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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 heterocycles possessing a propargyl 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 complimentary protocols for the synthesis of C-3 substituted⁶ and C-1 - C-2 disubstituted⁷ fused and non-fused pyrrole-containing heterocycles (Scheme 1). The first approach which ates *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 non-conjugated propargylic 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 propargyl 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 available⁹ propargyl-containing pyridine **1a** to the copper-catalyzed cycloisomerization conditions.^{6,10} It was found that **1a**, indeed, underwent the desired cycloisomerization, 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 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: AuCl₃ 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 AgBF₄ and AgPF₆ led to nearly quantitative yields of **2a** (entries 12, 13). In order to verify whether an eventual proton can serve as a catalyst,¹¹ 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 cycloisomerization 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 pyrrolothiazole **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 cycloisomerization of propargyl-heterocycles **1** (Scheme 2). π -Philic metal activates the 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 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 deuterium-labeling experiment employing isotopically pure propargyl pyridine **5** (Scheme 3). It was found that a severe proton-deuterium exchange took place upon cycloisomerization, thus, strongly supporting the deprotonation-protonation pathway **A**, and ruling out the possibility of a clean hydride shift (Path **B**).

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 complimentary to our previously developed methods^{6,7} as it allows for the synthesis of heterocycles with different substitution patterns.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.

Formation of differently substituted pyrrole ring by transition metal-catalyzed cycloisomerizations

Scheme 2.
Proposed mechanisms for cycloisomerization

Scheme 3.
Deuterium labeling experiment

Table 1

Catalyst optimization

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	AgBF₄	30 min	>99%
13	AgPF₆	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 10 mol % of catalyst were used.

Table 2

Scope of cycloisomerization

no.	substrate	product	yield, % ^a
1			95
2			76
3			83
4			64
5			94
6			87
7			52
8			72
9			82
10			85 ^c
11			89, ^{bc}
12			< 10, ^{cd}

^a Isolated yields.^b 10 mol % of catalyst was used.

^cReaction was performed at 40 °C.

^dNMR yield.