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A convenient synthesis of pyrrolopyridines and 2-substituted indoles by gold-catalyzed cycloisomerization

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ABSTRACT

We have developed a gold-catalyzed intramolecular cyclization of variously substituted acetylenic amines under mild conditions, which yields pyrrolopyridines and 2-substituted indoles, quantitatively. The cycloisomerization of acetylenic amines was achieved with $AuCl_3$ as catalyst without the use of base, acid or N-protecting group.

In the total synthesis of natural products, there is still significant interest in the construction of pyrrolopyridine and indole subunits because of their wide range of biological properties.[1] Many naturally occurring compounds possess indole as a key structural motif. Owing to the numerous applications of indoles in pharmaceutical research, the development of efficient and new synthetic protocols for their synthesis has attracted the attention of many chemists. Moreover, heterocycles possessing pyrrolopyridines have been used as modulators of kinase activity,[2] and are frequently used in the treatment of allergic, autoimmune, inflammatory, proliferative and hyperproliferative diseases and immune-mediated diseases such as the rejection of transplanted organs or tissues and AIDS.[3]

According to the literature,[4] there are only a few examples of the synthesis of pyrrolopyridines via Sonogashira coupling followed by oxidative cyclization. Among the different synthetic protocols developed, catalytic transformations using transition-metal catalysts are one of the more recent techniques for forming indoles.[5] Specifically, the use of highly functionalized acetylenic amines as the starting materials is some of most efficient approaches.[6] Rudisill and Still reported[7] the palladium-catalyzed intramolecular cyclization of 2-alkynylanilines to give 2-substituted indoles in high yield. Cacchi et al. have reported[8] a regioselective synthesis of 3-allylindoles via palladium-mediated cyclization of *O*-alkynyltrifluoroacetanilides with allyl esters. Subsequently, Knochel and co-workers described[9] the synthesis of polyfunctionalized indoles using cesium and potassium bases (e.g., CsO–*t*-Bu, KO–*t*-Bu and KH) in *N*-methylpyrrolidinone. Moreover, Hiroya et al. developed[10] an efficient Cu(II)-catalyzed indole synthesis and successfully applied the methodology to natural product synthesis. Recently, Yamamoto et al. reported[11] that in the presence of certain nucleophiles, for example, allyl carbonate and alcohol, tandem cyclization of 2-alkynylanilines proceeded smoothly to afford the nucleophile-incorporated indoles.

On the other hand, many synthetic methods for the preparation of acetylenic amines have been reported.[9,12,6a] The cyclization of acetylenic amines with various transition-metal catalysts gave the corresponding 2-substituted indoles. The synthesis of indoles with functional groups at any position except for the 3-position seems to be a widely useable method. Furthermore, the 3-position of indole is most prone to electrophilic aromatic substitution and there are many reports on the synthesis of 3-substituted indole derivatives, but access to 2-substituted derivatives are a challenge to the synthetic community. So far, only a few methods for the synthesis of 2-substituted indoles have been reported. [9,13]

In continuation of our efforts on palladium-mediated heterocyclizations[14] we recently reported[15] the regioselective synthesis of pyrrolopyridine derivatives **2** in moderate yields via base-promoted cyclization of variously substituted acetylenic *N*-$COCF_3$-protected amines **1**. Initially, we attempted the cyclization with the free acetylenic amine **3** but which failed to cyclize due to the fact that an electron-withdrawing group is required for the cyclization of the acetylenic free amine to increase the nucleophilicity[13a,16] of the nitrogen atom of the amine functionality. Therefore, we protected the free amines using trifluoroacetic anhydride (TFAA) and cyclized the amines by using CuI/DMF–Et_3N at 100 °C (Scheme 1).

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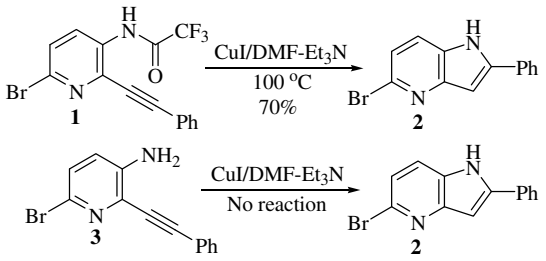
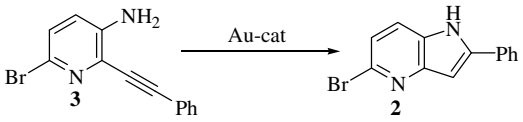


Scheme 1. CuI- or base-mediated heterocyclization.

Our interest towards the development of resource-saving and safe synthetic protocols led us to explore $AuCl_3$ as green catalysts.[16,17] Until now, very little attention[18] has been paid to gold-catalyzed cycloisomerizations of acetylenic free amines and to our knowledge, this is the first report for the synthesis of potentially bioactive pyrrolopyridine derivatives via gold-catalyzed cycloisomerization.

Here we report that the gold catalyst, $AuCl_3$ can catalyze cyclization at ambient temperature leading to potentially bioactive pyrrolopyridine derivatives in a very simple fashion. Our aim was to develop a synthetic protocol involving the use of environmentally benign solvents and avoiding the requirement of protecting groups

Table 1
Optimization of gold-catalyzed cycloisomerization



Entry	Catalyst	Solvents[a]	Temperature (°C)	Time (h)	Yields[b] (%)
1	1% $AuCl_3$	PhMe	rt	24	NR[c]
2	1% $AuCl_3$	PhMe	100	24	NR[c]
3	3% $AuCl_3$	PhMe	100	24	NR[c]
4	1% $AuCl_3$	MeCN	80	10	31
5	3% $AuCl_3$	MeCN	80	10	~35
6	3% $AuCl_3$	DMF	80	10	NR[c]
7	3% $AuCl_3$	1,4-Dioxane	80	10	NR[c]
8	3% $AuCl_3$	PhMe + MeCN (1:1)	100	10	45
9	1% $AuCl_3$	EtOH + MeCN (1:1)	80	10	55
10	3% $AuCl_3$	EtOH + MeCN (2:1)	80	10	64
11	3% $AuCl_3$	EtOH + MeCN (3:1)	80	6	81
12	3% $AuCl_3$	EtOH + MeCN (4:1)	70	5	~85
13[d]	**3% $AuCl_3$**	**EtOH**	**70**	**4**	**98**

[a] In each case the total amount of solvent is 10 ml.
[b] Isolated yield.
[c] NR = no reaction.
[d] Optimized reaction conditions.

Table 2
Synthesis of pyrrolopyridines and 2-substituted indoles by Au-catalyzed cycloisomerization

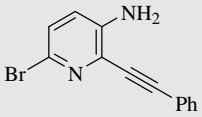
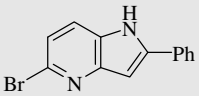
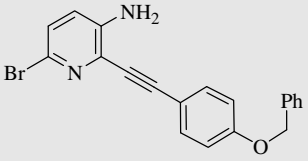
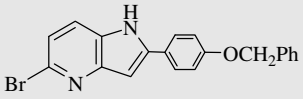
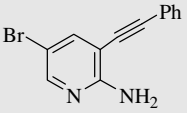
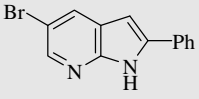
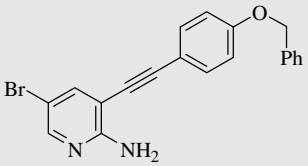
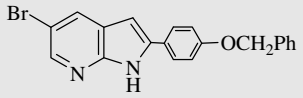
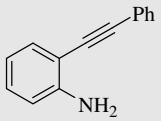
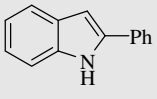
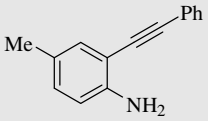
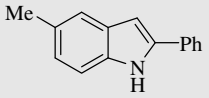
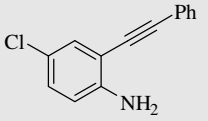
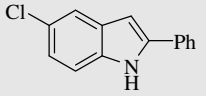
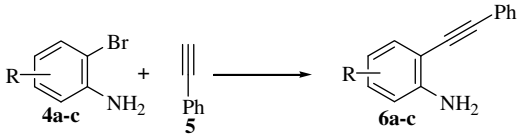
Entry	Acetylenic amines	Catalytic compositions[a]	Time (h)	Products	Yields[b] (%)
1	 **3a**	$AuCl_3$ (3%)/EtOH/70 °C	4	 **2a**	98
2	 **3b**	$AuCl_3$ (3%)/EtOH/70 °C	4.5	 **2b**	97
3	 **3c**	$AuCl_3$ (3%)/EtOH/70 °C	4.5	 **2c**[23]	98
4	 **3d**	$AuCl_3$ (3%)/EtOH/70 °C	4	 **2d**	96
5	 **6a**[20,22]	$AuCl_3$ (3%)/EtOH/70 °C	4.5	 **2e**	98

Table 2 (*continued*)

Entry	Acetylenic amines	Catalytic compositions[a]	Time (h)	Products	Yields[b] (%)
6	 **6b**	$AuCl_3$ (3%)/EtOH/70 °C	5	 **2f**	99
7	 **6c**[20,22]	$AuCl_3$ (3%)/EtOH/70 °C	4.5	 **2g** [20,22]	98

[a] In each case ethanol (10 ml) and 50 mg of the acetylenic amine were used.
[b] Isolated yields.



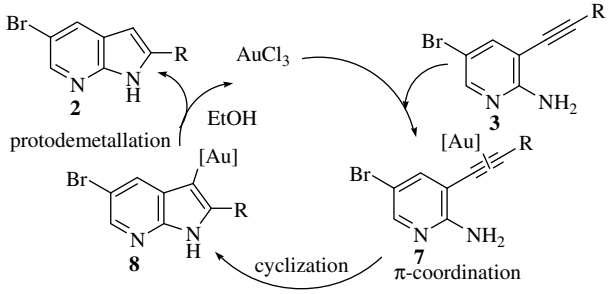
Scheme 2. Reagents and conditions: $Pd(PPh_3)_2Cl_2$, CuI, DMF–Et_3N (5:2, 7 ml), 100 °C, 2 h. Preparation of acetylenic amines **6a–c**.

and harsh reaction conditions. We selected compound **3** as a model substrate to study its cycloisomerization under a variety of reaction conditions, for example, varying the catalytic loading, the solvent system and composition and the reaction temperature. The results of this investigation are presented in Table 1.

The results show that toluene, 1,4-dioxane and DMF are ineffective solvents for the cycloisomerization irrespective of the temperature, catalyst or the reaction duration. Acetonitrile was effective as it gave a 31% yield of **2** in the presence of 1 mol % of $AuCl_3$. Increasing the catalytic load gave a small increase of the yield in 5 h, but after an additional 5 h, there was no further improvement in the yield. Interestingly, when the reaction was carried out in a mixed solvent in various ratios, the results obtained were more promising. Ethanol plays an important role in allowing rapid reaction in the presence of 3 mol % $AuCl_3$. Increasing the amount of ethanol and decreasing the amount acetonitrile, the reaction proceeds smoothly with greater efficiency. Finally, when the reaction was conducted in ethanol alone as the solvent at 70 °C, the reaction yield was quantitative in 4 h.

Next, this protocol was extended to various acetylenic free amines 3**b–d**. Substrates **3b–d** were reacted under the optimized conditions to afford the corresponding cycloisomerized products **2b–d** in excellent yields (96–98%) (Table 2).

Since 2-substituted indoles are the versatile building blocks for the assembly of various complex molecules, we also attempted the gold-catalyzed cycloisomerization of the substrates **6a–c**. The starting materials **6a–c** were prepared in moderate to good yields by Sonogashira coupling[19] of the free amines **4a–c** with phenylacetylene using $Pd(PPh_3)_2Cl_2$ as catalyst and CuI as co-catalyst in dry DMF–Et_3N (5:2) at 100 °C for 2 h (Scheme 2). A variety of methods are available for the synthesis of 2-substituted indole derivatives from N-protected amines by gold-catalyzed cycloisomerization using Ag salts as co-catalysts.[20] We have carried out the reaction without protecting the amine functionality and also in the absence of any silver salt.



Scheme 3. Probable mechanistic pathway of the gold-catalyzed cycloisomerization.

Applying the optimized reaction conditions of the substrates **6a–c** afforded the 2-substituted indoles **2e–g** in excellent yields (98–99%). The results are summarized in Table 2. The mechanistic rationale for the reaction is outlined in Scheme 3. The Lewis acidic Au(III) coordinates to alkynyl moiety of substrate **3/6**. The resulting electron-deficient triple bond in **3/6** undergoes intramolecular nucleophilic attack by the poorly basic nitrogen atom of the free amine moiety leading to the intermediate **8** via a 5-*endo-dig* cyclization in preference to a 4-*exo-dig* mode of cyclization, which is disfavored according to the Baldwin rules.[21] Finally, protodemetallation by EtOH affords the cycloisomerized products **2** (Scheme 3).

In conclusion, we have shown that gold catalysis enables a mild and convenient synthetic protocol for the synthesis of pyrrolopyridine and 2-substituted indole derivatives in excellent yields. This protocol is simple to carry out and does not require the use of base, acid or N-protecting group. The isolation of the products is simple and avoids extractive work-up.

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23. General procedure for the preparation of compounds **2**:To a magnetically stirred solution of **3c** (50 mg, 0.183 mmol) in ethanol, $AuCl_3$ (1.66 mg, 3 mol%) was added and the reaction heated on an oil bath at 70 °C for 4.5 h. The mixture was cooled to rt and ethanol was removed under reduced pressure. The crude mass was then purified by flash column chromatography (silica gel 230–400 mesh) using ethyl acetate–petroleum ether (1:4) as eluant to give the product **2c** in 98% yield.
Selected spectral data:
Compound **2c**: White solid; mp above 200 °C; yield 98%. IR (KBr, cm^{-1}): 3135. ^1H NMR (DMSO-d_6, 400 MHz): δ 6.91 (d, 1H, C*H*=C, *J* = 1.6 Hz), 7.37 (t, 1H, Ar*H*, *J* = 7.3 Hz), 7.48 (t, 2H, Ar*H*, *J* = 7.5 Hz), 7.94 (d, 2H, Ar*H*, *J* = 7.6 Hz), 8.17 (d, 1H, Ar*H*, *J* = 1.6 Hz), 8.26 (d, 1H, Ar*H* *J* = 1.9 Hz), 12.37 (s, 1H, N*H*). MS (*m/z*): 272 (M^+), 274. Anal. Calcd for $C_{13}H_9BrN_2$: C, 57.17; H, 3.32; N, 10.26. Found: C, 56.98; H, 3.48; N, 10.29.
Compound **2f**: Solid, mp 210–211 °C; yield 99%. IR (KBr, cm^{-1}): 3443. ^1H NMR ($CDCl_3$, 400 MHz) δ 2.43 (s, 3H, *Me*), 6.74 (s, 1H, =C*H*), 7.00 (d, 1H, *J* = 8.1 Hz, Ar*H*), 7.27 (d, 1H, *J* = 7.4 Hz, Ar*H*), 7.30 (d, 1H, *J* = 2.8 Hz, Ar*H*), 7.40–7.44 (m, 3H, Ar*H*), 7.64 (d, 2H, *J* = 7.6 Hz, Ar*H*), 8.33 (br s, 1H, N*H*). MS (*m/z*): 207 (M^+). Anal. Calcd for $C_{15}H_{13}N$: C, 86.92; H, 6.32; N, 6.76. Found: C, 86.77; H, 6.45; N, 6.89.