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Tandem cyclization-[3+3] cycloaddition reactions of 2-alkynylbenzaldoxime: synthesis of fused 1,2-dihydroisoquinolines

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ABSTRACT

Tandem cyclization-[3+3] cycloaddition of 2-alkynylbenzaldoximes with dimethyl cyclopropane-1,1-dicarboxylate co-catalyzed by AgOTf and $Yb(OTf)_3$ is described, which provides an useful method for the synthesis of tetrahydro-1,2-oxazine fused 1,2-dihydroisoquinolines.

The increasing significance of combinatorial chemistry in pharmaceutical sciences demands the development of new strategies to synthesize a collection of natural product-like compounds.[1] As a privileged fragment, the 1,2-dihydroisoquinoline skeleton is an important substructure in both natural products and therapeutic agents, as well as the wide application of 1,2-dihydroisoquinolines in pharmaceutical research.[2] Typical examples include papaverine (smooth muscle relaxant),[2e] saframycin-B (antitumor agent),[2f] indenoisoquinoline (topoisomerase I inhibitor),[2g] and narciclasine (antitumor agent).[2h] Thus, significant effort continues to be given to the development of new 1,2-dihydroisoquinoline-based structures and new methods for their construction.[3–5] As part of a program in our laboratory for synthesis of biologically relevant heterocyclic compounds,[5,6] we became interested in developing novel and efficient methods to construct the new 1,2-dihydroisoquinoline-based structures, with a hope of finding active hits for our particular biological assays. Herein, we present our recent efforts for the synthesis of tetrahydro-1,2-oxazine-fused 1,2-dihydroisoquinoline derivatives via AgOTf and $Yb(OTf)_3$ co-catalyzed tandem cyclization-[3+3] cycloaddition reaction of 2-alkynylbenzaldoximes with dimethyl cyclopropane-1,1-dicarboxylates.

Among the strategies used for the construction of small molecules, design and synthesis of natural product-like compounds via tandem reactions have attracted much attention, and the development of tandem reactions has been a fertile area in organic synthesis.[7] In particular, the development of tandem reactions for the efficient construction of small molecules is an important goal in combinatorial chemistry from the viewpoints of operational simplicity and assembly efficiency. Recently, we and others discovered that in the presence of electrophiles (such as iodine or bromine) or Lewis acids, 2-alkynylbenzaldoxime could be transferred to isoquinoline-N-oxide via electrophilic cyclization.[6b,8] Prompted by these results, we envisioned that the tandem cyclization-cycloaddition reaction might occur since the generated isoquinoline-N-oxide could undergo further dipolar cycloaddition in the presence of dipolarophiles, leading to the fused 1,2-dihydroisoquinoline derivatives. Recently, donor–acceptor cyclopropanes as dipolarophiles have been successfully applied in the [3+3] cycloaddition of nitrones developed by Kerr and others.[9,10] The generated tetrahydro-1,2-oxazine core is also found in many natural products and pharmaceuticals that exhibit remarkable biological activities.[11] They also serve as valuable synthetic intermediates in total synthesis.[12,13] Based on these results, we started to investigate the possibility of this tandem reaction of 2-alkynylbenzaldoxime with dimethyl cyclopropane-1,1-dicarboxylate.

The reaction was initially studied with 2-alkynylbenzaldoxime **1a** and dimethyl cyclopropane-1,1-dicarboxylate **2a**, which were selected as suitable substrates for reaction development (Scheme 1). As described above, in the presence of Lewis acid, 2-alkynylbenzaldoxime could be transferred to isoquinoline-N-oxide via electrophilic cyclization. At the outset, various Lewis acids were

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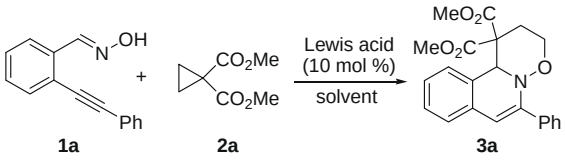


Scheme 1.

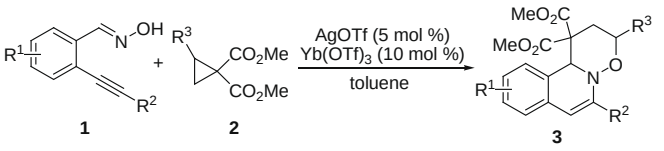
screened, and AgOTf (5 mol %) was demonstrated as the best choice for isoquinoline-N-oxide formation.[8b] However, this catalyst was not effective for the subsequent [3+3] cycloaddition reaction. Thus, additional Lewis acid catalyst was added to the reaction system. To our delight, we observed the formation of the desired fused 1,2-dihydroisoquinoline **3a**, when the reaction was performed in toluene co-catalyzed by AgOTf (5 mol %) and $Yb(OTf)_3$ (10 mol %) at 80 °C (77% yield). Following an extensive investigation, we observed that the yields were inferior when other solvents (THF, CH_3CN, DMF, CH_2Cl_2, and DCE) were employed in the reaction. Decreasing the amount of catalyst diminished the yield of product **3a**.

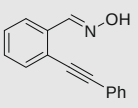
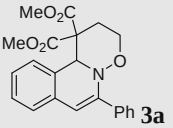
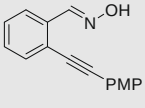
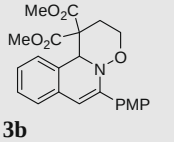
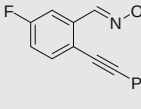
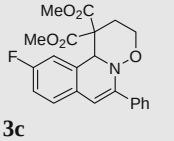
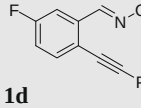
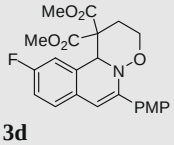
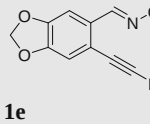
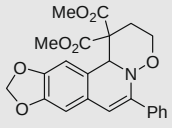
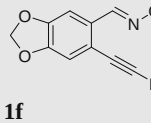
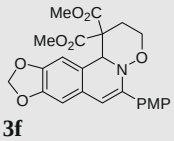
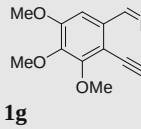
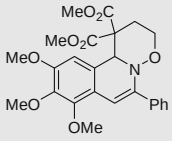
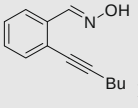
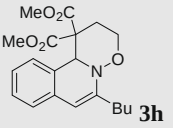
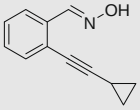
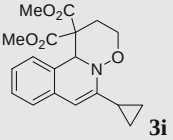
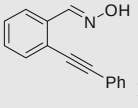
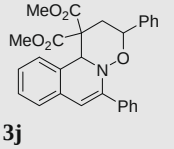
To test the effectiveness of this catalytic system, a range of 2-alkynylbenzaldoximes **1** were examined using the preliminary optimized reaction conditions [toluene as the solvent, 5 mol % of AgOTf, 10 mol % of $Yb(OTf)_3$, 80 °C], and the results are summarized in Table 1. 2-Alkynylbenzaldoxime **1b** reacted with dimethyl cyclopropane-1,1-dicarboxylate **2a**, leading to the formation of 1,2-dihydroisoquinoline **3b** in 74% yield (Table 1, entry 2). Complete conversion and excellent isolated yield (92%) were observed, when fluoro-substituted 2-alkynylbenzaldoxime **1c** was employed in the reaction (Table 1, entry 3). Reaction of 2-alkynylbenzaldoxime **1d** with dimethyl cyclopropane-1,1-dicarboxylate **2a** also furnished the desired product **3d** in good yield (78% yield, Table 1, entry 4). However, inferior results were displayed, when substrates with electron-donating groups attached on the aromatic ring of 2-al kynylbenzaldoxime were employed. For instance, substrate **1e** reacted with dimethyl cyclopropane-1,1-dicarboxylate **2a**, which gave rise to the corresponding product **3e** in 38% yield (Table 1, entry 5). Similar yields were observed when 2-alkynylbenzaldoxime **1f** or **1g** was utilized in the reaction (36% or 42% yield, respectively, Table 1, entries 6 and 7). We also found that, in this kind of transformation, the R^2 group attached on the triple bond is crucial. When R^2 was replaced by aliphatic group, such as butyl (**1h**) and cyclopropyl groups (**1j**), the reaction was complicated and no desired product was isolated (Table 1, entries 8 and 9). We also tested the reaction of 2-alkynylbenzaldoxime **1a** with phenyl-substituted dimethyl cyclopropane-1,1-dicarboxylate **2b**, which generated the desired product **3j** in 47% yield (Table 1, entry 10).

In the reaction process, the intermediate isoquinoline-N-oxide should be formed from 2-alkynylbenzaldoxime in the presence of silver triflate.[8b] It was well known that 1,1-cyclopropane diesters behaved very much like α,β-unsaturated carbonyl compounds in their ability to react with nucleophiles,[10a–d] and the strained bonds in 1,1-cyclopropane diesters can be polarized and further weakened by coordination of a Lewis acid to one or both of the ester moieties. Thus, [3+3] cycloaddition of isoquinoline-N-oxide with 1,1-cyclopropane diester occurred, which was similar to the reports of Kerr and others.[9,10]

In summary, we have described a tandem cyclization-[3+3] cycloaddition reaction of 2-alkynylbenzaldoxime with dimethyl cyclopropane-1,1-dicarboxylate catalyzed by the combination of AgOTf and $Yb(OTf)_3$, which provide a facile and useful protocol for the synthesis of tetrahydro-1,2-oxazine-fused 1,2-dihydroisoquinolines. Introducing enantioselectivity in the scaffold and screening for biological activity of these small molecules are under

Table 1
Tandem cyclization/[3+3] cycloaddition of 2-alkynylbenzaldoximes with dimethyl cyclopropane-1,1-dicarboxylate[14]



Entry	2-Alkynyl benzaldoxime	R^3	Product	Yield[a] (%)
1	 **1a**	H (**2a**)	 **3a**	77
2	 **1b**	H (**2a**)	 **3b**	74
3	 **1c**	H (**2a**)	 **3c**	92
4	 **1d**	H (**2a**)	 **3d**	78
5	 **1e**	H (**2a**)	 **3e**	38
6	 **1f**	H (**2a**)	 **3f**	36
7	 **1g**	H (**2a**)	 **3g**	42
8	 **1h**	H (**2a**)	 **3h**	–
9	 **1i**	H (**2a**)	 **3i**	–
10	 **1a**	Ph (**2b**)	 **3j**	47

[a] Isolated yield based on 2-alkynylbenzaldehydes **1**.

investigation in our laboratory, and the results will be reported in due course.

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14. *General procedure for AgOTf and Yb(OTf)$_3$ co-catalyzed tandem cyclization-[3+3] cycloaddition reaction of 2-alkynylbenzaldoximes with dimethyl cyclopropane-1,1-dicarboxylate*: 2-Alkynylbenzaldoxime (0.30 mmol) was added to a mixture of AgOTf (5 mol %) and Yb(OTf)$_3$ (10 mol %) in toluene (2.0 mL) at 80 °C under nitrogen atmosphere. After 5 min, dimethyl cyclopropane-1,1-dicarboxylate (0.36 mmol, 1.2 equiv) was added. After completion of the reaction as indicated by TLC, the reaction mixture was cooled to room temperature, quenched with water (10 mL), and extracted with EtOAc (2 × 10 mL). Evaporation of the solvent followed by purification of the residue on silica gel afforded fused 1,2-dihydroisoquinoline **3**.