AgOTf-catalyzed tandem reaction of N'-(2-alkynylbenzylidene)hydrazide with alkyne[†]

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AgOTf-catalyzed tandem reactions of N'-(2-alkynylbenzylidene)hydrazides with various alkynes under mild conditions are described, which generate fused 1,2-dihydroisoquinolines in good to excellent yields.

As a privileged fragment, the 1,2-dihydroisoquinoline (including isoquinoline) core is found in many natural products and pharmaceuticals that exhibit remarkable biological activities.1 Recently, the method development and small library generation of 1,2-dihydroisoquinolines were established by us and others.²⁻⁴ For instance, Yamamoto and Takemoto described that functionalized 1,2-dihydroisoquinoline skeletons could be generated through the direct addition of various carbon pronucleophiles to ortho-alkynylaryl aldimines catalyzed by Lewis acids.^{3a,c} Larock and co-workers reported the transition-metal catalyzed cyclization of ortho-alkynylaryl aldimines for the synthesis of isoquinoline derivatives.⁴ We also developed 1,2-dihydroisoquinoline synthesis via tandem reactions starting from 2-alkynylbenzaldehyde, amine, and various nucleophiles.² Screening in a HCT-116 inhibition assay led to the identification of a hit with a promising IC_{50} value of 0.18 µM. With a hope for finding better lead anti-tumor compounds by evaluations of analogous structures, we need to develop an efficient method for rapid syntheses of new 1,2-dihydroisoquinoline-based structures. Herein, we disclose our recent efforts for the generation of fused 1,2-dihydroisoquinolines via tandem reactions of N'-(2-alkynylbenzylidene)hydrazides with various alkynes. This transformation is highly effective under mild conditions, which probably proceeds through 6-endo cyclization, alkyne addition, 5-endo cyclization and aromatization.

Among the strategies used for preparation of small molecules, utilizing tandem reactions for design and synthesis of natural product-like compounds has attracted much attention, and the development of tandem reactions has been a fertile area in organic synthesis.^{5,6} In our previous reports,² we found that 2-alkynylbenzaldehyde was a versatile building

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block in tandem reactions for the construction of heterocycles. Prompted by the results, we envisioned that N'-(2-alkynylbenzylidene)hydrazide might have similar functionality for further elaboration due to the structural similarity with 2-alkynylbenzaldehyde. Recently, we have discovered that N'-(2-alkynylbenzylidene)hydrazide 1 can be converted to isoquinolinium-2-yl amide A in the presence of Lewis acids or electrophiles.⁷ Based on this result, we conceived that a nucleophilic addition might occur in the presence of nucleophiles. To identify the practicability of this proposed route, we started to investigate the possibility for one-pot tandem cyclization-nucleophilic addition of N'-(2-alkynylbenzylidene)hydrazide 1.

The starting material N'-(2-alkynylbenzylidene)hydrazide was easily accessible via condensation of 2-alkynylbenzaldehyde with hydrazine. The reaction was initially studied with N'-(2-alkynylbenzylidene)hydrazide **1a** and phenylacetylene 2a (Scheme 1). As described above, in the presence of Lewis acid, N'-(2-alkynylbenzylidene)hydrazide could be transferred to the intermediate A via electrophilic cyclization. Indeed, after screening various Lewis acids, the intermediate could be isolated and AgOTf (10 mol%) was demonstrated as the best choice when this reaction was performed in dichloroethane. Encouraged by this result, the AgOTf-catalyzed one-pot reaction of N'-(2-alkynylbenzylidene)hydrazide 1a with phenylacetylene 2a in the presence of base was performed. Surprisingly, no further transformation was observed when NaOAc was used as the base. Gratifyingly, the formation of a product was detected when potassium phosphate was employed as the base. Further screening revealed that DBU was the most efficient base for the transformation (59% yield). However, structural identification revealed that the product generated was compound 3a, instead of the desired product 4a. Since AgOTf is one of the most popular reagents for inducing transformations, which take advantage of its affinity



Scheme 1 One-pot tandem reaction of N'-(2-alkynylbenzylidene)hydrazide 1a with phenylacetylene 2a

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[†] Electronic supplementary information (ESI) available: 1: General experimental methods (S2). 2: General experimental procedure and characterization data (S2–S9). 3: ¹H and ¹³C spectra of compounds **3** (S10-S41). CCDC 722722. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b904498a



Scheme 2 Possible mechanism of the one-pot tandem reaction of N'-(2-alkynylbenzylidene)hydrazide 1 with alkyne 2.

for halogen and carbon–carbon unsaturated bonds, we reasoned that initially the triple bond coordinated to the silver salt, and subsequently the nitrogen atom of N'-(2-alkynyl-benzylidene)hydrazide **1** attack on the triple bond *via* 6-endo-cyclization afforded isoquinolinium intermediate **A** (Scheme 2). Following nucleophilic addition of alkyne to the isoquinolinium intermediate **A** afforded the corresponding product **B**, which then underwent the intramolecular 5-endo cyclization leading to the intermediate **C**. Finally, aromatization occurred to generate the unexpected product **3**. With this promising result in hand, we subsequently screened different solvents in the reaction. We realized that the combination of dichloroethane (DCE) and CCl₄ gave rise to the best result and the product was generated in 80% yield.

Having demonstrated the viability of this catalytic strategy we next investigated the scope of the transformation under the preliminary optimized conditions [AgOTf (10 mol%), DBU, DCE-CCl₄, rt]. The results are summarized in Table 1. To assess the impact of the structural and functional motifs on the reaction we tested a range of linking units between N'-(2-alkynylbenzylidene)hydrazides and alkynes. For all cases, N'-(2-alkynylbenzylidene)hydrazide 1 reacted with alkyne 2 leading to the corresponding fused 1,2-dihydroisoquinoline 3 in good to excellent yields. For instance, reaction of N'-(2-alkynylbenzylidene)hydrazide 1a with 4-methoxyphenyl acetylene 2b under the standard conditions gave rise to the desired product **3b** in 74% yield (Table 1, entry 2). A similar yield was isolated when substrate 1b was employed in the reaction of 4-methoxyphenylacetylene 2b (70% yield, Table 1, entry 3). When N'-(2-alkynylbenzylidene)hydrazide 1c was utilized in the reaction, we rapidly noticed the broad field of application of the process and its remarkable functional group compatibility on alkynes (Table 1, entries 4-8). All the expected products were generated under our standard experimental conditions, whatever the nature of the substituents. For example, almost quantitative yield of product 3d was generated when phenylacetylene 2a was involved as a partner (Table 1, entry 4). The structure of **3d** was also verified by 1 H

and ¹³C NMR, mass spectroscopy, as well as X-ray diffraction analysis (Fig. 1).‡ Excellent yield was observed when 4-methoxyphenyl acetylene **2b** was used as a replacement in the reaction (Table 1, entry 5). When \mathbb{R}^3 was changed to *n*-butyl or cyclopropyl group, the reactions also occurred smoothly to generate the corresponding products in good yields (Table 1, entries 6, 7). Interestingly, it was found that a hydroxy group as substituent in the substrate **2e** was well tolerated under these conditions and the fused

Table 1 AgOTf-catalyzed tandem reaction of N'-(2-alkynylbenzylidene)hydrazide 1 with alkynes



^{*a*} Isolated yield based on N'-(2-alkynylbenzylidene)hydrazide 1.



Fig. 1 X-Ray ORTEP illustration of fused 1,2-dihydroisoquinoline **3d** (30% probability ellipsoids).

1,2-dihydroisoquinoline **3h** could be isolated in 64% yield (Table 1, entry 8). The conditions have also proven to be useful for other N'-(2-alkynylbenzylidene)hydrazide substrates. As expected, the substrates **1e–1i** are suitable partners in this process and the desired 1,2-dihydroisoquino-lines were generated in good yields (Table 1, entries 11–16).

In conclusion, we have described an efficient tandem reaction of N'-(2-alkynylbenzylidene)hydrazide with alkynes catalyzed by silver triflate, which generated the highly functionalized fused 1,2-dihydroisoquinolines in good to excellent yields. Small library construction as well as biological screening of these small molecules is ongoing, and the results will be reported in due course.

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Notes and references

‡ Crystal data and structure refinement for compound **3d**. Empirical formula: $C_{21}H_{20}N_2$, $M_r = 300$, monoclinic, space group $Pca2_1$, a = 11.8040(2), b = 13.1961(3), c = 23.5991(4) Å, V = 3675.96(12) Å³, Z = 8, $D_c = 1.239$ Mg m⁻³, T = 296(2) K, Reflections collected/unique: 19108/10218 ($R_{int} = 0.0251$), Final *R* indices [$I > 2\sigma(I)$]: R1 = 0.0911, wR2 = 0.2659; *R* indices (all data): R1 = 0.1410, wR2 = 0.3158.

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