Programmed Heterocycle Synthesis Using Halomuconononitriles as Zincke Nitrile Precursors

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ABSTRACT: The isomeric imidazo[1,2-*a*]pyridines and pyrrolo[2,3-*b*]-pyridine (7-azaindole) heterocyclic cores are "privileged structures" due in part to their ability to interact with a multitude of different receptors, making them essential to the drug discovery process. Imidazo[1,2,-*a*]pyridine and 7-azaindole, though structurally related, are typically independently synthesized from 2-aminopyridine starting materials. Herein we report a method to convert primary amines, ubiquitous motifs found in pharmaceutical libraries, to either imidazo[1,2-*a*]pyridines or 7-alkyl azaindoles in two steps. Using halomuconononitrile reagents, we can directly access 5-bromo-6-imino-1-alkyl-1,6-dihydropyridine-2-carbonitriles (pyridinimines) in a single step from primary amines (25–95% yield) through a cyclization of transient Zincke nitrile intermediates. We then demonstrate that these compounds can be readily converted to 7-alkylazaindoles using Sonogashira cross-coupling conditions (14 examples, up to 91% yield). Under oxidative conditions, the pyridinimines serve as directing groups for C–H functionalization reactions to afford imidazo[1,2-*a*]pyridines. We have studied the mechanism of the cyclization event using DFT calculations and propose this takes place via ketenimine intermediates.

Imidazo[1,2-*a*]pyridines[1,2] and the isomeric pyrrolo[2,3,*b*]pyridines (7-azaindoles) are privileged heterocycles – compounds that have found applications as therapeutics for multiple diseases because of their ability to bind to different receptors.[3] The activity of imidazo[1,2-*a*]pyridines ranges from $GABA_A$ receptor modulators as exemplified by the flagship imidazo[1,2-*a*]pyridine compound zolpidem **1a** (brand name Ambien®), to compounds which treat tuberculosis.[4] The 7-azaindoles have also found broad medicinal applications as bioisosteres of indole,[5,6] are indispensable tools in chemical biology,[7] and have beneficial luminescence properties (Figure 1a).[8]

Most established methods to construct imidazo[1,2-*a*]pyridines and 7-azaindoles frequently employ 2-aminopyridines as common synthetic precursor.[9] Although numerous robust methods for 2-aminopyridine synthesis from pyridine-derived starting materials have been disclosed, a noteworthy gap in the synthetic chemist's toolbox is a conceptually different approach that involves the *de novo* construction of 2-aminopyridines from other aromatic feedstock compounds.[10,11] Such an approach is valuable in light of the recent developments in arene skeletal remodeling reactions.[12] When considering the construction of 2-aminopyridines from other arenes, we gravitated toward the Zincke reaction, which accomplishes the tandem deconstruction of activated pyridinium ions with primary amines **1d** to "Zincke imines" **1e**, which then cyclize to yield alkylpyridinium products **1g** in a single step.[13,14] We identified a conceptual parallel between Zincke imines **1e** and the more highly oxidized Zincke nitriles **1i** that we believed would cyclize in an analogous fashion to afford pyridinimines (2-aminopyridine tautomers) allowing one to, in principle, decouple the deconstruction and construction steps of the traditional Zincke process.

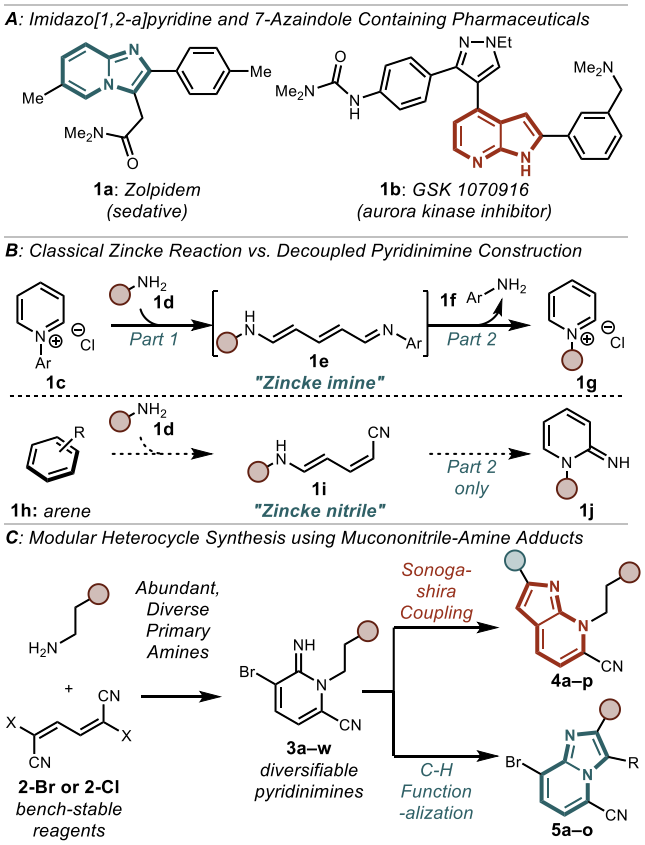

Figure 1: a) Representative heterocycle-containing drugs. b) Ar = 2,4-dinitrophenyl. Part 1 = deconstruction and Part 2 = reconstruction. c) Our approach toward these motifs.

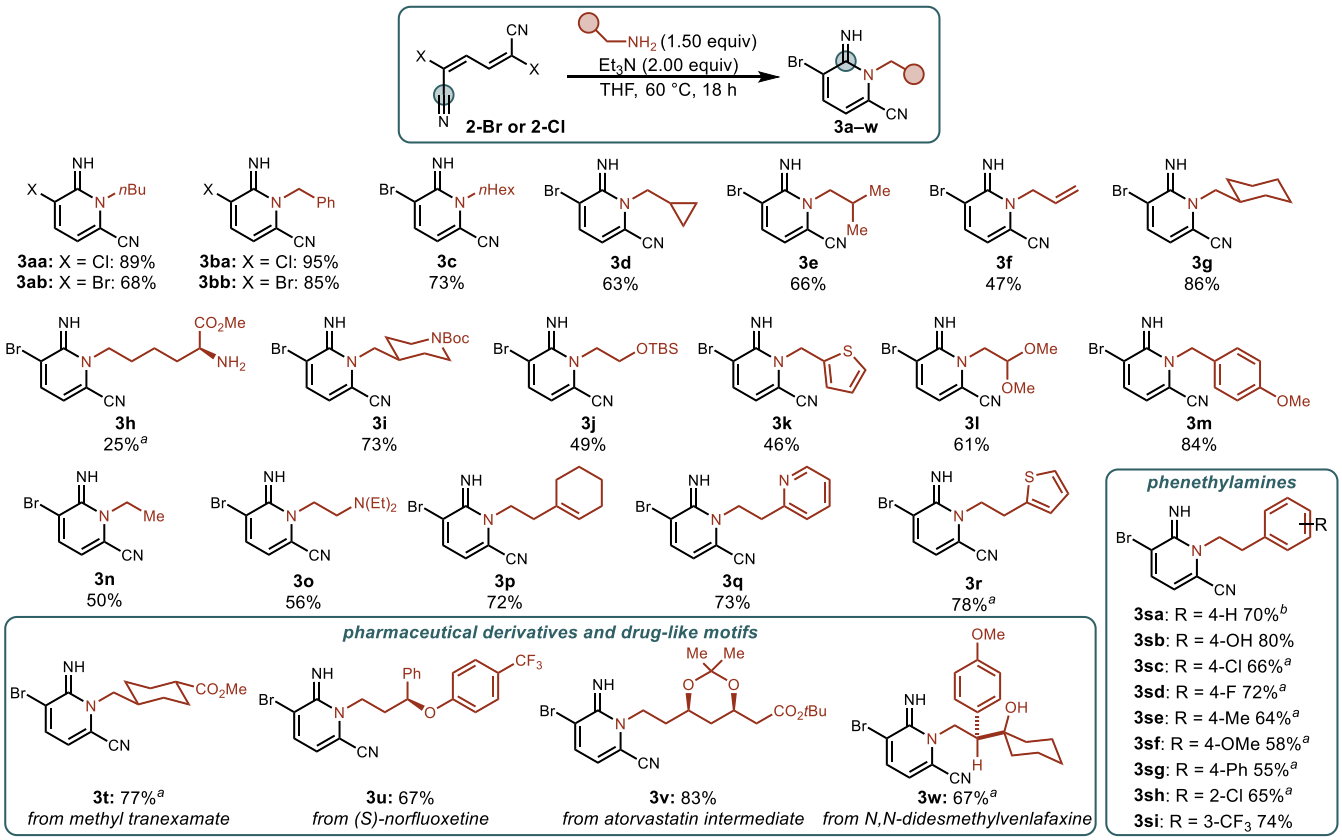

Figure 2: Scope of primary amine nucleophiles. [a]Amine hydrochloride salt was used with 5.00 equiv of Et_3N. [b]Reaction run on 5.00 mmol scale.

Recently, we disclosed the ability of halomuconononitriles to functionalize a variety of secondary amines, including a suite of saturated amine-containing heterocycles (e.g., piperidine, piperazines and azapanes).[15] It occurred to us that halomuconononitriles could also be useful substrates to enable the *de novo* construction of heterocycles. This idea was supported by studies by Cheng[16] and McQuade[17], employing *N*-propargylic-β-enaminone and ylidine-malononitriles respectively, as acyclic pyridinimine precursors. Moreover, muconononitriles are easily synthesized through the oxidative "cracking" of arene precursors.[18] Herein, we demonstrate a method for the construction of pyridinimines *via* the intramolecular cyclization of "Zincke nitrile" intermediates – species transiently formed from the coupling of primary amines with dihalomuconononitrile reagents (Figure 1c). Our strategy is especially advantageous, given the prevalence of primary amines in active pharmaceutical ingredients and pharmaceutical compound libraries,[19] and the stated challenge of selective functionalization of amine-containing compounds in drug molecules.[20] Furthermore, the resulting pyridinimines possess basic cyclic amidines and an aryl halide which can both be leveraged to obtain both imidazo[1,2-*a*]pyridines and 7-azaindoles respectively.

A variety of amines reacted with **2-Br** or **2-Cl** to afford *N*-alkylpyridinimines **3a**–**3w** (Figure 2).[21] The products were obtained by simply mixing 1.0 equivalent of halomuconononitrile with a slight excess of amine (1.50 equiv) and Et_3N (2.00 equiv) in THF at 60 ºC. Aliphatic amines provided products **3aa**–**3g**, **3n**, and **3p** in 47–95% yield. *L*-Lysine methyl ester dihydrochloride provided adduct **3h**, albeit in low yield (25%). However, there was no evidence of reaction at less nucleophilic amine. Silyl-protected aminoalcohols and 1,2-diamines produced **3j** and **3o** in 49% and 56% yield, respectively. Notably, there was no evidence of reaction with the 3º amine when *N*,*N*-diethylethylene diamine was used. Linear phenethylamines, privileged pharmacophores, reacted with ease to provide compound **3sa**–**3si** in high yield.[22] Finally, we sought to demonstrate the generality of this method by reacting **2-Br** with structurally complex primary amines that would be more representative of those found in drug libraries. Methyl tranexamate, and (*S*)-norfluoxetine give their corresponding pyridinimines, **3t**, **3u** in 77% and 67% yield, respectively. Using an amine intermediate common to the statin class of therapeutics gave product **3v** in 83% isolated yield. Lastly, *N*,*N*-didesmethylvenlafaxine gave the corresponding pyridinimine **3w** in 67% yield.

Next, we tested the ability of *N*-alkylpyridine imines to react with alkynes to afford their corresponding 2,6-disubstituted 7-alkylazaindoles (Figure 3). There are few methods that achieve the selective synthesis of C2,C6-functionalized 7-azaindole derivatives.[23] Traditional methods to functionalize the N7 position of azaindoles, affording the more unstable aromatic form, rely on alkylation reactions under neutral conditions and often results in mixtures N1 and N7 alkylation products. The corresponding reaction under basic conditions is highly selective for the N1 position. Recent methods using Ru-catalysis have been developed to address these pitfalls; however, substrates containing non-hydrogen functional groups at the 6-position on the azaindole yield no product.[24]

We found that the pendant bromine atom on these *N*-alkyl pyridinimine intermediates can be used to construct alkylated

azaindole derivatives. *N*-(Boc)-piperidine derivative **3i** and *para*-methoxybenzyl substrate **3m** participated well in a Larock-type indolization reaction, affording products **4a** and **4b**

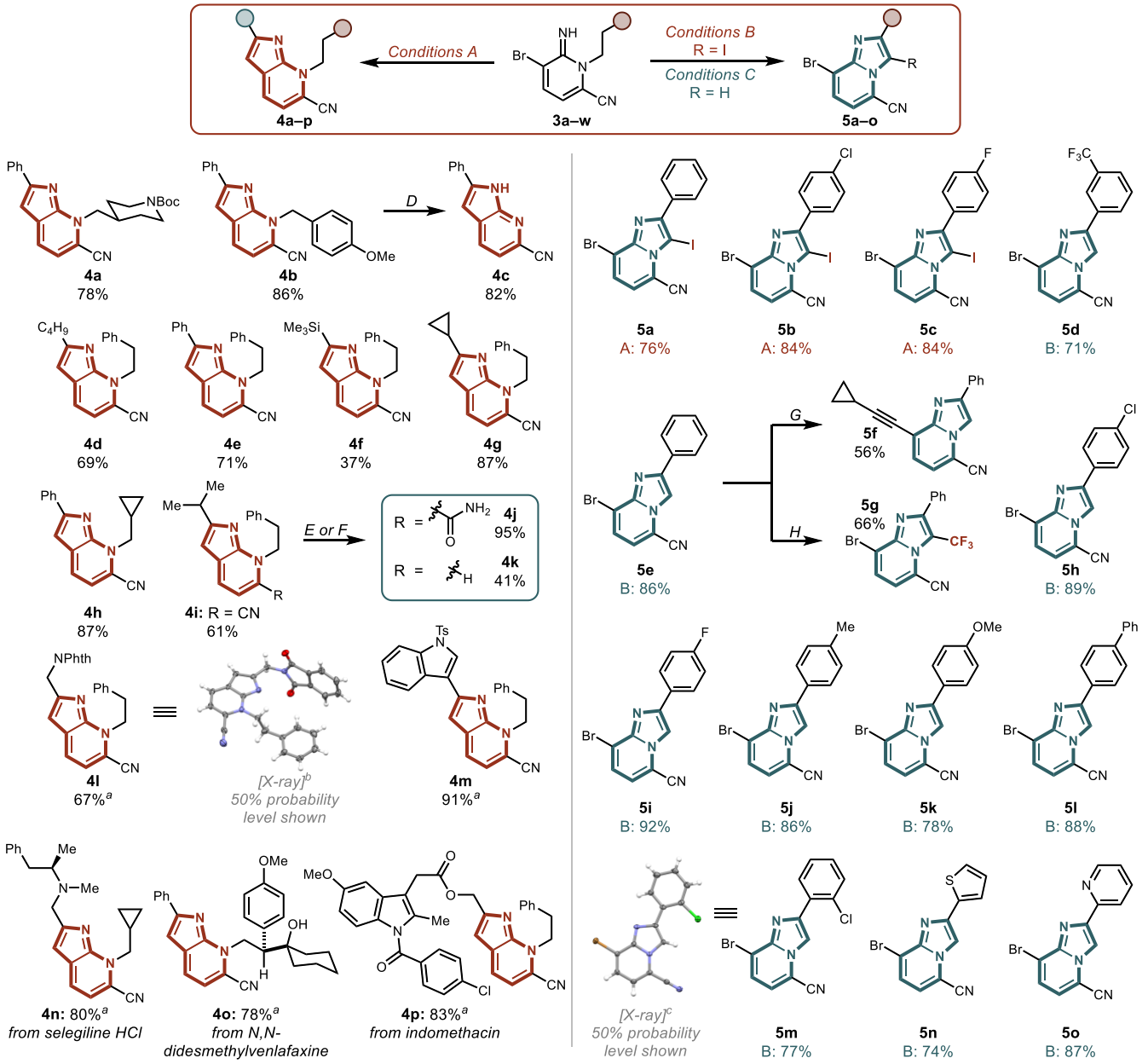

Figure 3: Conditions A: **3d**, **3i**, **3m**, **3sa**, or **3w** (1.00 mmol), $Pd(PPh_3)_4$ (5.00 mol%), CuI (15.0 mol%), Et_3N (10.0 equiv), alkyne (5.00 equiv) in 1,4-dioxane (300 mL) at 60 °C for 18 h. Conditions B: **3sa**, **3sc**, or **3sd** (1.00 mmol), $PhI(OAc)_2$ (4.00 equiv), NaI (4.00 equiv), $NaHCO_3$ (5.00 equiv), 5Å mol. sieves (50.0 mg) in CH_3CN (2.00 mL) irradiated with 23 W compact fluorescent light (CFL) at 30 °C for 3 h. Conditions C: **3q**, **3r**, **3sa**, or **3sc**–**3si** (1.00 mmol), 1,3-diiodo-5,5-dimethylhydantoin (4.00 equiv), $NaHCO_3$ (5.00 equiv), 5Å mol. sieves (50.0 mg) in PhMe (2.00 mL) irradiated with 23 W CFL at 30 °C for 3 h. Conditions D: **4b** (1.00 mmol) and anisole (5.00 equiv) in TFA (500 mL) at 80 °C for 30 min. Conditions E: **4i** (1.00 mmol), NaOH (5.00 equiv) in *i*PrOH (200 mL) at 80 °C for 30 min. Conditions F: **4i** (1.00 mmol), $Ni(PCy_3)_2Cl_2$ (30.0 mol%), Me_3Al (3.00 equiv), TMDSO (2.00 equiv) in *p*-xylene (1.00 mL) at 130 °C for 18 h. Conditions G: **5e** (1.00 mmol), $Pd(PPh_3)_4$ (5.00 mol%), CuI (15.0 mol%), Et_3N (10.0 equiv), cyclopropylacetylene (5.00 equiv) in 1,4-dioxane (300 mL) at 60 °C for 18 h. Conditions H: **5e** (1.00 mmol), $PhI(OAc)_2$ (2.00 equiv), CsF (4.00 equiv), and $TMSCF_3$ (4.00 equiv) in CH_3CN (750 mL) at 30 °C for 3 h. [a]2.00 equiv of alkyne was used. [b]CCDC 2205913. [c]CCDC 2205914.

respectively, that both possess the elusive C6, N7 alkylation pattern. The *para*-methoxybenzyl group in **4b** was removed by heating compound **4b** in TFA at 80 ºC for 30 minutes, revealing the N–H moiety that is crucial in the kinase inhibitory activity for a variety of 7-azaindole containing therapeutics.[25] Using phenethylamine adduct **3sa**, we found 7-alkyl azaindoles **4d**–**4g**, **4i**, **4l**, and **4m** were obtained in good yields, demonstrating a wide degree of functional group compatibility including alkyl, aryl, heteroaryl, and silyl substitution on the alkyne coupling partner. In addition to the alkyne and amine components, we showcase the nitrile's potential for diversification by hydrating **4i** to afford carboxamide **4j** in 95% yield and a nickel-catalyzed reductive decyanation that provided N7, C2-substituted azaindole **4k** in 41% yield.[26,27] Additionally, we obtained X-ray

crystallographic data for phthalimide-containing compound **4l**, which confirms the connectivity of these substrates.

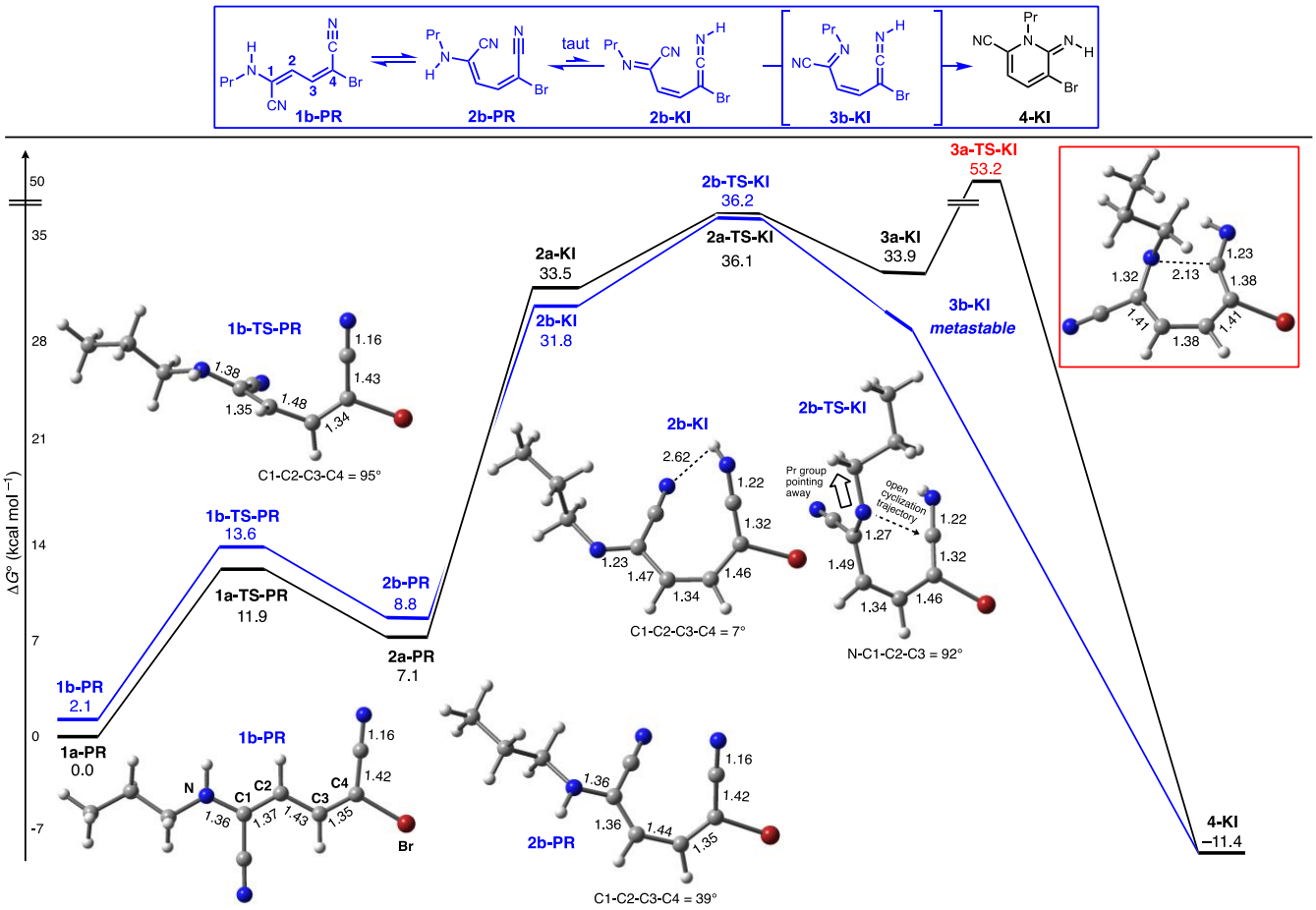

Figure 4: Free energy surface and selected optimized structures for the cyclization of *E,E*-propylaminodienedinitrile to *N*-propylpyridinimine. Distances are reported in Å.

We next demonstrated this reactivity on a variety of drug-like compounds to showcase the amenability of these compounds for late-stage diversification. For example, selegiline hydrochloride, containing a pendant alkyne, can readily be incorporated into *N*-cyclopropylmethyl pyridininimine **3d**, to afford adduct **4n** in 80% yield. We then coupled adduct **3w** and phenylacetylene to obtain complex azaindole **4o** in 78% yield. Finally, indomethacin propargyl ester afforded azaindole **4p** in 83% yield. Notably, these complex azaindoles would be difficult to synthesize selectively using traditional N-alkylation approaches for azaindole synthesis with alkyl halides.

Next, we turned our attention to the development of a modular approach toward the imidazopyridine scaffold from pyridinimines. C–H functionalization emerged as an optimal strategy to achieve this goal because it obviates the need for prior functionalization of the primary amine component, allowing for the incorporation of "native" amine fragments. Furthermore, we surmised that the cyclic amidine substructure common to pyridinimines **3a-w** could serve as a *N*-centered radical precursor that can enable a tandem β C–H amination and hydrogen atom transfer (HAT) cyclization cascade.[28] This approach represents a new paradigm for imidazo[1,2-*a*]pyridines synthesis, deviating from the classical approaches.[29] Recapitulation of reaction conditions developed by Nagib and coworkers using pyridinimines **3sa**, **3sc**, and **3sd** as substrates provided 3-iodo-imidazo[1,2-*a*]pyridines **5a-c** in good yields (76–84%), likely through the proposed HAT cascade followed by electrophilic aromatic iodination *via* transiently generated acetyl hypoiodite.[30] Interestingly, changing the iodine source to 1,3-diiodo-5,5-dimethylhydantoin (DIH) and using toluene as solvent mitigated the iodination reaction completely. Phenyl-substituted imidazo[1,2-*a*]pyridine **5e** was synthesized in 86% yield and could be readily derivatized using a Sonogashira cross-coupling reaction to produce adduct **5f**, or through radical-trifluoromethylation to form imidazo[1,2-*a*]pyridine **5g**.[31] The HAT cascade reaction proved to be tolerant of substitution at the *para* (**5h–l**), *meta* (**5d**), and *ortho* positions (**5m**), and we were able to confirm the structure of **5m** through single crystal X-ray crystallography. Moreover, pendant heterocycles such as thiophene **3r** and 2-pyridyl **3q** provided imidazo[1,2-*a*]pyridines **5n** and **5o** in 74% and 87% yields respectively. Alkyl-substituted pyridinimines participated in the HAT cascade in modest yields and further optimization using these substrates is underway.

Finally, we sought to understand the mechanism of pyridine imine formation using quantum chemical calculations (Figure 4). Using *E,E*-propylaminodienedinitrile **1-PR** as a model system, we considered four elementary steps that must occur to produce *N*-propylpyridinimine **4-KI**: i) rotation about the central C2–C3 bond of the diene (i.e., *s-trans/s-cis*

isomerization), ii) proton transfer from the amine to the distal nitrile, iii) rotation about the C1-C2 double bond of the diene (i.e., substrate preorganization), and iv) cyclization to form a new C–N bond (Figure 4). We considered that the barrier for these steps would likely be affected by the protonation state of substrate over the course of the reaction, so we studied Steps 1–4 using different models, including protonated cyano dienamine (**PR**), anionic enamine diene (**AN**), protonated keteneimine (**KI**) and an anionic enamine diene-propyl ammonium ion pair (**IP**). Here we discuss the most likely pathway, which involves more than one tautomer of the cyano dienamine. Energies are computed at the B2PLYPD3/def2-TZVPPD//M06-2x/6-31G(d) level of theory.[32] Refined energies include a PCM model to incorporate solvent effects with THF as the solvent and are corrected to a 1M standard state. See the Supporting information for full description of computational methods.[33]

Before discussing the proposed mechanism, it should be noted that two minimum energy conformations of **1-PR** were located by rotation about the C1–N bond that differed in their positioning of the propyl group–either pointed away from (**1a-PR**), or toward (**1b-PR**) the C1 nitrile group. These conformational differences eventually affect the height of the cyclization barrier of tautomers **3a** and **3b** (Step 4), which varies substantially due to the geometry of the propyl group (i.e., *E* versus *Z*) on the resulting imine (*vide infra*). So, although structure **1a-PR** has a lower Gibbs energy than **1b-PR** by 2.1 kcal mol^{-1}, **1b-PR** is likely the isomer that leads to productive cyclization. We found that isomers **1a-PR** and **1b-PR** otherwise have similar reaction profiles until Step 4, so we will focus our discussion of the cyclization reaction through isomer **1b-PR**.

Step 1: Rotation about the C2–C3 bond of the diene (i.e., *s-trans*/*s-cis* isomerization) to form **2b-PR** is endergonic ($\Delta G°$ = 6.7 kcal mol^{-1}) and occurs with a modest barrier ($\Delta G°^{‡}$ = 11.5 kcal mol^{-1}). Step 2: The tautomerization of **2b-PR** to produce a ketenimine intermediate **2b-KI** is also endergonic ($\Delta G°$ = 23.0 kcal mol^{-1}). Step 3: From **2b-KI** rotation about the C1-C2 bond (i.e., substrate preorganization) occurs through a low free energy barrier ($\Delta G°^{‡}$ = 4.4 kcal mol^{-1}) but then leads directly to the cyclized product **4-KI** indicating that the intermediate **3b-KI** is metastable. The occurrence of tautomerization prior to E/Z isomerization is important because it leads to a redistribution of the π-electrons along the diene structure as evidenced by lengthening of the C1-C2 bond from 1.36Å in **2b-PR** to 1.47Å in **2b-KI**.

Step 4: The finding that intermediate **3b-KI** is metastable and directly produces **4-KI** suggests that the reaction proceeds through a *barrierless 6π-electrocyclization reaction.* The Z geometry of the imine places the propyl group away from the nitrile group, resulting in an open trajectory for cyclization. In contrast, the propyl substituent in intermediate **3a-KI** is pointed toward the nitrile group and severely hinders the path of the amine leading to a significant barrier for cyclization ($\Delta G°^{‡}$ = 19.3 kcal mol^{-1}). Computed relative to **1a-PR**, the overall barrier to cyclization through **3a-KI** is prohibitively high ($\Delta G°^{‡}$ = 53.2 kcal mol^{-1}), which suggests the cyclization product is only accessible through the isomer **1b-PR**.

The barrierless cyclization of **3b-KI** to product **4** means that the overall barrier for the reaction is based on the sequence of the first three steps (*s-cis*/*s-trans* isomerization, ketenimine formation and substrate preorganization). From this sequence, the predicted Gibbs energy barrier for cyclization is 36.2 kcal mol^{-1}. The IP pathway predicts a lower overall barrier for cyclization at 30.8 kcal mol^{-1} but has the same overall mechanistic features as the KI pathway (See the SI for more details). The formation of pyridinimine **4-KI** provides sufficient driving force for the reaction (**1** → **4**, $\Delta G°$ = –11.4 kcal mol^{-1}). Since only one isomer leads to product, all of the steps should be reversible to allow the enamine diene to react through **1b-PR**.

In summary, we have demonstrated halomuconononitriles are useful bench stable reagents to obtain *N*-alkylpyridinimines through "Zincke nitrile" intermediates on demand. We show that these compounds can be readily converted to 2,6-substituted *N*7-alkylazaindoles or 2,4,7-substituted imidazo[1,2-*a*]pyridines. We also show that pyridinimines likely arise from a 6π-electrocyclization reaction of the corresponding ketenimine intermediates. Future studies will be aimed at developing novel methods for the conversion of a diverse array of arenes to halomuconononitriles, which will enable the rapid incorporation of *N*-atoms to arenes through the intermediacy of Zincke nitrile intermediates.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details, spectroscopic data, computational details, and energies (PDF)

X-ray crystallographic data for **4l** and **5m** (.cif)

Cartesian coordinates for all optimized structures (XYZ)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interests.

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