Organic LETTERS

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Lewis Acid Catalyzed Cascade Reaction to Carbazoles and Naphthalenes via Dehydrative [3 + 3]-Annulation

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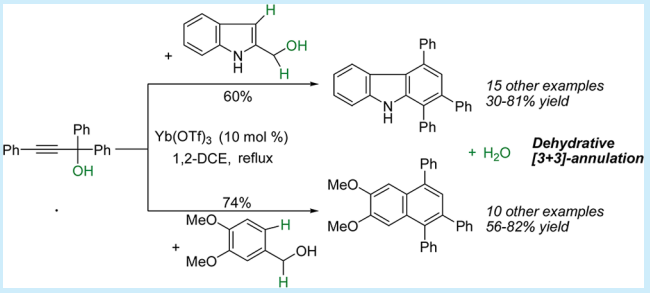
Supporting Information

ABSTRACT: A novel Lewis acid catalyzed dehydrative [3 + 3]-annulation of readily available benzylic alcohols and propargylic alcohols was developed to give polysubstituted carbazoles and naphthalenes in moderate to good yields with water as the only byproduct. The reaction was presumed to proceed via a cascade process involving Friedel−Crafts-type allenylation, 1,5-hydride shift, 6π-eletrocyclization, and Wagner−Meerwein rearrangement.



Carbazoles are important scaffolds present in numerous biologically and pharmaceutically active compounds.[1] For example, complex alkaloids tubingensin A and B have shown antiviral and anticancer activity as well as potent activities against agriculturally important pests;[2] clausenine and clausenol have shown antibiotic activities;[3] and P7C3 and its analogues have shown promising neuroprotective properties for drug discovery in rodent models of Parkinson's disease, age-related cognitive decline, amyotrophic lateral sclerosis, and traumatic brain injury (Figure 1).[4] Moreover, carbazoles are also widely

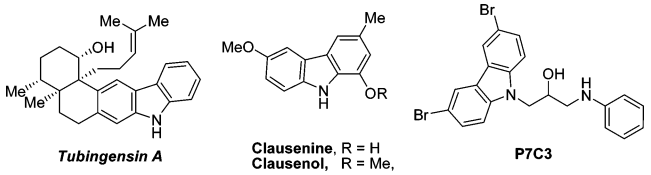


Figure 1. Representative carbazole-containing natural products.

used in photorefractive materials and organic dyes for solar cells and have found applications in the design of single-molecule circuits and sensors.[5] Consequently, a large number of procedures have been developed with varied degrees of success for the construction of this highly useful structure.[6−8] However, current methods more or less suffer from limited substrate scope, complicated catalyst or noble metal catalyst systems, not-easily accessible starting materials, and/or multistep manipulations. Therefore, there is still great room for the development of a simple and efficient method for the syntheses of structurally diverse carbazoles.

Cascade reaction systems enable the construction of complex molecules from relatively simple and easily available starting materials with excellent atom- and step-economy.[9] Recently, our group has been interested in the development of cascade processes using simple electron-rich benzylic alcohols as a versatile three-carbon synthon for the construction of useful cyclic structures, such as tetrahydro-β-carbolines and tetrahydroisoquinolines.[10] This type of process involves direct dehydrative couplings between a C−OH bond and a C−H bond to construct new C−C bonds with water as the only byproduct, and therefore, it has been recognized as an environmentally benign process and has prompted significant research interest recently.[11] In this context, we envisaged that 2-indolyl methanols and propargylic alcohols would be two three-carbon building blocks for the construction of carbazoles in a [3 + 3]-annulation manner (Scheme 1). We report herein the details of this research.

The reaction of 1*H*-indole-2-methanol **1a** and propargylic alcohol **2a** was selected as a model reaction for optimization of reaction conditions (Table 1). Using 1,2-dichloroethane (1,2-DCE) as solvent, four different rare-earth metal triflates were screened, and $Yb(OTf)_3$ was found to be the most efficient catalyst for this reaction (Table 1, entries 2−5). No reaction occurred in the absence of the catalyst or when the reaction was performed at room temperature (Table 1, entries 1 and 6). Changing the solvent to DCM, toluene, DMF, 1,4-dioxane, or THF gave inferior results (Table 1, entries 7−10). Further screen of catalyst loading amount revealed that 10 mol % was

Received: June 4, 2014

   dx.doi.org/10.1021/ol501605h | *Org. Lett.* XXXX, XXX, XXX−XXX

Scheme 1. Lewis Acid Catalyzed Dehydrative [3 + 3]-Annulation Path to Useful Heterocycles

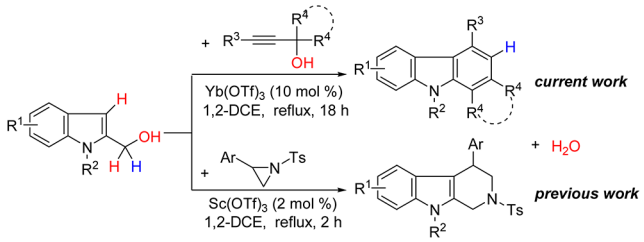
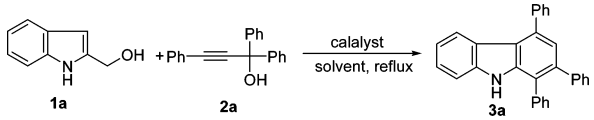


Table 1. Screening of Reaction Conditions[a]



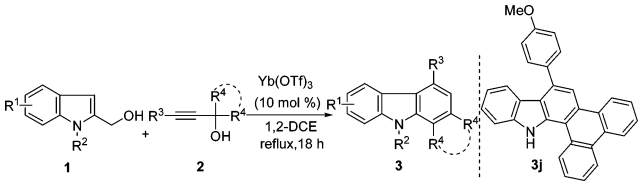
entry	catalyst (mol %)	solvent	time (h)	yield (%)[b]
1	no catalyst	1,2-DCE	24	0
2	$Sc(OTf)_3$ (10)	1,2-DCE	16	43
3	$Y(OTf)_3$ (10)	1,2-DCE	16	55
4	$La(OTf)_3$ (10)	1,2-DCE	24	50
5	$Yb(OTf)_3$ (10)	1,2-DCE	16	60
6[c]	$Yb(OTf)_3$ (10)	1,2-DCE	18	nr
7[d]	$Yb(OTf)_3$ (10)	toluene	18	25
8[d]	$Yb(OTf)_3$ (10)	DMF	24	0
9[d]	$Yb(OTf)_3$ (10)	1,4-dioxane	18	44
10	$Yb(OTf)_3$ (10)	THF	18	56
11	$Yb(OTf)_3$ (5)	1,2-DCE	18	55
12	$Yb(OTf)_3$ (20)	1,2-DCE	18	59

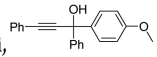
[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), solvent (5 mL). [b]Yield of the isolated pure product. [c]Reaction was run at 25 °C. [d]Reaction was run at 90 °C.

optimal for the reaction, while lower (5 mol %) or higher (20 mol %) all led to reduced yields (Table 1, entries 11 and 12). It is worth mentioning that the reaction is tolerant of moisture and air and could be performed in commercial solvents under open air.

With the optimized reaction conditions in hand, the scope of the reaction was then examined with a series of indole-2-methanols **1** and propargylic alcohols **2** (Table 2). First, a series of substituted **2** were reacted with **1a** to examine the substituent effect (Table 2, entries 1−8). In general, propargylic alcohols **2** bearing electron-donating substituents on either of the two aryl groups (R^3, R^4) provided higher yields than those with electron-withdrawing ones. Such a phenomenon suggests the intermediacy of carbocation species in this reaction. Notably, when the propargylic alcohol **2i** with two different aryl groups (R^4) was employed, the electron-rich aryl group migrated predominantly to give the product **3i** (Table 2, entry 9). Moreover, when 9-fluorenyl-substituted **2l** was subjected to the reaction conditions, a polycyclic heteroaromatic product **3j** could be formed in an acceptable 31% yield (Table 2, entry 10). Differently substituted 2-indolyl methanols **1** were then examined in the reaction (Table 2, entries 11−16). While the presence of an electron-donating substituent on the benzene ring of indole seemed to be detrimental to the reaction (Table 2, entry 11 vs entry 7), the presence of an electron-withdrawing one seemed favored (Table 2, entries 13, 14 vs entry 1). This might be because the presence of electron-donating substituents would render the corresponding indole substrates

Table 2. Syntheses of Carbazoles 3[a]



entry	**1**, R^1/R^2	**2**, R^3/R^4	**3**	yield[b]
1	**1a**, H/H	**2a**, Ph/Ph	**3a**	60
2	**1a**, H/H	**2b**, 4-MeC_6H_4/Ph	**3b**	69
3	**1a**, H/H	**2c**, 4-$MeOC_6H_4$/Ph	**3c**	76
4	**1a**, H/H	**2d**, 3-ClC_6H_4/Ph	**3d**	46
5	**1a**, H/H	**2e**, 4-ClC_6H_4/Ph	**3e**	38
6	**1a**, H/H	**2f**, Ph/4-MeC_6H_4	**3f**	77
7	**1a**, H/H	**2g**, Ph/4-$MeOC_6H_4$	**3g**	81
8	**1a**, H/H	**2h**, Ph/4-ClC_6H_4	**3h**	30
9	**1a**, H/H	**2i**, 	**3i**	66
10	**1a**, H/H	**2l**, Ph/9-fluorenyl	**3j**	31
11	**1b**, 5-CH_3O/H	**2g**, Ph/4-$MeOC_6H_4$	**3k**	60
12	**1a**, 4-Cl/H	**2a**, Ph/Ph	**3l**	43
13	**1d**, 5-Cl/H	**2a**, Ph/Ph	**3m**	66
14	**1e**, 6-Cl/H	**2a**, Ph/Ph	**3n**	68
15	**1f**, H/CH_3	**2g**, Ph/4-$MeOC_6H_4$	**3o**	48[c]
16	**1g**, H/propargyl	**2g**, Ph/4-$MeOC_6H_4$	**3p**	36[c]

[a]Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), $Yb(OTf)_3$ (0.05 mmol), DCE (5 mL), 24 h. [b]Yield of the isolated product. [c]THF (5 mL) was used as solvent

more susceptible to other side reactions, as unidentified byproducts were observed in these cases. However, substrate **1c** having the electron-withdrawing substituent at the 4-position of the indole ring gave diminished yield (Table 2, entry 12). *N*-Substituted substrates (R^2 = methyl or propargyl) were also suitable for the reaction to produce the corresponding products in moderate yields by using THF as solvent (Table 2, entries 15 and 16). The structures of the products **3a** and **3i** were additionally confirmed by X-ray crystallographic analyses (see Supporting Information for details).

We then examined the reactivity of **6** and **8**, two sulfonamide analogues of 1-*H*-indole-2-methanol **1a**, under the same reaction conditions (Scheme 2). Not surprisingly, the same carbazole products **3h** and **3o** could be obtained with yields comparable to that obtained with **1a**. More importantly, in addition to the desired products, we isolated compound **7** (44% yield) and compound **9** (93% yield) when the two reactions were interjected at 8 and 1 h, respectively. These two compounds could be converted to the final products **3h** and **3o** under the same reaction conditions. Although attempts to isolate similar intermediates in the reactions of other indole-2-methanols failed, these results suggest that both **7** and **9** might be intermediates in this type of cascade process and thus provide important clues to the mechanism of the reaction.

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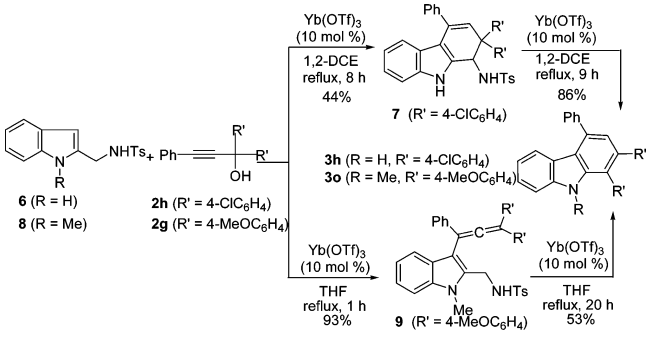
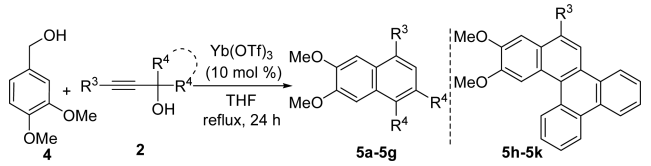
Scheme 2. Reaction of Indole-2-sulfonamides with Propargylic Alcohols



To further extend the scope of the current reaction, we then tested electron-rich primary benzylic alcohols **4** as substrates in lieu of indole-2-methanols **1**. To our delight, under very similar reaction conditions, the reaction of **4** with different propargylic alcohols **2** could provide various substituted naphthalene products in moderate to good yields (Table 3). Compared to

Table 3. Syntheses of Naphthalenes 5[a]



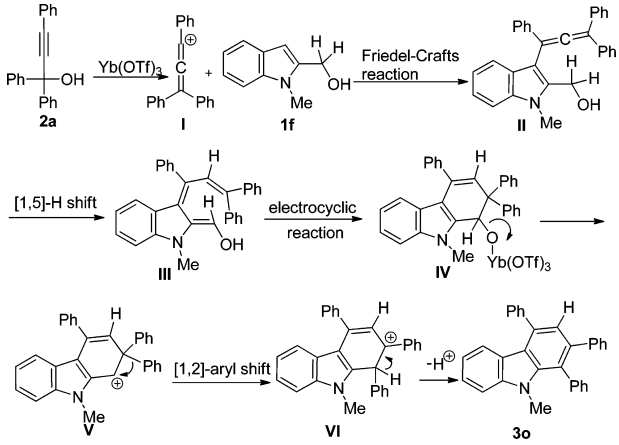
entry	2, R^3/R^4	5	yield[b]
1	**2a**, Ph/Ph	**5a**	74
2	**2b**, 4-MeC_6H_4/Ph	**5b**	71
3	**2c**, 4-$MeOC_6H_4$/Ph	**5c**	64
4	**2d**, 3-ClC_6H_4/Ph	**5d**	80
5	**2e**, 4-ClC_6H_4/Ph	**5e**	79
6	**2f**, Ph/4-MeC_6H_4	**5f**	73
7	**2h**, Ph/4-ClC_6H_4	**5g**	82
8	**2j**, Ph/9-fluorenyl	**5h**	66
9	**2k**, 4-MeC_6H_4/9-fluorenyl	**5i**	65
10	**2l**, 4-$MeOC_6H_4$/9-fluorenyl	**5j**	56
11	**2a**, 4-ClC_6H_4/9-fluorenyl	**5k**	71

[a]Reaction conditions: **4** (0.5 mmol), **2** (0.5 mmol), $Yb(OTf)_3$ (0.05 mmol), THF (5 mL), 24 h. [b]Yield of the isolated product.

indole-2-methanols **1**, the benzylic alcohols **4** were more stable and less susceptible to side reactions under the reaction conditions to give generally higher yields, although they are less reactive as nucleophile and a longer reaction time (24 h) was required. Moreover, compared to the reaction results of **2** with indole-2-methanols **1**, the electronic nature of the substituents on the R^4 group of propargylic alcohols **2** demonstrated reversed influence on the reaction: electron-withdrawing substituents were more favorable than electron-donating ones (Table 3, entries 1−7). This might be ascribed to the higher electrophilicity of the corresponding cationic species formed from **2** under Lewis acid catalysis in the presence of electron-withdrawing substituents, which is favored in the reaction with the less nucleophilic benzylic alcohol **4**. Notably, polyconjugated aromatic compounds **5h**−**5k** were also obtained in good yields when 9-fluorenyl propargylic alcohols were used (Table 3, entries 8−11). The structure of the product **5i** was unambiguously confirmed by X-ray crystallographic analysis.

On the basis of the above experimental results, a plausible mechanism for the present cascade reaction was proposed (Scheme 3). First, propargylic alcohol **2a** is converted to the

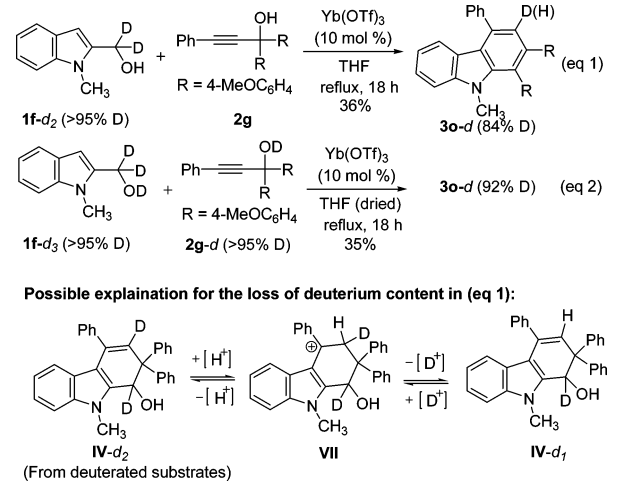
Scheme 3. Possible Mechanism for the Dehydrative [3 + 3]-Annulation



allenic carbocation **I** via Meyer−Schuster rearrangement,[12] which would then undergo Friedel−Crafts-type reaction with **1f** to form the allene intermediate **II**. The isolation of the compound **9** in Scheme 2 is in support of this assumption. Then allene **II** would be transformed to alcohol **III** via [1,5]-H shift, followed by 6π-eletrocyclization to provide intermediate **IV**, which is also supported by the isolation of the compound **7** in Scheme 2. The intermediate **IV** would undergo Wagner−Meerwein rearrangement following the loss of the hydroxyl group with assistance of the catalyst, and subsequent aromatization would deliver the final product.

To gain more support for the proposed reaction mechanism, two deuterium-labeling experiments were performed (Scheme 4). The reaction between deuterated *N*-methylindole-2-

Scheme 4. Deuterium-Labeling Reaction



methanol **1f**-d_2 and propargylic alcohol **2g** gave the desired product **3o**-*d* with 84% deuterium at the 3-position (eq 1). The failure of 100% deuterium transfer from **1f**-d_2 to **3o**-*d* was presumed to be due to the presence of the proton sources in the system including the two alcohol hydroxyl groups in the substrates, the proton released after the Friedel−Crafts-type

dx.doi.org/10.1021/ol501605h | *Org. Lett.* XXXX, XXX, XXX−XXX

reaction, and the trace residual water in the commercial solvent used. These proton sources might interact with the Lewis acid catalyst $Yb(OTf)_3$ to produce a small amount of a strong Brønsted acid such as HOTf. One possible explanation is that HOTf might protonate the intermediate **IV**-d_2 to form **VII** before the loss of the hydroxyl group and Wagner−Meerwein rearrangement. The intermediate **VII** might lose a deuteron to form **IV**-d_1, which would undergo subsequent process as outlined in Scheme 3 to produce the nondeuterated product **3o**. These three intermediates might be in equilibrium in the reaction system. Consistent with this explanation, when the reaction was performed with **1f**-d_3 and **2g**-d in dried solvent under dry argon atmosphere, the deuterium content in the final product was increased to 92% D (eq 2).

In summary, a novel Lewis acid catalyzed dehydrative [3 + 3]-annulation reaction for the construction of carbazoles and naphthalenes was developed. With readily available electron-rich benzylic alcohols and propargylic alcohols as starting materials, this reaction proceeds through a cascade process involving the cleavage and formation of multiple chemical bonds in a single operation releasing water as the only byproduct. A preliminary mechanism study revealed that the cascade reaction might proceed through a sequential process consisting of Friedel−Crafts-type allenylation, 1,5-hydride shift, 6π-eletrocyclization, and Wagner−Meerwein rearrangement. The excellent atom- and step-economy, easy operation, and mild reaction conditions render this method a good complement to the arsenal of synthetic methods for the construction of useful aromatic polycyclic structures such as carbazoles and naphthalenes. Efforts toward the utilization of the [3 + 3]-annulation strategy to the synthesis of other useful cyclic compounds are underway in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

Spectral and X-ray data, experimental procedures; CIF files for **3a**, **3i**, and **5h**; ^1H and ^{13}C NMR copies of all new compounds. 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

This work was supported by the National Natural Science Foundation of China (21372010, 21072004, 21202001), the National Basic Research Program of China (2012CB821604), the Science Foundation for Postdoctoral Scientists of Anhui Province, the Natural Science Foundation of Anhui Province (1308085QB25), and the Research Fund for the Doctoral Program of Wannan Medical College.

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