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Gold- and Silver-Mediated Cycloisomerizations of *N*-Propargylamides

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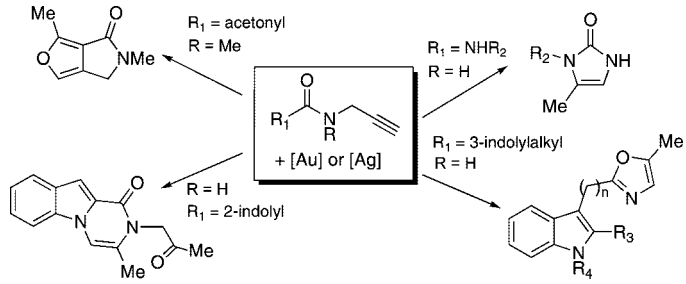
ABSTRACT



Substituted *N*-propargylamides have proven to be valuable substrates for alkyne-activated cycloisomerization reactions. *N*-Tosyl-*N*′-propargylurea underwent reaction with $AuCl_3$ to give the corresponding dihydroimidazolone, while *N*-propargyl-3-oxobutanamides and esters were used to construct furanyl fused pyrrolidinones and dihydrofuranones via Ag(I)-mediated alkyne activation.

During the past several years, the application of homogeneous gold catalysis in organic synthesis has emerged as a powerful tool for the preparation of a wide variety of carbo- and heterocyclic compounds.[1−4] The chemoselective alkynophilic properties of gold catalysts have been successfully exploited to develop mild and efficient synthetic strategies via alkyne activation and subsequent nucleophilic addition to the triple bond. Although gold-catalyzed intermolecular reactions of alkynes with nucleophiles have been reported,[5] the majority of recent examples have focused on the generation of new C−C and C−heteroatom bonds via cycloisomerization reactions as well as beneficial skeletal rearrangements.[1−4,6] A particularly promising field of research involves the intramolecular condensation of carbonyl compounds with alkynes which give rise to reactive intermediates that can then undergo structurally interesting rearrangements. In this respect, it has been shown that substituted 3-butyn-1-ones readily produce furans or 3-furanones by a $AuCl_3$-catalyzed 5-*endo-dig* cyclization.[7] *o*-Alkynylbenzaldehydes have also been used in Au-catalyzed 6-*endo-dig* cyclizations to generate pyrylium intermediates which readily undergo cycloaddition to generate a variety of polycyclic systems.[8] Propargylic esters have also been shown to be suitable substrates for intramolecular 5-*exo-dig* cyclizations. These cyclization reactions often result in a 1,2- or 1,3-acyl shift (cf. Rautenstrauch rearrangement) depending on the substitution pattern on the propargylic ester.[9] In many of these cases, the mechanistic understanding is often limited, and the exact reaction outcome is still hard to predict. Analogous cyclizations using carbonates or carbamates have

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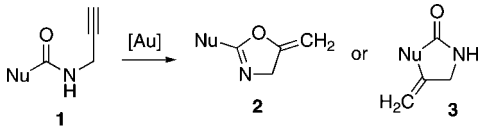
been found to afford the corresponding dioxolanone or oxazolidinone system bearing an *exo*-alkylidene substituent.[10]

An interesting example of the Au-catalyzed carbonyl−alkyne cycloisomerization involves 5-*exo*-*dig* oxazole formation starting from an *N*-propargyl-substituted amide. Since only two reports of this transformation can be found in the literature,[11] we decided to further investigate the synthetic potential of using substituted *N*-propargylamides and related derivatives for the metal catalyzed synthesis of various heterocyclic compounds. Catalytic alkyne cyclization of *N*-propargylamides and related urea derivatives **1** can occur either by cyclization of the carbonyl oxygen atom with the alkynyl group leading to structure **2** or by reaction at the

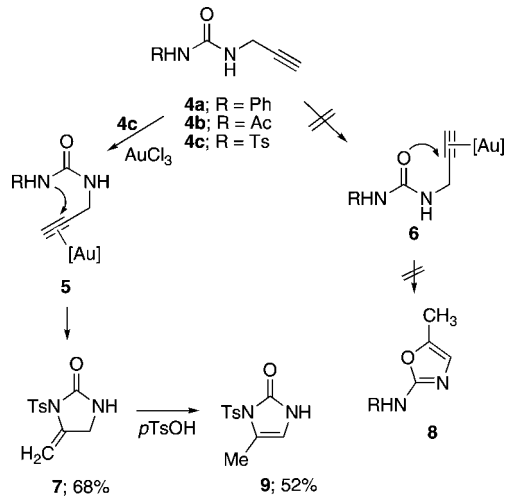
Scheme 1



nucleophilic center (Nu) to produce a cyclized compound such as **3** (Scheme 1).

In view of our group's interest in substituted aminooxazoles, urea derivatives **4** were evaluated as potential substrates for the gold-catalyzed formation of these structurally interesting oxazoles (i.e., **8**) (Scheme 2). We found that

Scheme 2



the reaction of *N*-phenyl- and *N*-acyl-*N*′-propargylureas **4a**,**b** with Au(I)(PPh_3)Cl or Au(III)Cl_3 did not lead to any oxazole formation as only starting material was recovered. However, when *N*-tosyl-*N*′-propargylurea **4c** was treated with $AuCl_3$, a clean conversion (68%) to the cyclic urea derivative **7** was observed. This represents the first example of imidazolidinone formation by a Au-catalyzed reaction. Upon heating in toluene in the presence of *p*-TsOH, the 4-methylene-2-imidazolidinone derivative **7** very slowly isomerized to the thermodynamically more stable 4-methyl-1,3-dihydroimidazol-2-one **9** (Scheme 2).

As a consequence of the preference of *N*-propargylureas to form dihydroimidazolones instead of aminooxazoles, our attention was next directed toward another class of *N*-propargylamides bearing two nucleophilic centers, both of which are capable of attacking the triple bond. With this in mind, 3-oxo-*N*-propargylbutanamides **10** were synthesized via standard procedures and were subjected to reaction using $AuCl_3$ as the catalyst in acetonitrile at room temperature (Scheme 3). Under these conditions, amide **10a** (R = H) was smoothly cyclized to the corresponding oxazole in 59% yield. In contrast, when the amido nitrogen atom contained a methyl group (i.e., **10b**), no reaction occurred even at elevated temperatures or by using other gold catalysts. Only when **10b** was allowed to react with in situ generated Au(PPh_3)OTf (derived from Au(PPh_3)Cl and AgOTf) was a small amount (<10%) of 5,6-dihydrofuro[3,4-*c*]pyrrol-4-one **14** detected in the crude reaction mixture by NMR spectroscopy. Since the other gold catalysts examined did not produce any of compound **14**, we thought that the presence of trace amounts of a Ag salt in the mixture might be responsible for the observed reactivity. Indeed, it is known in the literature that aside from gold catalysts, other π-Lewis

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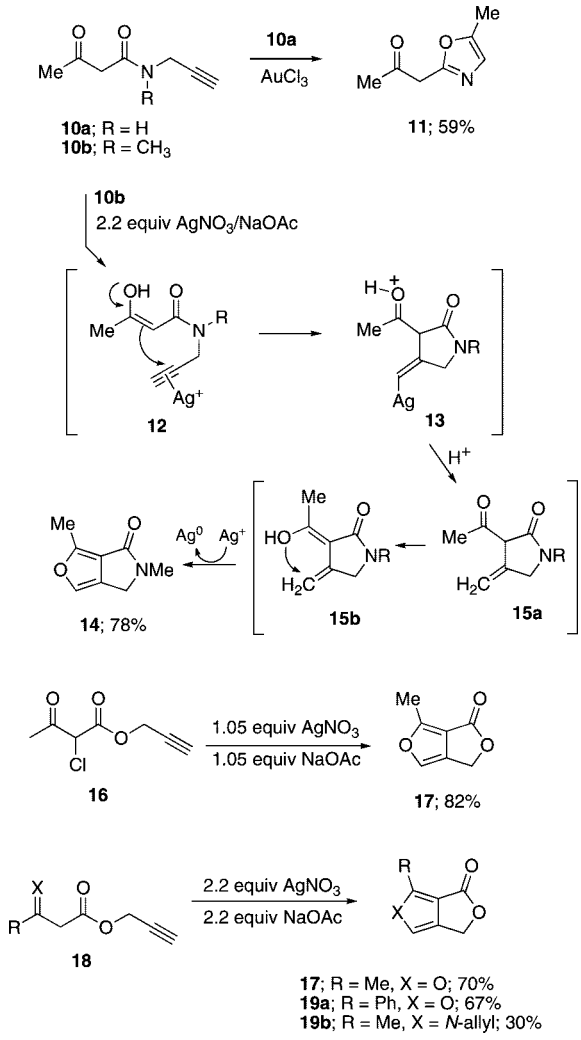
Scheme 3

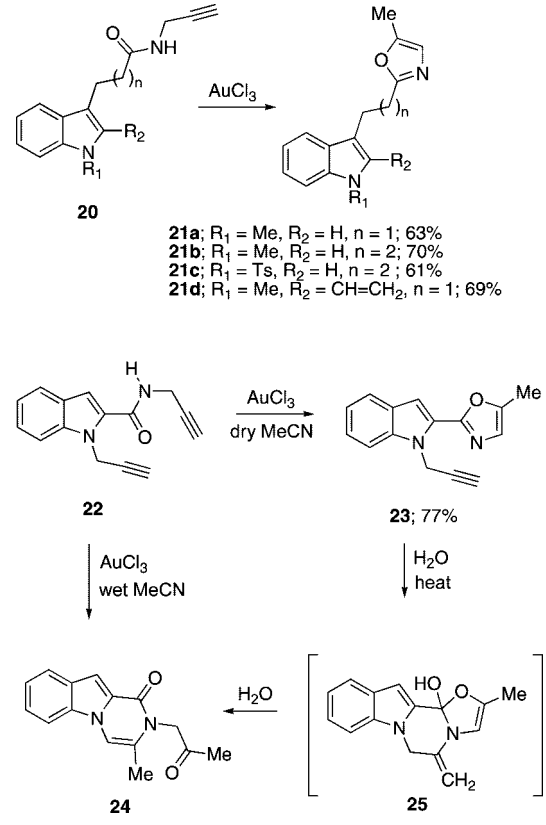


acids such as platinum and silver salts can be used for alkyne activation.[12]

After screening a variety of reaction conditions using **10b** with different Ag(I) salts, we found that an optimal yield of 78% of compound **14** could be obtained when 2.2 equiv of $AgNO_3$ was used in the presence of NaOAc (Scheme 3). A logical mechanism for this process would involve a Ag(I)-induced nucleophilic attack of the enol moiety of **12** onto the triple bond to initially give **13** followed by direct protonation of the vinyl metal bond to furnish **15a**. This is then followed by an oxidative cyclization of the transient enol intermediate **15b** to give **14**.[13] The subsequent oxidation step is presumably responsible for the need of 2 equiv of $AgNO_3$ in the reaction medium. In the case where compound **16**[14] is transformed into **17**,[15] only 1 equiv of $AgNO_3$ is needed for this cycloisomerization (Scheme 3). We also found that by using these optimal reaction conditions, *O*-propargyl esters of type **18**[16] gave rise to the corresponding furo- (**17**, **19a)** and pyrrolo-fused furanones (**19b**).

A very recent discovery in our laboratory showed that the Au(I)-catalyzed reaction of indole-2-carboxamides produces β-carbolines in good yield.[17] In order to further evaluate the potential of this transformation for heterocyclic synthesis, we prepared the indolyl-tethered amides **20** and **22** from readily accessible indoles[18] and studied their gold-catalyzed intramolecular cyclizations (Scheme 4). The reaction of

Scheme 4



amides of type **20** with $AuCl_3$ proceeded rapidly and furnished the oxazole tethered indoles **21a**−**d** in good yield. A most interesting reaction was encountered when the *N*-propargylamidoindole **22** was treated with 5 mol % $AuCl_3$.

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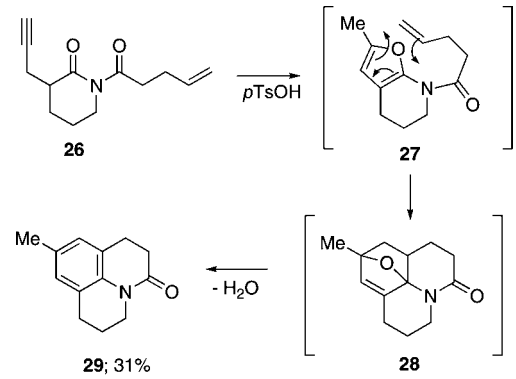
When dry acetonitrile was used as the reaction solvent, the expected oxazole **23** was formed in 77% yield. However, a 3:2 mixture of **23** and 2*H*-pyrazino[1,2-*a*]indolone **24** was obtained when aqueous acetonitrile was used as the solvent. A much higher yield of **24** was achieved by simply heating the crude oxazole **23** in aqueous dichlorobenzene. It would seem as though a trace of acid promotes cyclization of the oxazole nitrogen atom onto the adjacent alkyne to give **25** as a transient species which is further converted to the thermodynamically more stable product **24** under the aqueous conditions employed (Scheme 4).

We also thought it to be of interest to determine whether the Au(I)-catalyzed cycloisomerization of *N*-propargylamides can be extended to substituted 4-pentynamides. With this thought in mind, *N*-acyl-*δ*-valerolactam **26** was synthesized in two steps from *δ*-valerolactam. The reaction of **26** with a variety of gold catalysts did not lead to the formation of the desired amidofuran **27**, and only starting imide was recovered. However, the cyclization of **26** could be induced to occur by its treatment with *p*-TsOH in refluxing dichlorobenzene which gave rise to 9-methyl-1,2,6,7-tetrahydro-5*H*-pyrido[3,2,1-*ij*]quinolin-3-one (**29**) in 31% yield (Scheme 5).[19] We propose that this novel transformation occurs by an initial acid-promoted cycloisomerization to first give amidofuran **27** as a transient species which spontaneously undergoes an intramolecular [4 + 2]-cycloaddition followed by loss of water to eventually form tetrahydropyrido[3,2,1-*ij*]quinolin-3-one **29**.

In conclusion, substituted *N*-propargylamides proved to be valuable substrates for alkyne-activated cycloisomerization reactions. *N*-Tosyl-*N*′-propargylurea underwent reaction with $AuCl_3$ to give the corresponding dihydroimidazolone, while

Scheme 5



N-propargyl-3-oxobutanamides and esters were used to construct furanyl-fused pyrrolidinones and dihydrofuranones via Ag(I)-mediated alkyne activation. In addition, the Au-catalyzed cyclization of indolyl tethered *N*-propargylamides gave rise to both oxazoles as well as a pyrazinoindolone depending on the solvent system used. The applicability of the methodology to natural product synthesis is currently under study and will be the subject of future reports.

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Supporting Information Available: Spectroscopic data and experimental details for the preparation of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Although the formation of **29** proceeds in low yield, the acid-catalyzed reaction is of interest because it suggests, that in certain circumstances, an acid source can be a better catalyst than gold for alkyne activation.

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