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BF_3-Etherate-Promoted Cascade Reaction of 2-Alkynylanilines with Nitriles: One-Pot Assembly of 4-Amido-Cinnolines

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Supporting Information

ABSTRACT: A BF_3-etherate-promoted cascade reaction of nitriles with 2-alkynylanilines is described. This method achieves the formation of two new C−N bonds through a reaction sequence of diazotization with *t*-BuONO, nucleophilic addition of the alkyne to the BF_3-coordinated diazonium ion, followed by nitrile addition to the intermediary vinyl cation and hydrolysis. The method provides efficient and general access to a variety of 4-amido-cinnolines. Notable features of the method include its broad functional group tolerance and avoidance of transition metals.

Cinnolines and their derivatives are a pivotal class of aza-heterocycles with multifarious applications as bioactive cores (Figure 1).[1] They also play a role in organic synthesis[2]

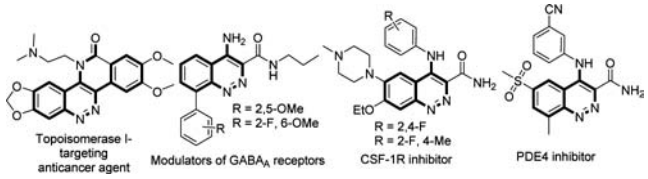


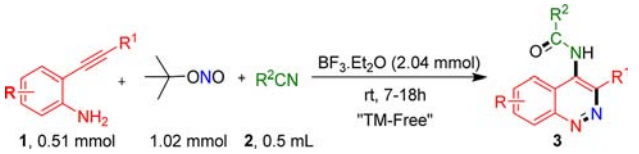
Figure 1. Biologically active cinnoline derivatives.

and electrochemistry,[3] and they have useful optical[4a] and luminescent properties.[4b] Despite this, the synthesis of cinnolines has been less frequently investigated.

Traditional methods for the synthesis of cinnolines utilize the ring-closure of in situ-generated phenyldiazonium ions onto ortho functionality.[5] In the case of the Ritcher cinnoline synthesis, the reaction proceeds via an intramolecular cyclization of the *ortho*-alkyne functionality in the presence of a hydrohalic acid, such as HBr or HCl and $NaNO_2$, to afford a mixture of halocinnolines and cinnolinones.[6] However, restricted substrate scope, activated alkynes, and strongly acidic conditions limit their application.[5,6] Aiming to improve the efficiency of substrate scope and mild reaction conditions, recently a few methodologies based on metals[7] and metal-free[8] strategies have been developed for the synthesis of cinnolines. Although these methods provide fruitful access to cinnoline derivatives, hitherto there has been no literature precedent for the straightforward construction of 4-amido/amino-cinnolines.[2a,9]

In recent decades, transition-metal-free reactions have become indispensable tools in organic synthesis.[10] The utilization of nitrile derivatives for the construction of heterocyclic rings is particularly well-established.[11] However, the addition of weak nucleophiles like nitriles onto π-electrophiles to form *N*-nitrilium ions followed by a cascade reaction is still an unexplored area of research.[12] In this context, and as part of our research into metal-free reactions,[13] herein we report an alternative method for cinnoline synthesis via BF_3-etherate-promoted cascade cyclization of *o*-alkynylanilines with nitriles in the presence of *tert*-butyl nitrite. The method allows for the construction of 4-amido-cinnolines via dual C−N bond formation for the first time (Scheme 1). We envision that the

Scheme 1. Our Approach for 4-Amido-cinnolines



reaction proceeds via diazotization,[14] the intramolecular nucleophilic addition of the alkyne to the diazonium ion to form a vinyl cation followed by nitrile addition to the vinyl cation and hydrolysis.

As shown in Table 1, our preliminary investigation began with easily accessible 2-(phenylethynyl)aniline **1a** and acetonitrile **2a** as model substrates. To our surprise, 4-amido-cinnoline **3aa** was obtained in 30% yield when these substrates were treated with $BF_3{\cdot}Et_2O$ (1.0 equiv), *t*-BuONO (2.0 equiv), and CH_3CN (0.5 mL) at room temperature for 18 h (Table 1, entry 1). The structure of compound **3aa** was confirmed unambiguously by X-ray analysis.[15] Subsequent work (Table 1, entries 2−4) eventually revealed that 4.0 equiv of $BF_3{\cdot}Et_2O$ and 7 h gave **3aa** in 90% yield (Table 1, entry 4). Other acids such as AcOH, benzoic acid, TFA, TfOH, TsOH, PivOH, and HCl resulted in low yields when evaluated in this process

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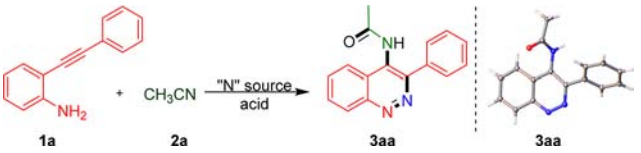
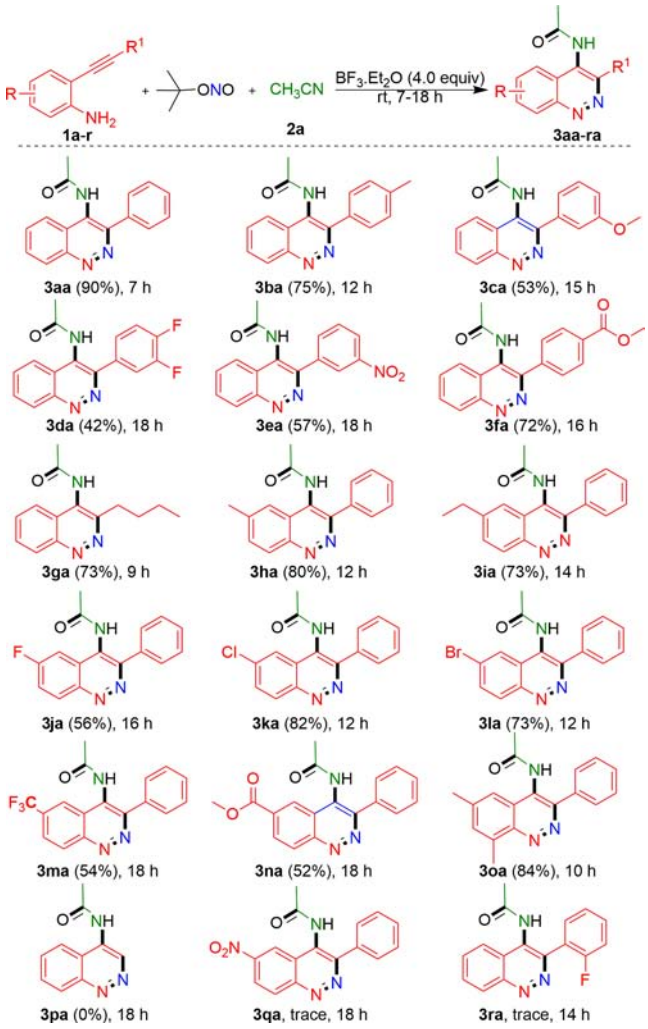
Table 1. Optimization of the Reaction Conditions[a]



entry	acid (equiv)	"N" source	solvent	time, h	yield (%)[b]
1	$BF_3{\cdot}Et_2O$ (1)	TBN	neat	18	30
2	$BF_3{\cdot}Et_2O$ (2)	TBN	neat	18	48
3	$BF_3{\cdot}Et_2O$ (4)	TBN	neat	14	64
4	**$BF_3{\cdot}Et_2O$ (4)**	**TBN**	**neat**	**7**	**90**
5	$BF_3{\cdot}Et_2O$ (5)	TBN	neat	7	73
6[c]	$BF_3{\cdot}Et_2O$ (4)	TBN	neat	7	71
7	AcOH (4)	TBN	neat	7	trace
8	PhCOOH (4)	TBN	neat	24	0
9	TFA (4)	TBN	neat	7	36
10	TfOH (4)	TBN	neat	7	65
11	TsOH (4)	TBN	neat	7	trace
12	PivOH (4)	TBN	neat	7	0
13	HCl (4)	TBN	neat	7	<20
14[d]	$BF_3{\cdot}Et_2O$ (4)	TBN	toluene	7	trace
15[d]	$BF_3{\cdot}Et_2O$ (4)	TBN	dioxane	7	trace
16[d]	$BF_3{\cdot}Et_2O$ (4)	TBN	DCE	7	45
17[d]	$BF_3{\cdot}Et_2O$ (4)	TBN	PhCl	7	32
18[d]	$BF_3{\cdot}Et_2O$ (4)	TBN	CH_3NO_2	7	<10
19[d]	$BF_3{\cdot}Et_2O$ (4)	TBN	THF	7	<10
20	$BF_3{\cdot}Et_2O$ (4)	amyl nitrite	neat	7	76
21	$BF_3{\cdot}Et_2O$ (4)	$NaNO_2$	neat	7	<10
22	HCl (4)	$NaNO_2$	neat	7	trace
23[e]	$BF_3{\cdot}Et_2O$ (4)	TBN	neat	7	73
24[f]	$BF_3{\cdot}Et_2O$ (4)	TBN	neat	7	30
25		TBN	neat	7	0

[a]All reactions were carried out using **1a** (0.51 mmol), **2a** (0.5 mL), acid, and "N" source (2.0 equiv) at room temperature (25 °C) unless otherwise noted. TBN = *tert*-butyl nitrite. PhCl = chlorobenzene. Entry in bold represents the optimized reaction conditions. Neat represents acetonitrile (0.5 mL) as reagent and solvent. TFA = trifluoroacetic acid. TfOH = trifluoromethanesulfonic acid. TsOH = *p*-toluenesulfonic acid. PivOH = pivalic acid. HCl = hydrochloric acid. [b]Isolated yields. [c]At 60 °C. [d]Used 2.0 equiv of acetonitrile and solvent (2.0 mL). [e]Added 2.0 equiv of H_2O. [f]Used 1.0 equiv of TBN.

Scheme 2. Scope of *o*-Alkynylanilines with Acetonitrile[a]



[a]Reaction conditions: Compounds (**1a-r**, 0.51 mmol), acetonitrile (**2a**, 0.5 mL), *t*-BuONO (1.02 mmol) and $BF_3{\cdot}Et_2O$ (2.04 mmol) at rt for indicated time. Isolated yields.

(Table 1, entries 7−13). The effect of solvents was tested by using CH_3CN (2.0 equiv) with toluene, 1,4-dioxane, 1,2-dichloroethane, chlorobenzene, nitromethane, and THF (Table 1, entries 14−19). However, none of them gave a better yield than entry 4. By replacing *t*-BuONO with amyl nitrite, **3aa** was formed in 76% yield (Table 1, entry 20). The reaction gave complex mixtures with $NaNO_2$ and HCl (Table 1, entries 21 and 22). For nitrilium hydrolysis, we presumed that the addition of water (2.0 equiv) could facilitate the reaction. However, we found no positive observation (Table 1, entry 23). Reducing the quantity of *t*-BuONO (1.0 equiv) led to a low yield (Table 1, entry 24). The reaction also failed to yield compound **3aa** in the absence of $BF_3{\cdot}Et_2O$ (Table 1, entry 25). Thus, the reaction conditions mentioned in Table 1, entry 4 were chosen as the optimum conditions.

As shown in Scheme 2, the scope and limitations of this method were investigated by systematic variation of the *o*-alkynylanilines (**1a−r**) with acetonitrile **2a** under standard conditions. A series of substituents on the R^1 functionality, such as *p*-Me-Ph (**1b**), *m*-OMe-Ph (**1c**), 3,4-di-F-Ph (**1d**), *m*-NO_2−Ph (**1e**), and *p*-COOMe-Ph (**1f**), worked well to afford the 4-amido-cinnoline derivatives **3ba−fa** in 42−75% yields. The reaction also proceeded smoothly for the alkyl (**1g**) derivative of the R^1 group to afford **3ga** in 73% yield. We next evaluated the scope of the R group with electron-donating and -withdrawing substituents like *p*-Me (**1h**), *p*-Et (**1i**) *p*-F (**1j**), *p*-Cl (**1k**), *p*-Br (**1l**), *p*-CF_3 (**1m**), *p*-COOMe (**1n**), and 2,4-di-Me (**1o**). The reaction proceeded well to give compounds **3ha−3oa** in 52−84% yields. In general, the reaction rate was comparatively slower when electron-withdrawing substituents were present in the R or R^1 group. However, terminal alkyne (**1p**) or *p*-NO_2 (**1q**) on R and *o*-F-Ph (**1r**) on the R^1 group gave trace amounts or no product at all.

In light of our success with *o*-alkynylaniline derivatives, we next envisioned the synthesis of 4-amido-cinnolines with various nitrile derivatives, as shown in Scheme 3. The reaction worked well with aromatic nitriles such as benzonitrile (**2b**) and 3-methoxybenzonitrile (**2c**) to afford the corresponding 4-amido-cinnoline derivatives **3ab** and **3ac** in 71−86% yields. Furthermore, the feasibility of the reaction was investigated with alkyl nitriles such as 4-phenylbutyronitrile (**2d**), propionitrile (**2e**), and isobutyronitrile (**2f**). The reaction

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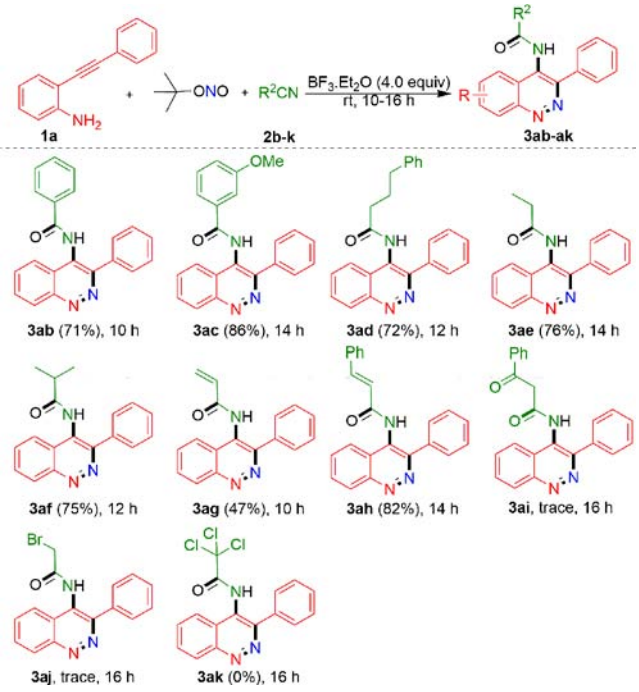
Scheme 3. Scope of nitriles with 2-(phenylethynyl)aniline[a]

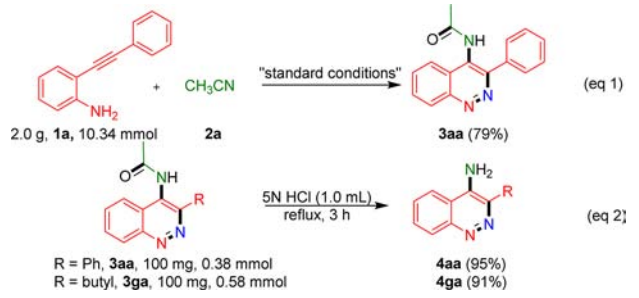


[a]Reaction conditions: Compound (**1a**, 0.51 mmol), nitriles (**2b-k**, 0.5 mL), *t*-BuONO (1.02 mmol) and $BF_3{\cdot}Et_2O$ (2.04 mmol) at rt for indicated time. Isolated yields.

smoothly afforded **3ad**–**af** in 72–76% yields. Interestingly, the reaction also worked well with acrylonitrile (**2g**) and cinnamonitrile (**2h**) to generate the corresponding acrylamide (**3ag**) and cinnamamide (**3ah**) derivatives, respectively, in 47–82% yields. However, the reactions of 3-oxo-3-phenylpropanenitrile (**2i**), bromoacetonitrile (**2j**), and trichloroacetonitrile (**2k**) gave traces or no product.

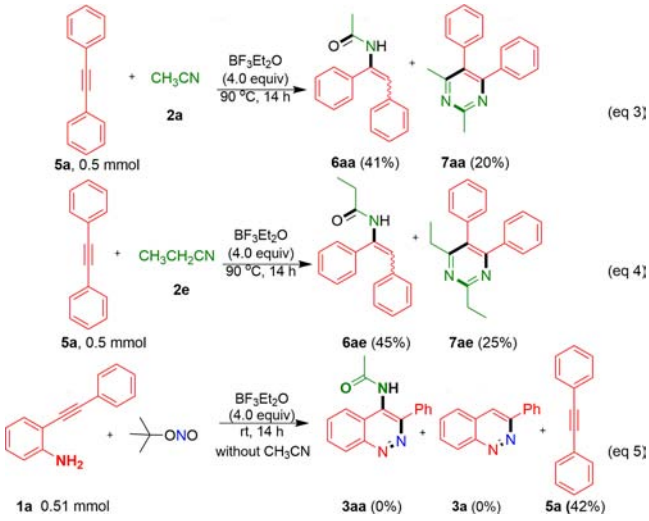
The practicality of this reaction has been investigated on a 2.0 g scale for the synthesis of compound **3aa**, as shown in Scheme 4. The reaction went smoothly, affording *N*-(3-phenylcinnolin-4-yl)acetamide in 79% yield (eq 1). Furthermore, we also hydrolyzed the *N*-acetyl group under acidic conditions to afford the amine for possible library work (eq 2).

Scheme 4. Gram Scale and Deacylation Reaction

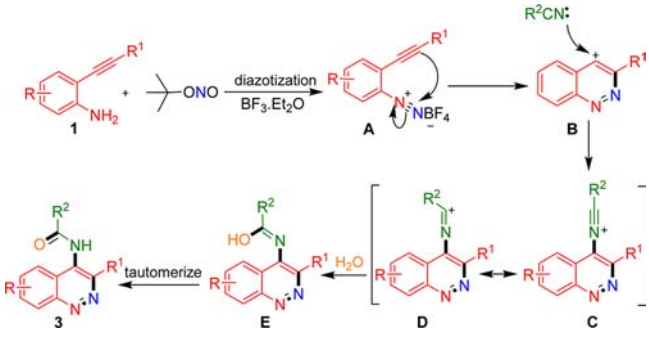


For some preliminary understanding of the reaction mechanism to be obtained, a few control experiments were carried out as shown in Scheme 5. The reaction of diphenylacetylene **5a** with acetonitrile **2a** under the standard conditions, without *t*-BuONO, gave enamide **6aa** as the major product and pyrimidine **7aa** as a minor product (eq 3). We presume that compound **7aa** was obtained by the reaction of enamide **6aa** with a second nitrile via an addition–elimination sequence.[16] Similar results were observed with propionitrile, as shown in eq 4. Next, we examined the reaction of **1a** without a nitrile source and isolated diphenyl acetylene **5a** in 42% yield (eq 5). The reason for the low yield of diphenylacetylene **5a** formation can be attributed to the lower stability of in situ-generated *o*-alkynylphenyldiazoniums in the absence of a nitrile. These results suggest that the reaction proceeds through diazotization followed by nucleophilic addition of the alkynes to the diazonium ions. A plausible mechanism is shown in Scheme 6.

Scheme 5. Control Experiments



Scheme 6. Plausible Reaction Mechanism



In conclusion, we have developed a one-pot cascade reaction strategy for the construction of 4-amido-cinnoline derivatives. The process involves two C–N bond formations under transition-metal-free conditions. The notable advantages are broad functional group tolerance, ambient reaction temperature, and moderate to good reaction yields alongside the introduction of an amide functional group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01207.

Experimental procedures, spectroscopic data and copies of NMR spectra for all new compounds (PDF)

X-ray crystallographic data for **3aa** (CIF)

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Notes

The authors declare no competing financial interest.

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