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# Gold Catalyzed Cyclization of Alkyne-Tethered Dihydropyrimidones

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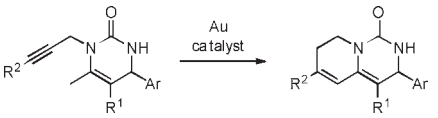
## ABSTRACT




**Dihydropyrimidones are an important class of biologically active heterocycles accessible from the multicomponent Biginelli condensation. Further manipulation of the dihydropyrimidone skeleton gives access to unique heterocycles. Presented herein is a Au-catalyzed cyclization of alkyne-tethered dihydropyrimidones to yield pyridopyrimidones.**

Dhydropyrimidones (DHPMs), the products of the classic Biginelli three-component reaction,[1] possess a wide range of intriguing pharmacological properties and thusly have attracted great synthetic interest.[2] Following our development of an organocatalytic route to access either enantiomer of the DHPM core and enantioenriched DHPM library collections,[3] we have been pursuing methods to further manipulate the scaffold. In addition to our discovery of a DHPM-derived guanidine chemotype which exhibits intriguing activity against select geographic isolates of *P. falciparum*,[4] we also recently reported the synthesis and identification of a DHPM-derived pyridopyrimidone that exhibits broad-spectrum activity against orthopoxviruses.[5] Herein we describe the discovery of a Au-catalyzed cyclization of propargyl-tethered DHPMs that gives rise to the tetrahydropyridopyrimidone motif.

Initial efforts focused on probing the intramolecular reactivity of DHPM derivatives **1** and **2** possessing alkynes attached to the N1 enamide nitrogen (Figure 1). Our initial screen[6] included a selection of alkynophilic metal catalysts, two different solvents (polar and nonpolar), and three different reaction conditions. All reactions were analyzed by TLC as well as UPLC/MS/ELSD. While substrate **2** was unreactive under all conditions screened, we were pleased to observe that a common product was formed

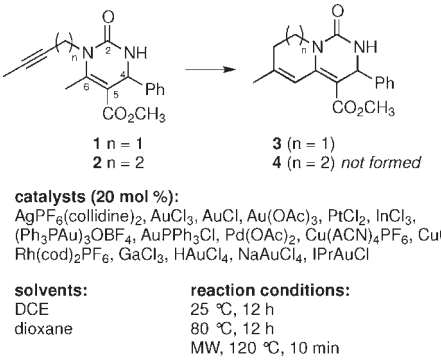



**Figure 1.** Screened catalysts and conditions.

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(6) Beeler, A. B.; Su, S.; Singleton, C. A.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2007**, *129*, 1413–1419.

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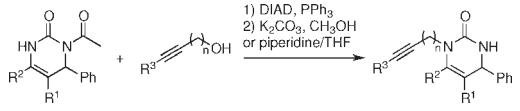
when **1** was heated in the presence of gold or platinum, as well as in trace amounts with $GaCl_3$. The product of the reaction was determined to be compound **3** by UPLC-MS and 2D NMR, bearing a unique bicyclic tetrahydropyridopyrimidone structural framework.[7]

Dihydropyrimidones analogous to **1** possessing N1 propargyl groups were synthesized to be evaluated in the cyclization reaction. However, our ability to prepare substrates with our previous methodology was limited by the necessity of employing propargyl isocyanates: preparation of low molecular weight isocyanates is inconvenient due to both volatility and the use of phosgene. Since the commercial availability of propargylic isocyanates and ureas is limited, substrate synthesis necessitated a more general route to N1-propargylated DHPMs.

**Table 1.** Synthesis of N1-Propargylated DHPMs

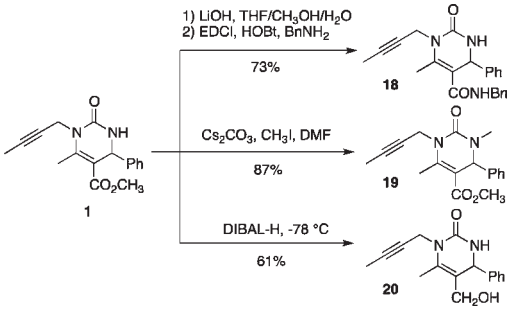



| DHPM | $R_1$ | $R_2$ | $R_3$ | $n$ | product | yield (%) |
|---|---|---|---|---|---|---|
| **5** | $CO_2CH_3$ | $CH_3$ | $CH_3$ | 1 | **1** | 69 |
| **5** | $CO_2CH_3$ | $CH_3$ | $CH_3$ | 2 | **2** | 56 |
| **5** | $CO_2CH_3$ | $CH_3$ | TMS | 1 | **9** | 67 |
| **5** | $CO_2CH_3$ | $CH_3$ | H | 1 | **10** | 85 |
| **5** | $CO_2CH_3$ | $CH_3$ | Ph | 1 | **11** | 46 |
| **5** | $CO_2CH_3$ | $CH_3$ | $C_5H_{11}$ | 1 | **12** | 84 |
| **6** | $COCH_3$ | $CH_3$ | $CH_3$ | 1 | **13** | 68 |
| **6** | $COCH_3$ | $CH_3$ | TMS | 1 | **14** | 76 |
| **6** | $COCH_3$ | $CH_3$ | H | 1 | **15** | 73 |
| **7** | CN | $CH_3$ | $CH_3$ | 1 | **16** | 72 |
| **8** | $CO_2CH_3$ | $CH_2CH_3$ | $CH_3$ | 1 | **17** | 83 |

Kappe and co-workers developed N1-selective alkylation of DHPMs using a Mitsunobu reaction employing TMAD and TBP.[8] While the reaction worked quite well for some substrates, in our hands the reaction proved problematic for the range of alkynols we utilized giving mixtures of N1 and N3 alkylation products. We therefore developed a modified protocol employing N3-acylated DHPMs **5**–**8**,[9] thus avoiding the inherent selectivity issue and making use of readily available propargylic alcohols.[10] Furthermore, by decreasing the p$K_a$ of the N1 proton, we are able to use common Mitsunobu reagents, instead of TMAD and pyrophoric TBP.[11] As depicted in Table 1, the protocol was employed to synthesize alkyne cyclization precursors from both known and novel DHPMs.[12]

Additional substrates were synthesized by subjecting compound **1** to hydrolysis/amide formation (**18**), N3-alkylation (**19**), and reduction (**20**) (Scheme 1).

**Scheme 1.** Synthesis of Additional Substrates for Reaction Screen




We then set out to determine the generality of the cyclization reaction. During the initial optimization using substrate **1**, we determined that 10 mol % AuCl provided the optimal yield. However, across AuCl sources we encountered a wide variance in reactivity on repetition of the parent reaction. Reproducibility issues led us to undergo a second screen of gold catalysts and conditions. We determined that, for consistently productive yields, certain substrates required an increased catalyst loading up to 30 mol %. We also identified $HAuCl_4$ as a similarly active and more dependable catalyst for a number of substrates.[13] Interestingly, while $AuClPPh_3$ alone gave trace product, cationic gold catalyst systems such as $AuClPPh_3/AgOTf$ and $AuClPPh_3/AgBF_4$ were wholly unreactive for substrates **1** and **14**.

Table 2 depicts the scope and limitations of the reaction. Aliphatic, aromatic, and silyl alkynes all cyclized in good to excellent yields (entries 1–2, 4–7). Notably, silyl alkynes **9** and **14** demonstrated the most efficient cyclization; while compound **1** required prolonged heating to induce cyclization, silyl alkyne **14** showed 91% conversion after 14 h at rt (20 mol % $HAuCl_4$, percent converson determined by crude $^1$H NMR).

The functionality at C5 proved to be critical to the outcome of the reaction. In addition to ester and ketone

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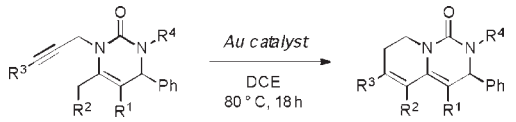
**Table 2.** Substrate Scope of Gold-Mediated Cyclization




| entry | substrate | catalyst[a,b] | product (yield) |
|---|---|---|---|
| 1 | **1** | C | **3** (63%) |
| 2 | **9** | B | **23** (93%) |
| 3 | **10** | A, B, C, D, E | No reaction |
| 4 | **11** | B | **24** (57%) |
| 5 | **12** | A | **25** (58%) |
| 6 | **13** | C | **26** (65%) |
| 7 | **14** | D | **27** (94%) |
| 8 | **15** | A, B, C, D, E | No reaction |
| 9 | **16** | B, D | No reaction |
| 10 | **17** | B, D | No reaction |
| 11 | **18** | E | **28** (27%) |
| 12 | **19** | E | **29** (20%) |
| 13 | **20** | B, D | Decomposed |
| 14 | **21** ($R^1$ = $COCH_3$, $R^2$ = H, $R^3$ = $CH_3$, $R^4$ = Ac) | C | **30** (50%) |
| 15 | **22** ($R^1$ = $COCH_3$, $R^2$ = H, $R^3$ = TMS, $R^4$ = Ac) | B | **31** (20%) |

[a] Catalyst loadings: (A) 10 mol % AuCl; (B) 20 mol % AuCl; (C) 10 mol % $HAuCl_4{-}3H_2O$; (D) 20 mol % $HAuCl_4{-}3H_2O$; (E) 30 mol % AuCl. [b] Loadings reported are for optimized yields.

substrates, amide **18** (entry 11) cyclized in low yield, while substrates lacking a carbonyl (entries 9, 13) failed to cyclize. We also investigated the effect of substituents at the N3 position of the DHPM. Acylated and alkylated substrates cyclized but with consistently lower conversions (entries 12, 14–15) and often requiring an increased catalyst loading.

While substitution of the alkyne was widely tolerated, terminal alkynes **10** and **15** showed erratic reactivity, with conversions generally below 5%. However, the target pyridopyrimidone products of these cyclizations could be reliably accessed via AgF-mediated desilylation[14] of cyclized vinylsilanes **23** and **27**.[5] Lastly, we observed that substitution of an ethyl group at the C6-DHPM position also shuts down the reaction (entry 10).

Our attention next turned to elucidating the mechanism of this transformation. A search for similar cyclizations of alkynyl enamides to give six-membered rings gave only one example: an undesired side reaction in the Au-catalyzed cycloisomerization of propargylated enamides to give pyrroles.[15] In addition, a number of examples of nucleophilic C–C bond formation at activated alkynes have been recently disclosed, employing $\beta$-dicarbonyls, silyl and alkyl enol ethers, and enamines as carbon nucleophiles.[16] There exist far fewer instances of such reactions employing unactivated enolizable carbonyls; the recent disclosure by Davies[17] is a notable example. For our system, we propose a vinylogous Conia-ene reaction[18] with dual activation, both oxophilic and alkynophilic, by the gold catalyst,[19] as depicted in Figure 2. A 6-*endo-dig* cyclization followed by protodemetalation and double bond isomerization gives rise to the observed product.

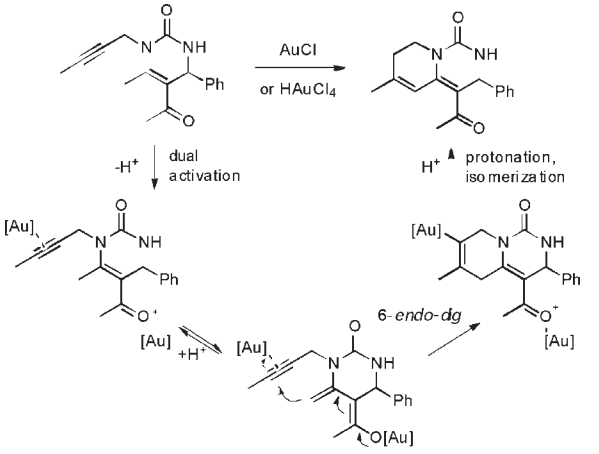



**Figure 2.** Proposed mechanism for pyridopyrimidone formation.

To investigate the proposed mechanism, we performed deuterium labeling experiments (Scheme 2). We first prepared deuterated substrate **19-d$_3$**, which cyclized in 14% yield with deuterium distribution as depicted. In addition, we performed the cyclization of compound **1** in the presence of $D_2O$. From these experiments, we can conclude that (1) significant enolization occurs prior to cyclization, as evidenced by the percent deuterium incorporation at the nonacidic $\gamma$-positions of **29-d$_6$** and **3-d$_6$**; (2) deuterium depletion at the acidic $\gamma$-protons of recovered starting materials **19-d$_3$** and **1-d$_3$** is suggestive of equilibration with the $\varepsilon$-protons of their respective cyclization products; and (3) the enolization of both **1** and **3** are gold-promoted, as there is no

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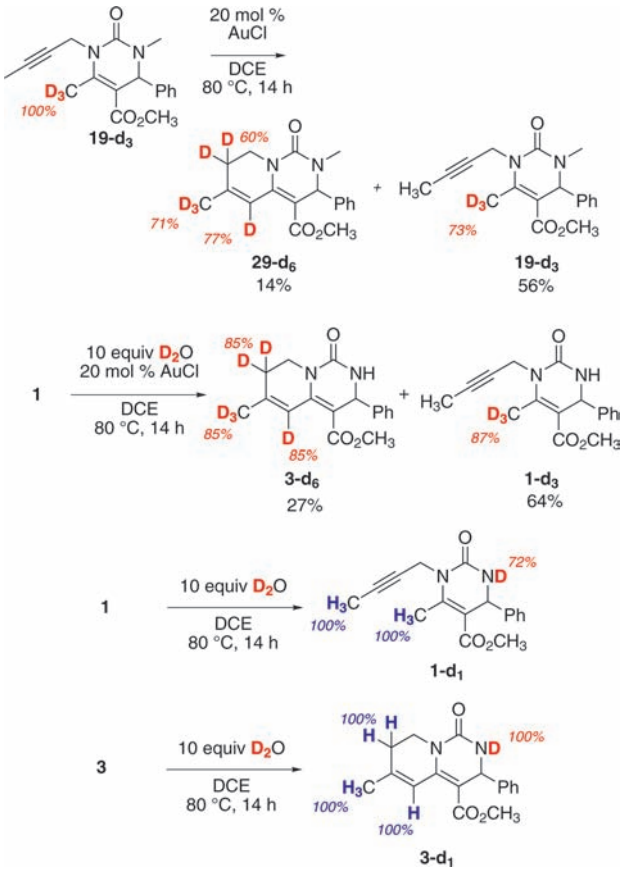
**Scheme 2.** Deuterium Labeling Studies




deuterium incorporation seen at any C−H position in two control experiments performed in the absence of catalyst.

Intrigued by the notion that the gold catalyst may serve a dual function in promoting the reaction, we then undertook a kinetic study to gain further insight. The third-order rate plot of the room-temperature cyclization of substrate **14** in the presence of auric acid is depicted in Figure 3. Kinetic data clearly indicate a multiple-order dependence on the catalyst, supporting our proposed dual catalyst activation. The apparent third-order dependence on the catalyst is intriguing and may arise from binuclear Au(III) Lewis acid activation of the carbonyl (Figure 4).[20]

We hypothesize that the challenges of reproducibility result from the relatively low catalytic activity of unstabilized gold(I) and (III) species under harsh reaction conditions, which is well-documented.[21] While gold is not generally known to cycle between oxidation states, AuCl will disproportionate to $AuCl_3$ and colloidal $Au_0$ upon heating.[22] The $\pi$-acidity of Au(I) and Au(III) are both well-established;

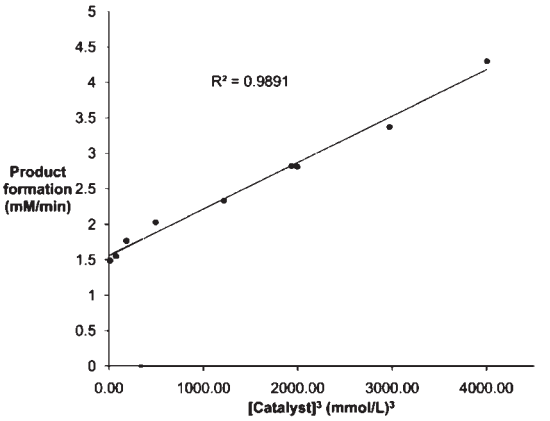



**Figure 3.** Plot of the steady-state initial rate of product formation vs auric acid concentration cubed for the conversion of **14** to **27** ($ClCH_2CH_2Cl$, 25 °C).

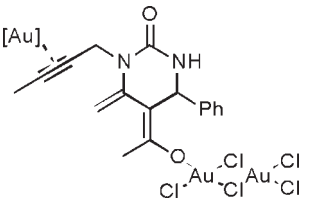



**Figure 4.** Proposed bimetallic Au(III) carbonyl activation.

calculations demonstrate Au(III) to be a superior oxophilic Lewis acid. Phosphine-ligated Au(I) salts, more broadly utilized due to their increased stability, may not be sufficiently oxophilic to promote the requisite enolization.[23]

In summary, we have discovered an interesting gold catalyzed cyclization of alkyne-tethered dihydropyrimidones. An effective protocol employing the Mitsunobu reaction was also developed to prepare a wide panel of reaction precursors. Mechanistic experiments suggest a dual role for the gold catalyst in this reaction, activating both the alkyne and nucleophile toward the desired reaction. Further studies, including applicability of this reaction to library synthesis and further biological evaluation of the pyridopyrimidones are currently under investigation and will be reported in due course.

**Acknowledgment.** Financial support from the NIH (P50 GM067041, P41 GM076263, and P41 GM086180) is gratefully acknowledged. We thank Professor Aaron Beeler (Boston University) for helpful discussions.

**Supporting Information Available.** Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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