Tetrahedron 69 (2013) 5744–5750

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Cationic dirhodium carboxylate-catalyzed synthesis of dihydropyrimidones from propargyl ureas

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ARTICLE INFO

Article history:
Received 11 March 2013
Received in revised form 9 April 2013
Accepted 11 April 2013
Available online 19 April 2013

Keywords:
Dihydropyrimidone
Heterocycle
Hydroamination
Rhodium catalysis
ARF 6

ABSTRACT

Cationic Rh(II) complexes are able to catalyze the regioselective hydroamination of propargyl ureas in a 6-*endo* fashion. This transformation permits access to interesting substitution patterns of dihydropyrimidines, which have found use as nucleotide exchange factor inhibitors.

1. Introduction

Accessible through multicomponent reactions, the dihydropyrimidone scaffold has been prevalent in both pharmaceutical and academic screening campaigns for decades.[1] Given the cornucopia of biological activities reported for this heterocyclic core,[2] methodologies have developed advancing the vetted Biginelli condensation[3] to include enantioselective variants and orthogonal substitution patterns.[4,5] Recently Rovis and co-workers reported an enantioselective Rh(I) catalyzed [4+2] cycloaddition of α,β-unsaturated imines and isocyanates to generate dihydropyrimidones, highlighting the continuing need for methodologies to access this core.[6]

Our group has recently been interested in the cyclization of propargylguanidines, particularly from the vantage of controlling the cyclization in either a 5-*exo* or 6-*endo* fashion.[7] The application of this strategy to propargyl ureas introduces an added level of selectivity, that is, not only are 5-*exo* and 6-*endo* modes of cyclization operable but they can occur through either the urea nitrogen or oxygen (Fig. 1).

The cyclization of propargyl ureas and related propargylcarbamates has been extensively studied, most frequently using salts of gold,[8] silver,[9] palladium,[10] and copper.[11] Kinetically favored, cyclization to form the five-membered ring is most commonly observed, both with N- and O-connectivity. Recently Toste and coworkers described the isolation of the dihydrooxazinoneimine in significant quantities from the cationic Au(I)-catalyzed cyclization of *N*-Ts-propargyl ureas,[8o] but without fail the six-membered rings are the minor component of the cyclization event. To the best of our knowledge the cyclization of propargyl ureas, selectively in a 6-*endo* fashion through the urea nitrogen, has not been observed. Achieving this selectivity would greatly add to our ability to create new substitution patterns of a biomedically significant small molecule scaffold.

2. Results and discussion

2.1. Cationic Rh(II) cyclizations of propargyl ureas

Having noted the ability of dirhodium(II)-carboxylates to selectively catalyze the 6-*endo* cyclization of propargylguanidines, in

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http://dx.doi.org/10.1016/j.tet.2013.04.071

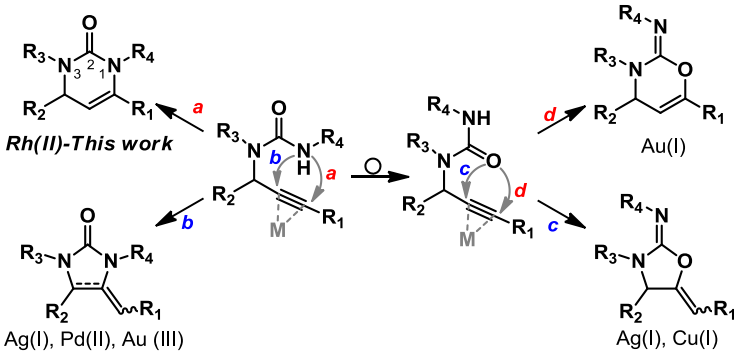
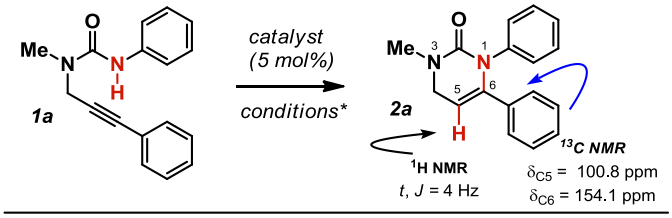


Fig. 1. Dihydropyrimidone strategy.

direct contrast to other π-Lewis acids, we were encouraged to explore the use of these catalysts in the cyclization of propargyl ureas.[7b] From our previous research AgOAc and $Rh_2(Oct)_4$ were preferred to selectively promote the 5-*exo* and 6-*endo* modes of cyclization, respectively.

We initially examined the ability of π-Lewis acids to catalyze the cyclization of propargylurea **1a** (Table 1). Surprisingly AgOAc failed to catalyze the cyclization at room temperature or 70 °C (entries 2 and 3) although Van der Eycken has recently reported that this transformation is possible with 20 mol % AgOTf at 110 °C, confirming that the propargyl ureas are much less nucleophilic than their di-Boc guanidine counterparts.[9e] More discouraging was the fact that $Rh_2(Oct)_4$ also failed to promote the cyclization (entries 4 and 5). The more Lewis-acidic $Rh_2(TFA)_4$ was then examined. While unreactive at room temperature (entry 6), formation of a single cyclization product (**2a**) occurred when the temperature was increased to 70 °C, albeit in 50% isolated yield (entry 7). Encouragingly, the product did appear to have cyclized in a 6-*endo* fashion as evidenced by the coupling constant of the vinylic proton at C5 (^3J=4.0 Hz). Further the ^{13}C chemical shifts of C5 and C6 were much more consistent with enamine connectivity versus that of an enol-ether. We anticipated that a suitable cationic Rh(II) complex, with more labile ligands, might lend the greater Lewis acidity and improve the reactivity. To test this assumption, we turned our attention to the cationic catalyst $[Rh_2(OAc)_2(MeCN)_6][BF_4]_2$.[12] To our

Table 1
Catalysts and solvents screen



Entry	Catalyst (5 mol %)	Solvent	Temp (°C)	Isolated yield (%) **2a**
1	N/A	CH_2Cl_2	80	NR
2	AgOAc	$HOAc/CH_2Cl_2$	rt	NR
3	AgOAc	$HOAc/CH_2Cl_2$	70	NR
4	$Rh_2(Oct)_4$	CH_2Cl_2	rt	NR
5	$Rh_2(Oct)_4$	CH_2Cl_2	70	NR
6	$Rh_2(TFA)_4$	CH_2Cl_2	rt	NR
7	$Rh_2(TFA)_4$	CH_2Cl_2	70	50
8	$[Rh_2(OAc)_2(MeCN)]_2[BF_4]_2$	CH_2Cl_2	80	94

*All reactions were run at 0.1 M in a Schlenk tube under a N_2 atmosphere for 24 h.

delight, this provided **2a** in 94% isolated yield with no trace of the other three possible cyclization products observable by ^1H NMR.

As mentioned, the competency of the more Lewis-acidic Rh(II) catalysts suggests that the propargyl ureas are inherently less nucleophilic than the related guanidines. Therefore it is likely that the nucleophilicity of the urea nitrogen and the electrophilicity of the metal–alkyne complex, might be critically coupled to the success of this reaction. Defining the limits of reactivity at these positions became the emphasis of our study on substrate scope (Table 2). With the phenyl substituted alkyne (R^1=Ph), cyclization is productive with urea substituents that span the electronic spectrum from *p*-MeOPh to *p*-NO_2Ph (e.g., **2a**–**e**). The *p*-NO_2–Ph substituted urea **2e** proved to be a highly crystalline solid, from which we were able to unambiguously prove the connectivity of these dihydropyrimidones via X-ray crystallography. Electron rich alkynes (e.g., *p*-MeOPh substituted) also reacted well with electron rich and poor ureas, **2f**–**h**. If the alkyne is electron poor (e.g., *p*-CF_3Ph substituted) it reacts well with most ureas (**2i**–**k**) but fails to react with an electron poor *p*-NO_2Ph substituted urea (e.g., **2n**). Other electron poor alkynes can also react as long as the urea is not extremely electron poor (**2l**–**m**). The reaction is also successful if the substrate is N^1,N^3-dialkyl substituted (**2o**,**p**) or N^1,N^3-alkyl/aryl substituted (**2q**). Alkyl substituted alkynes, while reactive gave complex mixtures that were intractable on a preparative scale. However, ene-ynes and yne-ynes react cleanly to give (**2r**–**t**), which are logical precursors to alkyl substitution patterns. Substrates bearing an N^3-Tosyl or N^3-Boc group are also not reactive, further defining that highly electron-withdrawing groups shut down the reaction. It is noteworthy that all of the successful cyclizations resulted in exclusive formation of the dihydropyrimidone.

When contemplating this unique reactivity, it is quite remarkable that Rh(II) catalyzes this bond forming event with two-fold thermodynamic selectivity: first to generate the 6-*endo* product and secondly to generate the C–N bond. One potential explanation for this is the Markovnikov-selective hydration of the alkyne followed by condensation of the urea on the resultant ketone. However, the addition of water (up to 1 equiv) or desiccants did not affect the efficiency of the reaction. Further, Rh(II) does not appear to be a competent Lewis acid for the condensation of a preformed urea–ketone.[13] Examples of alkyne activation by dirhodium(II) complex are quite rare.[14] Thus further investigations are warranted to understand this unique selectivity, and the potential reversibility of the initial amino- or oxo-rhodation.

2.2. Application of the resultant dihydropyrimidones

A testament to the value of these scaffolds, we identified compound **2k** capable of inhibiting proliferation of the LN-229 glioblastoma cell line (IC_{50}=25 μM) (Fig. 2). The EGF-dependent proliferation of glioblastoma cells has been directly linked to the activation of Adenosine diphosphate-ribosylation factor 6 (ARF6).[15] Known inhibitors of this enzyme, e.g., secin-44, are comprised of a 1,2-disubstituted triazole, which shares the diaryl-orientation as delivered by the methodology described above.[16] One drawback with the triazole inhibitors is their poor solubility. We reasoned