Organic LETTERS

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Construction of 1,2,4-Triazole Derivatives via Cyclocondensation of Alkylidene Dihydropyridines and Aryldiazonium Salts

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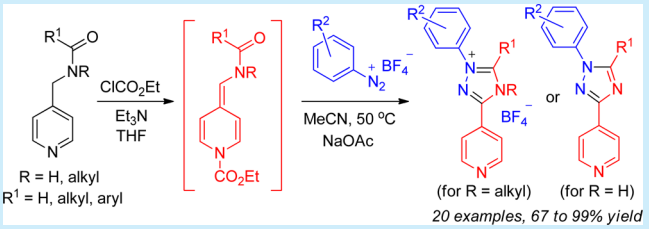
Supporting Information

ABSTRACT: Alkylidene dihydropyridines (anhydrobases) prepared via dearomatization of N-acylated 4-(aminomethyl)-pyridines participate in [3 + 2] cyclocondensation reactions with aryldiazonium cations to afford substituted 1,2,4-triazolium salts or neutral 1,2,4-triazoles in high isolated yield. The reaction proceeds in the presence of a variety of *N*-acyl groups and aryl-susbtituted diazonium salts and offers a general route to pyridyl-substituted 1,2,4-triazoles.

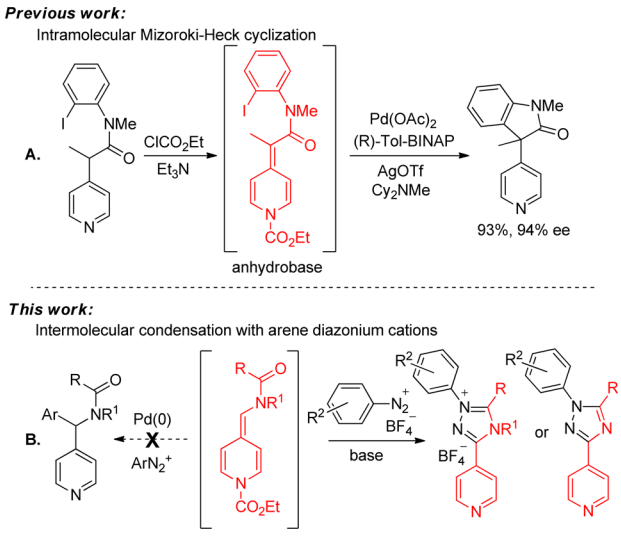


Nitrogen heterocycles, especially pyridines and piperidines, are ubiquitous structural components encountered in numerous natural products and synthetic pharmacophores.[1] Consequently, reliable methods to manipulate these ring systems are important to the synthetic community. In this context, addition of nucleophiles to activated pyridinium salts generated upon pyridine N-acylation or alkylation is widely used to construct substituted pyridines and piperidines.[2] Pyridinium salts also exhibit increased acidity at benzylic C–H groups located at the C2 and C4 positions. Deprotonation of appropriately substituted pyridinium salts under mild conditions then results in dearomatization of the pyridinium cations and affords neutral alkylidene dihydropyridines (anhydrobases).[3] While pyridine anhydrobases are established chemical entities, their use as synthetic intermediates in construction of functionalized pyridine or piperidine ring systems has not been extensively investigated.[4]

We have initiated studies examining the reactivity of 4-substituted alkylidene dihydropyridines and have reported intramolecular aldol-like reactions with attached carbonyl electrophiles.[5] More recently, we have demonstrated the use of anhydrobases as alkene partners in intramolecular Mizoroki–Heck cyclizations (Scheme 1A).[6] During attempts to develop intermolecular versions of this reaction, we screened aryldiazonium salts as organic electrophiles with the expectation that the high reactivity of aryldiazonium cations in Pd-catalyzed couplings would facilitate the desired Heck–Matsuda reaction.[7] Unexpectedly, we discovered that *N*-acyl-substituted 4-alkylidene dihydropyridines and aryldiazonium salts undergo spontaneous formal [3 + 2] cyclocondensation to afford 1,2,4-triazole derivatives in high yield (Scheme 1B).

Initial experiments (Table 1) involved activating pyridine **1** with $ClCO_2Et$ and Et_3N in refluxing THF for 30 min, after which time thin-layer chromatography (TLC) indicated complete conversion to the desired anhydrobase.[8] Excess $ClCO_2Et$ and Et_3N were removed in vacuo, and the residue consisting of **2** and Et_3NHCl (byproduct in formation of **2**) was taken up in MeCN and treated with diazonium salt **3**, NaOAc,

Scheme 1. Intramolecular Mizoroki–Heck Reaction of Pyridine Anhydrobases (A) and Attempted Intermolecular Heck–Matsuda Reactions of Anhydrobases Leading to Triazole or Triazolium Products (B)

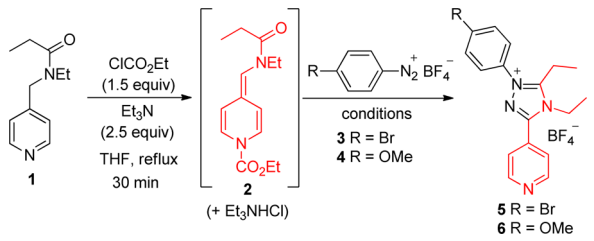


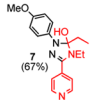
and a catalytic amount of $Pd(OAc)_2$. While **2** was completely consumed after 20 h (TLC), no products arising from a Heck reaction were observed. Instead, 1,2,4-triazolium salt **5** was obtained in ~90% isolated yield (entry 1, the structure was confirmed through X-ray crystallography; see the Supporting Information).[9] Screening of reaction conditions quickly established that $Pd(OAc)_2$ played no role as a similar result was obtained in its absence (entry 2). *p*-Methoxyphenyldiazonium salt **4** also gave the reaction (entry 3). Acetonitrile emerged as a convenient solvent, although less polar toluene was also suitable. Reaction in MeOH returned only rear-

Received: October 7, 2016

DOI: 10.1021/acs.orglett.6b03019
Org. Lett. XXXX, XXX, XXX–XXX

Table 1. Cyclization Reaction between Anhydrobase 2 and Aryldiazonium Salts[a]



entry	diazonium salt[b]	solvent	additive	t (°C)	time (h)[e]	product (%)[f]
1	**3**	MeCN	$Pd(OAc)_2$[c] NaOAc[d]	50	20	**5** (89)
2	**3**	MeCN	NaOAc[d]	50	20	**5** (98)
3	**4**	MeCN	NaOAc[d]	50	20	**6** (99)
4	**3**	MeCN	NaOAc[d]	90	20	**5** (99)
5	**3**	PhMe	NaOAc[d]	90	20	**5** (95)
6	**3**	MeOH	NaOAc[d]	70	1	--[g]
7	**4**	MeCN	NaOAc[d]	rt	20	nd[h]
8	**3**	MeCN	Et_3N[d]	50	48	nd[h]
9	**4**	MeCN	none	50	20	**6** (83)
10[i]	**4**	MeCN	none	50	20	--[j]
11[k]	**3**	THF	NaOAc[d]	50	20	--[j]
12	**4**	MeCN	NaOAc[d]	50	0.5	 7 (67%)

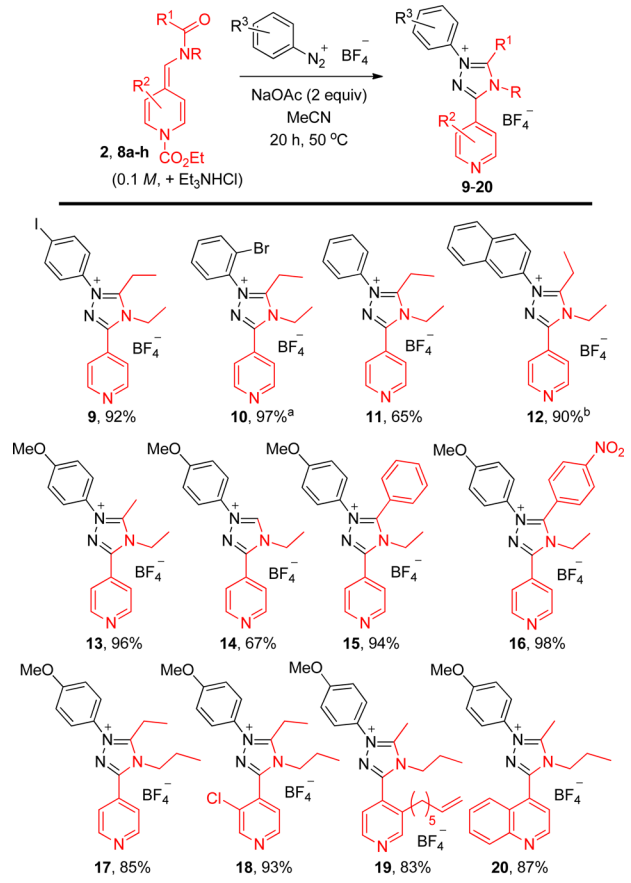
[a][2] = 0.1 M; equal amount of Et_3NHCl also present unless otherwise noted. [b]1.05 equiv. [c]10 mol %. [d]2 equiv. [e]Time at which no **2** was detected by TLC. [f]Isolated yield. [g]Pyridine **1** detected due to rearomatization of **2**. [h]Not determined. NMR indicated ~3:1 triazolium salt/anhydrobase mixture. [i]Et_3NHCl removed from **2** prior to reaction. [j]No product detected. [k]One-pot sequential reaction starting from **1**.

omatized pyridine **1**. Reactions performed between 50 and 90 °C proceeded smoothly, but reaction at room temperature was markedly slower (entries 4–7). Replacing NaOAc with Et_3N had a detrimental effect, and performing the reaction in the absence of NaOAc afforded triazolium salt **6** in slightly diminished yield (entries 8 and 9). Removal of Et_3NHCl from **2** by filtration prior to addition of **4** and NaOAc resulted in no reaction (anydrobase **2** remained unchanged, entry 10). Thus, the presence of both Et_3NHCl and NaOAc appears to be beneficial. Attempted conversion of **1** to **5** directly in a sequential one-pot reaction was unsuccessful (entry 11). When reaction between **2** and **4** was halted after only 30 min, the dihydrotriazole **7** was isolated as the major product (entry 12). Finally, a control experiment in which **1** was treated with **3** and NaOAc resulted in no reaction, demonstrating the requirement for alkylidene dihydropyridine **2** as a reactant.

1,2,4-Triazoles are valuable structural motifs in medicinal and agricultural chemistry due to wide-ranging anticancer, antimicrobial, and fungicidal activities.[10] Triazoles are also used in materials chemistry and as ligands in metal complexes and metal–organic frameworks.[11−13] Likewise, 1,2,4-triazolium salts have been investigated for applications in medicinal and materials chemistry,[14,15] as precursors to N-heterocyclic carbenes,[16] and as ionic liquids.[17] Several synthetic routes are commonly employed to access 1,2,4-triazole scaffolds, most involving condensations of hydrazides and activated amides.[18] 1,2,4-Triazole construction using aryldiazonium salts is limited to cyclocondensations with reactive 1,3-dipoles (azomethine ylides or ethyl isocyanoacetate).[19,20] Thus, the remarkably efficient condensation to afford **5** and **6** from readily accessible alkylidene dihydropyridine **2** is noteworthy for the presence of an unactivated amide as an apparent electrophilic component, leading to direct generation of highly substituted pyridine-functionalized triazolium salts.

Accordingly, we sought to examine the scope of this unusual cyclocondensation (Scheme 2). Using the conditions indicated

Scheme 2. Scope of Arenediazonium–Anhydrobase Cyclocondensation



[a]Reaction required 7 d. [b]Reaction required 48 h.

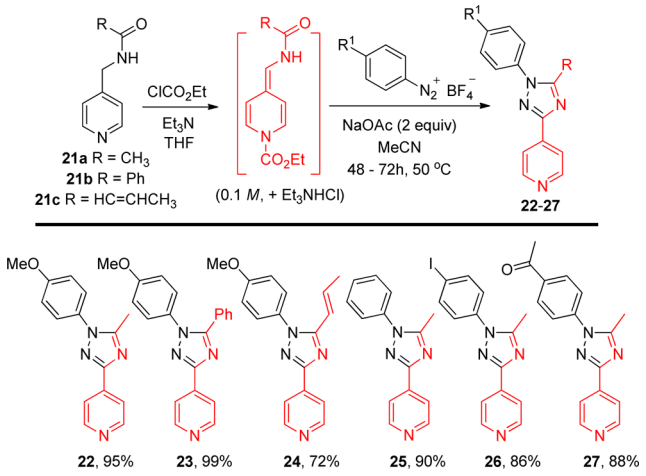
in Table 1, entry 2, we screened several different aryldiazonium salts for reactivity with **2**. *p*-Iodophenyl- and *o*-bromophenyldiazonium salts gave the expected triazolium products **9** and **10** in excellent isolated yield, although reaction leading to **10** required a longer time to reach completion. Phenyl- and 2-naphthyldiazonium salts also were compatible with the reaction (**11** and **12**), but no reaction occurred in the presence of 4-nitrophenyldiazonium salt. Variation in the anhydrobase component was probed in reactions with diazonium salt **4**. *N*-Ethyl- and *N*-propylalkyl/aryl and formyl amides all underwent smooth condensation (**13**–**17**), and the preparation of **14** is notable as this material may be a precursor to the

DOI: 10.1021/acs.orglett.6b03019
Org. Lett. XXXX, XXX, XXX–XXX

corresponding N-heterocyclic carbene. Substitution at the 3-position of the alkylidene dihydropyridine was tolerated (**18** and **19**),[21] and a quinoline analogue also gave the reaction (**20**).

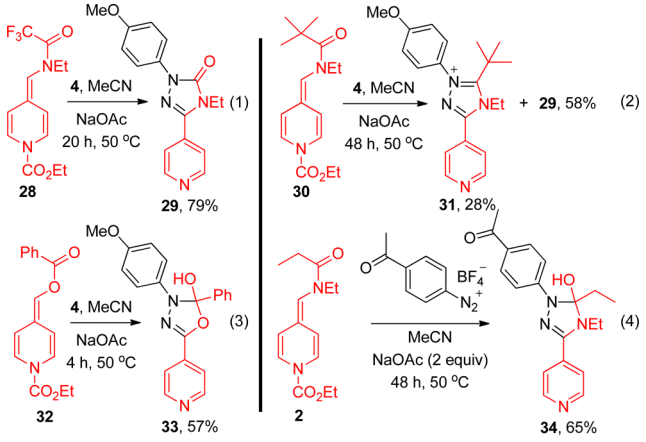
We further examined reactions between diazonium salts and pyridine anhydrobases possessing secondary amide groups in the 4-alkyl side chain. We envisioned that successful condensation would afford neutral 1,3,5-trisubstituted 1,2,4-triazole products (Scheme 3). Gratifyingly, pyridines **21a–c**

Scheme 3. Synthesis of Substituted 1,2,4-Triazoles



were smoothly converted to the corresponding alkylidene dihydropyridines, and treatment with aryldiazonium salts gave the desired 1,2,4-triazoles **22–27** in excellent isolated yield, although slightly longer reaction times were required.

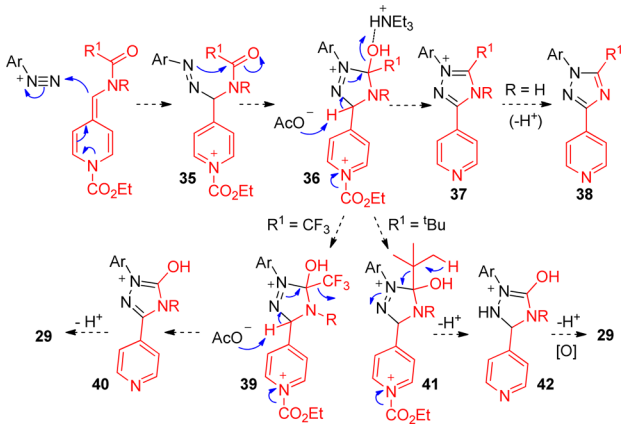
Several reactions gave unexpected products (eqs 1–4). Condensation between **4** and trifluoroacetamide **28** afforded



1,2,4-triazolone **29** as the sole isolable product (eq 1). Likewise, reaction of **4** and pivalamide **30** also returned **29** as the major product, along with triazolium salt **31** (eq 2). Reaction of ester-substituted anhydrobase **32** with **4** gave oxadiazole derivative **33** in good yield after 4 h (eq 3), but prolonged reaction led to decomposition. Lastly, condensation of **2** with *p*-acetylphenyldiazonium salt afforded dihydrotriazole **34**, which proved resistant to triazolium salt formation under the reaction conditions (eq 4).

A simple mechanistic rationale to account for the formation of 1,2,4-triazoles and triazolium salts is illustrated in Scheme 4. Nucleophilic addition of the alkylidene dihydropyridine to the

Scheme 4. Mechanistic Rationale



diazonium salt occurs initially to afford diazo intermediate **35**. Addition of the diazo group to the amide carbonyl (perhaps facilitated by the presence of Et_3NHCl as a Brønsted acid catalyst) gives **36** (consistent with isolation of **7**, **33**, and **34**). Benzylic deprotonation, again facilitated by the buffered reaction conditions, then leads to aromatization of the triazole ring with expulsion of water to provide triazolium salts **37** or, when R = H, neutral triazoles **38**. An electronically deactivated diazo group (i.e., Ar = *p*-acetylphenyl) appears to impede triazole aromatization upon reaction with **2** (in contrast to reaction with 2° amide **21a** to afford **27**), leading to isolation of dihydrotriazole **34**, despite prolonged reaction time (eq 4). Note that strongly deactivated *p*-nitrophenyldiazonium cation gives no reaction. In reactions involving a trifluoroacetamide group, aromatization of the triazole ring in **39** occurs via ejection of trifluoromethyl anion rather than water, ultimately leading to **29** via **40**.[22] A similar sequence in the pivalamide substrate requiring elimination of a *tert*-butyl anion seems highly unlikely. Instead, elimination of isobutylene from **41** may deliver **42**, which may convert to **29** upon loss of H^+ and oxidation (adventitious O_2 and/or air oxidation).

In summary, a novel route to 1,2,4-triazole derivatives via [3 + 2] cyclocondensation of dearomatized alkylidene dihydropyridines and aryldiazonium salts has been discovered. Anhydrobases substituted with tertiary or secondary amides yield functionalized 1,2,4-triazolium salts or 1,2,4-triazoles, respectively, in high yield under mild conditions. While products obtained in this study are derived from pyridine and quinoline anhydrobases, other substituted azine and azole ring systems (e.g., 2-alkylimidazole) can be converted to analogous alkylidene dihydroarenes that may exhibit similar reactivity toward aryldiazonium salts and other unconventional electrophiles.[23] Further studies examining the synthetic utility of azine and azole anhydrobases for construction of functionalized heterocyclic scaffolds are in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03019.

Experimental details, compound characterization data, and ^1H and ^{13}C NMR spectra (PDF)

X-ray data for compound **5** (CIF)

DOI: 10.1021/acs.orglett.6b03019
Org. Lett. XXXX, XXX, XXX–XXX

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank the US National Science Foundation for financial support (CHE-1265488) and the Graduate College, University of Iowa (fellowship to M.S.J.). We thank Dale Swenson and Michael Sinnwell (University of Iowa) for assistance with X-ray crystallography.

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(9) Structure deposited with the Cambridge Crystallographic Data Centre, CCDC no. 1508180.

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DOI: 10.1021/acs.orglett.6b03019
Org. Lett. XXXX, XXX, XXX−XXX