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An efficient route to 1-aminoisoquinolines *via* AgOTf-catalyzed reaction of 2-alkynylbenzaldoxime with amine†

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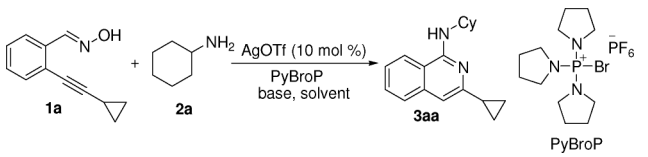
2-Alkynylbenzaldoxime reacts with amine catalyzed by silver triflate under mild conditions, leading to 1-aminoisoquinolines in good yield. This reaction proceeds efficiently with good functional group tolerance.

It is well recognized that *N*-heterocycles hold an important and special place among pharmaceuticals and natural products. Thus, significant efforts continue to be given to the methodologies development for the generation of nitrogen-containing heterocycles.[1] In the last few decades, intense attention has been paid continuously to isoquinoline derivatives due to their immense biological importance in many nature products and small molecule chemotherapeutics.[2] 1-Aminoisoquinoline is an important class of compounds among the family of isoquinolines, which shows remarkable biological activities. For example, 1-aminoisoquinoline derivatives have been reported as selective inhibitors of mutant protein kinase and anti-tumor reagents.[3] Additionally, due to their structural versatility, 1-aminoisoquinolines have been demonstrated as valuable intermediates in organic synthesis, which could be easily converted into functionalized isoquinolines. The methods for the preparation of 1-aminoisoquinolines include substitutional reaction of 1-haloisoquinolines by amines[4] and transition metal-catalyzed coupling reactions of amines with 1-haloisoquinolines.[5] However, these approaches usually suffered from harsh conditions, high temperature, strong base, or expensive metal catalysts. Moreover, a drawback associated with the methods is that a toxic compound such as $POCl_3$ has to be utilized for 1-haloisoquinolines formation.[6] Recently Londregan and co-workers described the reaction of pyridine-*N*-oxide with amine promoted by a phosphonium salt for the synthesis of 2-aminopyridines.[7] During our efforts for natural product-like compounds construction, we and others found that isoquinoline-*N*-oxide could be easily formed from 2-alkynylbenzaldoxime in the presence of electrophiles or suitable metal salts.[8,9] Inspired by these results, we conceived that 1-aminoisoquinoline scaffold could be generated *via* a reaction of 2-alkynylbenzaldoxime with amine in the presence of a metal catalyst and a suitable phosphonium salt. To demonstrate the feasibility of this projected route, we started to explore the possibility of this transformation.

Table 1 Initial studies for AgOTf-catalyzed reaction of 2-alkynylbenzaldoxime **1a** with cyclohexylamine **2a**



Entry	Base	PyBroP (equiv)	Solvent	Yield (%)[a]
1	$^{i}Pr_2NEt$	1.2	$ClCH_2CH_2Cl$	20
2	$^{i}Pr_2NEt$	0	$ClCH_2CH_2Cl$	NR
3	$^{i}Pr_2NEt$	2.0	$ClCH_2CH_2Cl$	77
4	$^{i}Pr_2NEt$	2.0	THF	64
5	$^{i}Pr_2NEt$	2.0	1,4-dioxane	80
6	$^{i}Pr_2NEt$	2.0	CH_2Cl_2	57
7	$^{i}Pr_2NEt$	2.0	Toluene	56
8	$^{i}Pr_2NEt$	2.0	MeCN	58
9	Et_3N	2.0	1,4-Dioxane	70
10	$^{n}Bu_3N$	2.0	1,4-Dioxane	69
11	DBU	2.0	1,4-Dioxane	29
12	pyridine	2.0	1,4-Dioxane	27
13	NaOAc	2.0	1,4-Dioxane	20

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

Our studies commenced with the reaction of 2-alkynylbenzaldoxime **1a** with cyclohexylamine **2a** (Table 1). As mentioned in our previous reports,[8] silver triflate was demonstrated as the best metal catalyst for isoquinoline-*N*-oxide formation *via* 6-*endo*-cyclization of 2-alkynylbenzaldoxime.[9] Thus, the reaction was catalyzed by 10 mol% of silver triflate in the presence of PyBroP (bromotrispyrrolidinophosphonium hexafluorophosphate, 1.2 equiv) and $^{i}Pr_2NEt$ (3.0 equiv) in dichloroethane. To our delight, the reaction proceeded to afford the desired product **3aa** in 20% yield (Table 1, entry 1). No reaction took replace in a blank experiment without the addition of PyBroP (Table 1, entry 2). This result highlights an important role of PyBroP for final outcome. With this promising lead in hand we next sought to improve the efficiency of the reaction. The yield was increased to 77% when 2.0 equiv of PyBroP was employed in the reaction (Table 1, entry 3). Further screens of

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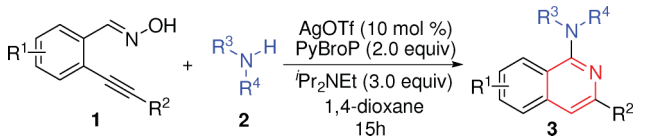
Table 2 Silver triflate-catalyzed reaction of 2-alkynylbenzaldoxime **1** with amine **2**



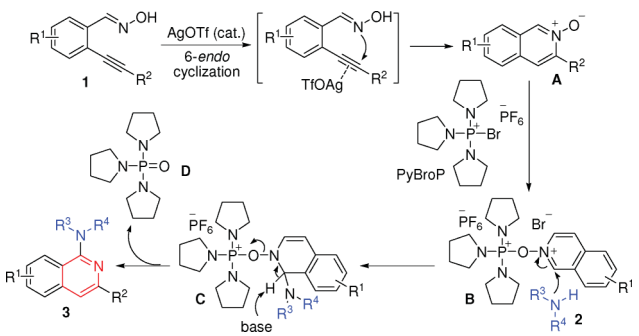
Entry	R^1, R^2	R^3, R^4	Yield (%)[a]
1	H, cyclopropyl (**1a**)	Cyclohexyl, H (**2a**)	80 (**3aa**)
2	H, cyclopropyl (**1a**)	*n*-Bu, H (**2b**)	70 (**3ab**)
3	H, cyclopropyl (**1a**)	*t*-Bu, H (**2c**)	66 (**3ac**)
4	H, cyclopropyl (**1a**)	Bn, H (**2d**)	63 (**3ad**)
5	H, cyclopropyl (**1a**)	-$(CH_2)_5$- (**2e**)	81 (**3ae**)
6	H, cyclopropyl (**1a**)	*n*-Pr, *n*-Pr (**2f**)	76 (**3af**)
7	H, cyclopropyl (**1a**)	C_6H_5, H (**2g**)	66 (**3ag**)
8	H, cyclopropyl (**1a**)	4-^{i}PrC_6H_4, H (**2h**)	77 (**3ah**)
9	H, cyclopropyl (**1a**)	4-ClC_6H_4, H (**2i**)	63 (**3ai**)
10	H, cyclopropyl (**1a**)	4-NCC_6H_4, H (**2j**)	54 (**3aj**)
11	H, cyclopropyl (**1a**)	4-$NO_2C_6H_4$, H (**2k**)	40 (**3ak**)
12	H, cyclopropyl (**1a**)	4-$EtO_2CC_6H_4$, H (**2l**)	62 (**3al**)
13	H, cyclopropyl (**1a**)	C_6H_5, Me (**2m**)	58 (**3am**)
14	H, cyclopropyl (**1a**)	H, 2-pyridinyl (**2n**)	50 (**3an**)
15	H, C_6H_5 (**1b**)	Cyclohexyl, H (**2a**)	55 (**3ba**)
16	H, 4-MeC_6H_4 (**1c**)	Cyclohexyl, H (**2a**)	52 (**3ca**)
17	H, 4-ClC_6H_4 (**1d**)	Cyclohexyl, H (**2a**)	60 (**3da**)
18	H, *n*-Bu (**1e**)	Cyclohexyl, H (**2a**)	60 (**3ea**)
19	4-F, *n*-Bu (**1f**)	Cyclohexyl, H (**2a**)	61 (**3fa**)
20	4-F, 4-MeC_6H_4 (**1g**)	Cyclohexyl, H (**2a**)	54 (**3ga**)
21	4-OMe, C_6H_5 (**1h**)	Cyclohexyl, H (**2a**)	68 (**3ha**)
22	5-F, C_6H_5 (**1i**)	Cyclohexyl, H (**2a**)	63 (**3ia**)
23	5-F, 4-MeC_6H_4 (**1j**)	Cyclohexyl, H (**2a**)	62 (**3ja**)
24	5-F, cyclopropyl (**1k**)	Cyclohexyl, H (**2a**)	84 (**3ka**)
25	5-Cl, C_6H_5 (**1l**)	Cyclohexyl, H (**2a**)	71 (**3la**)
26	5-Cl, cyclopropyl (**1m**)	Cyclohexyl, H (**2a**)	80 (**3ma**)
27	5-Me, C_6H_5 (**1n**)	Cyclohexyl, H (**2a**)	76 (**3na**)
28	4,5-$(OMe)_2$, cyclopropyl (**1o**)	Cyclohexyl, H (**2a**)	83 (**3oa**)

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

solvents indicated that the reaction worked the most efficiently in 1,4-dioxane to furnish the desired 1-aminoisoquinoline **3aa** in 80% yield (Table 1, entries 4–8). Additionally, survey of bases revealed that ^{i}Pr$_2$NEt was the best choice (Table 1, entries 9–13). The reactivity was diminished when the amount of base was reduced (data not shown in Table 1).

Having demonstrated the viability of this AgOTf-cayalyzed strategy we next investigated the scope of the transformation. To assess the impact of the structural and functional motifs on the reaction we tested a range of 2-alkynylbenzaldoxime **1** with amine **2** (Table 2). All the reactions were completed in 15 h. For the reaction of 2-(2-cyclopropylethynyl)benzaldehyde oxime **1a**, a variety of amines were examined (Table 2, entries 1–14). Not only aliphatic amines but also anilines were all good partners in the reactions. Additionally, different functional groups including chloro, cyano, nitro, and ester groups attached on the aromatic ring of anilines were all tolerated. Moreover, it was noticeable that reactions of 2-alkynylbenzaldoxime **1a** with secondary amines proceeded smoothly as well to afford the corresponding products. For instance, 2-alkynylbenzaldoxime **1a** reacted with piperidine **2e**, leading to 1-aminoisoquinoline **3ae** in 81% yield (Table 2, entry 5). A similar outcome was observed when diisopropylamine **2f** was utilized in the reaction (Table 2, entry 6). In extending this useful transformation, reactions of various 2-alkynylbenzaldoximes with cyclohexylamine **2a** were investigated (Table 2, entries 15–28). All reactions worked well to produce the expected 1-aminoisoquinolines in good yields. As we can see, the groups attached on the triple bond did not affect the final outcome. Moreover, substitutions including electron-withdrawing groups and electron-donating groups on the aromatic ring of 2-alkynylbenzaldoximes were well tolerated. For example, reaction of 2-(2-cyclopropylethynyl)-4,5-dimethoxybenzaldehyde oxime **1o** with cyclohexylamine **2a** gave rise to the desired 1-aminoisoquinoline **3pa** in 83% yield (Table 2, entry 28).

For the possible mechanism, according to Londregan' report[7] and our recent result,[8] we reasoned that isoquinoline-*N*-oxide **A** would be formed first *via* AgOTf-catalyzed 6-*endo*-cyclization of 2-alkynylbenzaldoxime **1**, which subsequently acted as a nucleophile to replace the bromide of PyBroP to afford intermediate **B** (Scheme 1). Then amine would be involved in the reaction. After intermolecular nucleophilic addition and deprotonation, the desired 1-aminoisoquinoline **3** would be generated with the release of 1-(dipyrrolidin-1-ylphosphoryl)pyrrolidine **D**. Actually, without the addition of silver catalyst, no formation of the desired product was observed for the reaction of 2-alkynylbenzaldoxime **1** with amine in the presence of PyBroP. Good conversion and yield were obtained when isoquinoline-*N*-oxide **A** was treated with PyBroP and amine, which provided a strong support for the proposed mechanism.



Scheme 1 Possible mechanism for silver triflate-catalyzed reaction of 2-alkynylbenzaldoxime **1** with amine **2**.

In conclusion, we have developed a novel and efficient approach to functionalized 1-aminoisoquinolines *via* silver triflate-catalyzed reaction of 2-alkynylbenzaldoxime with amine. The presence of PyBroP is essential for the successful transformation. The good functional groups tolerance at different positions of the substrates is demonstrated. The library of 1-aminoisoquinolines is under construction currently, due to the easy availability of starting materials and the efficiency of this method. The subsequent biological screens of these 1-aminoisoquinoline library members will be evaluated, and these results will be reported in due course.

Acknowledgements

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