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Domino Process in Silver-Catalyzed Reactions of *N*-Arylformimidates and Active Methylene Compounds Involving Cycloisomerization and 1,3-Alkenyl Shift

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Substituted indoles form the core skeletons of a wide range of pharmaceuticals and naturally occurring alkaloids.¹ To date, numerous elegant approaches have been developed to generate this unique ring system via transition-metal catalysis.² Recently, indole derivatives have been synthesized by employing inter- or intramolucular cyclization of alkynes and imines.³ In this communication, we report an atom-economical and highly efficient approach for the construction of 2,3-substituted indoles via silver-catalyzed condensation of *N*-arylformimidates and active methylene compounds followed by cycloisomerization and a novel and unprecedented 1,3-alkenyl shift to the Ag-activated site. Previously, Li and co-workers⁴ introduced an effective methodology for gold- and silver-catalyzed addition of active methylenes to alkenes. Later, Arcadi et al.⁵ reported goldcatalyzed coupling of active methylenes at the C3 position of indole. We considered the possibility of gold- and silver-catalyzed condensation of N-arylformimdate 1a and dimethyl malonate followed by in situ cycloisomerization with the triple bond, leading to the N-alkenylindole derivative. Our approach seemed to work well, but the reaction product turned out to be 3a, which was presumably formed via a 1,3-alkenyl shift in 2a or its equivalent. This result prompted us to examine 1,3-alkenyl migration from the synthetic and mechanistic points of view (Table 1).6

Several gold compounds did not catalyze this reaction, but those in conjunction with silver triflate catalyzed this reaction to furnish the product **3a** in moderate yields. We fortunately found that the Ag(I) cation itself (5 mol %) catalyzed this reaction effectively, with AgOTf showing much better catalytic activity than AgSbF₆ in toluene at 60 °C. Methanesulfonic acid did not act as a catalyst, and the role of PtCl₂ was insignificant in this reaction. To rationalize this domino process, we could propose a plausible mechanism by introducing unusual alkenyl migration (Scheme 1). Condensation of an enolate with activated alkynes is now quite general, as

Table 1.	Optimization of	f Catalysts for	or Constructing
2,3-Disub	ostituted Indole	s	÷

المراجع 1a	OEt V CH ₂ (CO ₂ Me) ₂ (2 eq.), Ag or Au Toluene, 80 °C	CO ₂ Me CO ₂ Me Ph 2a	e + CO ₂ Me CO ₂ Me
entry	catalyst (mol %)	time (h)	isolated % yield of 3a
1	$AuCl_3$ (5)	6	decomposition
2	$AuBr_3(5)$	6	decomposition
3	$NaAuCl_4 \cdot 2H_2O(5)$	6	decomposition
4	AuBr ₃ (5)/AgOTf (15)	12	82
5	AuCl ₃ (5)/AgOTf (15)	12	58
6	AuCl(PPh ₃)/AgOTf (5)	12	80
7	AgOTf (5)	12	91
8	$AgSbF_{6}(5)$	12	75
9	$CF_{3}SO_{3}H(10)$	12	10
10	$PtCl_2(5)$	12	5

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Scheme 1. Proposed Mechanism



proposed by Toste and co-workers.⁷ In our substrates, however, the electron-rich nitrogen in the imidate group should be activated prior to alkyne activation. Therefore, the Ag(I) cation might coordinate with the N-arylformimidate in the first step to give A, which would be susceptible to reaction with malonate to form **B**. The elimination of ethanol from \mathbf{B} via regeneration of Ag(I) would lead to C, which upon subsequent Ag(I)-induced 5-endo-dig cyclization would form the key intermediate D. Such an intermediate always has a provision to exist as a metal carbene intermediate E. Most probably, the captodative effect of the coordinated silver would increase the electron density on the nitrogen atom, which would drive the 1,3-alkenyl migration to the silver carbene \mathbf{F} , furnishing intermediate G. Similar 1,3-migrations of α-alkoxyalkyl and α -alkoxyacyl groups have been reported by the Nakamura group.⁸ In its final stage, simple protodemetalation would convert G into 2,3-disubstituted indole 3a.

Since such a 1,3-alkenyl transfer reaction has not been reported in any literature to date, we became interested in exploring its synthetic utility and finding evidence in support of the proposed mechanism for this novel phenomenon. First, we prepared **4a**, the tautomeric form of intermediate **C**, by simple condensation of *o*-alkynylaniline *Pro*-1**a** with dimethyl ethoxymethylenemalonate in the presence of acid catalyst. Enamine **4a** was then subjected to our reaction conditions, but only simple cyclization occurred, affording *N*-alkenylindole derivative **2a** as a major product (Scheme 2). This experiment supports the idea that it is not enamine **2a** but rather a metal-bound species like **C** that may be a possible intermediate during this domino process. The second experiment was done on the substrate **1b** having a carbene-trapping handle. The predicted Ag-carbene intermediate *F-b* formed from **1b** was



expected to undergo benzylic C-H insertion to provide the cyclized product 5b, but in practice, no such product was formed; instead, 1b smoothly underwent sequential cycloisomerization and 1,3alkenyl migration to furnish **3b** in moderate yield (67%).

The above two experiments revealed that this transformation would occur via a complicated concerted-metal-associated mechanism without forming the real intermediate 2a or Ag-carbene species such as F.

Next, turning our attention to the synthetic point of view, we prepared a series of indole derivatives (3c-m) from the corresponding N-arylformimidates (Figure 1). All of the substrates were transformed into the corresponding indoles 3c-m in good yields. The substituent at C2 in our products could vary from primary, secondary, or tertiary alkyl groups to phenyl, naphthyl, or substituted phenyl groups. These indole derivatives may have biological importance, since the two derivatives 3k and 3l are known to have antiproliferative activity on human MDA-MB 231 and MCF-7 breast cancer cells in a microplate assay.9 This methodology may provide a general entry to the synthesis of various indole derivatives. Since the present 1,3-alkenyl transfer is a new observation in the organic chemistry field, we confirmed the structure of a representative product (3a) by X-ray analysis as well as its full spectral data.¹⁰



Figure 1. 2,3-Substituted indoles from this study.

In conclusion, we have developed an efficient domino process for the synthesis of 2,3-disubstituted indoles from alkyne iminoethers 1 that employs a silver-catalyzed two-component condensation followed by a tandem Ag-induced cycloisomerization and 1,3alkenyl shift to the Ag-activated carbon. This methodology may be an ideal protocol for in situ metal-mediated synthesis of olefin and its regioselective migration to the metal-activated site and can be useful in constructing 3-alkylated indoles, which are part of the structures of biologically active compounds and important alkaloids. The scope of this reaction is currently under investigation in our laboratories.

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Supporting Information Available: Full experimental details, compound characterization data, complete ref 1e, and a CIF file for 3a. This material is available free of charge via the Internet at http:// pubs.acs.org.

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- The X-ray data for 3a have been deposited at the Cambridge Crystal-(10)lographic Data Centre and allocated the deposition number CCDC 757660.

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