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One-Pot Cascade Approach to Phenanthridine-Fused Quinazoliniminiums from Heteroenyne-Allenes

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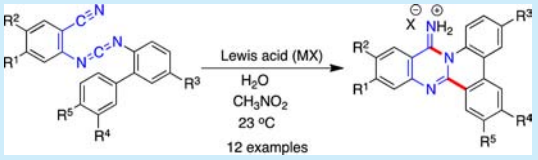
Supporting Information

ABSTRACT: A one-pot cascade method to obtain functionalized phenanthridine-fused quinazoliniminiums from a variety of heteroenyne-allenes is described. This protocol involves formation of C−N and C−C bonds in a single step in the presence of a Lewis acid and trace water to afford pentacyclic title compounds in moderate to good yields.



Naturally occurring or synthetically produced fused heterocyclic compounds play an important role in pharmaceutics, agriculture, and material science. Therefore, the development of quick, efficient, and versatile methods for the synthesis of new classes of fused heterocycles are in high demand. As an important structural motif, phenanthridine ring system **1** (Figure 1) is represented in several bioactive natural products,[1] and many synthetic compounds containing this molecular framework are known to exhibit potent anticancer,[2] antituberculosis,[3] antitrypanosomiasis,[3] antihepatitis,[4] and pesticidal[5] activities. Recently, it has been reported that phenanthridine derivatives also show promise as radiotracers for imaging of brain 5-HT_4 receptors by single photon emission computed tomography.[6] Similarly, the 4(3*H*)-quinazolinimine framework **2** is an important pharmacophore with cholinesterase inhibitory,[7] antihypertensive,[8] antimicrobial,[8] and antiproliferative[9] activities. Further interest in **2** stems from its role as a key precursor to 4(3*H*)-quinazolinones.[10] The latter are regarded as "privileged" skeletons,[11] widely distributed in natural products[12] and synthetic compounds with a broad spectrum of biological activities such as antimicrobial,[13] antioxidant,[13a] antimalarial,[14] anticonvulsive,[15] anti-inflammatory,[16] anticancer,[17] antihypertensive,[18] and analgesic.[19] Furthermore, molecules containing the quinazoline and phenanthridine motifs show promise as electroluminescent materials[20] and organic dyes.[21]

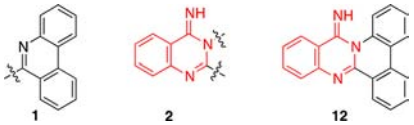


Figure 1. Phenanthridine **1**, 4(3*H*)-quinazolinimine **2**, and phenanthridine-fused quinazolinimine **12** scaffolds.

Several routes for the independent construction of phenanthridine **1** or quinazolinimine **2** cores exist in the literature;[10,22] however, the phenanthridine-fused quinazolinimine molecular framework has not been previously reported. In view of the aforementioned applications of the phenanthridine and quinazolinimine skeletons in biology and materials, the development of concise, versatile, and efficient protocols that fuse these two ring systems in one molecular skeleton **12** (Figure 1) are highly desirable, as that may ease the search of promising new structures for medicine and materials with increased efficacy and improved performance, respectively. Furthermore, derivatives of phenanthridine-fused quinazolinimine **12** would provide useful building blocks for another new class of heterocycles, the phenanthridine-fused quinazolinones. Fused quinazolinones are important targets because of their interesting architectures and promising bioactivities.[23]

A cascade or tandem cyclization reaction that leads to the formation of multiple bonds in a single synthetic event represents a powerful tool to construct complex heterocyclic ring structures. Herein we report the one-pot Lewis acid assisted cascade/tandem cyclization of 2-((([1,1′-biphenyl]-2-ylimino)methylene)amino)benzonitriles **3** to phenanthridine-fused quinazoliniminium salts **5** (protonated **12**) that involves C−N and C−C bond formation *via* nucleophilic addition and Friedel−Crafts reactions, respectively (Scheme 1). The highlights of this approach are the following: (a) the construction of a new class of *N*-fused heterocycles can be achieved from commercially available substrates in only 3−4 steps, (b) the tandem/cascade cyclization is carried out at rt and requires no special setup or workup to isolate the product, (c) this method is versatile and provides a straightforward way to obtain functionalized *N*-fused heterocycles by selecting appropriately substituted starting materials, and (d) the cascade cyclization reaction is atom economical.

We have previously reported that a series of heteroenyne-allenes, namely 2-(((phenylimino)methylene)amino)benzonitriles undergo facile intramolecular cyclization to 2-halo-3-

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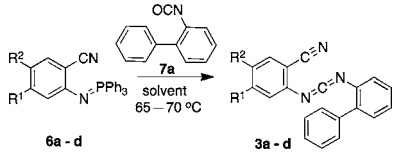
Scheme 1. Tandem/Cascade Cyclization of 3 to 5

arylquinazolin-4(3*H*)-iminium salts upon reaction with hydrogen halide, generated *in situ* from a Lewis acid and trace water.[22b] In our attempts to further explore the synthetic potential of heteroenyne-allenes, we synthesized 2-((([1,1′-biphenyl]-2-ylimino)methylene)amino)benzonitriles **3** and investigated their cyclization to phenanthridine-fused quinazoliniminium salts **5** through two sequential intramolecular cyclizations (Scheme 1). We envisaged that reaction would involve intermediacy of 2-halo-3-((1,1′-biphenyl)-2-yl)-quinazolin-4(3*H*)-iminiums **4**,[22b] and once formed the presence of a halogen atom at C2 of **4** will prompt Friedel–Crafts type cyclization with the biphenyl ring under Lewis acid conditions to form **5**. To examine this possibility, 2-((([1,1′-biphenyl]-2-ylimino)methylene)amino)benzonitrile (**3a**) (R^1, R^2, R^3, R^4, R^5 = H) was synthesized. Briefly, iminophosphorane **6a** (R^1, R^2 = H) was reacted with commercially obtained 2-isocyanato-1,1′-biphenyl (**7a**) to afford **3a** (Scheme 2).

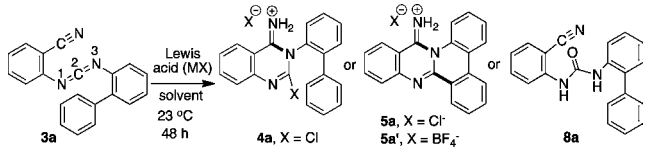
Scheme 2. Synthesis of 3a–d



In order to study the cyclization to *N*-fused heterocycle **5a**, **3a** was treated with TMSCl in CH_2Cl_2 at rt that resulted in the formation of a white solid over 48 h. The product was isolated. ^1H and ^{13}C NMR spectroscopy and high resolution mass spectrometry (HRMS) revealed that the solid obtained was not the desired 14*H*-quinazolino[3,2-*f*]phenanthridin-14-iminium chloride (**5a**) but the partially cyclized compound, 3-([1,1′-biphenyl]-2-yl)-2-chloroquinaz-olin-4(3*H*)-iminium chloride (**4a**) (Table 1, entry 1). The cyclization of **3a** was also attempted in the presence of TMSBr and $SnCl_4$ in CH_2Cl_2; however, the product obtained was 1-([1,1′-biphenyl]-2-yl)-3-(2-cyanophenyl)urea (**8a**) (entries 2 and 3). The reaction of **3a** with $BF_3{\cdot}OEt_2$ in CH_2Cl_2 furnished the desired 14*H*-quinazolino[3,2-*f*]phenanthridin-14-iminium tetrafluoroborate (**5a′**) in 50% yield (entry 4). The structure characterization of **5a′** was carried out by NMR spectroscopy and HRMS. The final confirmation of the molecular structure was obtained from X-ray crystallography (Figure 2). The C(14)–N(14) and C(14)–N(13) bond lengths were 1.319 and 1.376 Å, respectively, that confirmed an exocyclic C=N bond in **5a′**.

The above result encouraged us to further investigate the reaction conditions with the goal of increasing the yield of **5a′**. Because the reaction mechanism is believed to involve the formation of polar intermediates, we examined the cascade cyclization in high polarity solvent, nitromethane (anhydrous). However, a reaction of **3a** in $BF_3{\cdot}OEt_2/CH_3NO_2$ resulted in no product (entry 5). We hypothesized that the failure to obtain **5a′** may be attributed to the lack of a Bronsted acid (HBF_4) in the mixture, which is required for the protonation of the CN group of **3a**, and subsequent nucleophilic attack from N3 of its carbodiimide to form the C–N bond. HBF_4 would be formed by the reaction of BF_3 with water. In the case of the reaction with $BF_3{\cdot}OEt_2/CH_2Cl_2$ (entry 4), this water is provided by the solvent (CH_2Cl_2, 95% purity) resulting in the generation of HBF_4, while anhydrous CH_3NO_2 (entry 5) did not contain enough water to form the required Bronsted acid. Therefore, we attempted the cyclization of **3a** in $BF_3{\cdot}OEt_2/CH_3NO_2$ by adding two drops of water (entry 6). To our delight, **5a′** was produced, albeit in low yields. Next, we carefully studied the

Table 1. Reaction of 3a with Different Lewis Acids



					product (%)		
entry	Lewis acid	S[a]	H_2O (equiv)	X^-	4	5	8
1	TMSCl	A		Cl^-	**4a**: 78		
2	TMSBr	A		Br^-			**8a**: 57
3	$SnCl_4$	A		Cl^-			**8a**: 65
4	$BF_3{\cdot}OEt_2$	A		BF_4^-		**5a′**: 50	
5	$BF_3{\cdot}OEt_2$	B		BF_4^-		none[b]	
6	$BF_3{\cdot}OEt_2$	B[c]		BF_4^-		**5a′**: < 20	
7	$BF_3{\cdot}OEt_2$	B	2	BF_4^-		**5a′**: 43	
8	$BF_3{\cdot}OEt_2$	B	4	BF_4^-		**5a′**: 60	
9	$BF_3{\cdot}OEt_2$	B	8	BF_4^-		**5a′**: 56	
10	$BF_3{\cdot}OEt_2$	B	10	BF_4^-		**5a′**: 43	
11	$SnCl_4$	B	4	Cl^-		**5a**: 75[d]	
12	$BF_3{\cdot}OEt_2$	B	4	BF_4^-		**5a′**: 63[e]	
13	$SnCl_4$	B	4	Cl^-		**5a**: 75[f]	

[a]Solvent: (A) CH_2Cl_2 or (B) CH_3NO_2. [b]A complex mixture of products formed which were not identified. [c]Two drops of H_2O added. [d]Reaction completed in 16 h. [e]5 °C, 72 h. [f]5 °C, 20 h.

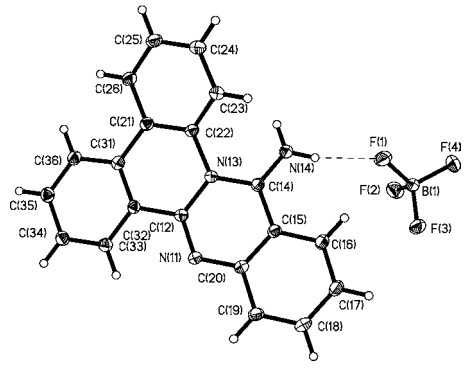


Figure 2. ORTEP diagram of **5a′**.

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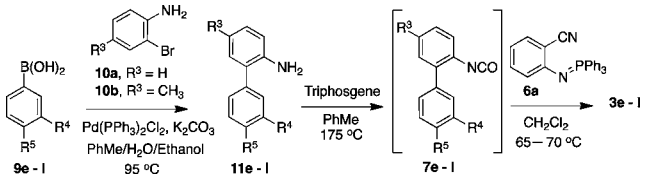
effect of addition of different equivalents of water on the yield of **5a′** (entries 7−10), and the best results were obtained with 4 equiv of the added water. Further, we screened different Lewis acids under these conditions (see Table 1s, Supporting Information). Reaction of **3a** with TMSCl, $AlCl_3$, and BCl_3 in CH_3NO_2/4 equiv H_2O gave **4a**. TMSBr and SnF_4 gave **8a**, and TMSI and BBr_3 yielded a complex mixture of products that was not characterized (Table 1s). Pleasingly, treatment of **3a** with $SnCl_4$ in CH_3NO_2/4 equiv of H_2O furnished **5a** in very good yields (Table 1, entry 11). Lewis acids (BF_3·OEt_2 and $SnCl_4$) that showed promise were also investigated at low temperature (entries 12−13), but the reaction was slow and yields were not significantly different from the case at room temperature.

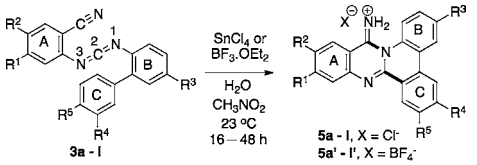
Next, the scope of this protocol was explored under the optimized conditions (Table 2). A variety of 2-((([1,1′-biphenyl]-2-ylimino)methylene)amino)benzonitriles **3** were synthesized. **3b−d** were obtained as shown in Scheme 2, while **3e−l** were prepared as described in Scheme 3. Briefly, phenyl boronic acids **9e−l** were subjected to Suzuki coupling with 2-bromoanilines **10a,b** to obtain [1,1′-biphenyl]-2-amines **11e−l**. Treatment of the latter with triphosgene afforded the isocyanates **7e−l** which were not isolated, and reacted with iminiphosphoranes **6a** *in situ* to yield the desired compounds **3e−l**.

Scheme 3. Synthesis of 3e−l



Cyclization to the respective phenanthridine-fused quinazoliniminiums **5** proceeded smoothly in the presence of $SnCl_4$/4 equiv of H_2O for **3b,c** carrying an electron-donating methyl group on ring A (Table 2, entries 2 and 3). Compound **3d**, substituted with an electron-withdrawing bromo group, also produced the desired heterocycle **5d**, although it afforded somewhat lower yields. The effect of an electron-donating methyl group on ring B of **3e** was also examined. **5e** was formed in excellent yields upon reaction of **3e** with $SnCl_4$ (entry 5). Next, the effect of substitution on ring C of **3** was investigated. The reaction of compound **3f** carrying a methyl group at R^4 with $SnCl_4$ proceeded efficiently to afford *N*-fused heterocycle **5f** in excellent yield (entry 6). However, the reaction of **3g,h,i** bearing a methoxy, fluoro, and chloro group with $SnCl_4$ led to the formation of a mixture of products with only a trace amount of the desired *N*-fused heterocycles **5g,h,i**. The heterocyclic salts **5g′,h′,i′** were successfully obtained with BF_3·OEt_2, although in somewhat lower yields (entries 7−9). The treatment of **3j** carrying a trifluoromethyl group with $SnCl_4$ or BF_3·OEt_2 did not result in the formation of **5j** or **5j′** (entry 10). The reduced yields and no product formation in the case of cyclizations of **3g,h,i** and **3j**, respectively, may be attributed to the electron-withdrawing inductive effect of the $-OCH_3$, −F, −Cl, and $-CF_3$ groups that retards or prevents the Friedel−Crafts type cyclization. The reaction of $SnCl_4$ with compound **3k** displaying a methyl group at R_5 afforded the desired *N*-fused heterocycle **5k** albeit in 44% yield; however, the reaction of **3k** with BF_3·OEt_2 produced **5k′** in very good yields (entry 11). The disubstituted **5l′** was also obtained from

Table 2. Scope of Cyclization of Heteroenyne-Allenes 3 to *N*-Fused Quinazoliniminiums 5



entry	3	R^1	R^2	R^3	R^4	R^5	yield (%)
1	**3a**[a]	H	H	H	H	H	**5a:** 75
2	**3b**[a]	Me	H	H	H	H	**5b:** 63
3	**3c**[a]	H	Me	H	H	H	**5c:** 61
4	**3d**[a]	H	Br	H	H	H	**5d:** 54
5	**3e**[a]	H	H	Me	H	H	**5e:** 79
6	**3f**[a]	H	H	H	Me	H	**5f:** 81
7	**3g**[b]	H	H	H	OMe	H	**5g′**: 51
8	**3h**[b]	H	H	H	F	H	**5h′**: 45
9	**3i**[b]	H	H	H	Cl	H	**5i′**: 39
10	**3j**[c]	H	H	H	CF_3	H	**5j,j′**: 0
11	**3k**[b]	H	H	H	H	Me	**5k′**: 70
12	**3l**[b]	H	H	Me	OMe	H	**5l′**: 37

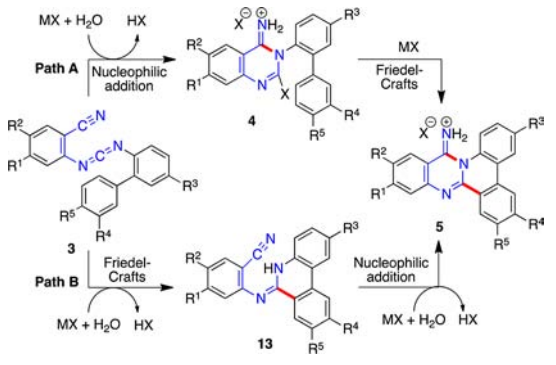
[a]Reaction carried out in $SnCl_4$. [b]Reaction carried out in BF_3·Et_2O. [c]Reaction attempted in $SnCl_4$ and BF_3·Et_2O.

the corresponding heteroenyne-allene **3l** upon treatment with BF_3·OEt_2, however in somewhat low yields (entry 12).

In Scheme 4, we propose two mechanistic pathways for this cascade cyclization. Path A involves C−N bond formation prior to C−C bond formation *via* the intermediacy of 2-halo-3-((1,1′-biphenyl)-2-yl)quinazolin-4(3*H*)-iminiums **4** as proposed (Scheme 1), while Path B shows an alternative route in which C−C bond formation precedes C−N bond formation through the intermediacy of (*Z*)-2-(phenanthridin-6(5*H*)-ylideneamino)benzonitriles **13**. We synthesized compound **4a** (Table 1, entry 1), and all our attempts to cyclize it to **5a** upon treatment with $SnCl_4$ in nitromethane with or without water were unsuccessful. This suggests that the mechanism of the reaction may not involve the formation of **4**; however intermediacy of a pyrimidinium type cation (precursor to **4** before the attack by halide) in the formation of **5** may not be ruled out at this stage. Our computational investigations to gain insights into the mechanism of this cascade/tandem cyclization are in progress.

In summary, we have demonstrated a concise, facile, and a versatile protocol for the construction of a novel class of heterocycles, namely the phenanthridine-fused quinazoliniminium salts **5** from heteroenyne-allenes **3** *via* $SnCl_4$ or BF_3·OEt_2

Scheme 4. Proposed Pathways for Cascade Cyclization



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mediated cascade intramolecular cyclization. The reaction conditions are compatible with most of the tested functional groups and effectively afford the desired *N*-fused heterocycles **5** in moderate to excellent yields. Since electrophilic aromatic substitution is a critical step in the formation of **5**, the cyclization outcome and its yields seem to be dependent on the electronic nature of the substituents and their respective positioning on the heteroenyne-allene **3** scaffold. Furthermore, this method offers a promising new way to construct different types of ring fusions to the quinazolinimine scaffold by varying the nature of the aryl group on the N3 of the carbodiimide. These investigations will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, optimization of reaction conditions table, ^{1}H and ^{13}C NMR spectra of all new compounds; X-ray data and cif files of **5a′** and **5k′**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

All authors have approved the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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