Review Article

Chemical Review and Letters
journal homepage: www.chemrevlett.com
ISSN (online): 2645-4947 (print) 2676-7279

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

Sepideh Farshbaf [a], Lakshmaiah Sreerama [b,*], Torkan Khodayari [c], Esmail Vessally [d]

[a] *Department of Chemistry, Center for Photochemical Sciences, Bowling Green State University, Bowling Green, Ohio 43403, USA*
[b] *Department of Chemistry and Earth Sciences, College of Arts and Science, Qatar University, P.O. Box 2713, Doha, Qatar*
[c] *Department of Chemistry, Tabriz Branch, Islamic Azad University, Tabriz, Iran*
[d] *Department of Chemistry, Payame Noor University, P. O. Box: 19395-4697, Tehran, Iran*

ARTICLE INFO

Article history:
Received 30 July 2018
Received in revised form 8 September 2018
Accepted 18 September 2018
Available online 19 September 2018

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

ABSTRACT

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.

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. 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]. Propargylic 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 1*H*-imidazol-2(3*H*)-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

* Corresponding author, Tel: +974 7070 6746; email: lsreerama@qu.edu.qa

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.

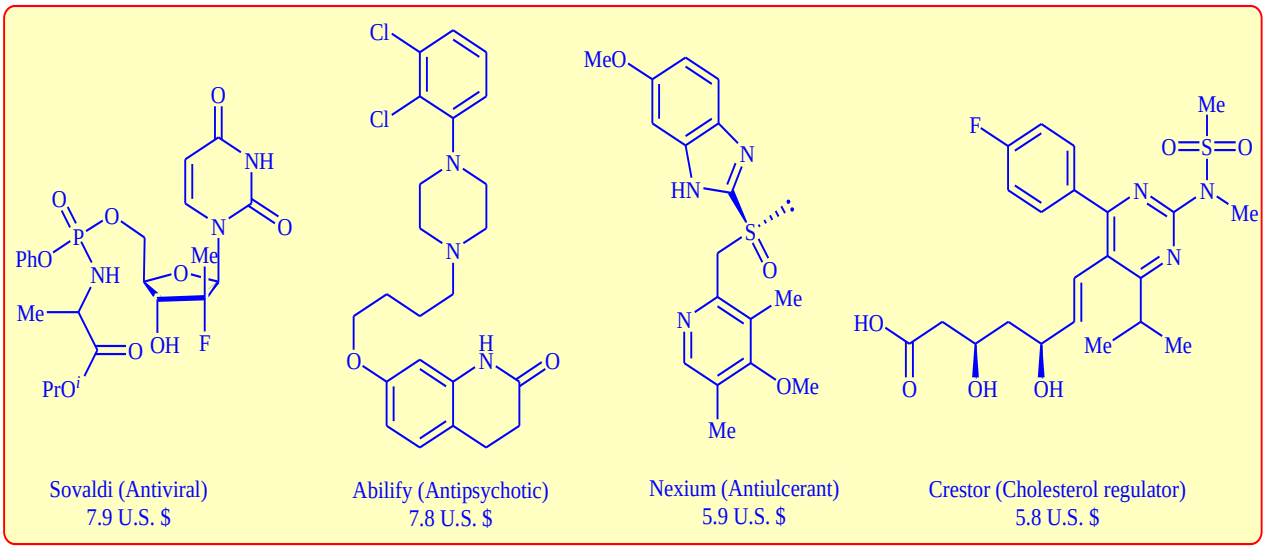


Fig. 1 N-heterocycle molecule drugs present in the US top five prescription drugs and respective retail sales in 2014 (in billions of U.S. $)

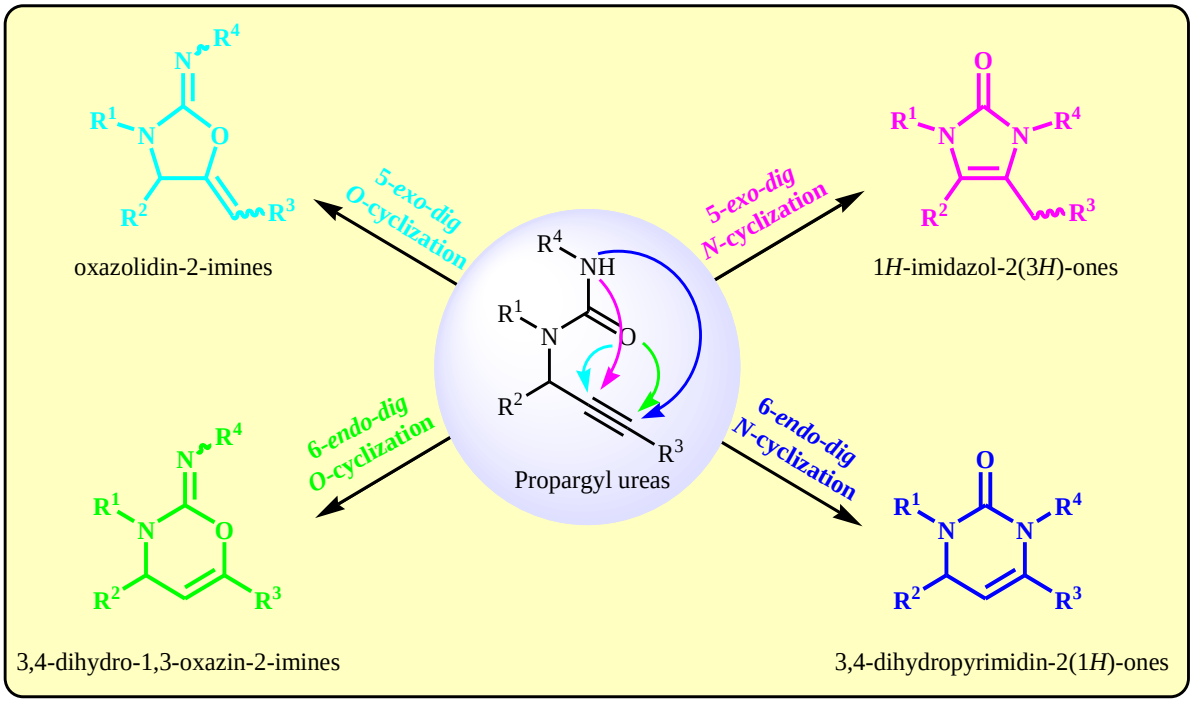


Fig. 2 Synthesis of heterocyclic compounds from propargylic ureas through regio- and chemoselective 5-*exo-dig* and 6-*endo-dig* modes of *N*- and *O*-cyclization reactions.

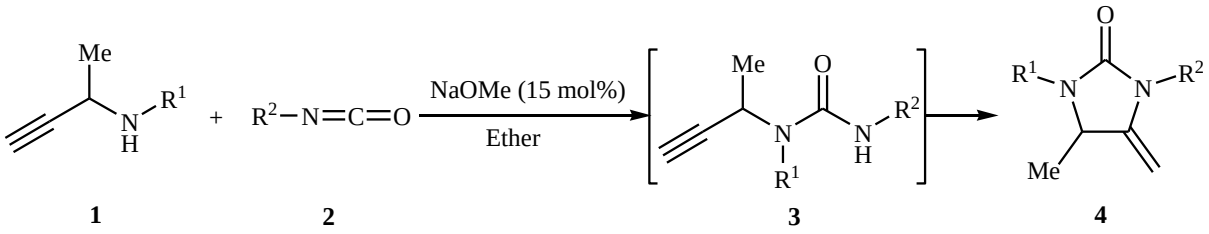
2. Imidazolones

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 anti-bacterial, anti-tubercular, anti-parasitic, anti-cancer, anti-neuropathic, anti-convulsant, anti-histaminic, anti-inflammatory, and anti-obesity activity [19]. Among those known are several 1*H*-2-imidazolone derivatives, such as citronamide A and B [20], domperidone [21], and IACS-9571 [22]. Regio- and chemoselective cyclization reactions of propargylic ureas provide an interesting and practical route for the preparation of 2-

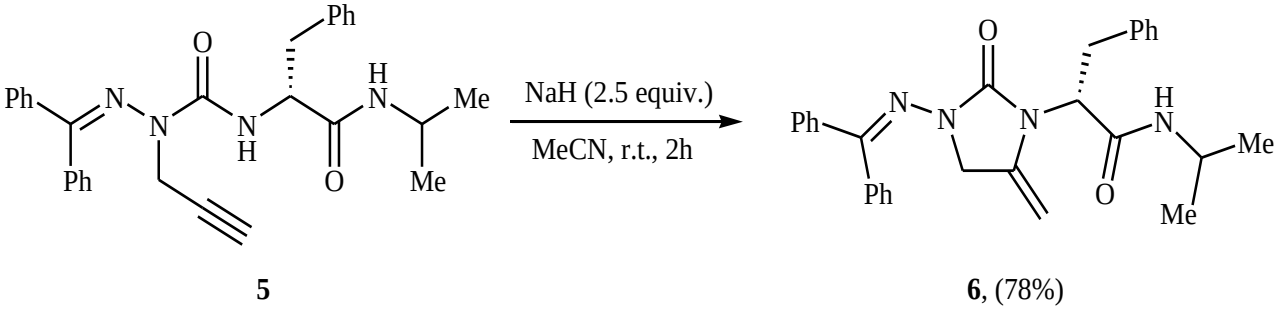
imidazolone core structures.

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].

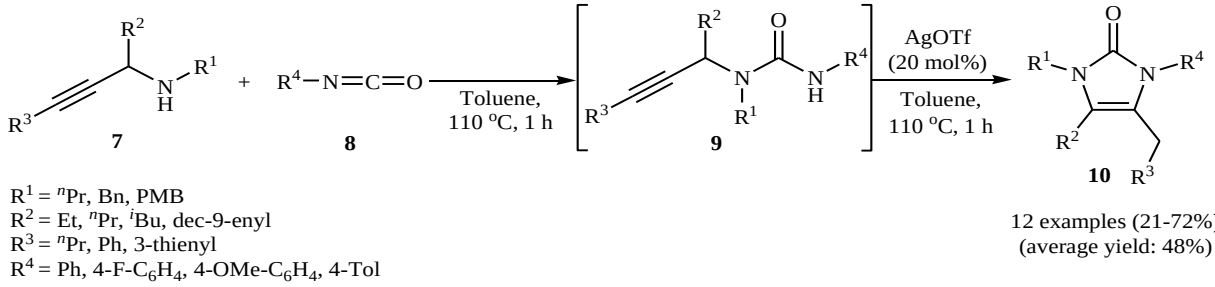
In 2011, Ermolat'ev and Eycken along with their co-workers studied the possibility of synthesizing highly substituted 2-imidazolones **10** from secondary propargylamines **7** and isocyanates **8** *via* a one-pot acylation, Ag(I)-catalyzed 5-*exo*-*dig* cyclization procedure. Thus, the careful analysis 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.*, $AgSbF_6$, $AgNO_3$, $AgOOCCF_3$); 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. Intramolecular 5-*exo*-*dig* *N*-cyclization of propargylic ureas **3** developed by Shachat and Bagnell.



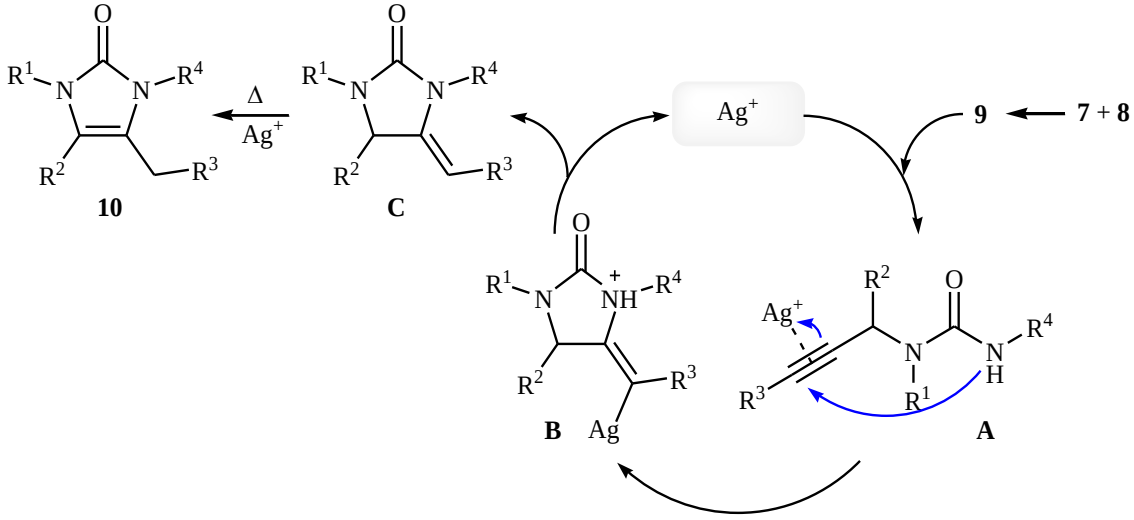
Scheme 2. Synthesis of *N*-amino-imidazolin-2-one peptide mimic **6** from corresponding propargylic urea **5**.



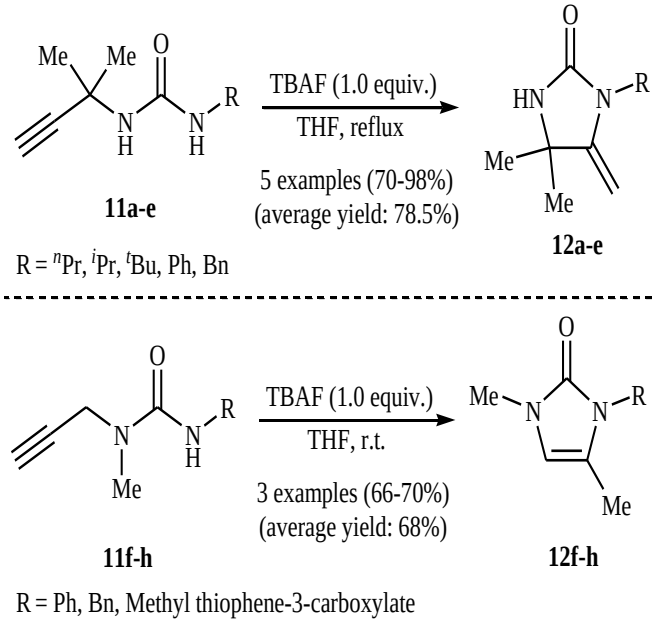
Scheme 3. Synthesis 2-imidazolones **10** from secondary propargylamines **7** and isocyanates **8** *via* a one-pot acylation, Ag(I)-catalyzed 5-*exo*-*dig* cyclization.

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].

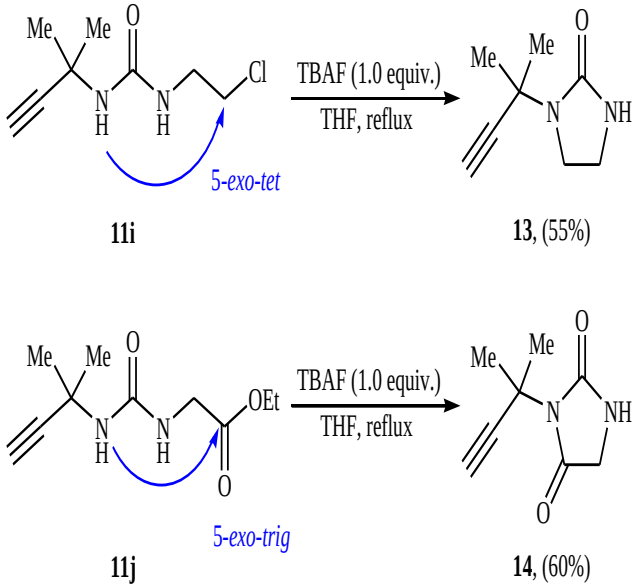
Recently, an interesting gold-catalyzed cycloisomerization of immobilized propargyl urea derivatives toward the regioselective synthesis of 2-imidazolidinones was reported by La-Venia *et al*. Thus, the treatment of solid-supported terminal propargylic ureas **15** with 5 mol% of simple gold salt AuCl 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.*, Ph_3PAuCl, $Ph_3PAuNTf_2$, $Ph_3PAuCl/AgSbF_6$, $Ph_3PAuCl/AgOTf$, $AuCl_3$); however, the use of AgCl gave the best results [28].



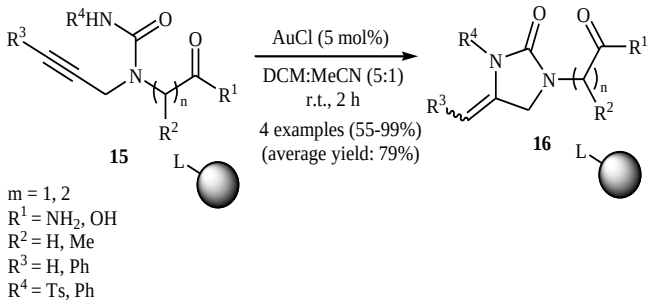
Scheme 4. Mechanistic proposal for the reaction in Scheme 3.



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**.

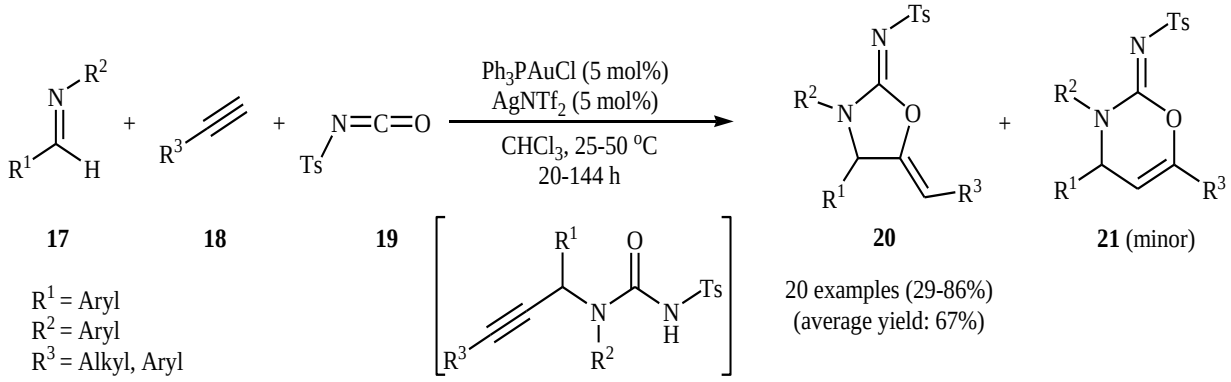


Scheme 7. Au(I)-catalyzed solid-phase synthesis of 2-imidazolidinones **16**.

3. Oxazolines

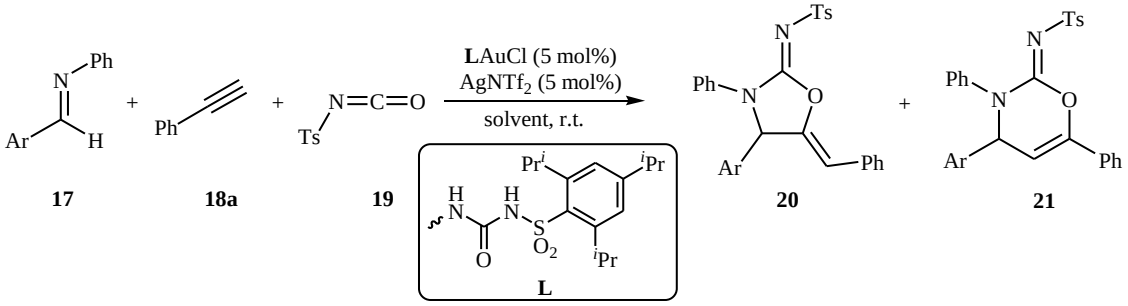
Oxazoline derivatives are of great interest to medicinal chemistry due to their broad range of biological activity [29]. Among a variety of oxazolines, oxazolidin-2-imines are currently attracting considerable attention due to their significant biological features [30]. For instance, they show strong 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].

5-*exo-dig O*-cyclization of propargylic urea derivatives is a straightforward route to the oxazoline cores. One of the earliest report of the applicability of such reactions, has been reported by Campbell and Toste in 2011. They showed that *O*-attack-5-*exo-dig* cyclization of *in situ* generated propargyl ureas bearing an internal alkyne **20** (*via* a three-component reaction from imines **17**, terminal alkynes **18**, and sulfonylisocyanates **19**) in the presence of catalytic amount of $Ph_3PAuCl/AgNTf_2$ 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 catalyst, 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*-toluenesulfonylisocyanate **19**.

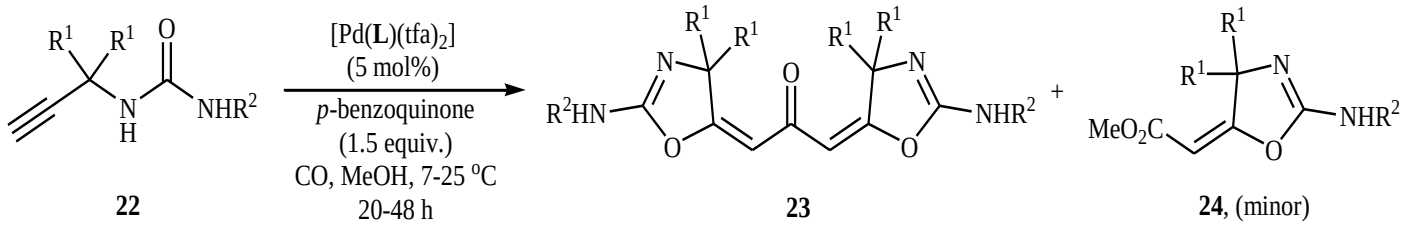


Entry	Ar	Solvent	Time (h)	Yield[a]%	Regio (**20**:**21**)[b]	ee[c]%
1	Ph	C7H8	21	27 (37)	4.5:1	85
2	Ph	DCM	48	75 (0)	5:1	81
3	4-Cl-C_6H_4	DCM	24	30 (51)	3:1	83
4	4-Cl-C_6H_4	DCM	168	52 (14)	3:1	82

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

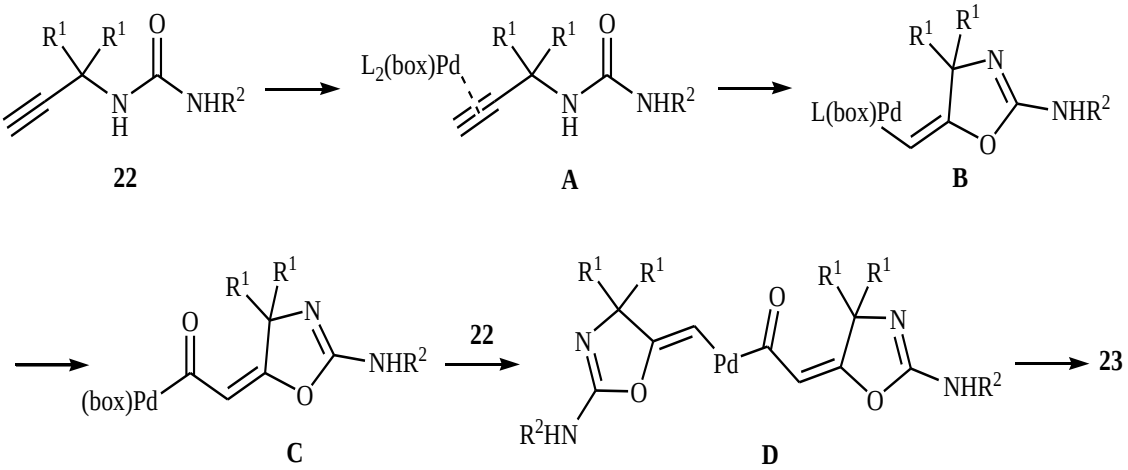
Subsequently, an efficient one-pot synthesis of the dimeric 2-oxazoline scaffold has been developed by Kato *et al*. They showed that α,α-disubstituted terminal propargyl ureas **22** underwent a tandem cyclization-carbonylation-cyclization coupling reaction in the presence of palladium(II)-bisoxazoline **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-oxazoline 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 haloalkyliene **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].

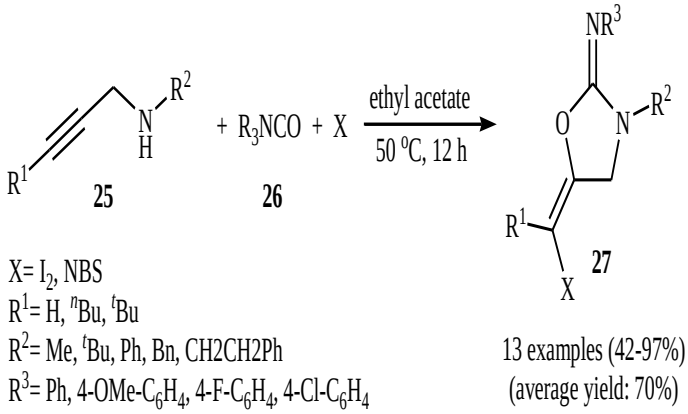


L: (*S*)-4,5-dihydro-2-(2-((*S*)-4,5-dihydro-4-phenyloxazol-2-yl)propan-2-yl)-4-phenyloxazole

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



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

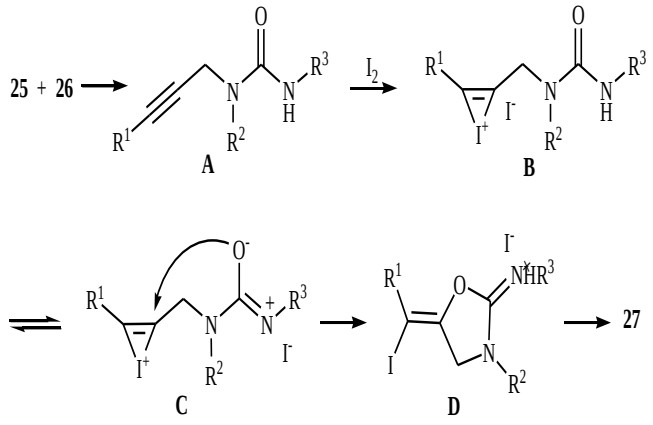


Scheme 11. Synthesis of oxazolidin-2-imine derivatives **27** *via* direct halocyclization between propargylamines **25**, aryl isocyanates **26** and I_2 (NBS)**.**

4. Pyrimidinone and 1,3-oxazine derivatives

2-Pyrimidinone derivatives are important structural motifs found in many biologically active structures and medicinally relevant compounds [37].

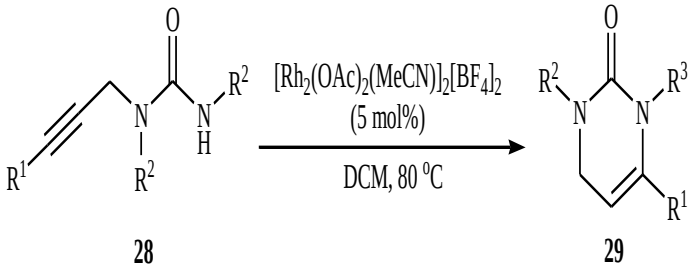
Compounds containing these cores have widespread biological applications as anticancer, antimicrobial, antihypertensive, antiulcer, anti-inflammatory, antitubercular, antimalarial, and antioxidant agents [38]. Several commercially available drugs, including flucytosine, capreomycin, fluorouracil and butabarbital are derived from 2-pyrimidinone core entities. In a similar way, 1,3-oxazine-2-imine derivatives are



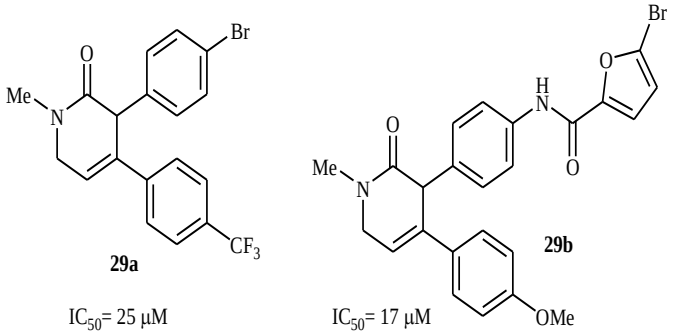
Scheme 12. Mechanism that accounts for the formation of **27**.

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 $[Rh_2(OAc)_2(MeCN)]_2[BF4]_2$ 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).

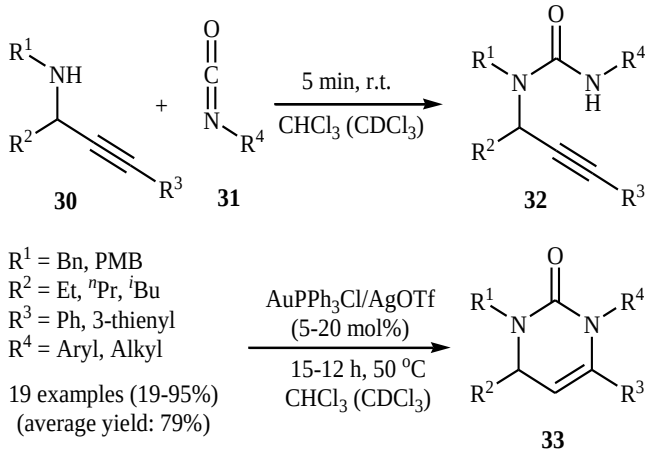


Scheme 13. Rh(II)-catalyzed synthesis of dihydropyrimidones **29** from propargyl ureas **28**.



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.

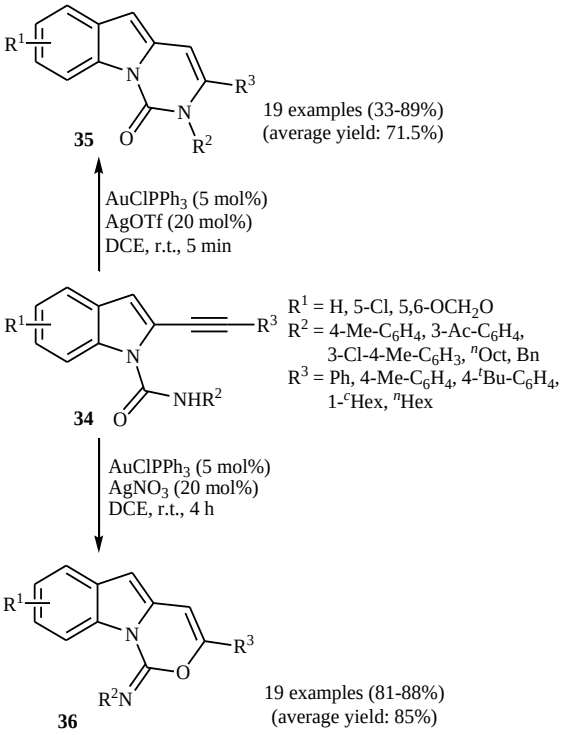
Shortly afterward, a similar regio- and chemoselective cycloisomerization was used by the group of Van der Eycken in the synthesis of tetrasubstituted 3,4-dihydropyrimidin-2(1H)-ones **33** *via* heating of *in situ* generated internal propargylic ureas **32** in the presence of cationic gold(I) catalyst $AuPPh_3Cl/AgOTf$ 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].



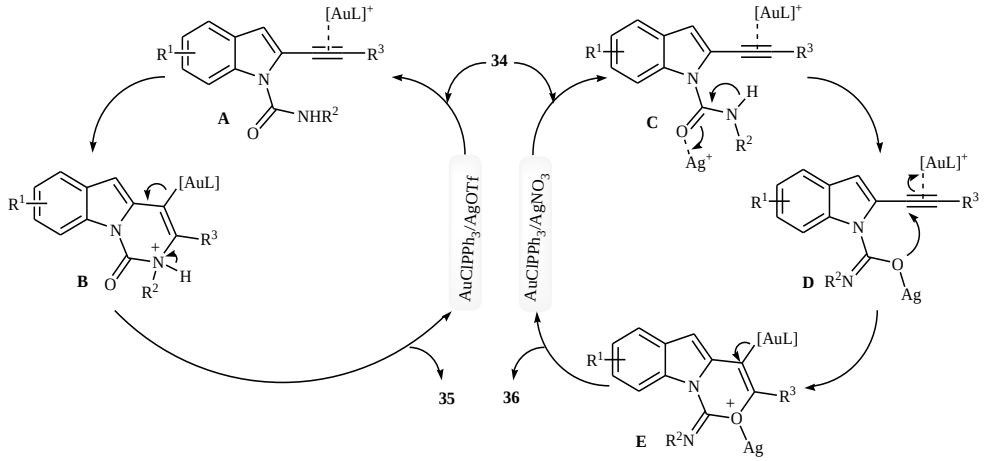
Scheme 15. Synthesis of tetrasubstituted 3,4-dihydropyrimidin-2(1H)-ones **33** *via* heating of *in situ* generated internal propargylic ureas **32** in the presence of a cationic gold(I) catalyst.

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-ethynyl-1*H*-indole-1-carboxamides **34** in the presence of 5 mol% of $AuClPPh_3$ 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 $AuClPPh_3/AgNO_3$ 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 $[Ph_3P–Au]^+TfO^-$, 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, $AuClPPh_3/AgNO_3$ combination simultaneously activates both 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].



Scheme 16. Au/Ag catalyzed chemoselective 6-*endo-dig* *N*- and *O*-cyclizations of 2-ethynyl-1H-indole-1-carboxamides **34**.



Scheme 17. Mechanistic proposal for the reactions in Scheme 16.

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 1*H*-imidazol-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 rgio-, stereo-, and chemoselective procedures for the synthesis of biologically important N-heterocyclic compounds.

References

[1] a) S. Shahidi, P. Farajzadeh, P. Ojaghloo, A. Karbakhshzadeh, A. Hosseinian, Nanocatalysts for conversion of aldehydes/alcohols/amines to nitriles: A review, *Chem. Rev. Lett.* 1 (2018) 37-44;

b) S. Mohammadi, M. Musavi, F. Abdollahzadeh, S. Babadoust, A. Hosseinian, Application of Nanocatalysts in C-Te Cross-Coupling Reactions: An Overview, *Chem. Rev. Lett.* 1 (2018) 49-55;

[2] a) E. Vessally, M. Abdoli., Oxime ethers as useful synthons in the synthesis of a number of key medicinal heteroaromatic compounds. *J. Iran. Chem. Soc.*, 13 (2016) 1235-1256;

b) V. Bhardwaj, D. Gumber, V. Abbot, S. Dhiman, P. Sharma. Pyrrole: a resourceful small molecule in key medicinal hetero-aromatics. *RSC Adv*., 5 (2015) 15233-15266;

c) A. Marella, O.P. Tanwar, R. Saha, M. R. Ali, S. Srivastava, M. Akhter, M. Shaquiquzzaman, M. M. Alam. Quinoline: A versatile heterocyclic. *Saudi. Pharm. J*., 21 (2013) 1-12;

d) M. Baumann, I. R. Baxendale. An overview of the synthetic routes to the best selling drugs containing 6-membered heterocycles. *Beilstein J. Org. Chem*., 9 (2013) 2265-2319;

e) S. B. Ferreira, C. R. Kaiser. Pyrazine derivatives: a patent review (2008–present). *Expert Opin. Ther. Pat*., 22 (2012) 1033-1051;

f) N.K. Kaushik, N. Kaushik, P. Attri, N. Kumar, C.H. Kim, A.K. Verma, E.H. Choi. Biomedical importance of indoles. Molecules., 18 (2013) 6620-6662;

g) S. Y. Essack. The development of β-lactam antibiotics in response to the evolution of β-lactamases, *Pharm. Res*., 18 (2001) 1391-1399.

[3] R. Dua, S. Shrivastava, S. Sonwane, S. Srivastava, Pharmacological significance of synthetic heterocycles scaffold: a review. *Adv. Biol. Res*., 5 (2011) 120-144.

[4] P. Martins, J. Jesus, S. Santos, L. R. Raposo, C. Roma-Rodrigues, P. V. Baptista, A.R. Fernandes. Heterocyclic anticancer compounds: recent advances and the paradigm shift towards the use of nanomedicine's tool box. *Molecules*., 20 (2015) 16852-16891.

[5] a) G. Zeni, R. C. Larock. Synthesis of heterocycles via palladium π-olefin and π-alkyne chemistry. *Chem. Rev*., 104 (2004) 2285-2310;

b) N. T. Patil, Y. Yamamoto. *Chem. Rev*., 108 (2008) 3395-3442;

c) X. -F. Wu, H. Neumann, M. Beller. Synthesis of heterocycles via palladium-catalyzed carbonylations. *Chem. Rev*., 113 (2012) 1-35;

d) B. Stanovnik, J. Svete. Synthesis of heterocycles from alkyl 3-(dimethylamino) propenoates and related enaminones. *Chem. Rev*., 104 (2004) 2433-2480;

e) G. Balme, E. Bossharth, N. Monteiro. Pd-assisted multicomponent synthesis of heterocycles. *Eur. J. Org. Chem*., (2003) 4101-4111.

[6] a) B. Godoi, R. F. Schumacher, G. Zeni. Synthesis of heterocycles via electrophilic cyclization of alkynes containing heteroatom. *Chem. Rev*., 111 (2011) 2937-2980;

b) S. A. Vizer, E. S. Sycheva, A. A. A. Al Quntar, N. B. Kurmankulov, K. B. Yerzhanov, V. M. Dembitsky. *Chem. Rev*., 115 (2014) 1475-1502;

c) Y. Hu, X. Xin, B. Wan. Cyclization reactions of propargylic amides: mild access to N-heterocycles. *Tetrahedron Lett.*, 56 (2015) 32-52.

[7] S. Sarhandi, M. Daghagheleh, M. Vali, R. Moghadami, E. Vessally, New insight in Hiyama cross-coupling reactions: Decarboxylative, denitrogenative and desulfidative couplings: A review, *Chem. Rev. Lett.* 1 (2018) 9-15.

[8] M. Daghagheleh, M. Vali, Z. Rahmani, S. Sarhandi, E. Vessally, A review on the CO2 Incorporation Reactions Using Arynes, *Chem. Rev. Lett.* 1 (2018) 23-30.

[9] a) E. Vessally, A new avenue to the synthesis of highly substituted pyrroles: synthesis from N-propargylamines, *RSC Adv*., 6 (2016) 18619-18631;

b) E. Vessally, H. Saeidian, A. Hosseinian, L. Edjlali, A. Bekhradnia, A review on synthetic applications of oxime esters, *Curr.Org. Chem.*, 21 (2017) 249-271;

c) E. Vessally, L. Edjlali, A. Hosseinian, A. Bekhradnia, M.D. Esrafili, Novel routes to quinoline derivatives from N-propargylamines, RSC Adv., 6 (2016) 49730-49746;

d) E. Vessally, A. Hosseinian, L. Edjlali, A. Bekhradnia, M.D. Esrafili, New page to access pyridine derivatives: synthesis from N-propargylamines, *RSC Adv.*, 6 (2016) 71662-71675;

e) E. Vessally, A. Hosseinian, L. Edjlali, A. Bekhradnia, M. D Esrafili, New page to access pyrazines and their ring fused analogues: Synthesis from N-propargylamines, *Curr.Org. Synth*., 14 (2017) 557-567;

f) E. Vessally, A. Hosseinian, L. Edjlali, A. Bekhradnia, M.D. Esrafili, New route to 1, 4-oxazepane and 1, 4-diazepane derivatives: synthesis from N-propargylamines, *RSC Adv.*, 6 (2016) 99781-99793;

g) E. Vessally, S. Soleimani-Amiri, A. Hosseinian, L. Edjlali, A. Bekhradnia, New protocols to access imidazoles and their ring fused analogues: synthesis from N-propargylamines, *RSC Adv.*, 7 (2017) 7079-7091;

h) M. Babazadeh, S. Soleimani-Amiri, E. Vessally, A. Hosseinian, L. Edjlali, Transition metal-catalyzed [2+ 2+ 2] cycloaddition of nitrogen-linked 1, 6-diynes: a straightforward route to fused pyrrolidine systems, *RSC Adv.*, 7 (2017) 43716-43736;

i) S. Arshadi, E. Vessally, L. Edjlali, R. Hosseinzadeh-Khanmiri, E. Ghorbani-Kalhor, N-Propargylamines: versatile building blocks in the construction of thiazole cores, *Beilstein J. Org. Chem.*, 13 (2017) 625-638;

j) E. Vessally, A. Hosseinian, L. Edjlali, E. Ghorbani-Kalhor, R. Hosseinzadeh-Khanmiri, Intramolecular cyclization of N-

propargyl anilines: a new synthetic entry into highly substituted indoles, *J. Iran. Chem. Soc.*, 14 (2017) 2339-2353;

k) S. Arshadi, E. Vessally, L. Edjlali, E. Ghorbani-Kalhor, R. Hosseinzadeh-Khanmiri, N-Propargylic β-enaminocarbonyls: powerful and versatile building blocks in organic synthesis, *RSC Adv.*, 7 (2017) 13198-13211;

l) E. Vessally, A. Hosseinian, L. Edjlali, M. Babazadeh, R. Hosseinzadeh-Khanmiri, New strategy for the synthesis of morpholine cores: synthesis from N-propargylamines, *Iran. J. Chem. Chem. Eng.*, 36 (2017) 1-13;

m) S. Arshadi, E. Vessally, M. Sobati, A. Hosseinian, A. Bekhradnia, Chemical fixation of CO2 to N-propargylamines: a straightforward route to 2-oxazolidinones, *J. CO2 Util.*, 19 (2017) 120-129.

[10] (a) S. Soleimani-Amiri, E. Vessally, M. Babazadeh, A. Hosseinian, L. Edjlali, Intramolecular cyclization of N-allyl propiolamides: a facile synthetic route to highly substituted γ-lactams (a review), *RSC Adv.*, 7 (2017) 28407-28418;

b) E. Vessally, M. Babazadeh, A. Hosseinian, L. Edjlali, L. Sreerama, Recent Advances in Synthesis of Functionalized β-Lactams through Cyclization of N-Propargyl Amine/Amide Derivatives, *Curr. Org. Chem.*, 22 (2018) 199-205;

c) E. Vessally, A. Hosseinian, M. Babazadeh, L. Edjlali, R. Hosseinzadeh-Khanmiri, Metal Catalyzed Carboxylative Coupling of Terminal Alkynes, Organohalides and Carbon Dioxide: A Novel and Promising Synthetic Strategy toward 2-Alkynoates (A Review), *Curr. Org. Chem.*, 22 (2018) 315-322;

d) E. Vessally, M. Nikpasand, S. Ahmadi, P.D.K. Nezhad, A. Hosseinian, Transition metal-catalyzed intramolecular cyclization of N-Boc-protected propargyl/ethynyl amines: a novel and convenient access to 2-oxazolidinone/oxazolone derivatives, *J. Iran. Chem. Soc.*, (2018) DOI: 10.1007/s13738-018-1542-5;

e) S. Arshadi, E. Vessally, A. Hosseinian, S. Soleimani-amiri, L. Edjlali, Three-component coupling of CO2, propargyl alcohols, and amines: An environmentally benign access to cyclic and acyclic carbamates (A Review), *J. CO2 Util.*, 21 (2017) 108-118;

f) E. Vessally, S. Soleimani-Amiri, A. Hosseinian, L. Edjlali, M. Babazadeh, Chemical fixation of CO2 to 2-aminobenzonitriles: a straightforward route to quinazoline-2, 4 (1H, 3H)-diones with green and sustainable chemistry perspectives, *J. CO2 Util.*, 21 (2017) 342-352;

g) E. Vessally, M. Babazadeh, A. Hosseinian, S. Arshadi, L. Edjlali, Nanocatalysts for chemical transformation of carbon dioxide, *J. CO2 Util.*, 21 (2017) 491-502.

[11] a) A. Hosseinian, S. Farshbaf, L.Z. Fekri, M. Nikpassand, E. Vessally, Cross-Dehydrogenative Coupling Reactions Between P (O)–H and X–H (X= S, N, O, P) Bonds, *Top. Curr. Chem.*, 376 (2018) 23;

b) F.A.H. Nasab, L.Z. Fekri, A. Monfared, A. Hosseinian, E. Vessally, Recent advances in sulfur–nitrogen bond formation via cross-dehydrogenative coupling reactions, *RSC Adv.*, 8 (2018) 18456-18469;

c) S. Farshbaf, L.Z. Fekri, M. Nikpassand, R. Mohammadi, E. Vessally, Dehydrative condensation of β-aminoalcohols with CO 2: An environmentally benign access to 2-oxazolidinone derivatives, *J. CO2 Util.*, 25 (2018) 194-204;

d) A. Hosseinian, S. Ahmadi, A. Monfared, P.D. Nezhad, E. Vessally, Nano-structured Catalytic Systems in Cyanation of Aryl Halides with K4[Fe(CN)4], *Curr. Org. Chem.*, 22 (2018) 1862-1874;

e) A. Hosseinian, L. Zare Fekri, A. Monfared, E. Vessally, M. Nikpassand, Transition-metal-catalyzed C–N cross-coupling reactions of N-unsubstituted sulfoximines: a review, *J. Sulfur Chem.*, 39 (2018) 674-698;

f) K. Nejati, S. Ahmadi, M. Nikpassand, P.D.K. Nezhad, E. Vessally, Diaryl ethers synthesis: nano-catalysts in carbon-oxygen cross-coupling reactions, *RSC Adv.*, 8 (2018) 19125-19143;

g) A. Hosseinian, S. Ahmadi, F.A.H. Nasab, R. Mohammadi, E. Vessally, Cross-Dehydrogenative C–H/S–H Coupling Reactions, *Top. Curr. Chem.*, 376 (2018) 39;

h) A. Hosseinian, F.A.H. Nasab, S. Ahmadi, Z. Rahmani, E. Vessally, Decarboxylative cross-coupling reactions for P (O)–C bond formation, *RSC Adv.*, 8 (2018) 26383-26398.

[12] a) K. Didehban, E. Vessally, A. Hosseinian, L. Edjlali, E.S. Khosroshahi, Nanocatalysts for C–Se cross-coupling reactions, *RSC Adv.*, 8 (2018) 291-301;

b) E. Vessally, R. Mohammadi, A. Hosseinian, K. Didehban, L. Edjlali, S-arylation of 2-mercaptobenzazoles: a comprehensive review, *J. Sulfur Chem.*, 39 (2018) 443-463;

c) A. Hosseinian, S. Farshbaf, R. Mohammadi, A. Monfared, E. Vessally, Advancements in six-membered cyclic carbonate (1, 3-dioxan-2-one) synthesis utilizing carbon dioxide as a C1 source, *RSC Adv.*, 8 (2018) 17976-17988.

[13] a) A. Hosseinian, M. Babazadeh, L. Edjlali, Z. Rahmani, E. Vessally, Intramolecular Cyclization of Aryl Propargyl Ethers: A Straightforward and Convenient Approach to Benzofuran Derivatives, *Curr. Org. Synth.*, 15 (2018) 972-981;

b) K. Didehban, E. Vessally, M. Salary, L. Edjlali, M. Babazadeh, Synthesis of a variety of key medicinal heterocyclic compounds via chemical fixation of CO2 onto o-alkynylaniline derivatives, *J. CO2 Util.*, 23 (2018) 42-50;

c) E. Vessally, R. Mohammadi, A. Hosseinian, L. Edjlali, M. Babazadeh, Three component coupling of amines, alkyl halides and carbon dioxide: An environmentally benign access to carbamate esters (urethanes), *J. CO2 Util.*, 24 (2018) 361-368;

d) E. Vessally, K. Didehban, R. Mohammadi, A. Hosseinian, M. Babazadeh, Recent advantages in the metal (bulk and nano)-catalyzed S-arylation reactions of thiols with aryl halides in water: a perfect synergy for eco-compatible preparation of aromatic thioethers, *J. Sulfur Chem.*, 39 (2018) 332-349.

[14] E. Vessally, R. Hosseinzadeh-Khanmiri, E. Ghorbani-Kalhor, M. Es' haghi, A. Bekhradnia, Domino carbometalation/coupling reactions of N-arylpropiolamides: a novel and promising synthetic strategy toward stereocontrolled preparation of highly substituted 3-methyleneindolinones, *RSC Adv.*, 7 (2017) 19061-19072.

[15] E. Vessally, M. Babazadeh, K. Didehban, A. Hosseinian, L. Edjlali, Intramolecular ipso-Cyclization of N-Arylpropiolamides: A Novel and Straightforward Synthetic Approach for Azaspiro [4.5] decatrien-2-ones, *Curr. Org. Chem.*, 22 (2018) 286-297.

[16] E. Vessally, M. Babazadeh, K. Didehban, A. Hosseinian, L. Edjlali, Intramolecular Cyclization of N-Arylpropiolamides: A New Strategy for the Synthesis of Functionalized 2-Quinolones, *Curr. Org. Chem.*, 21 (2017) 2561-2572.

[17] E. Vessally, K. Didehban, M. Babazadeh, A. Hosseinian, L. Edjlali, Chemical fixation of CO2 with aniline derivatives: A new avenue to the synthesis of functionalized azole compounds (A review), *J. CO2 Util.*, 21 (2017) 480-490.

[18] E. Vessally, A. Hosseinian, L. Edjlali, M. Babazadeh, K. Didehban, Chemical Fixation of CO2 to Allylic (α-Allenylic) Amines: A Green Route to Synthesis of Functionalized 2-Oxazolidones, *Mini-Rev. Org. Chem.*, 15 (2018) 315-323.

[19] L. Zhang, X. M. Peng, G. L. Damu, R. X. Geng, C. H. Zhou. Comprehensive review in current developments of imidazole-based medicinal chemistry. *Med. Res. Rev*., 34 (2014) 340-437.

[20] A. R. Carroll, S. Duffy, V. M. Avery. Citronamides A and B, Tetrapeptides from the australian sponge *Citronia astra*. *J. Nat. Prod*., 72 (2009) 764-768.

[21] S. C. Reddymasu, I. Soykan, R. W. McCallum. Domperidone: Review of pharmacology and clinical applications in gastroenterology. *Am. J. Gastroenterol*.. 102 (2007) 2036-2044.

[22] Palmer, W. S.; Poncet-Montange, G.; Liu, G.; Petrocchi, A.; Reyna, N.; Subramanian, G.; Theroff, J.; Yau, A.; Kost-Alimova, M.; Bardenhagen. J.P. Structure-guided design of IACS-9571, a selective high-affinity dual TRIM24-BRPF1 bromodomain inhibitor. *J. Med. Chem*., 59 (2015) 1440-1454.

[23] N. Shachat, J. J. Bagnell Jr. Reactions of propargyl alcohols and propargylamines with isocyanates. *J. Org. Chem*., 28 (1963) 991-995.

[24] C. Proulx, W. D. Lubell. N-amino-imidazolin-2-one peptide mimic synthesis and conformational analysis. *Org. Lett*., 14 (2012) 4552-4555;

[25] V. A. Peshkov, O. P. Pereshivko, S. Sharma, T. Meganathan, V. S. Parmar, D. S. Ermolat'ev, E. V. Van der Eycken. Tetrasubstituted 2-imidazolones *via* Ag (I)-catalyzed cycloisomerization of propargylic ureas. *J. Org. Chem*., 76 (2011) 5867-5872.

[26] A. Ranjan, R. Yerande, P. B. Wakchaure, S.G. Yerande, D. H. Dethe. Base-mediated hydroamination of propargylamine: A regioselective intramolecular 5-*exo-dig* cycloisomerization en route to imidazole-2-thione. *Org. Lett*., 16 (2014) 5788-5791.

[27] F. Huguenot, C. Delalande, M. Vidal. Metal-free 5-*exo-dig* cyclization of propargyl urea using TBAF. *Tetrahedron Lett*., 55 (2014) 4632-4635.

[28] A. La-Venia, N. S. Medran, V. Krchňák, S. A. Testero. Synthesis of a small library of imidazolidin-2-ones using gold catalysis on solid phase. *ACS. Comb. Sci*., 18 (2016) 482-489.

[29] a) S. P. Gaine, L. J. Rubin, J. J. Kmetzo, H. I. Palevsky, T. A. Traill. Recreational use of aminorex and pulmonary hypertension. *Chest*., 118 (2000) 1496-1497;

b) R. A. Glennon, B. Misenheimer. Stimulus properties of a new designer drug: 4-methylaminorex ("U4Euh"). *Pharmacol. Biochem. Behav*., 35 (1990) 517-521;

c) S. Bansal, A. Halve. Oxazolines: Their synthesis and biological activity. *Int. J. Pharm. Sci. Res*., 5 (2014) 4601-4616.

[30] a) Z. M. Ištuk, A. Čikoš, D. Gembarovski, G. Lazarevski, I. Đilović, D. Matković-Čalogović, G. Kragol, G. Novel 9a, 11-bridged azalides: One-pot synthesis of N′-substituted 2-imino-1, 3-oxazolidines condensed to an azalide aglycone. *Bioorg. Med. Chem.*, 19 (2011) 556-566;

b) A. A. Nirschl, Y. Zou, S. R. Krystek Jr, J. C. Sutton, L. M. Simpkins, J. A. Lupisella, J. E. Kuhns, R. Seethala, R. Golla, P. G. Sleph, N-Aryl-oxazolidin-2-imine muscle selective androgen receptor modulators enhance potency through pharmacophore reorientation. *J. Med. Chem.*, 52 (2009) 2794-2798;

c) J. Castilla, R. Rísquez, D. Cruz, K. Higaki, E. Nanba, K. Ohno, Y. Suzuki, Y. Díaz, C. Ortiz Mellet, J. M. García Fernández, Conformationally-locked N-glycosides with selective β-glucosidase inhibitory activity: identification of a new non-iminosugar-type pharmacological chaperone for Gaucher disease. *J. Med. Chem.*, 55 (2012) 6857-6865.

[31] S. Ueda, H. Terauchi, A. Yano, M. Ido, M. Matsumoto, M. Kawasaki, 4, 5-Disubstituted-1, 3-oxazolidin-2-imine derivatives: a new class of orally bioavailable nitric oxide synthase inhibitor. *Bioorg. Med. Chem. Lett.*, 14 (2004) 313-316.

[32] G. Wegener, V. Volke, Nitric oxide synthase inhibitors as antidepressants. *Pharmaceuticals*., 3 (2010) 273-299.

[33] a) C. Larksarp, H. Alper, Highly enantioselective synthesis of 1, 3-oxazolidin-2-imine derivatives by asymmetric cycloaddition reactions of vinyloxiranes with unsymmetrical carbodiimides catalyzed by palladium (0) complexes. *J. Org. Chem.*, 63 (1998) 6229-6233;

b) T. Munegumi, I. Azumaya, T. Kato, H. Masu, S. Saito, [3+2] Cross-coupling reactions of aziridines with isocyanates catalyzed by nickel (II) iodide. *Org. Lett.*, 8 (2006) 379-382;

c) M. A. Tabarki, R. Besbes, Ring expansion of aziridine-2-carboxylates. An efficient entry to imidazolidin-2-ones and oxazolidin-2-imines. *Tetrahedron Lett.*, 56 (2015) 1837-1839.

[34] M. J. Campbell, F. D. Toste. Enantioselective synthesis of cyclic carbamimidates *via* a three-component reaction of imines, terminal alkynes, and p-toluenesulfonylisocyanate using a monophosphine gold(I) catalyst. *Chem. Sci*., 2 (2011) 1369-1378.

[35] T. Kusakabe, K. Kawaguchi, M. Kawamura, N. Niimura, R. Shen, H. Takayama, K. Kato. Cyclization-carbonylation-cyclization coupling reaction of propargyl ureas with palladium (II)-bisoxazoline catalyst. *Molecules*., 17 (2012) 9220-9230.

[36] S. Huang, Y. Shao, R. Liu, X. Zhou. Facile access to oxazolidin-2-imine, thiazolidin-2-imine and imidazolidin-2-imine derivatives bearing an exocyclic haloalkyliene via direct halocyclization between propargylamines, heterocumulenes and I_2 (NBS). *Tetrahedron*., 71 (2015) 4219-4226.

[37] (a) C. O. Kappe, Biologically active dihydropyrimidones of the Biginelli-type—a literature survey. *Eur. J. Med. Chem.* 2000, *35*, 1043-1052;

(b) Â. de Fátima, T. C. Braga, L. d. S. Neto, B. S. Terra, B. G. Oliveira, D. L. da Silva, L. V. Modolo, A mini-review on Biginelli adducts with notable pharmacological properties. *J. Adv. Res.*, 6 (2015) 363-373.

[38] K. Beena, R. Suresh, A. Rajasekaran, P. Manna, Dihydropyrimidinones-a versatile scaffold with diverse biological activity. *J. Pharm. Sci. Res.*, 8 (2016) 741-746.

[39] a) M. R. de Brito, W. J. Peláez, M. S. Faillace, G. C Militão, J. R. Almeida, G. A. Argüello, Z. Szakonyi, F. Fülöp, M. C. Salvadori, F. S. Teixeira, Cyclohexene-fused 1, 3-oxazines with selective antibacterial and antiparasitic action and low cytotoxic effects. *Toxicol In Vitro*., 44 (2017) 273-279;

b) K. Fuchino, Y. Mitsuoka, M. Masui, N. Kurose, S. Yoshida, K. Komano, T. Yamamoto, M. Ogawa, C. Unemura, M. Hosono, Rational design of novel 1, 3-oxazine based β-secretase (BACE1) inhibitors: Incorporation of a double bond to reduce P-gp efflux leading to robust Aβ reduction in the brain. *J. Med. Chem*., 61 (2018) 5122-5137.

[40] M. Yang, S. J. Odelberg, Z. Tong, D. Y. Li, R. E. Looper. Cationic dirhodium carboxylate-catalyzed synthesis of dihydropyrimidones from propargyl ureas. *Tetrahedron*., 69 (2013) 5744-5750.

[41] O. P. Pereshivko, V. A. Peshkov, A. A. Peshkov, J. Jacobs, L. Van Meervelt, E. V. Van der Eycken. Unexpected regio- and chemoselectivity of cationic gold-catalyzed cycloisomerizations of propargylureas: access to tetrasubstituted 3, 4-dihydropyrimidin-2 (1 H)-ones. *Org. Biomol. Chem*., 12 (2014) 1741-1750.

[42] S. Gupta, D. Koley, K. Ravikumar, B. Kundu. Counter ion effect in Au/Ag-catalyzed chemoselective 6-endo-dig N- and O-cyclizations of enyne–urea system:

Diversity-oriented synthesis of annulated indoles. *J. Org. Chem*., 78 (2013) 8624-8633.

How to Cite This Article

Sepideh Farshbaf; Lakshmaiah Sreerama; Torkan Khodayari; Esmail Vessally. "Propargylic ureas as powerful and versatile building blocks in the synthesis of various key medicinal heterocyclic compounds". Chemical Review and Letters, 1, 2, 2018, 56-67. doi: 10.22034/crl.2018.85120