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ARTICLE TYPE

Silver Triflate and Triflic Anhydride-Promoted Expedient Synthesis of Acylated 1-Aminoisoquinolines

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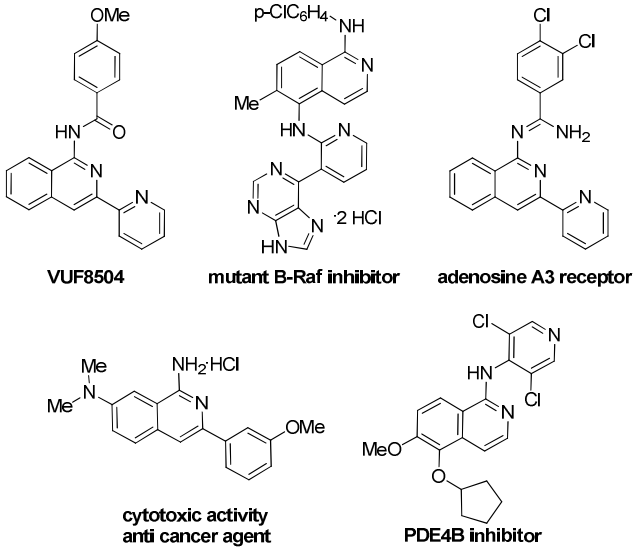
A practical and convergent synthesis of biologically active 1-(*N*-acyl)-1-aminoisoquinolines from the reaction of 2-alkynylbenzaldoximes with amides has been realized. The readily available amides could be activated by triflic anhydride (Tf_2O) and efficiently participate in the domino reaction of 2-alkynylbenzaldoximes when catalyzed by AgOTf, thus providing various acylated 1-aminoisoquinolines with up to 98% yields.

The substituted aminoisoquinolines are widely found in many natural products and pharmaceutically active compounds. For example, compounds that containing 1-aminoisoquinoline core structures are well-recognized as efficacious inhibitors of mutant B-Raf enzyme,[1a] mutant protein kinase, and PDE4B,[1d] adenosine A3 receptor,[1e] or as anti-cancer agents due to their strong cytotoxic activities. [2] Furthermore, 1-aminoisoquinoline derivatives are also useful synthetic building blocks in the generation of functionalized isoquinoline derivatives.[1-2]



Scheme 1. Biologically active compounds that containing 1-aminoisoquioline core structures.

For the preparation of such type of nitrogen-containing heterocycles, traditional synthesis relies on the nucleophilic displacement reaction between 1-haloisoquinolines and the corresponding amines. [3] Transition-metal-catalyzed C-N cross-coupling reactions at a late stage as represented by Buchwald-Hartwig amination reactions have been intensively studied as well, and practiced as prominent strategy for the formation of functionalized isoquinolines. [4] However, although the methods may be of interest, manipulations for these "prefunctionalization" notions, particularly on unactivated 1-haloisoquinolines, are frequently devious and in most cases require toxic reagents such as $POCl_3$ or expensive noble metal catalysts.

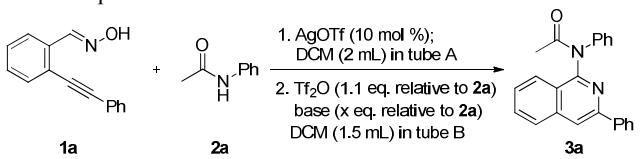
It is well known that domino reactions are fascinating tools in modern drug discovery processes, because they could provide straightforward access to complex molecules, simply by mixing several starting materials together and waiting for them to connect into a multipart molecule in a one-pot reaction vessel.[5] The types of reactions possess several benefits such as efficiency of time and cost saving, avoidance of intermediate isolation and minimum the production of chemical wastes. Recently, the group of Wu developed an efficient domino synthesis of 1-aminoisoquinolines via a silver triflate and bismuth triflate co-catalyzed reaction of 2-alkynylbenzaldoximes with isocyanides.[6a] Later, a silver triflate-catalyzed/PyBrop-promoted tandem reaction of 2-alkynylbenzaldoximes with amines to give functionalized 1-aminoisoquinolines was described.[6b] The phosphonium salt (PyBrop) was assumed to act as an energetic activator toward the in situ formed isoquinoline-*N*-oxide intermediate **A** (in scheme 3, *vide infra*), thus introducing secondary or tertiary amines onto the heterocyclic frameworks.[7] Stimulated by the studies, we envisioned that when activated by a favorable reagent, the readily available amides mignt participate in the domino reaction of 2-alkynylbenzaldoximes, and as a result the structurally useful 1-(*N*-acyl)-1-aminoisoquinolines should be conveniently generated. Note that currently no general protocol for the synthesis of acylated 1-aminoisoquinolines has been found.

Recently, the groups of Charette[8] and Movassaghi[9] reported seminar works on the electrophilic activation of readily available amides with trifluoromethanesulfonic anhydride (Tf_2O) in the presence of pyridines as the base additive.[10] The resulting highly reaction pyridinium cation could be quickly trapped by weak π-nucleophilic agents such as nitriles,[9b] alkynes and vinyl ethers.[8c,9c] Inspired by the results and our recent achievements around domino reactions,[11] we conceived that the functionalized 1-aminoisoquinoline derivatives could be delivered via a reaction

of 2-alkynylbenzaldoxime with the activated amides in the presence of a metal catalyst.

We started to explore the practicability of this transformation using 2-alkynylbenzaldoxime **1a** (0.4 mmol) and *N*-phenylacetamide **2a** (0.2 mmol) as the substrates of model reactions. Silver triflate was selected as the optimal metal catalyst because it had previously been recognized as the most efficient catalyst for the formation of isoquinoline-*N*-oxide **A** (in scheme 3) from 2-alkynylbenzaldoxime.[6] The reaction of 2-alkynylbenzaldoxime **1a** with AgOTf (10 mol%), *N*-phenylacetamide **2a**, Tf_2O (0.22 mmol) and 2-F-pyridine (0.24 mmol) were carried out in various solvents at different temperature. However, these initial investigations all failed to proceed, the reaction became complex and no expected product **3a** could be detected. We realized that the highly electrophilic trifluoromethanesulfonic anhydride (Tf_2O) would be consumed away firstly by 2-alkynylbenzaldoxime **1** in the reaction condition, thus it failed to activate the targeted amide **2a**.

Table 1. Reaction Optimization for the generation of 1-aminoisoquinoline **3a**

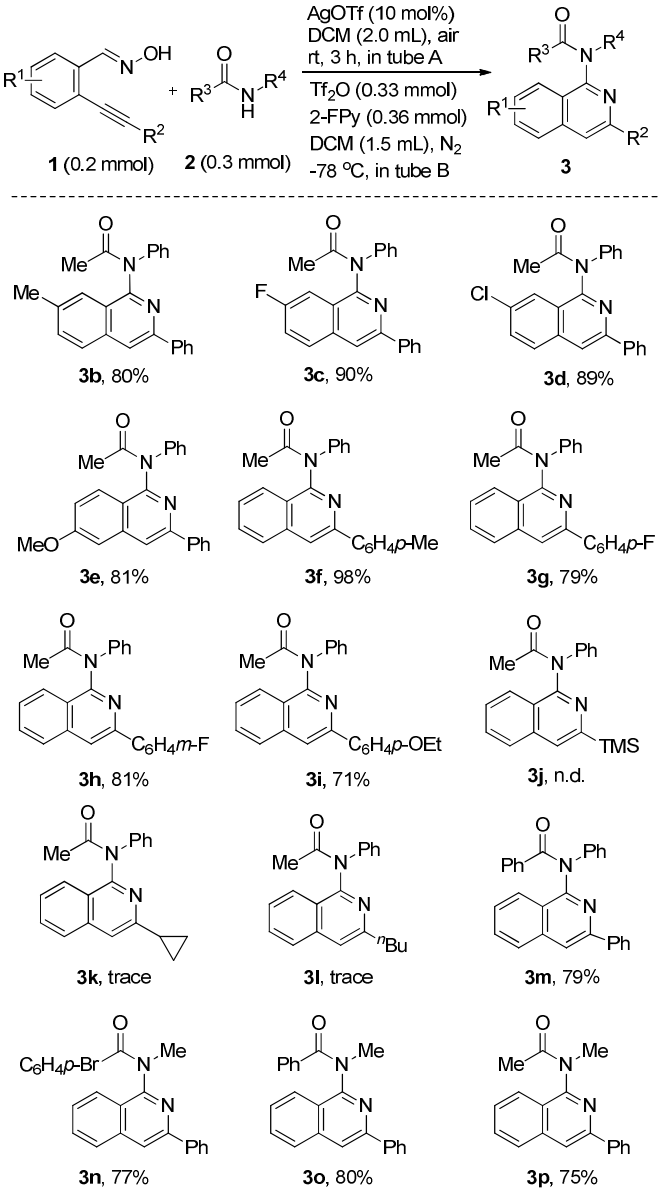


1a **2a** **3a**

entry	**1a: 2a**	base (x equiv.)	**3a** (%)[a]
1	2 : 1	2-FPy (1.2)	72
2	2 : 1	Et_3N (1.2)	28
3	2 : 1	Pyridine (1.2)	31
4	2 : 1	2-BrPy (1.2)	48
5	2 : 1	3-ClPy (1.2)	61
6	2 : 1	2,6-lutidine (1.2)	53
7	2 : 1	2,6-Cl_2Py (1.2)	54
8	2 : 1	3-BrPy (1.2)	64
9	2 : 1	-	13
10	2 : 1	2-FPy (1.5)	70
11	2 : 1	2-FPy (3.0)	58
12	1 : 1.5	2-FPy (1.2)	89[b]
13	1 : 2	2-FPy (1.2)	92[b]

[a]Reaction condition: **1a** (0.4 mmol), **2a** (0.2 mmol), AgOTf (10 mol%), Tf_2O (0.22 mmol), base (equiv. as relative to **2a**), rt. Isolated yield based on **2a**. [b]**1a** (0.2 mmol) was used. Isolated yield based on **1a**.

Therefore, in an improved experiment, we carefully modified the reaction by mixing 2-alkynylbenzaldoxime **1a** with silver catalyst in DCM in one reaction tube A, and simultaneously compound **2a** reacted with Tf_2O and 2-FPy in another test tube B, after a period of time, the solution in test tube A was slowly transferred into the test tube B by a syringe, and the resulting reaction mixture was allowed to stir at room temperature for about 4h. From this way we were delighted to obtain the desired product **3a** in 72% yield (Table 1, entry 1). This result demonstrated that the designed reaction was theoretically feasible, and prompted us to investigate the reaction conditions further. Different bases were examined subsequently, however, no improvement was observed and 2-FPy was again shown to be the optimal choice (Table 1, entries 2-8). A poor reaction was obtained while in the absence of base (Table 1, entry 9), which highlighted the importance of pyridine salt in the activation progress of amide **2a**. Finally, a nice reaction was observed when using 2-alkynylbenzaldoxime **1a** as the limiting reagent with an excess of *N*-phenylacetamide **2a** (2.0 equiv.), the yield could be improved to 92% (Table 1, entry 12).

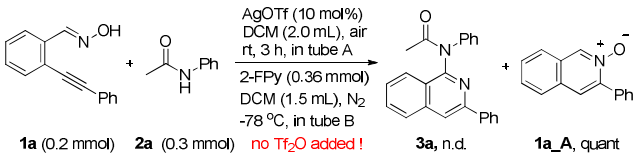


[a]Isolated yield based on **1**.

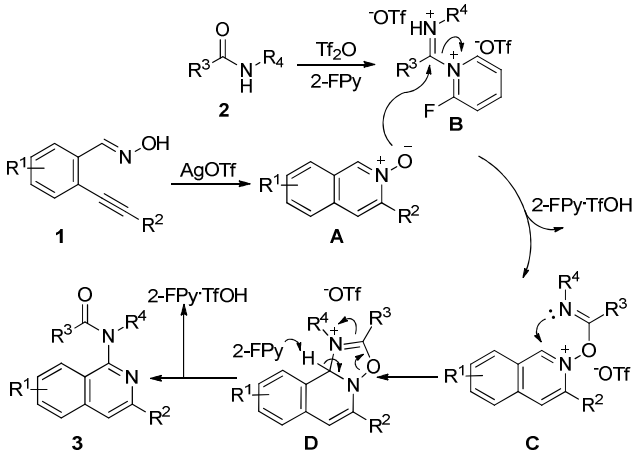
Scheme 2. Generation of 1-aminoisoquinolines by the reaction of 2-alkynylbenzaldoximes with amides.

We next explored the substrate scope of this reaction under the optimized reaction conditions (Scheme 2). When 2-alkynylbenzaldoxime **1** and silver catalyst were combined with each amide **2** in dichloromethane and treated with Tf_2O and 2-

FPy, we were pleased to obtain the corresponding acylated 1-aminoisoquinolines **3** with good functional groups tolerance. As shown in Scheme 2, the 2-alkynylbenzaldoxime **1** bearing either electron-rich (Me, MeO, and EtO) or electron-deficient halide substituents (F, Cl) on the R^1 or R^2 position of aromatic rings were all compatible under the standard conditions, providing the desired products **3a-3i** in excellent yields. Since the *N*-acetyl amide moiety could be easily hydrolyzed under basic conditions to give the corresponding secondary amines, these results indicated that the methods could be potentially applied in the synthesis of some valuable secondary 1-aminoisoquinoline derivatives. Unfortunately, for the reaction of trimethylsilyl group (TMS) substituted compound **1j** with *N*-phenylacetamide **2a**, a poor reaction was observed and the expected product **3j** could not be isolated. During this preliminary screening of the reaction, the limitation we found was related to the substitution pattern of R^2 which attached at the triple bond of substrate **1**: the aromatic moiety is required; otherwise complex mixtures are obtained while alkyl or cycloalkyl groups were present at R^2 position (**3j-3l**). Moreover, different *N*-substituted amides were employed in the tandem reaction, and the corresponding acylated products (**3m-3p**) were nicely furnished in serviceable yields. Note that for the reaction of 2-alkynylbenzaldoxime **1a** with nonsubstituted amide, such as acetamide (R = Me) or benzamide (R = Ph), the starting materials were full consumed as shown by TLC, however, the reactions were complex and no desired product was identified.



Scheme 3. Reaction of **1a** with **2a** in the absence of Tf_2O.



Scheme 4. Proposed mechanism for the reaction of 2-alkynylbenzaldoximes **1** with acetamides **2**.

To probe an insight into the mechanism, we have tried the reaction of **1a** with **2a** in the absence of Tf_2O (Scheme 3). No desired product **3a** was detected while the 3-phenylisoquinoline-2-oxide **1a_A** largely existed in the reaction condition. This result indicated that the Tf_2O played an important role in the activation of amide. Based on the previous 1-aminoisoquinoline synthesis[6] and the current activation chemistry of amides,[8-10] we depicted the following possible mechanism for the formation of 1-(*N*-acyl)-1-aminoisoquinolines **3** in Scheme 4. We assumed that the isoquinoline-*N*-oxide **A** would be generated from 2-alkynylbenzaldoximes via a silver triflate-catalyzed *6-endo-dig* cyclization reaction.6 Meanwhile, the pyridinium cation species **B** would be generated from the electrophilic addition reaction of acetamides **2** with trifluoromethanesulfonic anhydride in the presence of 2-F-pyridine.[9b,c] The subsequent addition reaction of **A** to the highly activated electrophile **B** should result in the formation of an isoquiolinium intermediate **C** accompanied by expulsion of 2-FPy·TfOH. **C** undergoes an intramolecular electrophilic substitution to give **D**, which subsequently isomerizes to acylated 1-aminoisoquinoline **3**.

Conclusions

In conclusion, we have successfully developed an efficient synthesis of valuable 1-(*N*-acyl)-1-aminoisoquinolines from 2-alkynylbenzaldoximes and various readily available amides. The advantages of this domino approach lie not only in fruitful expedient synthesis of potentially biologically active and naturally occurring aminoisoquinoline derivatives, but also in its economical use of reagents in simple procedures. Ongoing studies focus on the extension of substrate scopes and extension of this methodology to natural products and drug synthesis are currently underway.

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Notes and references

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‡ Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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