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Base- and Ligand-free Room-Temperature Synthesis of N-Fused Heteroaromatic Compounds via the Transition Metal-Catalyzed Cycloisomerization Protocol

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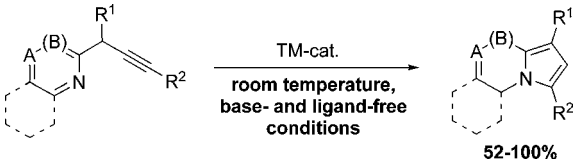
ABSTRACT



A new practical method for the synthesis of N-fused heterocycles via the transition metal-catalyzed cycloisomerization of heterocyles possessing a propagyl group has been developed. This very mild, base- and ligand-free method allows for the synthesis of diverse fused heterocyclic cores in good to excellent yields.

Heteroaromatic molecules containing N-fused bicyclic fragments and their partially or completely reduced analogues are pharmaceutically important scaffolds, widely found in naturally occurring, as well as synthetic biologically active, molecules.[1] For instance, it was shown that molecules containing indolizine and other closely related cores exhibit strong anti-inflammatory,[2] anti-HIV,[3] and anti-leukemia activities.[4] Although few routes toward substituted fused pyrrolo-heterocycles exist,[5] new methods allowing for the efficient construction of these heterocycles with different substitution patterns are of high demand.

We have recently developed two complementary protocols for the synthesis of C-3 substituted[6] and C-1−C-2 disubstituted[7] fused and nonfused pyrrole-containing heterocycles (Scheme 1). The first approach which operates via a copper-assisted cycloisomerization of conjugated alkynyl imines into pyrrole ring (eq 1) was demonstrated to be very general and efficient, though requires excess base and elevated temperatures, and is limited to C-3 monosubstituted products.[6] Another protocol is based on a gold-catalyzed cascade alkyne−vinylidene isomerization/1,2-metalloid migration in

(1) For review, see: Michael, J. P. *Nat. Prod. Rep*. **1999**, *16*, 675.
(2) For studies on sPLA$_2$ inhibition activity, see: Hagishita, S.; Yamada, M.; Shirahase, K.; Okada, T.; Murakami, Y.; Ito, Y.; Matsuura, T.; Wada, M.; Kato, T.; Ueno, M.; Chikazawa, Y.; Yamada, K.; Ono, T.; Teshirogi, I.; Ohtani, M. *J. Med. Chem.* **1996**, *39*, 3636.
(3) For studies on biological activity of Lamellarin family, see: (a) Facompre, M.; Tardy, C.; Bal-Mahieu, C.; Colson, P.; Perez, C.; Manzanares, I.; Cuevas, C.; Bailly, C. *Cancer Res.* **2003**, *63*, 7392. (b) Reddy, M. V.; Rao, M. R.; Rhodes, D.; Hansen, M. S.; Rubins, K.; Bushman, F. D.; Venkateswarlu, Y.; Faulkner, D. J. *J. Med. Chem.* **1999**, *42*, 1901. (c) Østby, O. B.; Dalhus, B.; Gundersen, L.-L.; Rise, F.; Bast, A.; Haenen, G. R. M. M. *Eur. J. Org. Chem.* **2000**, 3763.
(4) (a) Anderson, W. K.; Heider, A. R.; Raju, N.; Yucht, J. A. *J. Med. Chem.* **1988**, *31*, 2097. (b) Anderson, W. K.; DeRuiter, J.; Heider, A. R. *J. Org. Chem.* **1985**, *50*, 722.
(5) For a general review, see: (a) Behnisch, A.; Behnisch, P.; Eggenweiler, M.; Wallenhorst, T. Indolizine. In *Houben-Weyl;* Thieme: Stuttgart, Germany, 1994; Vol. E6b/1, 2a, pp 323−450. See also: (b) Marchalin, S.; Baumlova, B.; Baran, P.; Oulyadi, H.; Daich, A. *J. Org. Chem.* **2006**, *71*, 9114. (c) Kaloko, J., Jr.; Hayford, A. *Org. Lett.* **2005**, *7*, 4305.
(6) Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074.
(7) Seregin, I. V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2006**, *128*, 12050.

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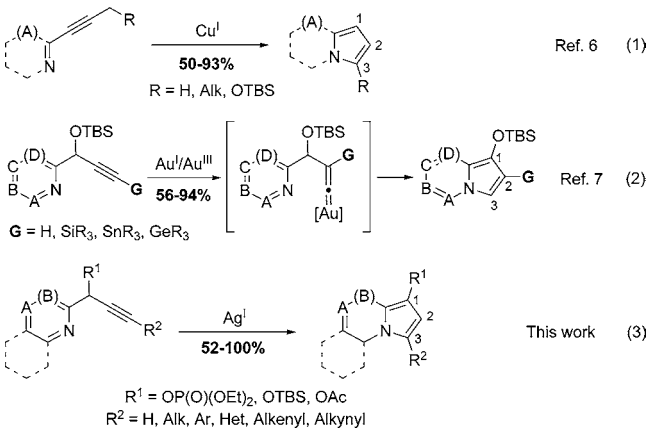
Scheme 1. Formation of Differently Substituted Pyrrole Ring by Transition Metal-Catalyzed Cycloisomerizations

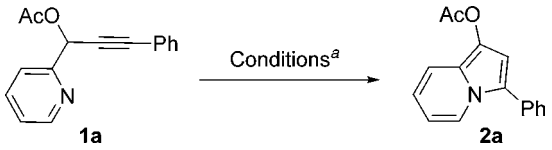


nonconjugated propargyic systems (eq 2).[7] This method does not require base and can be efficiently used at 60 °C to construct C-1−C-2 bifunctional scaffolds. Herein, we wish to report a room temperature, base- and additive-free transition metal-catalyzed cycloisomerization of propagyl heterocycles leading to the formation of C-1−C-3 disubstituted N-fused heterocycles in good to excellent yields (eq 3).[8]

We hypothesized that a π-philic metal would coordinate to the propargylic moiety of the heterocycle rendering its triple bond electrophilic, thus provoking cyclization via an intramolecular nucleophilic attack of heterocyclic nitrogen (Scheme 1, eq 3). To test this hypothesis, we first subjected easily available[9] propargyl-containing pyridine **1a** to the copper-catalyzed cycloisomerization conditions.[6,10] It was found that **1a**, indeed, underwent the desired cycloizomerization, affording indolizine **2a** in good yield. After brief optimization, we were pleased to find that this reaction can be performed equally well at room temperature, the base can be omitted, and DMA can be substituted with easier to handle dichloromethane.

Next, catalyst optimization for this transformation was performed. Thus, it was found that dramatic decrease of the catalyst load to 3 mol % of CuI or CuCl had virtually no effect on the reaction course, producing indolizine **2a** in 77% and 83% yields respectively (Table 1). Similarly, gold catalysts were found to be efficient in this transformation: $AuCl_3$ afforded 71% yield, while AuI gave 95%, though the reaction was slower. In contrast, employment of Al, Sn, In, Mg, Pt, and Pd catalysts under these conditions resulted in moderate yields only, and the reactions were generally much more sluggish. Gratifyingly, switching to $AgBF_4$ and $AgPF_6$ led to nearly quantitative yields of **2a** (entries 12, 13). To verify whether an eventual proton can serve as a catalyst,[11]

Table 1. Catalyst Optimization



1a **2a**

no.	catalyst	reaction time	yield, %[b]
1	CuI	3 h	77%
2	**CuCl**	**30 min**	**83%**
3	$AuCl_3$	30 min	71%
4	**AuI**	**3 h**	**95%**
5	$AlCl_3$	48 h	64%[c]
6	$Sn(OTf)_2$	48 h	31%
7	$Mg(OTf)_2$	48 h	52%
8	$In(OTf)_2$	48 h	33%
9	$PtCl_2$	48 h	41%
10	$PdCl_2(PPh_3)_2$	30 min	61%
11	$Pd(OAc)_2$	30 min	74%
12	**$AgBF_4$**	**30 min**	**>99%**
13	**$AgPF_6$**	**30 min**	**>99%**
14	$AgSbF_6$	30 min	52%
15	HOTf	30 min	9%

[a] Reactions were run in the presence of 3 mol % of catalyst in DCM (0.25 M) at room temperature. Most reactions work equally well in toluene. [b] GC−MS yields. [c] Reaction run using 10 mol % of catalyst.

we tested this reaction in the presence of triflic acid. However, it was found that only small amounts of **2a** were produced under Brønsted catalysis (entry 15).

Next, the scope of this cycloisomerization was examined under the optimized conditions (Table 2). To our delight, acetyloxy, diethylphosphatyloxy, and O−TBS-protected propargylic substrates **1a**−**k** bearing alkyl (entries 2, 8, 10), aryl (entries 1, 5, 9), heteroaryl (entry 11), and alkenyl (entries 3, 7) substituents at the triple bond, as well as those possessing terminal alkyne moiety (entries 4, 6), underwent very smooth cycloizomerization to give corresponding heterocycles **2a**−**k** in good to excellent yields. In contrast, the reaction of diyne-containing substrate **1l** gave a very low yield of pyrrolo-thiazole **2l** (entry 12).[12] It deserves mentioning that this cycloisomerization protocol appeared to be general with regard to the heterocyclic core: C-1−C-3 disubstituted indolizines (entries 1−6), pyrrolo-quinoxalines (entries 7, 8), and pyrrolothiazoles (entries 9−11) can efficiently be synthesized via this method from readily available precursors.[9]

We propose the following mechanistic rationale for the transition metal-catalyzed cycloizomerization of propargyl-heterocycles **1** (Scheme 2). π-Philic metal activates the

(8) When this project was underway, a report on a related Pt-catalyzed 1,2-migration/cyclization toward indolizine core appeared, see: Smith, C. R.; Bunnelle, E. M.; Rhodes, A. J.; Sarpong, R. *Org. Lett.* **2007**, *9*, 1169.

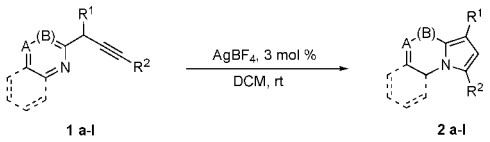
(9) See Supporting Information for detailed preparative procedures.

(10) The reactions were performed in *N*,*N*-dimethylacetamide (DMA) at 130 °C in the presence of 30 mol % CuI.

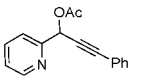
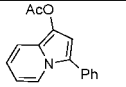
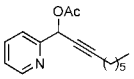
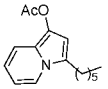
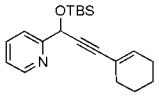
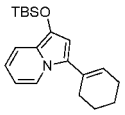
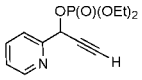
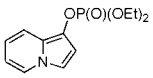
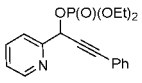
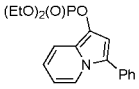
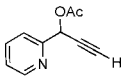
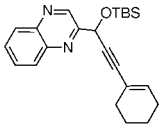
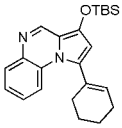
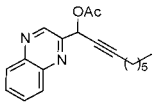
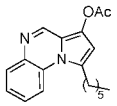
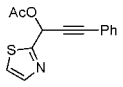
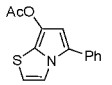
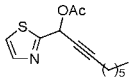
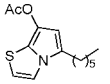
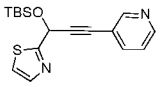
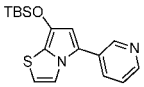
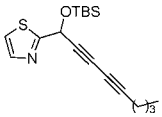
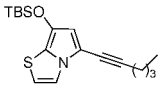
(11) For recent discussions on the role of Brønsted acids in transition metal-catalyzed transformations, see: (a) Hashmi, A. S. K. *Catal. Today* **2007**, *122*, 211. (b) Li, Z.; Zhang, J.; Brouwer, C.; Yang, C.-G.; Reich, N. W.; He, C. *Org. Lett.* **2006**, *8*, 4175. (c) Rosenfeld, D. C.; Shekhar, S.; Takemiya, A.; Utsunomiya, M.; Hartwig, J. F. *Org. Lett.* **2006**, *8*, 4179. (d) Rhee, J. U.; Krische, M. J. *Org. Lett.* **2005**, *7*, 2493.

(12) Alkynyl N-fused heterocycles can be alternatively accessed via our recently developed direct C-H alkynylation approach: Seregin, I. V.; Ryabova, V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, *129*, 7742.

Table 2. Scope of Cycloisomerization



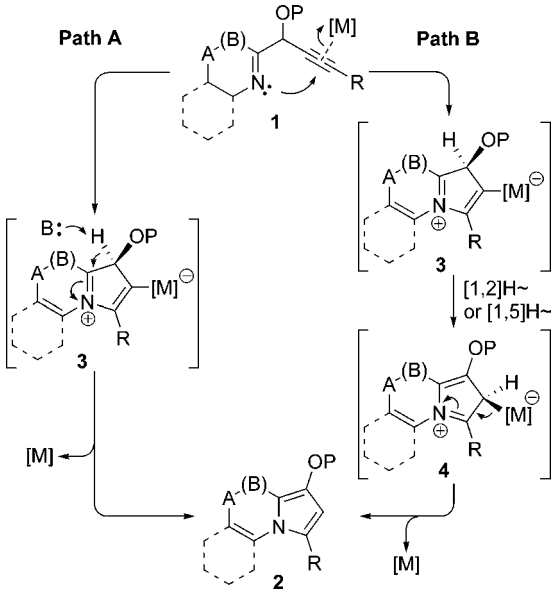
1 a-l 2 a-l

no.	substrate		product		yield, %[a]
1		**1a**		**2a**	95
2		**1b**		**2b**	76
3		**1c**		**2c**	83
4		**1d**		**2d**	64
5		**1e**		**2e**	94
6		**1f**		**2f**	87
7		**1g**		**2g**	52
8		**1h**		**2h**	72
9		**1i**		**2i**	82
10		**1j**		**2j**	85[c]
11		**1k**		**2k**	89[b,c]
12		**1l**		**2l**	< 10[c,d]

[a] Isolated yields. [b] Reaction run using 10 mol % of catalyst. [c] Reaction was performed at 40 °C. [d] NMR yield.

triple bond toward an intramolecular nucleophilic attack of the heterocyclic nitrogen,[13] leading to the formation of a bicyclic zwitterionic adduct **3**. The latter can rearomatize into product **2** via two different ways: through a deprotonation−protonation sequence (Path A), or via 1,2- or 1,5-hydride shift (Path B). In the former scenario, heterocyclic nitrogen of **1** serves as a base, as there is no other base present in the

Scheme 2. Proposed Mechanisms for Cycloisomerization



reaction mixture. Thus, we hypothesized that if deprotonation−protonation event indeed takes place (Path A), a substantial deuterium scrambling would be observed.[14] On the other hand, if the rearomatization proceeds via a hydride shift (Path B), deuterium would cleanly end up at the C-2 position of the cyclized product **2**.[15] To test the above idea, we performed a deuterium-labeling experiment employing isotopically pure propargyl pyridine **5** (Scheme 3). It was

Scheme 3. Deuterium-Labeling Experiment

5 6

found that a severe proton-deuterium exchange took place upon cycloizomerization, thus, strongly supporting the deprotonation−protonation pathway A, and ruling out the possibility of a clean hydride shift (Path B).

(13) For selected examples on nucleophilic attack of heteroatom at alkyne activated by Au and Ag complexes, see: (a) Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc*. **2005**, *127*, 11260. (b) Dubé, P.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 12062. (c) Shapiro, N. D.; Toste, N. D. *J. Am. Chem. Soc.* **2007**, *129*, 4160. (d) Hashmi, A. S. K.; Rudolph, M.; Schymura, S.; Visus, J.; Frey, W. *Eur. J. Org. Chem.* **2006**, 4905. (e) Hashmi, A. S. K.; Weyrauch, J. P.; Frey, W.; Bats, J. W. *Org. Lett.* **2004**, *6*, 4391. (f) Belting, V.; Krause, N. *Org. Lett.* **2006**, *8*, 4489. (g) Sun, J.; Kozmin, S. A. *Angew. Chem., Int. Ed*. **2006**, *45*, 4991. (h) Wang, S.; Zhang, L. *J. Am. Chem. Soc*. **2006**, *128*, 14274. (i) McDonald, F. E.; Gleason, M. M. *J. Am. Chem. Soc.* **1996**, *118*, 6648. (j) McDonald, F. E.; Burova, S. A.; Huffman, L. G. *Synthesis* **2000**, 970.

(14) For an example of a base-assisted substantial deuterium scrambling upon cycloisomerization in conjugated propargylic systems, see ref 6.

(15) For an example of a clean 1,2-deuterium shift upon cycloisomerization, see: Sromek, A. W.; Rubina, M.; Gevorgyan, V. *J. Am. Chem. Soc*. **2005**, *127*, 10500.

In summary, we have developed an exceptionally mild, practical, and efficient method en route to C-1−C-3 disubstituted N-fused heterocycles, including indolizines, pyrroloquinoxalines, and pyrrolothiazoles. This approach is complementary to our previously developed methods[6,7] as it allows for the synthesis of heterocycles with different substitution patterns.

Acknowledgment. The support of the National Institutes of Health (Grant GM-64444) is gratefully acknowledged.

Supporting Information Available: Preparative procedures, analytical and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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