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Carbazoles via $AuCl_3$-Catalyzed Cyclization of 1-(Indol-2-yl)-3-alkyn-1-ols

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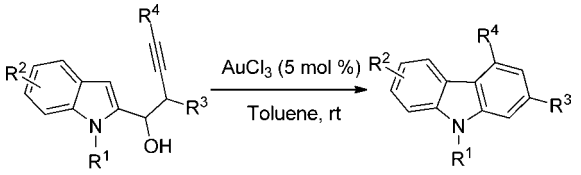
ABSTRACT



$AuCl_3$-catalyzed reaction of 1-(indol-2-yl)-3-alkyn-1-ols occurred smoothly in toluene at room temperature to form a benzene ring leading to a series of carbazole derivatives efficiently. A possible mechanism has been proposed for the formation of carbazoles.

Carbazoles are important heteroaromatic compounds in many biologically active products.[1] They also serve as building blocks for potential electroluminescent materials[2] due to their electrical[3] and thermal[4] properties and host materials for triplet emitters in organic light-emitting diodes.[5] Therefore, they are attractive targets for organic synthesis. Although there are a number of useful synthetic procedures to prepare carbazoles,[6−9] there remain some limitations such as low yields, poor atom economy, and harsh reaction conditions in these methods. Thus, a simple, mild, efficient, regiocontrolled, and diversified preparation of carbazole alkaloids with specific substitution patterns is still highly desirable.

On the other hand, the intramolecular hydroarylation reaction of alkyne is of particular interest, since valuable carbo- and heterocycles can be readily formed under relatively mild conditions.[10−12] For example, gold- or platinum-catalyzed cyclization reactions of indoles with alkynes are

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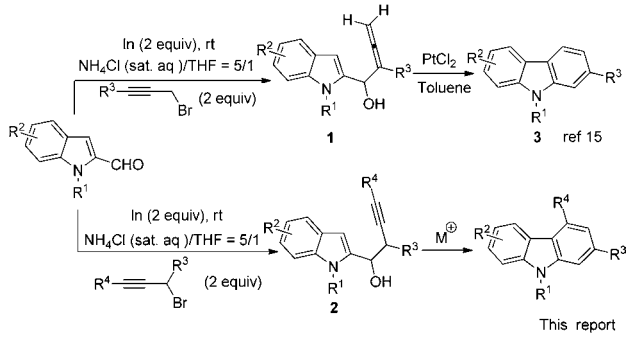
important because significant molecular complexity can be obtained in one step starting from an easily accessible system.[13,14]

Recently, we developed a route to construct carbazole alkaloids via the Pt-catalyzed cyclization of terminal 1-(indol-2-yl)-2,3-allenols **1** (Scheme 1),[15] which may be easily prepared from the In-mediated reaction of indole-2-carbaldehydes and primary 1-alkynyl bromides in an aqueous phase.[15,16] Interestingly, 1-(indol-2-yl)-3-alkyn-1-ols **2** were formed when non-terminal secondary 1-alkynyl bromides were used.[17] Considering our interests in synthesis of heterocyclic compounds, we reasoned that cyclization of homoproparylic alcohols **2** may also afford carbazole alkaloids following a similar elimination of water to form the aromatic ring[15] (Scheme 1). In this paper, we report our observation of such a reaction.

Scheme 1



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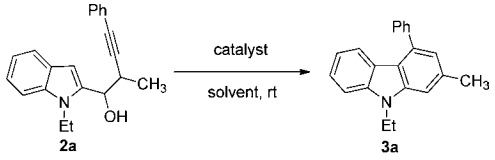
Our initial investigation focused on the reaction of 1-(1-ethyl-1*H*-indol-2-yl)-2-methyl-4-phenyl-3-butyn-1-ol (**2a**) in toluene under the catalysis of $PtCl_2$ (5 mol %). Interestingly, 9-ethyl-2-methyl-4-phenyl-9*H*-carbazole (**3a**) was indeed formed in 62% NMR yield (entry 1, Table 1). When AgOTf was used instead of $PtCl_2$, the yield of this reaction was only 35% (entry 2, Table 1), and $Zn(OTf)_2$ was totally inactive (entry 3, Table 1). However, the combined use of $AuCl(PPh_3)$ and AgOTf as catalyst could improve the yield to 87% (entry 4, Table 1). AuCl-(*t*-Bu_3P)/AgOT catalyzed this transformation affording **3a** in 88% yield (entry 5, Table 1). Further study showed that $AuCl_3$[18] is the best catalyst for this reaction, affording **3a** in 93% yield (entry 6, Table 1)! Several solvents were also tested for the $AuCl_3$-catalyzed reaction of **2a** at room temperature with toluene still being the best (entries 7−9, Table 1). When 1 mol % of $AuCl_3$ was used, the yield of **3a** was slightly lower (entry 10, Table 1). Thus, we defined the standard conditions as follows: 5 mol % of $AuCl_3$ in toluene at room temperature (entry 6, Table 1). The structure of **3a** was further confirmed by the X-ray crystal diffraction study (Figure 1).[19]

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst (5 mol %)	solvent	time (h)	yield[b] of **3a** (%)
1	$PtCl_2$	toluene	36	62
2	AgOTf	toluene	23	35
3	$Zn(OTf)_2$	toluene	12	0
4	$AuCl(PPh_3)$/AgOTf	toluene	12	87
5	AuCl(*t*-Bu_3P)/AgOTf	toluene	12	88
6	$AuCl_3$	toluene	3	93
7	$AuCl_3$	CH_2Cl_2	5	36
8	$AuCl_3$	CH_3CN	5	51
9	$AuCl_3$	acetone	5	85
10[c]	$AuCl_3$	toluene	12	82

[a] The reaction was conducted with 0.2 mmol of **2a** and 0.01 mmol of catalyst in 1 mL of solvent. [b] Determined by ^1H NMR of crude product using dibromomethane as internal standard. [c] $AuCl_3$(1 mol %) was used.

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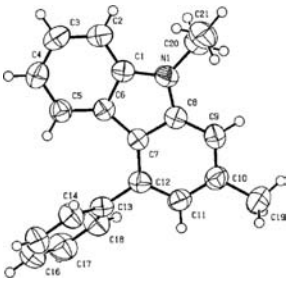
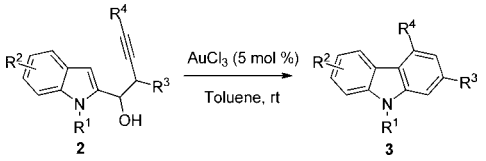


Figure 1. ORTEP representation of **3a**.

This new transformation is quite general, and some typical results are listed in Table 2. The 1-position of indoles may be substituted with alkyl (entries 1−7, 9 and 10, Table 2) or benzyl groups (entries 8, 11 and 12, Table 2). Substituents on the 5-position could be methyl (entries 4−6, Table 2), methoxy, which is the vital functional group for the synthesis of many natural tricyclic carbazole alkaloids[21] (entry 7, Table 2), or bromine,[20] which could easily transform to many useful functional groups in the synthesis of biologically active carbazole alkaloids[21] (entry 8, Table 2). Substituents may also be introduced to the 4- or 7-position (entries 9−10, Table 2). R^3 could be an alkyl (entries 1−5 and 7−12, Table 2) or an aryl group (entry 6, Table 2). Moreover, R^4 could be an alkyl (entries 2−4, 6, 7, 9, and 11, Table 2) or an aryl group (entries 1, 5, 8, 10, and 12, Table 2).

Table 2. $AuCl_3$-Catalyzed Cyclization Reaction of 1-(Indol-2-yl)-3-alkyn-1-ols **2**[a]

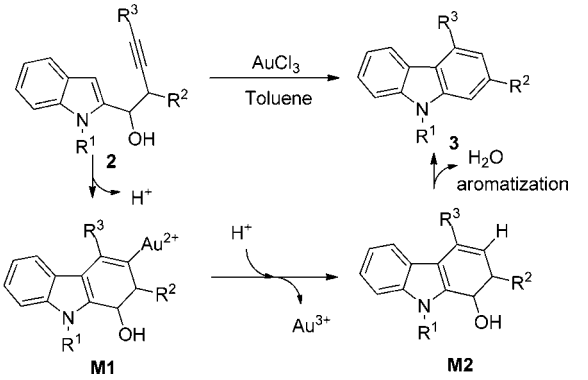


entry	**2**	R^1, R^2, R^3, R^4	time (h)	yield[b] of **3** (%)
1	**2a**	Et, H, Me, Ph	3	**3a**, 90
2	**2b**	Et, H, Me, Et	12	**3b**, 81
3	**2c**	Et, H, Me, n-C_4H_9	19.5	**3c**, 74
4	**2d**	Et, 5-Me, Me, n-C_4H_9	11.5	**3d**, 72
5	**2e**	Et, 5-Me, Et, Ph	14	**3e**, 79
6	**2f**	Et, 5-Me, Ph, n-C_4H_9	11	**3f**, 64
7	**2g**	Et, 5-OMe, Me, n-C_4H_9	11.5	**3g**, 60
8	**2h**	Bn, 5-Br, Et, Ph	13	**3h**, 72
9	**2i**	Et, 4-Me, Me, n-C_4H_9	3	**3i**, 65
10	**2j**	Et, 7-Me, Me, Ph	12	**3j**, 90
11	**2k**	PMB, H, Me, n-C_4H_9	12	**3k**, 58
12	**2l**	Bn, H, Et, Ph	12	**3l**, 62

[a] Reaction conditions: 0.2 mmol of 1-(indol-2-yl)-3-alkyn-1-ols **2**, 0.01 mmol of $AuCl_3$ in 1 mL of toluene. [b] Isolated yield.

A mechanism is proposed for the reaction (Scheme 2).[10,15,22] The reaction of Au^{3+} with **2** would form intermediate **M1** via the coordination of the alkyne with the Au^{3+} species followed by nucleophilic attack of indolyl C3 to the metal-activated electrophilic C−C triple bonds. The six-membered intermediate **M2** may be afforded via demetalation of **M1** regenerating the catalytically active Au^{3+} species. Subsequent elimination of H_2O would afford the target carbazole **3**.[15,12l,23]

Scheme 2



In conclusion, we have developed a simple and mild $AuCl_3$-catalyzed reaction of 1-(indol-2-yl)-3-alkyn-1-ols to provide an efficient route to differently substituted carbazoles in moderate to good yields under very mild conditions. A rationale has also been proposed for the formation of carbazoles. Because of the easy availability of the starting materials and potential of the products, this method would be useful in organic synthesis and medicinal chemistry. Further studies on the synthetic applications of this reaction are being carried out in our laboratory.

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(19) Crystal data for compound **3a**: $C_{21}H_{19}N$, MW = 285.37, monoclinic, space group $P21$, final R indices $[I > 2\sigma(I)]$, $R1$ = 0.0395, $wR2$ = 0.0972, R indices (all data) $R1$ = 0.0590, $wR2$ = 0.0889, a = 8.9461(6) Å, b = 8.9810(6) Å, c = 20.0010(13) Å, α = 90°, β = 90.115(5)°, γ = 90°, V = 1606.98(18) Å^3, T = 293(2) K, Z = 4, reflections collected/unique: 8159/4822 (R_{int} = 0.0252), number of observations [> $2\sigma(I)$] 3681, parameters: 402. CCDC 906003.

(20) For the orthogonality of gold and palladium catalysis, see: Hashmi, A. S. K.; Lothschütz, C.; Döpp, R.; Ackermann, M.; Becker, J. D. B.; Rudolph, M.; Scholz, c.; Rominger, F. *Adv. Synth. Catal.* **2012**, *354*, 133.

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Supporting Information Available. General procedure and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.