing an exocyclic double bond. Finally, double-bond migration yields the observed 2-imidazolone 10 (Scheme 4) [25]. Ranjan and coworkers showed subsequently that this method for 2-imidazolone synthesis was much improved in terms of yield when the reaction was carried out in the presence of sodium hydroxide in DMF at room temperature. Under these conditions, the reaction tolerated both isocyanates and isothiocyanates and gave the corresponding imidazole-2-(thi)ones in good to almost quantitative yields. Beside high yields, short reaction time, broad substrate scope, and mild reaction conditions were other advantages of this base catalyzed reaction [26].

![Scheme 1](image1)

Scheme 1. Intramolecular 5-exo-dig N-cyclization of propargylic ureas 3 developed by Shachat and Bagnell.

![Scheme 2](image2)

Scheme 2. Synthesis of N-amino-imidazolin-2-one peptide mimic 6 from corresponding propargylic urea 5.

![Scheme 3](image3)

Scheme 3. Synthesis 2-imidazolones 10 from secondary propargylamines 7 and isocyanates 8 via a one-pot acylation, Ag(I)-catalyzed 5-exo-dig cyclization.

In a closely related investigation, the group of Huguenot also described that tetra-n-butylammonium fluoride (TBAF) catalyzed 5-exo-dig N-cyclization of α,α-disubstituted terminal propargyl ureas 11a-e produced corresponding substituted 2-imidazolidinones 12a-e in good to excellent yields (Scheme 5). The results demonstrated that depending on the nature of the propargyl moiety, the imidazolidin-2-one is quickly converted into the aromatic 2-imidazolone ring. Thus, in the case of α,α-unsubstituted terminal propargyl ureas 11f-h, the corresponding 2-imidazolones 12f-h were formed in good yields, as a single isomer, using 1.0 equiv of TBAF, in THF at room temperature. The authors also elegantly showed that under the standard conditions the 5-exo-tet and 5-exo-trig cyclization processes predominated over the 5-exo-dig cyclization process (Scheme 6) [27].
Recently, an interesting gold-catalyzed cycloisomerization of immobilized propargyl urea derivatives toward the regioselective synthesis of 2-imidazolidinones was reported by La-Venia et al. Thus, the treatment of solid-supported terminal propargyl ureas 15 with 5 mol% of simple gold salt AuCl in binary solvent DCM/MeCN with ratio 5:1 afforded highly substituted 2-imidazolidinones 16 in moderate to excellent yields (Scheme 7). It should be mentioned that in the optimization study, the authors found that other gold catalysts also promoted the reaction (e.g., Ph₃PAuCl, Ph₃PAuNTf₂, Ph₃PAuCl/AgSbF₆, Ph₃PAuCl/AgOTf, AuCl); however, the use of AgCl gave the best results [28].

Oxazoline derivatives are of great interest to medicinal chemistry due to their broad range of biological activity [29]. Among a variety of oxazolines, oxazolidin-2-imines are currently attracting considerable attention due to their significant biological features [30]. For instance, they show strong inhibitory activity against nitric oxide synthase enzymes [31]. It was recently found that the nitric oxide synthase inhibitors have antidepressant and anxiolytic properties [32]. As a consequence, nowadays the preparation of oxazolidin-2-imine derivatives is one of the hot topics in synthesis organic chemistry research [33].

**Scheme 4.** Mechanistic proposal for the reaction in Scheme 3.

**Scheme 5.** TBAF-catalyzed synthesis of 2-imidazolidinones 12 from terminal propargylic ureas 11.

**Scheme 6.** Selective 5-exo-tet and 5-exo-trig cyclization reactions of propargylic ureas 11.

**Scheme 7.** Au(I)-catalyzed solid-phase synthesis of 2-imidazolidinones 16.

3. Oxazolines
amount of Ph₃PAuCl/AgNTf₂ in chloroform gave corresponding oxazoline derivatives 20 in moderate to very good yields together with a trace amount of six-membered product 21 formed by a 6-endo-dig cyclization (Scheme 8). The same authors also carried out the enantioselective version of this reaction using a chiral gold complex as a cataly, however, the results were not very good (Table 1) [34].

Scheme 8. Toste’s synthesis of oxazolines 20.

Table 1. Enantioselective synthesis of oxazolines 20 via a gold-catalyzed three-component reaction of imines 17, phenylacetylene 18a, and p-toluenesulfonyl isocyanate 19.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield%</th>
<th>Regio (20:21)</th>
<th>ee%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>C7H8</td>
<td>21</td>
<td>27 (37)</td>
<td>4.5:1</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>DCM</td>
<td>48</td>
<td>75 (0)</td>
<td>5:1</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>4-Cl-C₆H₄</td>
<td>DCM</td>
<td>24</td>
<td>30 (51)</td>
<td>3:1</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
<td>4-Cl-C₆H₄</td>
<td>DCM</td>
<td>168</td>
<td>52 (14)</td>
<td>3:1</td>
<td>82</td>
</tr>
</tbody>
</table>

a Determined with the use of an internal standard (mesitylene) by 1H NMR. The value in parentheses is the yield of the corresponding uncyclized urea. b Determined by 1H NMR. c Determined by chiral HPLC.

Subsequently, an efficient one-pot synthesis of the dimeric 2-oxazoline scaffold has been developed by Kato et al. They showed that α,α-disubstituted terminal propargyl ureas 22 underwent a tandem cyclization-carbonylation-cyclization coupling reaction in the presence of palladium(II)-bisoxazoline A as a catalyst in methanol under a carbon monoxide atmosphere at room temperature. Under optimized conditions, the reaction is tolerant toward a variety of functional groups and gave the corresponding symmetrical ketones bearing two 2-amino-2-oxazole groups 23 in good yields (Scheme 9). However, α-mono substituted substrates failed to form the desired products. It should be mentioned that the unexpected monomeric esters 24 were also detected during the chromatographic purification in low yields. The author proposed mechanism for the formation of dimeric ketone 23 is depicted in Scheme 10. The intermediate A, formed from the coordination of palladium(II) to the triple bond of propargyl urea 22, undergoes intramolecular cyclization to generate the 2-oxazoline derivative B. This intermediate can then be converted into the intermediate C by a formal CO insertion. Coordination of the C-C triple bond of a second propargylic urea induces the second cyclization and forms intermediate D. This intermediate undergoes reductive elimination to produce desired products 23 [35].

More recently, to develop an efficient and practical protocol for the synthesis of oxazolidin-2-imine derivatives bearing an exocyclic haloalkylene 27 from propargylic ureas, Zhou and co-workers have investigated the three-component halocyclization of propargyl amines 25, aryl isocyanates 26, and iodine (or NBS) in ethyl acetate, and moderate to excellent yields of desired oxazolines was observed (Scheme 11). The reaction is noteworthy in that both terminal and internal propargyl amines is tolerated. These compounds could be used as coupling partners in transition metal
catalyzed cross-coupling reactions to the synthesis of more functionalized oxazoline scaffolds. The mechanistic course of this reaction sequence is shown in Scheme 12, and involves the initial formation of the propargylic urea intermediate A from the reaction of propargyl amine 25 and isocyanate 26. The electrophilic addition of \( I_2 \) (or NBS) to the triple bond of this intermediate gives halonium intermediate B, which undergoes isomerization to produce intermediate C. Subsequently, an intramolecular cyclization and HX elimination to afford corresponding oxazolines 27 [36].

\[
R^1 = \text{Me, } -\text{(CH}_2\text{)}_3-, \quad R^2 = ^{1}Pr, ^{1}Bu, ^{1}Hex, \text{Ph, OPh, Bn, Bn}
\]

Scheme 9. Synthesis of the dimeric 2-oxazolines 23 from corresponding \( \alpha,\alpha \)-disubstituted terminal propargyl ureas 22 through a Pd-catalyzed tandem cyclization-carbonylation-cyclization coupling reaction.

\[
\begin{align*}
R^1 + R^2NCO + X &\rightarrow \text{ethyl acetate} \quad 50°C, 12 h \\
&\rightarrow \text{oxazoline derivative 27} \\
&\text{13 examples (42-97%) (average yield: 70%)}
\end{align*}
\]

Scheme 11. Synthesis of oxazolidin-2-imine derivatives 27 via direct halocyclization between propargylamines 25, aryl isocyanates 26 and \( I_2 \) (NBS).

\[
\begin{align*}
25 + 26 &\rightarrow \text{oxazolidin-2-imine derivatives 27} \\
&\text{8 examples (58-89%) (average yield: 66%)}
\end{align*}
\]

Scheme 10. Mechanism that accounts for the formation of 23.

4. 2-Pyrimidinone and 1,3-oxazine derivatives

2-Pyrimidinone derivatives are important structural motifs found in many biologically active structures and medicinally relevant compounds [37]. Compounds containing these cores have widespread biological applications as anticancer, antimicrobial, antihypertensive, antiulcer, anti-inflammatory, antitubercular, antimarial, and antioxidant agents [38]. Several commercially available drugs, including flucytosine, capreomycin, fluorouracil and butabarbital are derived from 2-pyrimidinone core entities. In a similar way, 1,3-oxazine-2-imine derivatives are ubiquitous structural motifs in various biologically active pharmaceuticals [39]. Therefore, the development of novel and truly efficient synthetic methods for their preparation is of prime importance in organic synthesis.

The possibility of regioselective 6-endo-dig \( N \)-cyclization of propargyl ureas to dihydropyrimidones was first realized by Looper and co-workers [40], who synthesized a series of 1,3,6-trisubstituted 3,4-dihydropyrimidin-2(1H)-one derivatives 29 from internal propargyl ureas 28 in the presence of \([\text{Rh}_2(\text{OAc})_2(\text{MeCN})]_2[\text{BF}_4]_2\) as a cationic rhodium catalyst in DCM. Under optimized conditions, the
reaction showed remarkable flexibility and desired products were formed in moderate to excellent yields with both aryl and alkyl substituted propargylic ureas. As shown in Scheme 13, the reaction tolerated a variety of functional groups, such as chloro, bromo, nitro, methoxy, and vinyl functionalities. This made possible the further derivatization of the products to more complex systems. On a separate note, it was discovered that synthesized compounds 29a,b could inhibit the proliferation of the LN-229 glioblastoma cell line (Scheme 14).

Scheme 13. Rh(II)-catalyzed synthesis of dihydropyrimidones 29 from propargyl ureas 28.

Scheme 14. Chemical structure of 1,3,6-trisubstituted 3,4-dihydropyrimidin-2(1H)-ones 29a and 29b that capable of inhibiting proliferation of the LN-229 glioblastoma cell line.

Shortly afterward, a similar regio- and chemoselective cycloisomerization was used by the group of Van der Eycken in the synthesis of tetrasubstituted 3,4-dihydropyrimidin-2(1H)-ones 33 via heating of in situ generated internal propargylic ureas 32 in the presence of cationic gold(I) catalyst AuPPh3Cl/AgOTf in chloroform. Under these conditions, the corresponding dihydropyrimidones 33 were obtained in relatively low to excellent yields (Scheme 15). Interestingly, in the case of terminal propargyl ureas the 6-endo-dig pathway was not realized and, corresponding 5-exo-dig products were formed [41].

Scheme 15. Synthesis of tetrasubstituted 3,4-dihydropyrimidin-2(1H)-ones 33 via heating of in situ generated internal propargylic ureas 32 in the presence of a cationic gold(I) catalyst.

An interesting and rare example for synthesis of indole fused 2-pyrimidinones 35, which were prepared because of their potential pharmaceutical interest, has been developed by Kundu and co-workers, and is based on the regioselective intramolecular cyclization of corresponding 2-ethyl-1H-indole-1-carboxamides 34 in the presence of 5 mol% of AuClPPh3 as catalyst and 20 mol% of AgOTf as co-catalyst. The reaction was run in DCM at room temperature and generally provided the highly substituted pyrimido[1,6-a]indolones 36 in moderate to high yields. Interestingly, When the reaction was carried out in the presence of AuCIPPh3/AgNO3 combination as a catalytic system, the N-[1,3]oxazino[3,4-a]indol-1-ylideneamine products 36 was obtained exclusively (Scheme 16). The differentiation between the mechanisms of this two cyclizations is shown in Scheme 17. In one way, the mechanism proposed for the formation of pyrimido[1,6-a]indolones 35 involves the key intermediate [PhP= (Au)TFO], generated in situ, which forms the soft electrophilic intermediate A by the coordination to the C-C triple bond of alkyne 34. Next, the nitrogen of the urea, being less electronegative than oxygen, favorably attacks as a relatively softer nucleophile onto the electron-deficient alkyne to afford observed pyrimidinone core 35. In the other way, AuCIPPh3/AgNO3 combination simultaneously activates the alkyne by Au catalyst along with coordination of Ag with the oxygen of the urea to furnish the intermediate D which upon cyclization and protodeauration delivers the corresponding O-cyclized product 36 [42].
5. Conclusions

Heterocyclic compounds are not only prevalent in an extensive number of natural products and synthetic pharmaceuticals but also used as building blocks in organic synthesis. Although many synthetic approaches are reported to make this special class of organic compounds, still there is a demand for new methods. The examples discussed above showed that propargylic ureas are interesting precursors for the synthesis of various biologically important heteroaromatic compounds. Titled compounds were successfully transformed to the corresponding 1H-imidazo-2(3H)-ones, 2,4-dihydropyrimidin-2(1H)-ones, oxazolidin-2-
imines, 3,4-dihydro-1,3-oxazin-2-imines through regio-
and chemoselective 5-exo-dig and 6-endo-dig modes of N- and O-cyclization reactions depending on the nature of starting propargyl urea, the used catalyst, and reaction conditions. We conclude this review by hoping that it will stimulate researchers to develop highly regio-, stereo-, and chemoselective procedures for the synthesis of biologically important N-heterocyclic compounds.

References


