Heterocycles

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Aniline Dearomatization and Silver-Catalyzed [3+3] Dipolar Cycloaddition: Efficient Construction of Oxocino[4,3,2-*cd*]indoles from 2-Alkynylanilines and 2-Alkynylbenzaldoximes

Dandan Han, Qiuqin He, and Renhua Fan**

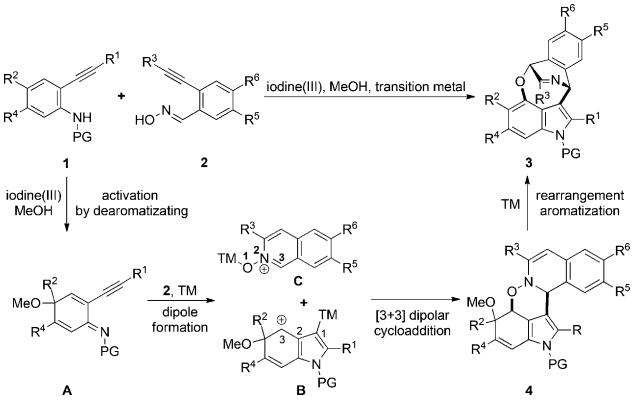
Dedicated to Professor Xue-Long Hou on the occasion of his 60th birthday

Abstract: *2-Alkynylanilines are attractive starting materials in indole synthesis because of their ready availability. Herein, a one-pot stepwise procedure is reported for efficient construction of multisubstituted oxocino[4,3,2-cd]indoles from 2-alkynylanilines and 2-alkynylbenzaldoximes. The method comprises the oxidative dearomatization of 2-alkynylanilines, the silver-catalyzed [3+3] cycloaddition with 2-alkynylbenzaldoximes, and subsequent thermal radical skeletal rearrangement and aromatization.*

Among the family of indoles, 3,4-fused indoles such as **3** (for structure see Scheme 1) are highly valuable synthetic targets owing to their remarkable biological activities.[1] In recent decades, synthetic chemists have devoted great effort to the exploration of effective protocols for building the fused tricyclic structure, and have examined transition-metal-catalyzed intramolecular cross-coupling reactions,[2] intramolecular Fischer indole syntheses,[3] Witkop photocyclizations,[4] Pictet–Spengler reactions,[5] Diels–Alder reactions,[6] electrocyclizations,[7] and addition of indolynes.[8] These elegant tactics have enabled the highly efficient and selective construction of 3,4-fused indoles. However, in many cases, these methods suffer from difficulty in preparing the corresponding precursors. For example, 4-substituted indoles are commonly used precursors in many synthetic strategies. But the preparation of 4-substituted indoles normally requires multistep synthesis because the C4-position in indoles is not a preferred reactive site for electrophilic substitution. In contrast, 2-alkynylanilines are attractive starting materials in indole synthesis because of their ready availability. Although a plethora of cyclization or cascade cyclization/coupling reactions of 2-alkynylanilines have been developed for the synthesis of 2-substituted or 2,3-disubstituted indoles,[9] methods that allow rapid access to 3,4-fused indoles from 2-alkynylanilines still remain scarce.

In connection with our recent research on the synthesis of 3,4-difunctionalized benzofurans from 2-alkynylphenols,[10] we focused our attention on developing methods that directly convert 2-alkynylanilines into 3,4-fused indoles.[11] For a medicinal chemistry project, we were interested in the synthesis of oxocino[4,3,2-*cd*]indoles (**3**) because of their structural similarity to many natural products and potential biological activities.[12]

We originally conceived that this skeleton could be constructed by from 2-alkynylanilines (**1**) and 2-alkynylbenzaldoximes (**2**) as starting materials by the process shown in Scheme 1. Oxidative dearomatization could convert 2-alkynylanilines into the electron-deficient 2-alkynyl cyclohexadienimines **A**.[13,14] In the presence of a transition-metal catalyst, the 5-*endo* or the 6-*endo* cyclization of 2-alkynylcyclohexadienimines and 2-alkynylbenzaldoxime might lead to the in situ generation of the metal-associated dipoles **B** and **C**, respectively. Subsequent [3+3] cycloaddition between these two dipoles would form compound **4**, in which the C4-position is connected to the C3-position by means of a six-membered ring. The unstable N–O bond in **4** can go through a homolytic cleavage and, after a radical rearrangement, the six-membered ring might be expanded to an eight-membered ring. Final aromatization could restore the aromaticity and complete the construction of oxocino[4,3,2-*cd*]indole skeleton.



Scheme 1. Construction of oxocino[4,3,2-*cd*]indoles from 2-alkynylanilines and 2-alkynylbenzaldoximes. PG = protecting group. TM = transition metal.

The main challenge to implementation of this strategy was the realization of an efficient [3+3] dipolar cycloaddition. Indeed, compared with extensively studied [3+2] or [4+2] cycloadditions, successful examples of transition-metal-cata-

[*] D. Han, Prof. Dr. Q. He, Prof. Dr. R. Fan
Department of Chemistry, Fudan University
220 Handan Road, Shanghai, 200433 (China)
E-mail: rhfan@fudan.edu.cn

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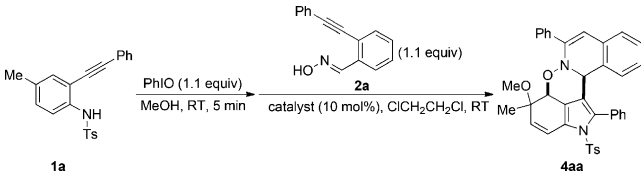
lyzed [3+3] dipolar cycloadditions are far fewer because of the limited availability of suitable 1,3-dipolar species.[15,16] The major competitive side reaction would be a [1,2] methoxy group transfer reaction of intermediate **B**, and it would lead to the formation of a 4-methoxy-substituted indole. In a search for potential catalysts and suitable reaction conditions, the crude dearomatization product of 4-methyl-2-(2-phenylethynyl)benzenamine (**1a**) was used directly to test the [3+3] dipolar cycloaddition with 2-(phenylethynyl)benzaldehyde oxime (**2a**). Initial screening of various metal salts revealed that only silver salts are effective catalysts for the [3+3] dipolar cycloaddition (Table 1, entries 1–9). A 4-methoxy-substituted indole was isolated as the major product from reactions using other metal salts. Amongst a variety of silver catalysts (entries 9–17), silver trifluoroacetate proved to be the best catalyst for the formation of the cycloaddition product **4aa**. Further screening of solvents, temperatures, and the ratio of reagents improved the yield of **4aa** to 76% (see the Supporting Information).

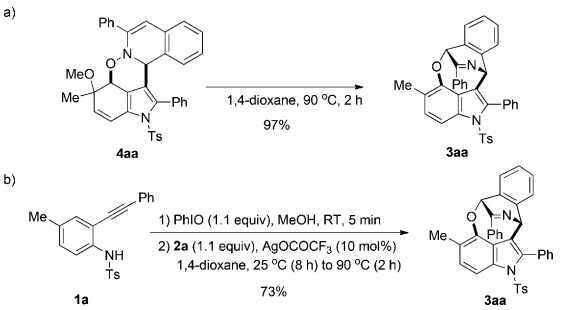
Table 1: Evaluation of catalysts for [3+3] dipolar cycloaddition.



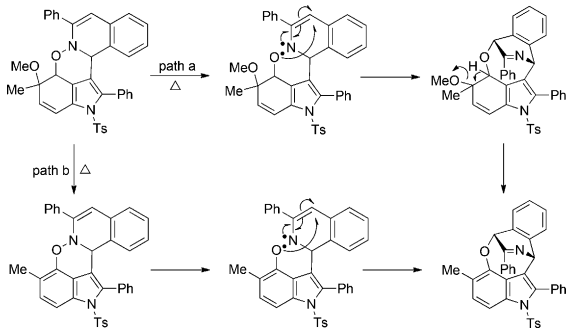
Entry	Catalyst	Yield [%][a]	Entry	Catalyst	Yield [%][a]
1	$[Au(PPh_3)Cl]$	0	10	$AgNTf_2$	17
2	$Pd(OAc)_2$	0	11	$AgSbF_6$	38
3	$PtCl_2$	0	12	AgF	32
4	$Cu(OTf)_2$	0	13	$AgNO_3$	40
5	CuI	0	14	Ag_2CO_3	27
6	$Zn(OTf)_2$	0	15	AgSCN	<5
7	$NiCl_2$	0	16	AgOAc	16
8	$Bi(OTf)_3$	0	17	$AgOCOCF_3$	53
9	AgOTf	31	18	$AgOCOCF_3$	76[b]

[a] Yield of isolated product. [b] 1,4-Dioxane was used as solvent. Tf = trifluoromethanesulfonyl, Ts = 4-toluenesulfonyl.

No catalyst was required for subsequent rearrangement and aromatization. Heating of **4aa** in 1,4-dioxane at 90 °C for 2 hours led to the formation of the oxocino[4,3,2-*cd*]indole **3aa** in an almost quantitative yield (Scheme 2a). Because the $AgOCOCF_3$-catalyzed [3+3] dipolar cycloaddition at 90 °C was complex, the one-pot construction of oxocino[4,3,2-*cd*]indole was carried out in a stepwise manner and gave rise to **3aa** in 73% yield (Scheme 2b).

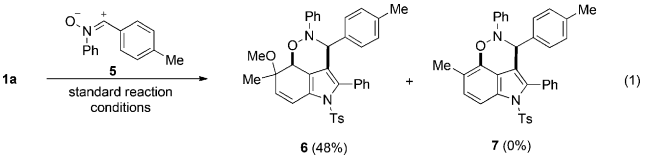


Scheme 2. Formation of the oxocino[4,3,2-*cd*]indole **3aa**.

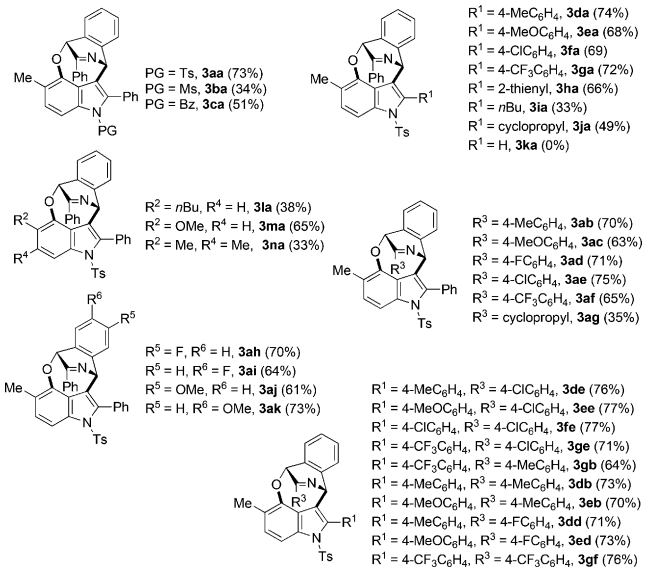


Scheme 3. Plausible pathway for conversion of **4aa** into **3aa**.

As depicted in Scheme 3, there are at least two plausible pathways for the conversion of **4aa** into **3aa**. Path a refers to the radical skeletal rearrangement followed by the aromatization reaction, and path b features the same steps but in reverse order. To gain more insight into the conversion, control experiments were conducted. When 2 equivalents of TEMPO were added into the reaction, no formation of **3aa** was observed, and **4aa** was recovered in 96% yield. Such high recovery of **4aa** indicated that the radical rearrangement reaction might be the first step (Scheme 3, path a). Additional evidence emerged from the failure of the aromatization of the [3+3] dipolar cycloaddition product of **1a** with the nitrone **5**, which is a simplified version of the in situ generated dipole from 2-alkynylbenzaldoxime [Eq. (1)]. This result meant that the direct aromatization to form a six-membered ring fused indole is difficult as a result of the high torsion strain.



With the optimized reaction conditions in hand, the scope of this transformation was investigated, and representative results are shown in Scheme 4. The tosyl group was a better protecting group for 2-alkynylanilines in this transformation. Reaction of 2-alkynylanilines bearing an aryl group at the alkynyl moiety proceeded smoothly, thus providing oxocino-[4,3,2-*cd*]indoles in moderate to good yields, no matter whether the substituent on the aryl ring is an electron-donating or an electron-withdrawing group. When R^1 was an alkyl group, lower yields were obtained for the compounds **3ia** and **3ja**. The steric hindrance caused by the *n*-butyl group at the C4-position or the second methyl group at the C5-position of 2-alkynylanilines anilines tended to diminish the yield of compounds **3la** and **3na**, respectively. When R^2 was a methoxy group, the product **3ma** was formed in a reasonable yield. A variety of 2-alkynylbenzaldoximes were suitable partners in this process, and the reaction was found to tolerate a range of groups on 2-alkynylbenzaldoximes with different



Scheme 4. Construction of oxocino[4,3,2-*cd*]indoles. Bz = benzoyl, Ms = methanesulfonyl.

electronic demands. The cross-experiments also gave rise to a set of products which were isolable in moderate to good yield. The structure of the oxocino[4,3,2-*cd*]indole **3ga** was confirmed by single-crystal diffraction analysis.[17]

In conclusion, we have developed a one-pot stepwise procedure for efficient construction of multisubstituted oxocino[4,3,2-*cd*]indoles from 2-alkynylanilines and 2-alkynylbenzaldoximes. The protocol involves the oxidative dearomatization of 2-alkynylanilines, the silver-catalyzed [3+3] cycloaddition with 2-alkynylbenzaldoximes, and subsequent thermal radical skeletal rearrangement and aromatization. The use of this method in the synthesis of natural products and the investigation of the biological activities of oxocino-[4,3,2-*cd*]indoles are currently underway in our laboratory.

Experimental Section

PhIO (0.22 mmol) was added to a solution of 4-methyl-2-(2-phenylethynyl)benzenamine **1a** (0.2 mmol) in MeOH (2.0 mL) at 25 °C. After 5 min, the reaction mixture was concentrated in vacuo. The resulting crude reaction mixture was mixed with a solution of 2-(phenylethynyl)benzaldehyde oxime (**2a**; 0.22 mmol) and AgO-$COCF_3$ (0.02 mmol) in 1,4-dioxane (2.0 mL), and the resulting mixture was stirred at 25 °C for 8 h. After the substrates were completely consumed (monitored by TLC analysis), the reaction mixture was warmed to 90 °C and stirred for 2 h. The mixture was passed through a short silica gel column and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate 5:1) to furnish the desired compound **3aa**.

Acknowledgements

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Keywords: cycloaddition · heterocycles · rearrangements · silver · synthetic methods

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[17] CCDC 1415338 (**3ga**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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