Organic LETTERS

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Synthesis of 5,6-Dihydropyrazolo[1,5-*c*]quinazolines through Gold-Catalyzed Chemoselective Bicyclization of *N*-Propargylic Sulfonylhydrazones

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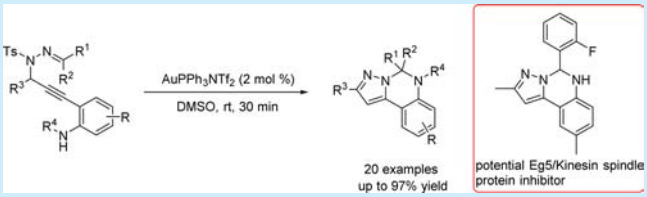
Supporting Information

ABSTRACT: An efficient method for the preparation of 5,6-dihydropyrazolo[1,5-*c*]quinazolines via gold(I)-catalyzed chemoselective bicyclization of *N*-propargylic sulfonylhydrazones has been developed. This process relies on the chemoselective cyclization of the hydrazone nitrogen instead of the usually favored aniline nitrogen onto the alkyne. The synthetic utility of the current strategy is demonstrated through the synthesis of a potential Eg5/Kinesin spindle protein inhibitor.

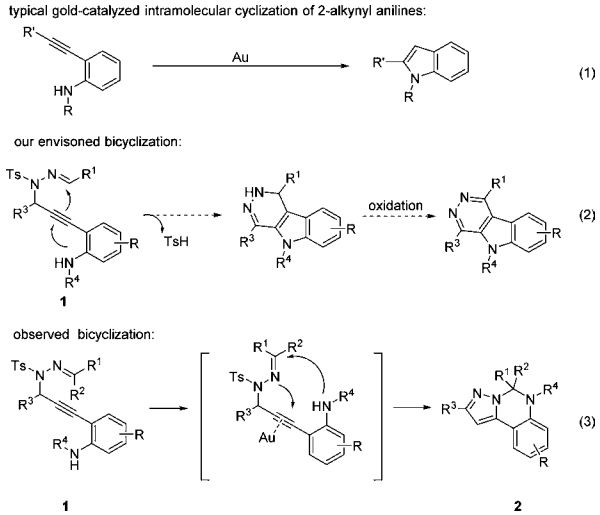


Pyrazoles are widely present in ligands for organic synthesis,[1] agrochemicals,[2] and bioactive compounds.[3] Among those pyrazole derivatives, 5,6-dihydropyrazolo[1,5-*c*]quinazolines have been used as antagonists for a number of biological targets such as Gly/NMDA receptor,[4a,b] excitatory amino acid,[4c] AMPA and kainate receptor,[4d] and adenosine receptor,[4e] as well as inhibitors for IKK[4f] and phosphodiesterase 10A.[4g] Although several strategies have been developed for the synthesis of 5,6-dihydropyrazolo[1,5-*c*]quinazolines, they usually rely on the functionalization of substrates with the pyrazole ring preinstalled.[5,4c,e−g] To the best of our knowledge, methods that form both rings of the 5,6-dihydropyrazolo[1,5-*c*]quinazoline in a single operation have not been reported.[6]

We have been interested in employing *N*-propargylic sulfonylhydrazones for organic synthesis and recently reported the selective transformations of these structures to (1*E*,3*E*)-2-sulfonyl-1,3-dienes[7] and pyrazoles.[8] Gold-catalyzed intramolecular cyclization of 2-alkynyl anilines to prepare indoles has been well-studied (Scheme 1, eq 1).[9] Considering the fact that the nucleophilicity of the amino group is stronger than that of the imine group, we surmised that gold-promoted cyclization of 2-alkynyl aniline **1** that contains a propargylic hydrazone moiety may lead to the formation of a tricylic indole derivative (Scheme 1, eq 2). However, when **1** was treated with a gold catalyst, none of the indole product was observed. Instead, 5,6-dihydropyrazolo[1,5-*c*]quinazolines **2** was obtained in moderate to excellent yields (Scheme 1, eq 3). We report herein the development of this gold(I)-catalyzed chemoselective bicyclization reaction for the synthesis of a wide variety of 5,6-dihydropyrazolo[1,5-*c*]quinazolines, which outcompetes the generation of indole scaffolds.

The cyclization of *N*-propargylic sulfonylhydrazone **1a** was used to optimize the reaction conditions. Treating **1a** with different metal catalysts such as AgOTf, $In(OTf)_3$, $Cu(OTf)_2$, $Sm(OTf)_3$, and $Pd(PPh_3)_2Cl_2$ or trifluoroacetic acid in DMF at room temperature did not yield any of the cyclized product (Table 1, entries 1−6). When we carried out the reaction in the presence of 10 mol % of $AuPPh_3NTf_2$ for 30 min, the desired 5,6-dihydropyrazolo[1,5-*c*]quinazoline **2a** was isolated in 66% yield (Table 1, entry 7). The structure of **2a** is further confirmed by single crystal X-ray structure analysis (Figure 1). Other gold species such as $AuCl_3$ and $AuPPh_3Cl$ were not effective (Table 1, entries 8 and 9). However, the latter did catalyze the cyclization to form **2a** in moderate yields in the presence of silver salts such as AgOTf, $AgSbF_6$, or $AgBF_4$, suggesting the importance of the Lewis acidity of the gold

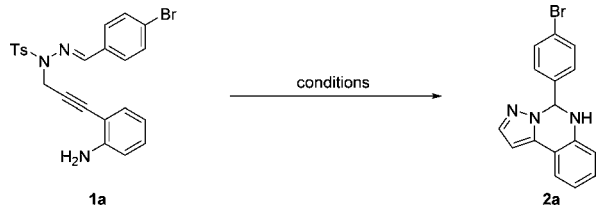
Scheme 1. Possibilities for Forming Different Fused Tricyclic Scaffolds



Received: November 27, 2014
Published: December 26, 2014

DOI: 10.1021/ol503437n
Org. Lett. 2015, 17, 326−329

Table 1. Optimization of the Reaction Conditions[a,b]



1a **2a**

entry	catalyst	solvent	time	yield (%)
1	AgOTf	DMF	2 h	NR[c]
2	$In(OTf)_3$	DMF	2 h	NR
3	$Cu(OTf)_2$	DMF	2 h	NR
4	$Sm(OTf)_3$	DMF	2 h	NR
5	CF_3COOH	DMF	2 h	NR
6	$Pd(PPh_3)_2Cl_2$	DMF	2 h	NR
7	$AuPPh_3NTf_2$	DMF	30 min	66%
8	$AuCl_3$	DMF	2 h	trace
9	$AuPPh_3Cl$	DMF	2 h	trace
10	$AuPPh_3Cl/AgOTf$	DMF	30 min	61%
11	$AuPPh_3Cl/AgSbF_6$	DMF	30 min	47%
12	$AuPPh_3Cl/AgBF_4$	DMF	30 min	62%
13	$AuPPh_3NTf_2$	THF	1 h	trace
14	$AuPPh_3NTf_2$	DCM	1 h	trace
15	$AuPPh_3NTf_2$	DMSO	30 min	86%
16	$AuPPh_3NTf_2$	DMA	30 min	60%
17	$AuPPh_3NTf_2$	CH_3NO_2	1 h	25%
18	$AuPPh_3NTf_2$	CH_3CN	1 h	30%
19	**$AuPPh_3NTf_2$**	**DMSO**	**30 min**	**85%**[d]

[a]Reaction conditions: The reaction was carried out using **1a** (0.5 mmol) and catalyst (10 mol %) in the solvent (5 mL) at room temperature. [b]Isolated yields. [c]NR = no reaction. [d]The amount of catalyst was decreased to 2 mol %.

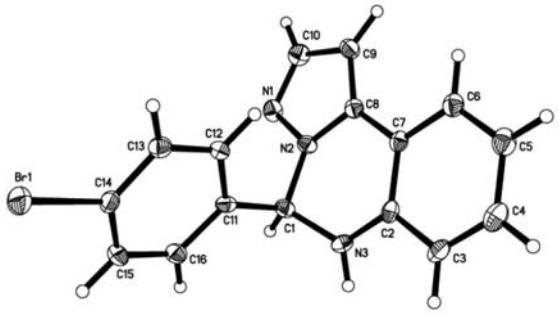
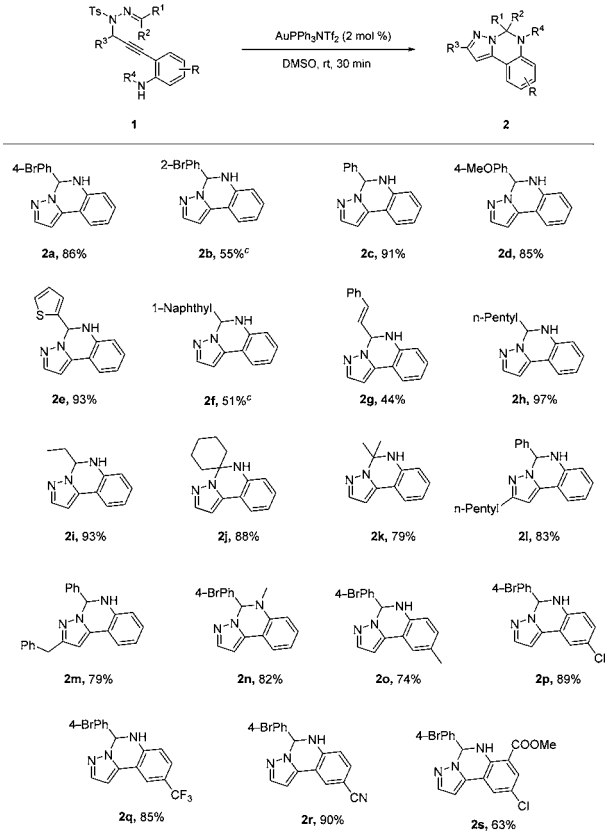


Figure 1. Single crystal X-ray structure for **2a**.

catalyst for the reaction (Table 1, entries 10−12). Given these data, $AuPPh_3NTf_2$ was chosen as the catalyst for further optimization. The screening of various solvents revealed that DMSO was the optimal solvent for the cyclization and the yield could be improved to 86% (Table 1, entry 15). Reducing the catalyst loading to 2 mol % did not affect the yield (Table 1, entry 19). Hence, the optimal reaction conditions were determined to be carrying out the cyclization in the presence of 2 mol % of $AuPPh_3NTf_2$ in DMSO at room temperature (Table 1, entry 19).

The scope of the bicyclization reaction was investigated and is summarized in Scheme 2. Hydrazones derived from numerous aldehydes including aryl aldehydes, cinnamaldehyde, and alkyl aldehydes were all suitable substrates (Scheme 2, products **2a-i**, 44−97% yields). However, the reaction was

Scheme 2. Synthesis of 5,6-Dihydropyrazolo[1,5-*c*]quinazolines 2 from *N*-Propargylic Sulfonylhydrazones 1[a,b]



[a]Reaction conditions: The reaction was carried out using **1** (0.5 mmol) and catalyst (2 mol %) in DMSO (5 mL) at room temperature. [b] Isolated yields. [c] The reaction was run at 120 °C.

somewhat sensitive to *ortho* substitution of the aryl aldehydes. Due to the steric effect, the yields of **2b** and **2f** were much lower. Notably, hydrazones synthesized from ketones also cyclized nicely (Scheme 2, products **2j−k**, 79−88% yields). Branching at the propargylic position were tolerated (Scheme 2, products **2l−m**, 79−83% yields). Additionally, substrates bearing a methyl group at the aniline nitrogen or a variety of substituents with different electronic properties at the aniline phenyl ring all reacted smoothly to afford the desired products (Scheme 2, products **2n−s**, 63−90% yields).

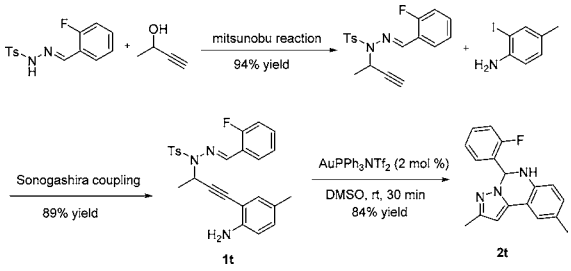
The synthetic utility of the current method was illustrated through the preparation of **2t**, a potential Eg5/Kinesin spindle protein inhibitor.[10] Fan's group recently reported the synthesis of **2t** by assembling the quinazoline ring from a pyrazole-containing precursor.[5b] We were gratified to demonstrate that **2t** could be obtained in 84% yield in a single step by using the gold-catalyzed chemoselective bicyclization of *N*-propargylic sulfonylhydrazone **1t** (Scheme 3).

5,6-Dihydropyrazolo[1,5-*c*]quinazolines synthesized from aldehyde-derived hydrazones can be oxidized to afford pyrazolo[1,5-*c*]quinazolines.[5a] Hence, **1a** was subjected to gold-catalyzed bicyclization followed by copper-catalyzed aerobic oxidation in situ to produce **3a** in 77% yield (Scheme 4).

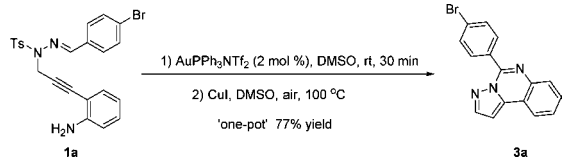
To gain some insight into the reaction mechanism, sulfonylhydrazone **4** without an amino group and **5** with an amino group positioned away from the alkyne were prepared

DOI: 10.1021/ol503437n
Org. Lett. 2015, 17, 326−329

Scheme 3. Synthesis of 5-(2-Fluorophenyl)-2,9-dimethyl-5,6-dihydropyrazolo[1,5-*c*]quinazoline 2t

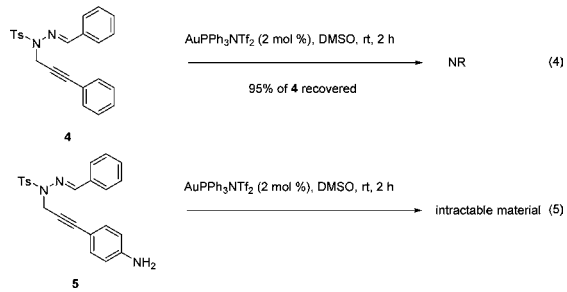


Scheme 4. Synthesis of Pyrazolo[1,5-*c*]quinazoline 3a



and reacted under the standard conditions (Scheme 5). These substrates either failed to react (Scheme 5, eq 4) or led to

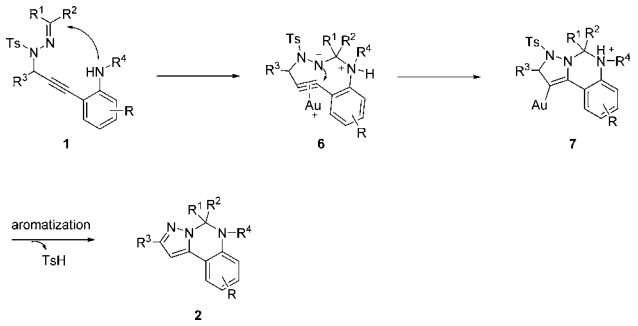
Scheme 5. Mechanistic Studies



intractable material (Scheme 5, eq 5). These results indicated that the *o*-amino group might play a key role in promoting the chemoselective bicyclizations.

A plausible mechanism for the reaction is proposed and depicted in Scheme 6. First, nine-membered ring cyclic aminal

Scheme 6. Proposed Mechanism



intermediate **6** is formed by the intramolecular nucleophilic attack of the aniline nitrogen to the imino group. Second, coordination of the gold catalyst with the alkyne activates the triple bond for nucleophilic attack by the nitrogen anion, leading to the tricyclic intermediate **7**. Proto-demetalation and aromatization through eliminating a molecule of *p*-toluenesulfinic acid result in the regeneration of the gold catalyst and the 5,6-dihydropyrazolo[1,5-*c*]quinazoline product. Other possible pathways cannot be ruled out, such as concerted aminal formation and cyclization, as well as cyclization after imine transfer.

In summary, we have developed a highly efficient and chemoselective gold(I)-catalyzed method for the synthesis of 5,6-dihydropyrazolo[1,5-*c*]quinazolines. This method offers rapid access to a wide variety of dihydropyrazolo[1,5-*c*]quinazolines from easily available *N*-propargylic sulfonylhydrazones under mild reaction conditions. The reversed reactivity in the highly selective formation of 5,6-dihydropyrazolo[1,5-*c*]quinazolines instead of the formation of the usually favored indole scaffolds is observed. Application of the bicyclization protocol for the synthesis of other heterocycles is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization of compounds **1a–t**, **2a–t**, **3a**, and crystallographic data (CIF) of **2a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the National Natural Science Foundation of China (No. 21272190), PCSIRT in University is gratefully acknowledged.

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