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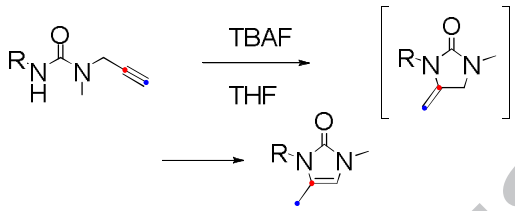

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Metal-free 5-exo-dig cyclization of propargyl urea using TBAF

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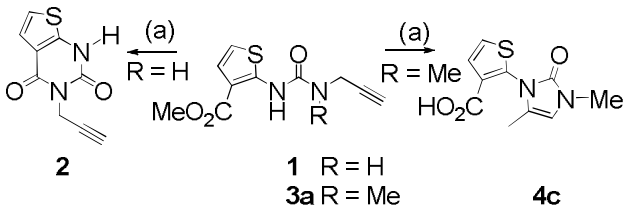
ABSTRACT

We present the first results of the intramolecular cyclization of propargyl ureas catalyzed by TBAF. Depending on the substituents close to the triple bond, imidazolone or methylene-imidazolidinone was obtained. The dual activation of the triple bond by interaction with TBAF via the cation-π is thought to be responsible.

Substituted imidazol-2-ones and other cyclic ureas are of considerable interest in pharmaceutical and medicinal chemistry, as many biologically active compounds contain these moieties. [1] Cyclic five-membered ring ureas have been demonstrated to act as HIV protease inhibitors,[2] receptor antagonists or antagonists, and these structures have also been employed as monomeric units for biopolymer scaffolds that exhibit greater stability than typical peptides.[3] In addition, substituted imidazolidin-2-ones have found applications in organic synthesis as chiral auxiliaries,[4] and as precursors to α-amino acids[5] and vicinal diamines.[6]

Due to the utility of imidazolidin-2-ones, a number of methods have been developed for their construction. The most commonly employed method for the synthesis of these compounds involves the generation of 1,2-diamines, which are then converted to cyclic ureas by treatment with phosgene or phosgene equivalents such as carbonyl diimidazole,[7] or through other carbonylation methods.[8] However, the preparation of 1,2-diamines frequently requires several steps. Several alternative strategies for the synthesis of imidazolidin-2-ones have been developed by diamination of alkene or aziridine ring extension.[6, 9]

Our recent investigations into the discovery of a disrupting reagent for the Vascular Endothelial Growth Factor (VEGF)//VEGF-receptor 1 interaction[10] required the synthesis of a propargyl urea skeleton attached to a thiophene carboxylic methyl ester. The alkyne moiety is used by click chemistry to design new molecules that can be quickly diversified. A specific reactivity of the carboxylic ester ureidothiophene **1** was rediscovered during the hydrolysis step in basic medium to lead to thienopyrimidinedione **2** (Scheme 1). [11] In order to avoid the formation of pyrimidinedione, nitrogen was replaced by a methyl group. However, the cycloisomerization of **3a** yielded the imidazolone derivative **4c** with the simultaneous hydrolysis of the methyl ester moiety.



2 **1** R = H **3a** R = Me **4c**

Scheme 1. Cyclization of the propargyl urea thiophene carboxylic ester. *Reagents and conditions*: (a) KOH_{aq} (1M), MeOH then HCl_{aq}

Intramolecular ring closure reactions are one useful method for constructing targeted cyclic or polycyclic skeletons. The ring size of the products can be predicted by Baldwin's rule,[12] based on stereoelectronic effects. Starting from propargyl carbamates, amides, amidines or amino alkynes, intramolecular ring closure reactions catalyzed by different metallic species have been widely described.[13] Despite these advances, few existing methods allow for ring closure of a simple, readily available acyclic urea derivative, with the formation of both a C–C and a C–N bond in the same step. Moreover, methods that accomplish this are limited by the use of metallic species.[9b]

We decided to study the cyclization reaction of the propargyl urea motif in a simpler model by replacing the thiophene-carboxylic acid phenyl moiety. Only compound **5b**, 1-methyl-4-methylene-3-phenylimidazolidin-2-one was formed starting from

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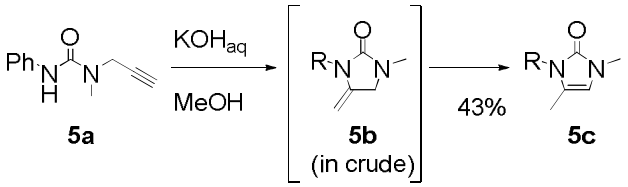
5a, characterized unambiguously by ^{1}H and ^{13}C NMR. Various attempts to purify compound **5b** led to the rapid formation of isomer **5c**, which is thermodynamically more stable (Scheme 2). This behavior has already been observed for methylidene-2-oxazolidinone.[14]

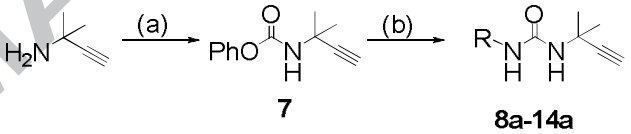


Scheme 2. Cyclization and isomerization of phenyl propargyl urea, **5a**

Initially, we undertook an examination of the base effect in order to apply this methodology to substrates that are more complex and therefore more sensitive to bases such as KOH or NaH. Thus we synthesized 3-benzyl-1-methyl-1-(prop-2-yn-1-yl) urea, **6a**. We observed that no organic compound tested allowed cyclization (Table 1, entries 1-5). The propargyl urea **6a** was fully recovered, even after a long time in refluxing MeOH or THF solvent in the presence of a large excess of base. The reactivity to KOH or other strong base appears to be limited to ureas bearing an aromatic ring (or an electron-withdrawing substituent) that can significantly reduce the pKa of the proton.[15] The increase in the pKa of the urea due to the replacement of the phenyl group by a benzyl group is responsible for the non-reactivity of **6a**. This aryl/alkyl selectivity should be of interest in the case of polyurea type molecules.

The best strategy was the activation of the triple bond through a cation-π interaction (Table 1).[16] Only TBAF was able to catalyze the intramolecular reaction at room temperature (Table 1, Entry 6). In 1995, Jacobi and Rajeswari reported the first TBAF-promoted 5-exo-dig cyclization reaction starting from alkynylamide.[17] However, in spite of its efficiency, the application of TBAF-promoted cyclization reactions to urea has not been reported.[18] We validated our strategy by transforming ureas **5a** and **3a**, which generated, respectively, the aromatic imidazol-2-ones **5c** in a 66% yield (Table 1, Entry 10), and **3c** in a 67% yield (Table 1, Entry 11), without reflux and while conserving the methyl ester moiety. The Bronsted basic activity of fluoride was necessary to catalyze the reaction. The activation of the triple bond was performed by the tetrabutylammonium cation, and the nucleophilicity of the nitrogen was increased by the fluoride anion. Although the lithium cation is described as an excellent activator of the triple bond,[16] LiF does not allow the cyclization of **5b** due to the very low dissociation of LiF in THF.

Next, we decided to focus our efforts on the preparation of an imidazolidin-2-one skeleton with an exocyclic double bond using ureas **8a-14a**, prepared from 2-methylbut-3-yn-2-amine. In this case, no isomerization of the double bond from the exocyclic to the endocyclic position is possible. These imidazolidin-2-ones can be evaluated by the formation of hydantoin (2,4-imidazolidinedione), by the alkylation or acetylation of the nitrogen NH, or by the reduction of the exocyclic double bond. Also, this structure has an enamine function that may be used as a nucleophile, or lead to hydrolysis and ring-opening. **8a** and **9a** were synthesized by the condensation of phenyl or benzyl isocyanate respectively with 2-methylbut-3-yn-2-amine. Compounds **10a-14a** were prepared in two steps using a phenyloxycarbonyl (Poc) strategy (Scheme 3). Phenylcarbamate **7** was prepared in large amounts by the condensation of phenyl chloroformate with 2-methylbut-3-yn-2-amine without the addition of a base, to avoid the release of the phenolate from the carbamate. Then compound **7** was converted into ureas **8a**–**14a** by the substitution of the phenolate moiety by alkylamines, in moderate to good yields.



Scheme 3. Strategy for the synthesis of ureas **8a-15a**. *Reagents and conditions*: (a) $PhCO_2Cl$, THF, r.t., 24 h, 82%; (b) RNH_2, Et_3N, $CHCl_3$, reflux, 24 h, R : nPr **10a** 98%, iPr **11a** 96%, tBu **12a** 88%, CH_2CO_2Et **13a** 94%, CH_2CH_2Cl **14a** 57%.

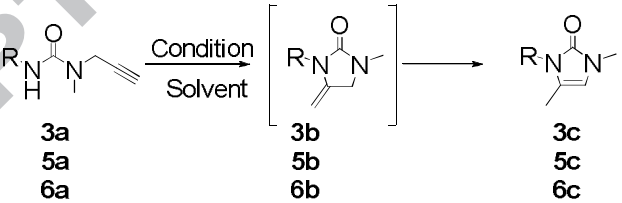


Table 1. Reagent screening for the synthesis of imidazol-2-one derivatives produced via imidazolidin-2-one

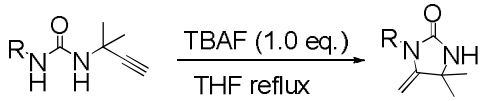
Entry	Compound	R	Reagent (1.0 equiv.)	Conditions	Ratio[b] **Xa**:**Xb**:**Xc**	Product	Yield %[c]
1	**6a**	Bn	KOH	THF or MeOH reflux, 48h	100:0:0	-	-
2	**6a**	Bn	NaH	THF or MeOH reflux, 48h	100:0:0	-	-
3	**6a**	Bn	DBU	THF or MeOH reflux, 48h	100:0:0	-	-
4	**6a**	Bn	DBN	THF or MeOH reflux, 48h	100:0:0	-	-
5	**6a**	Bn	MeONa	THF or MeOH reflux, 48h	100:0:0	-	-
6	**6a**	Bn	TBAF[a]	THF, RT, 8h	0:63:37	**6c**	70
7	**6a**	Bn	TBAI[a]	THF, reflux, 48h	100:0:0	-	-
8	**6a**	Bn	LiF	THF, reflux, 48h	100:0:0	-	-
9	**6a**	Bn	NH_4F	THF, reflux, 48h	100:0:0	-	-
10	**5a**	Ph	TBAF[a]	THF, RT, 8h	0:85:15	**5c**	66
11	**3a**	Methyl thiophene-3-carboxylate	TBAF[a]	THF, RT, 8h	0:100:0	**3c**	67

[a]Using freshly prepared 1M solution in THF.

[b]Determined by 1H NMR analysis of the crude mixture.

[c]**6c**, **5c** and **3c** as isolated products.

With these optimized reaction conditions in hand, we set out to examine the generality and scope of this cyclization reaction (Table 2). For all of ureas **8a-12a**, the cyclization reaction required refluxing THF. This suggests that the conformation of the urea influences cyclization conditions. **8a-12a** ureas are predominantly in *trans* conformation, while the cyclization requires the *cis* conformation. Despite the potential hydrolysis of the N-acyl enamine moiety,[19] imidazolidin-2-ones **8b-12b** were obtained in good yields after purification on silica gel. The cyclization was carried out with both linear and hindered substituents such as tert-butyl (Table 2, Entry 5).



8a-12a **8b-12b**

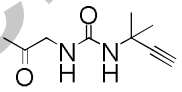
Table 2. Substituent effect for cyclization to imidazolidin-2-one **8b-12b**.

Entry	Substrate	R	Product	Yield %[a]
1	**8a**	Ph	**8b**	71
2	**9a**	CH_2Ph	**9b**	70
3	**10a**	$CH_2CH_2CH_3$	**10b**	81
4	**11a**	$CH(CH_3)_2$	**11b**	98
5	**12a**	$C(CH_3)_3$	**12b**	72[b]

[a] Yield of **8b-11b** as isolated products.

[b] Yield of **12b** in crude mixture by ^1H NMR.

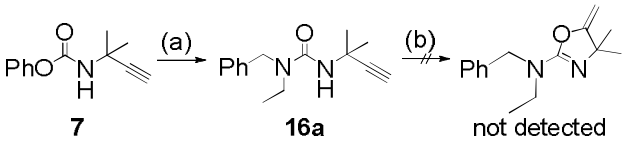
Interestingly, we did not observe the formation of a 6-membered ring by the 6-endo-dig process,[12] although the yield was sometimes quite low for **12b**. The reaction was very clean, with the crude reaction mixture containing only the 5-exo-dig cyclization product and TBAF. Almost quantitative presence of TBAF in the crude reaction mixture showed that TBAF was not consumed by the reaction and that it is thus possible to use it at catalytic concentration. To provide a mechanism for this catalytic cycloisomerization, **9a** was set in the presence of 0.2 equivalent of a freshly prepared TBAF solution in THF: after refluxing for 2 hours, ^1H NMR analysis showed the formation of **9b** in 54% yield. Upon purification by chromatography on silica gel, **12b** was relatively rapidly hydrolyzed to 3-oxo-urea **15** via ring opening (Figure 1). Spectroscopic and physical data were in agreement with the structure of **15**.[20]



15

Figure 1. 1-(*tert*-butyl)-3-(2-methyl-3-oxobutan-2-yl)urea **15**.

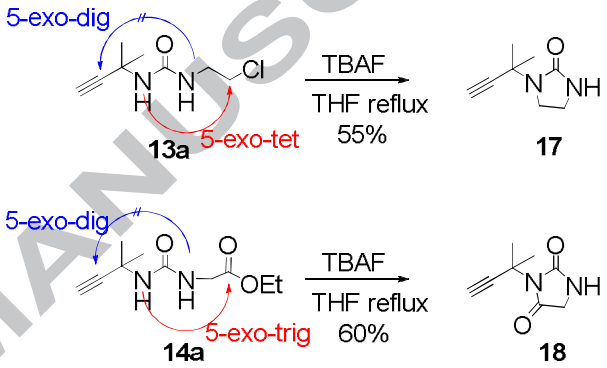
Although NMR analyses are consistent with the structure of imidazolidin-2-one,[21] we prepared urea **16a** to discriminate between the two possible 5-exo-dig reactions leading to the structures imidazolidin-2-one (through an O-cyclization) and 5 methyleneoxazolidin-2-imine (through an N-cyclization). The 5-exo-dig process via O-cyclization was characterized from propargyl-constrained urea, where the N-cyclization was geometrically impossible.[22] For **16a**, TBAF was not capable of activating the O-cyclization reaction, whereas this was the only 5-exo-dig process possible (Scheme 4).



7 **16a** not detected

Scheme 4. Synthesis and non-reactivity of propargyl urea **16a**. *Reagents and conditions*: (a) BnEtNH, Et_3N, $CHCl_3$, reflux, 24 h (b) TBAF, THF, reflux, 48h.

Finally, we looked at the outcome of the cyclization reaction from **13a** and **14a** (Scheme 5). **13a** leads to the exclusive formation of the imidazol-2-one **17** by a 5-*exo*-tet cyclization process. Similarly, hydantoin **18** is the only product obtained from **14a** through a 5-*exo*-trig cyclization process. It is very interesting to note that there is no competition between the cyclization processes authorized by the rules of Baldwin. This specificity may be of use later for the formation of a cyclic pharmacophore (imidazolone, hydantoin) functionalized by a triple bond.



Scheme 5. Selective 5-*exo*-tet and 5-*exo*-trig cyclization reactions of propargyl urea.

In summary, TBAF promotes the cyclization of propargyl urea to an imidazolidin-2-one core with an exocyclic double bond through a 5-exo-dig N-cyclization process. Depending on the nature of the propargyl moiety, the imidazolidin-2-one is quickly converted into the aromatic imidazol-2-one ring. The use of a gem-dimethylpropyne pattern allows the preparation of an imidazolidin-2-one core with a stable exocyclic double bond. We have also shown in our case that the 5-*exo*-tet and 5-*exo*-trig cyclization processes predominated over the 5-*exo*-dig cyclization process.

Acknowledgments

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