ORGANIC LETTERS

2011
Vol. 13, No. 15
3786–3789

Gold-Catalyzed Deacylative Cycloisomerization Reactions of 3-Acylindole/ynes: A New Approach for Carbazole Synthesis

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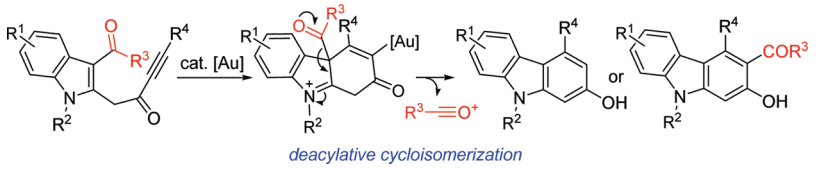
Received May 7, 2011

ABSTRACT



The synthesis of functionalized carbazoles through gold-catalyzed deacylative cycloisomerization of 3-acylindole/ynes is described. A mechanistic proposal for these transformations involving a novel carbonyl group facilitated heterolytic fragmentation upon the loss of an acylium ion intermediate is presented. The eliminated acylium ion species could be trapped by the organogold intermediate to afford acylcarbazoles.

In recent years, gold complexes have emerged as powerful homogeneous catalysts for inducing a wide variety of transformation reactions.[1] In particular, gold catalysts have been proven to be efficient alkynophilic Lewis acids to activate the π-systems toward nucleophilic attack. In this regard, gold-catalyzed inter- or intramolecular cycloisomerization of indolyl-tethered alkynes is of particular interest,[2] since these methodologies offer rapid access to indole-fused polycyclic structures which frequently occur in numerous natural products and indole-containing scaffolds with important biological and pharmaceutical properties. For example, Echavarren and co-workers reported that intramolecular cyclization of indoles with alkynes in the presence of gold catalysts led to the formation of azepino[4,5-*b*]indoles and indoloazocines.[2a−c] Padwa et al. developed a gold-catalyzed cycloisomerization of *N*-propargylamides to β-carbolinones.[2d,e] Cyclization of 2,3-disubstituted indoles to tetracyclic indolines[2f] and a novel 1,2-indole migration[2g] to indenyl indoles have also been reported. We have recently shown that indoles could undergo cascade Friedel−Crafts/hydroarylation reactions with (*Z*)-enynols catalyzed by gold.[3a] Soon after this study, we found a new gold-catalyzed cyclization of indole/ynes possessing hydroxyl groups[3b] through a heterolytic

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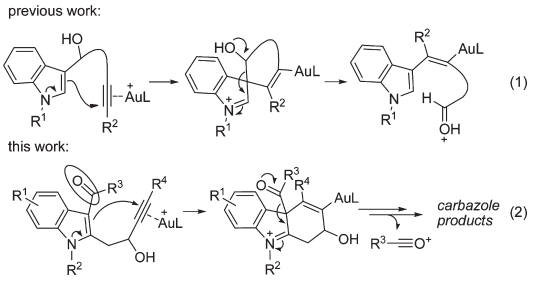
10.1021/ol2012154
Published on Web 07/06/2011

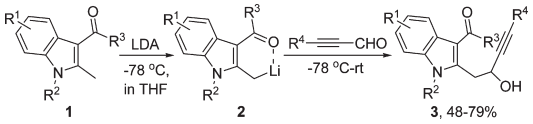
fragmentation, which results in 1,5-indole migration and C-3 allenylation of the indole nucleus (Scheme 1, eq 1). In this reaction, the hydroxyl group α to the indole ring was found to play an important role in initiating the C−C bond cleavage reactions.[4] We hypothesized that the fragmentation reactions might be facilitated by other nucleophilic substituents such as −COR, −NHR, or −SR groups bearing electron lone pairs on their heteroatoms. We then became interested in exploring further possibilities for the assembly of diverse indole-containing skeletons through heterolytic fragmentation reactions. Herein, we report a new Au-catalyzed deacylative cycloisomerization of 3-acylindole/ynes into carbazole derivatives[5] and demonstrating that a carbonyl group can be utilized for inducing fragmentation reactions[6] (Scheme 1, eq 2).

Scheme 1



To test this hypothesis, we designed the 3-acylindoles **3** for the cyclization reactions. Compound **3** was synthesized through a heteroatom-facilitated lateral lithiation of 2-methyl-3-acylindole **1** (Scheme 2). Treatment of ketone **1** with LDA freshly prepared by diisopropylamine/*n*-BuLi combination in THF at −78 °C resulted in the lithiation of the 2-methyl group to give a lithiated intermediate **2**. Subsequent reaction with acetylenic aldehyde afforded the substituted indoles **3** in 48−79% yields. The reaction works well with aryl and even alkyl groups with acidic α-protons as carbonyl substituents (R^3). It is noted that there is no report for ketone directed lateral lithiation of the indole system.[7] The methodology described here represents the first example of this type of reaction, and it is expected to be applicable for the synthesis of a wide variety of functionalized indoles through the reactions of lithium intermediates with various electrophiles.

Scheme 2



R^1 = H, OMe; R^2 = alkyl, allyl, Bn, H; R^3 = alkyl, aryl; R^4 = alkyl, aryl

With indole−ynes **3** in hand, we were interested in exploring the feasibility of **3** in gold-catalyzed cycloisomerization reactions. Indole−yne **3a** bearing an isopropylcarbonyl group was chosen as a model substrate for optimization studies. After examination of the reaction conditions, we were pleased to find that the reaction proceeded smoothly and provided a 73% yield of the carbazole **4a** at 60 °C in the presence of 5 mol % of $(p\text{-}CF_3C_6H_4)_3PAuOTf$ (Table 1, entry 1). $(PPh_3)AuOTf$ afforded **4a** in a lower yield of 66%. When AgOTf alone was used as a catalyst, only a trace amount of the anticipated **4a** was observed. The results indicated that **4** was formed by attack of the indolyl C-3-position onto the activated triple bond, and a deacylation occurred during the cyclization. It was noted that the presence of a phenyl group as the carbonyl substituent (R^3) in **3b** significantly decreased the yield of **4a** to 31%, possibly due to the weaker nucleophilicity of the indolyl C-3 position in this case (entry 2). Thus, 3-acylindoles **3** with an isopropyl group as R^3 were used as substrates in most cases. The effects of aryl substituents on the alkyne terminus (R^4) were first examined. The reaction proceeded satisfactorily with both electron-rich and electron-deficient substituents, furnishing the corresponding carbazoles **4c**−**e** in 69−86% yields (entries 3−5), in which a better yield was observed with an electron-rich group (−Me). A thienyl group was also compatible under the cyclization conditions, leading to **4f** in 84% yield (entry 6). Alkyl-substituted alkyne **3g** afforded the corresponding carbazole **4g** in a good yield of 76% (entry 7). The 5-MeO functionality on the indole ring can also be incorporated into the reaction process (entry 8). *N*-allyl- and *N*-benzyl-protected indoles **3i**−**j** were both found to be suitable for this reaction, as well as the nonprotected indole **3k** (entries 9−11). The structure of

(4) For hydroxy-group induced fragmentation, see: (a) Grob, C. A.; Schiess, P. W. *Angew. Chem., Int. Ed.* **1967**, *6*, 1. (b) Paquette, L. A.; Yang, J.; Long, Y. O. *J. Am. Chem. Soc.* **2002**, *124*, 6542.

(5) For transition-metal-catalyzed synthesis of carbazoles, see: (a) Hans-Knölker, J.; Reddy, K. R. *Chem. Rev.* **2002**, *102*, 4303. (b) Liu, Z.; Larock, R. C. *Org. Lett.* **2004**, *6*, 3739. (c) Cai, X.; Snieckus, V. *Org. Lett.* **2004**, *6*, 2293. (d) Kuwahara, A.; Nakano, K.; Nozaki, K. *J. Org. Chem.* **2005**, *70*, 413. (e) Zhao, J.; Larock, R. C. *Org. Lett.* **2005**, *7*, 701. (f) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560. (g) Kong, A.; Han, X.; Lu, X. *Org. Lett.* **2006**, *8*, 1339. (h) Jean, D. J., St. Jr.; Poon, S. F.; Schwarzbach, J. L. *Org. Lett.* **2007**, *9*, 4897. (i) Liégault, B.; Lee, D.; Huestis, M. P.; Stuart, D. R.; Fagnou, K. *J. Org. Chem.* **2008**, *73*, 5022. (j) Jordan-Hore, J. A.; Carin, C. C.; Gulias, M.; Beck, E. M.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 16184. (k) Tsang, W. C. P.; Munday, R. H.; Brasche, G.; Zheng, N.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 7603. (l) Ueno, K.; Kitawaki, T.; Chida, N. *Org. Lett.* **2008**, *10*, 1999. (m) Stokes, B. J.; Jovanović, B.; Dong, H.; Richert, K. J.; Riell, R. D.; Driver, T. G. *J. Org. Chem.* **2009**, *74*, 3225. (n) Kong, W.; Fu, C.; Ma, S. *Chem. Commun.* **2009**, 4572. (o) Hirano, K.; Inaba, Y.; Takahashi, N.; Shimano, M.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2011**, *76*, 1212. For recent paper on gold-catalyzed cyclization of 2-(enynyl)indoles to carbazoles, see: (p) Praveen, C.; Perumal, P. T. *Synlett* **2011**, 521.

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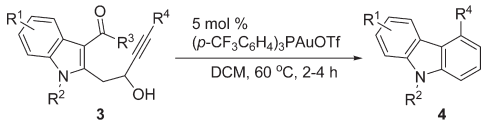
Table 1. Gold-Catalyzed Deacylative Cyclization of 3-Acylindole/ynes **3**

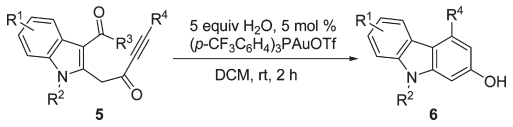


3 4

entry	substrate	R^1	R^2	R^3	R^4	products	yield[a] (%)
1	**3a**	H	Me	^{i}Pr	Ph	**4a**	73
2	**3b**	H	Me	Ph	Ph	**4a**	31
3	**3c**	H	Me	^{i}Pr	*p*-$CH_3C_6H_4$	**4c**	86
4	**3d**	H	Me	^{i}Pr	*p*-ClC_6H_4	**4d**	69
5	**3e**	H	Me	^{i}Pr	*p*-BrC_6H_4	**4e**	71
6	**3f**	H	Me	^{i}Pr	2-thienyl	**4f**	84
7	**3g**	H	Me	^{i}Pr	*n*-C_6H_{13}	**4g**	76
8	**3h**	5-OMe	Me	^{i}Pr	Ph	**4h**	80
9	**3i**	H	allyl	^{i}Pr	Ph	**4i**	48
10	**3j**	H	Bn	^{i}Pr	Ph	**4j**	64
11	**3k**	H	H	^{i}Pr	Ph	**4k**	56

[a] Isolated yields. All reactions were carried out in a sealed tube.

Table 2. Gold-Catalyzed Formation of 2-Hydroxycarbazoles **6**



5 6

entry	substrate	R^1	R^2	R^3	R^4	products	yield[a] (%)
1	**5a**	H	Me	^{i}Pr	Ph	**6a**	80
2	**5a**	H	Me	^{i}Pr	Ph	**6a**	30[b]
3	**5b**	H	Me	Ph	Ph	**6a**	85[c]
4	**5c**	H	Me	^{i}Pr	*p*-$CH_3C_6H_4$	**6c**	86
5	**5d**	H	Me	^{i}Pr	*p*-ClC_6H_4	**6d**	82
6	**5e**	H	Me	^{i}Pr	2-thienyl	**6e**	81
7	**5f**	H	Me	^{i}Pr	*n*-C_6H_{13}	**6f**	58[d]
8	**5g**	5-OMe	Me	^{i}Pr	Ph	**6g**	73
9	**5h**	H	allyl	^{i}Pr	Ph	**6h**	79[c]
10	**5i**	H	Bn	^{i}Pr	Ph	**6i**	78[c]

[a] Isolated yields. [b] Without H_2O. Reaction time is 24 h. [c] Reaction time is 5 h. [d] The C-3 acylated carbazole **7a** was also isolated in 34% yield.

carbazole **4h** was unambiguously confirmed by X-ray crystallographic analysis.[8]

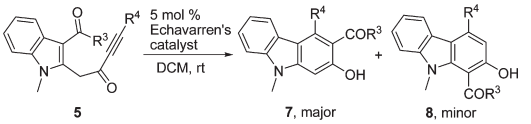
Encouraged by these results, we next prepared the ynones **5** with the enhanced electrophilicity of the alkyne moiety via DMP oxidation to examine their cyclization reactions. To our delight, we found that the desired 6-*endo*-*dig* cyclization reactions took place efficiently at room temperature in the presence of 5 mol % of (*p*-$CF_3C_6H_4)_3$PAuOTf and 5 equiv of H_2O, yielding the 2-hydroxycarbazole **6a** as the exclusive product in 80% yield within 2 h (Table 2, entry 1). It is noteworthy that the employment of water for this cycloisomerization reaction is essential. In the absence of water, **6a** was formed in 30% yield after 24 h (entry 2). The increased reaction rate in the presence of water was attributed to the facile demetalation facilitated by water. As shown in Table 2, the reactions tolerated a wide range of alkyne substitution with both aryl and alkyl groups, producing the cyclization products **6** in generally high yields at room temperature. Replacing the alkylcarbonyl group with a phenylcarbonyl group did not influence the efficiency of the reaction in this cyclization, leading to **6a** in 85% yield, albeit with a longer reaction time of 5 h (entry 3). Interestingly, when alkyl alkyne **5f** was used as a substrate, in addition to the major product of **6f**, a side product of C-3-acylated carbazole **7a** (see Table 3) resulting from a competing acylation was also isolated in 34% yield (entry 7). 2-Hydroxycarbazoles and its derivatives are of significant interest, as they exist as the core structures in a number of biologically active natural products;[9] for example, 3,6-disubstituted 2-hydroxycarbazoles exhibit HIV-inhibitory activity.[10]

It occurred to us that trapping the organogold intermediate through the reaction with the in situ formed acylium ion is feasible according to the results shown in Table 2, entry 7, which allows for the assembly of 2-hydroxy-3-acylcarbazoles. To this end, the possible cycloisomerization of ynone **5f** to acylcarbazole was tested in the presence of different gold catalysts. Best results were obtained upon treatment of **5f** with 5 mol % of Echavarren's catalyst in DCM, affording 3-acylcarbazole **7a** in 63% yield (Table 3, entry 1). To our surprise, 1-acylcarbazole **8a** was also isolated in 13% yield, which can be easily separated from the main product by column chromatography. Representative results are summarized in Table 3. The reaction accommodated various alkyl substituents on the alkyne terminus, such as *n*-hexyl, *n*-propyl, $(CH_2)_2$Ph, or benzyloxyethyl groups, and the desired 3-acylcarbazoles **7a**–**f** could be obtained in moderate to good yields. In addition, the corresponding 1-acylcarbazoles **8a**–**f** were also isolated in 13–27% yields (entries 1–6). Aryl- or heteroaryl-substituted alkynes worked well under the cyclization conditions, delivering a mixture of 3- and 1-acylated products **7** and **8** which could not be separated from each other through chromatography (entries 7 and 8). The structures of carbazoles **7a** and **8c** have been verified by X-ray crystallography.[8]

A possible reaction mechanism for the transformation of indolyl alkyne **5** into the 2-hydroxycarbazole **6** is shown in Scheme 3. In the first step, activation of the triple bond in **5** by forming a π-complex **9** with LAu^+ enhances the electrophilicity of the alkyne moiety, which facilitates a nucleophilic attack by the indole ring. Thus, the subsequent 6-*endo*-*dig* ring closure occurs to afford the intermediate **10**. Electron donation by the carbonyl oxygen lone

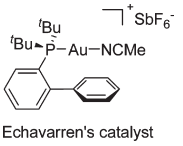
(8) See the Supporting Information.
(9) Knölker, H.-J.; Reddy, K. R. *Chem. Rev.* **2002**, *102*, 4303.
(10) Meragelman, K. M.; McKee, T. C.; Boyd, M. R. *J. Nat. Prod.* **2000**, *63*, 427.
(11) For the generation of acylium ions by fragmentation of the amide bond, see: (a) Li, G.; Huang, X.; Zhang, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 346. (b) Peng, Y.; Yu, M.; Zhang, L. *Org. Lett.* **2008**, *10*, 5187.

Table 3. Gold-Catalyzed Formation of 3-Acyl- or 1 -Acylcarbazoles **7** and **8**



entry	substrate	R^3	R^4	time (h)	yield (%) of **7**[a]		yield (%) of **8**[a]	
1	**5f**	^{i}Pr	n-C_6H_{13}	1	**7a**	63	**8a**	13
2	**5j**	Ph	n-C_6H_{13}	2	**7b**	58	**8b**	21
3	**5k**	$CH_2{}^i$Pr	n-C_6H_{13}	1	**7c**	48	**8c**	27
4	**5l**	^{i}Pr	n-C_3H_7	1	**7d**	67	**8d**	19
5	**5m**	^{i}Pr	$(CH_2)_2Ph$	1	**7e**	81	**8e**	15
6	**5n**	^{i}Pr	$(CH_2)_2OCH_2Ph$	1	**7f**	71	**8f**	20
7	**5a**	^{i}Pr	Ph	4	**7g** + **8g** 68(1:1.7)[b,c]			
8	**5e**	^{i}Pr	2-thienyl	6	**7h** + **8h** 67(1.1:1)[b]			

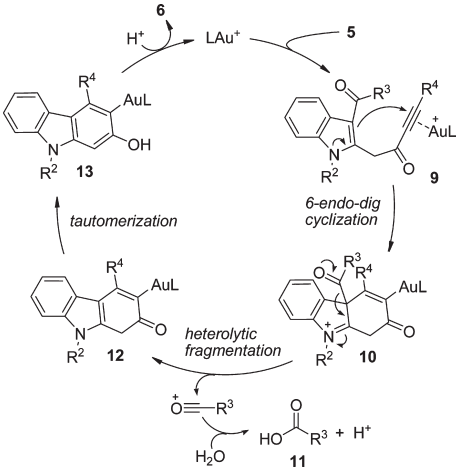
[a] Isolated yields. [b] A mixture of two inseparable products were obtained. The ratio of the two products is shown in parentheses. [c] In this case, **8g** is the major product.



pair triggers the heterolytic fragmentation to give the gold species **12** along with the loss of an acylium ion.[11] Tautomerization of **12** facilitated by a proton or metal ion delivers the aryl gold species **13**; this is followed by deauration to furnish the carbazole **6** and regenerate the gold catalyst.[12] In a similar catalytic cycle to acylated carbazoles, reaction of the Au–C bond in gold intermediate **13** with the highly electrophilic acylium ion would give the 3-acylcarbazole **7**. We speculate that the byproduct of 1-acylcarbazole **8** might be formed by competitive acylation on the C-1 position of the carbazolyl gold species **13**.[13]

In summary, we have developed a gold-catalyzed cycloisomerization of 3-acylindole/ynes for the synthesis of multiply substituted carbazoles, which are very important building blocks in natural product synthesis[9,14] and material science.[15] A mechanism involving a novel reaction pattern of carbonyl group facilitated heterolytic fragmentation is proposed. Clarification of the reaction mechanism and further application of this chemistry are in progress.

Scheme 3



Acknowledgment. We thank the National Natural Science Foundation of China (Grant Nos. 20872163, 20732008, 20821002), Chinese Academy of Science, and the Major State Basic Research Development Program (Grant No. 2011CB808700) for financial support.

Supporting Information Available. Experimental details, spectroscopic characterization of all new compounds, and X-ray crystallography of compounds **4h**, **6g**, **7a**, and **8c**. This material is available free of charge via the Internet at http://pubs.acs.org.

(12) As suggested by one reviewer, we also tried the gold-catalyzed cyclization of **5a** in the presence of 5 equiv of D_2O in a sealed tube. The amounts of deuterium incorporation on C-1 and C-3 are 65% and 37%, respectively. The results indicated that a hydrogen–deuterium exchange occurred during keto–enol tautomerization. The low deuterium incorporation on C-3 might be due to the fast demetalation by H^+ produced in situ.

(13) At present, a mechanism that involves the acylation of the neutral final product **6** by an acylium ion for the formation of **7** and **8** cannot be ruled out.

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