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Aza-Annulation of Enynyl Azides: A New Approach to Substituted Pyridines

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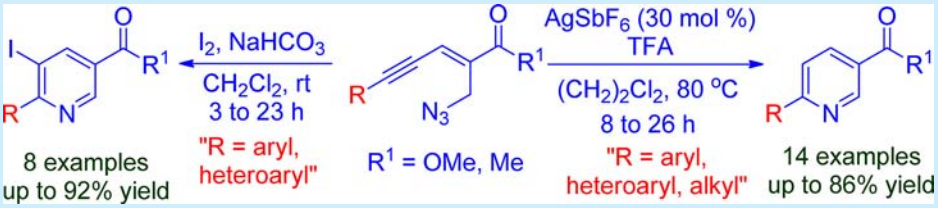
Supporting Information



ABSTRACT: Synthesis of substituted pyridines through a novel aza-annulation of 2-en-4-ynyl azides, derived from MBH-acetates of acetylenic aldehydes, is described. A variety of enynyl azides having aryl, heteroaryl, and alkyl groups on the alkyne functionality successfully participated in the Ag-mediated annulation reaction to provide the corresponding 3,6-disubstituted pyridines. I_2-Mediated cyclization was found to be controlled by the substituent on the alkyne functionality, which offered the 5-iodo-3,6-disubstituted pyridines from enynyl azides having an electron-rich substituent on the alkyne functionality.

Substituted pyridines are an important class of *N*-heterocycle that are widely distributed in natural products, bioactive molecules, functional materials, and pharmaceuticals.[1] They also play a vital role in organic synthesis as building blocks and find use in catalysis and coordination chemistry.[2] Consequently, diverse strategies have been successfully established for the synthesis of substituted pyridines. Conventionally, the condensation of amines and carbonyl compounds has been used to access these compounds.[3] Various other methods have also been developed based on cycloaddition reactions,[4] transition-metal catalysis,[5] and C−H functionalization.[6] The majority of them rely on intermolecular reactions between two or more components. Recently, the reaction between alkynes and nitrogen-derivatives such as nitriles, oximes, imines, etc. has received considerable attention.[7] Although these methods are efficient, sometimes regioselectivity and product selectivity difficulties may arise. Therefore, intramolecular cyclizations serve as an attractive protocol for the synthesis of pyridines.[8]

Our continuing interest in enyne-based annulation reactions[9] prompted us to explore the synthesis of substituted pyridines from (*E*)-2-en-4-ynyl azides. These are easily accessible from Morita−Baylis−Hillman acetates of acetylenic aldehydes.[9b,10] In 2007, Yamamoto et al. reported the cyclization of 2-alkynyl benzyl azides for the synthesis of 4-iodo-isoquinoline derivatives.[11a] Later, this interesting work was further explored by the Yamamoto, Liang, and Li research groups for the preparation of diversely substituted isoquinolines (Figure 1a).[11] Encouraged by these reports, we anticipated that the 2-en-4-ynyl azides would readily undergo intramolecular aza-annulation to give the corresponding substituted pyridines. Herein, we present a novel aza-annulation approach to substituted pyridines from (*E*)-2-en-4-ynyl azides (Figure 1b).

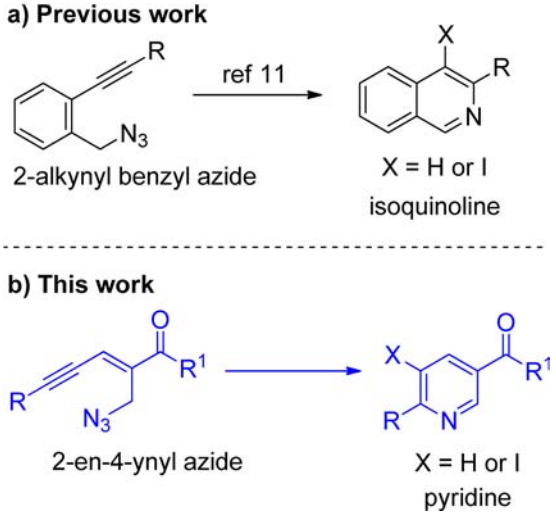


Figure 1. Intramolecular aza-annulation reactions.

At the outset, 2-en-4-yn-1-azide **1a**, obtained from the corresponding MBH-acetate, was chosen to check our hypothesis. Based on the literature report,[11d] aza-annulation **1a** was tested in the presence of $AgSbF_6$ (30 mol %) and TFA (2 equiv) in DCE at 80 °C. To our delight, the reaction proceeded smoothly to completion in 10 h, providing 6-phenyl nicotinate **2a** in 82% yield (entry 1, Table 1). Encouraged by this result, the scope of the reaction was then explored using a variety of enynyl azides (Table 1). A facile aza-annulation was

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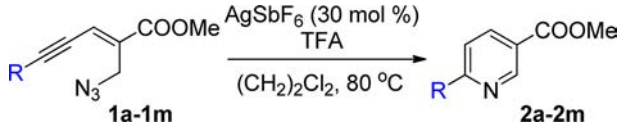
Table 1. Substrate Scope for Ag-Catalyzed Aza-Annulation of (*E*)-2-En-4-ynyl Azides[a]



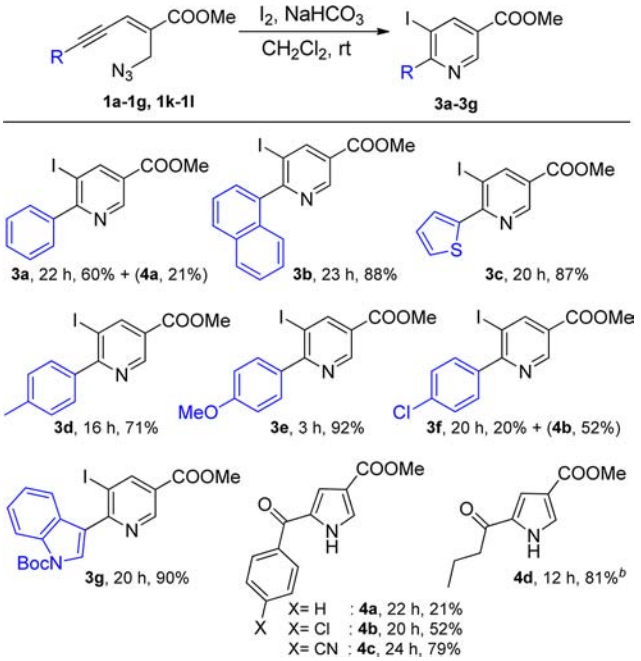
entry	enynyl azide (**1**)	time (h)	pyridine (**2**)[b]	yield (%)[c]
1	R = Ph, **1a**	10	**2a**	82
2	R = 1-Naphthyl, **1b**	22	**2b**	79
3	R = 2-Thiophenyl, **1c**	8	**2c**	78
4	R = 4-Me-C_6H_4, **1d**	10	**2d**	81
5	R = 4-MeO-C_6H_4, **1e**	8	**2e**	86
6	R = 4-Cl-C_6H_4, **1f**	10	**2f**	66
7	R = 4-CN-C_6H_4, **1g**	14	**2g**	60
8	R = 4-NO_2-C_6H_4, **1h**	18	**2h**	62
9	R = 3-CF_3-C_6H_4, **1i**	16	**2i**	69
10	R = 4-$COCH_3$-C_6H_4, **1j**	18	**2j**	75
11	R = 3-*NBoc*-Indole, **1k**	18	**2k**	80[d]
12	R = nC_3H_7, **11**	20	**21**	84
13	R = nC_6H_{13}, **1m**	26	**2m**	86

[a]Reaction conditions: Enynyl azide **1** (0.20 mmol), $AgSbF_6$ (30 mol %), TFA (0.4 mmol), DCE, 80 °C. [b]All the products were characterized by ^1H, ^{13}C NMR, IR, and MS spectra. [c]Isolated yield. [d]Boc-deprotected product **2k** was obtained.

observed for the reaction of 1-naphthyl-enynyl azide **1b** under the aforementioned Ag-catalyzed conditions to obtain the corresponding pyridine **2b** in 79% yield (entry 2, Table 1). Similarly, 2-thiophenyl-enynyl azide **1c** was also effective in the cyclization to provide pyridine **2c** in 78% yield (entry 3, Table 1). All (*E*)-2-en-4-yn-1-azides bearing aryl groups with either electron-donating (Me, MeO, Cl) or electron-withdrawing substituents (CN, NO_2, CF_3, $COCH_3$), **1d−1j**, underwent the Ag-catalyzed aza-annulation, furnishing the desired products **2d−2j** in good yields (entries 4 to 10, Table 1). Notably, 3-(NBoc)indole enynyl azide **1k** was also found to be a suitable substrate to provide the Boc-deprotected indoloylpyridine **2k** in 80% yield (entry 11, Table 1). Enynyl azides containing aliphatic substituents tethered to the alkyne moiety, **1l** (*n*-propyl) and **1m** (*n*-hexyl), were found to afford the corresponding 6-alkyl nicotinates, **2l** (84%) and **2m** (86%), respectively (entries 12 and 13, Table 1).

Next, the intramolecular aza-annulation was investigated under iodine-mediated electrophilic reaction conditions[11a] to obtain 5-iodo-3,6-disubstituted pyridines (Scheme 1), which are suitable for further elaboration. Treatment of **1a** under I_2/$NaHCO_3$ conditions provided the desired 5-iodo pyridine derivative **3a** as the major product (60%) along with the 5-*exo*-dig-cyclized product, 2-benzoylpyrrole-4-carboxylate **4a** (21%). Other enynyl azides, 1-naphthyl-enynyl azide **1b** and 2-thiophenyl-enynyl azide **1c**, exclusively gave the corresponding 5-iodo pyridines **3b** (88%) and **3c** (87%), respectively, under identical conditions. The above results suggest that the electronic factors in the aryl substituent on the alkyne affect the regiochemistry of cyclization. To further verify this, substrates containing both electron-donating and -withdrawing groups on the phenyl substituent of the alkyne were explored for iodine-mediated annulation. Enynyl azides with the phenyl group having an electron-donating substituent, **1d** and **1e**, afforded the corresponding 5-iodo pyridines **3d** and **3e**, respectively, in good yields. The substrate having a 4-Cl-phenyl group on the alkyne, **1f**, gave a mixture of iodo-pyridine **3f** and

Scheme 1. Substrate Scope for I_2-Mediated Aza-Annulation of (*E*)-2-En-4-ynyl Azides[a]

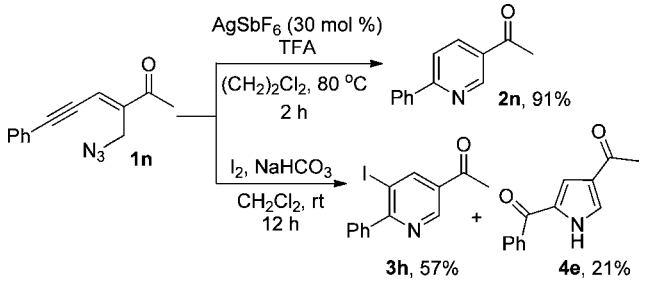


[a]Reaction conditions: Enynyl azide **1** (0.20 mmol), I_2 (1.0 mmol), $NaHCO_3$ (0.20 mmol), CH_2Cl_2, rt. [b] Reaction was carried out in DCE at 80 °C.

benzoyl-pyrrole **4b**. Enynyl azides with a strong electron-withdrawing substituent (CN) on the phenyl group **1g** underwent 5-*exo*-dig-cyclization exclusively to furnish the benzoyl-pyrrole **4c** in 79% yield. Unfortunately, the enynyl azide bearing an aliphatic group on the alkyne, **1l**, also underwent 5-*exo*-dig-cyclization exclusively to furnish the *n*-butanoyl pyrrole **4d** in 81% yield under heating conditions.

Gratifyingly, the annulation reaction of enynyl azide **1n** containing keto functionality worked well to furnish the 3-acetylpyridine **2n** in 91% yield under the Ag-catalyzed reaction. Treatment of substrate **1n** with I_2/$NaHCO_3$ provided the desired 5-iodo pyridine derivative **3h** as the major product (57%) along with the benzoyl pyrrole **4e** (Scheme 2).

Scheme 2. Aza-Annulation of (*E*)-2-En-4-ynyl Azide 1n



Based on the results shown in Table 1, Ag-catalyzed aza-annulation reactions of (*E*)-2-en-4-ynyl azides (**1**) were found to be highly regioselective in providing the corresponding pyridines via 6-*endo*-dig cyclization through the activation of the alkyne with a silver catalyst. Further steps in the mechanism to give the pyridine **2** through the intermediates **A** and **B** are

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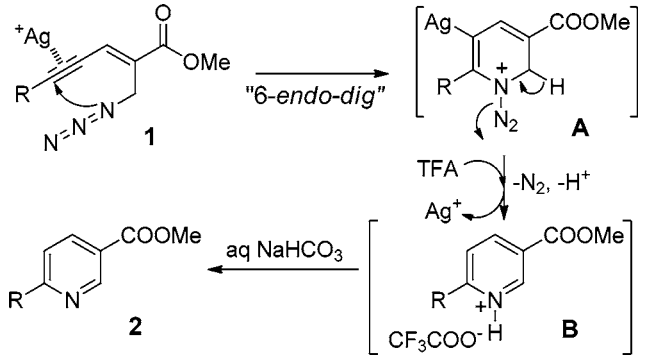
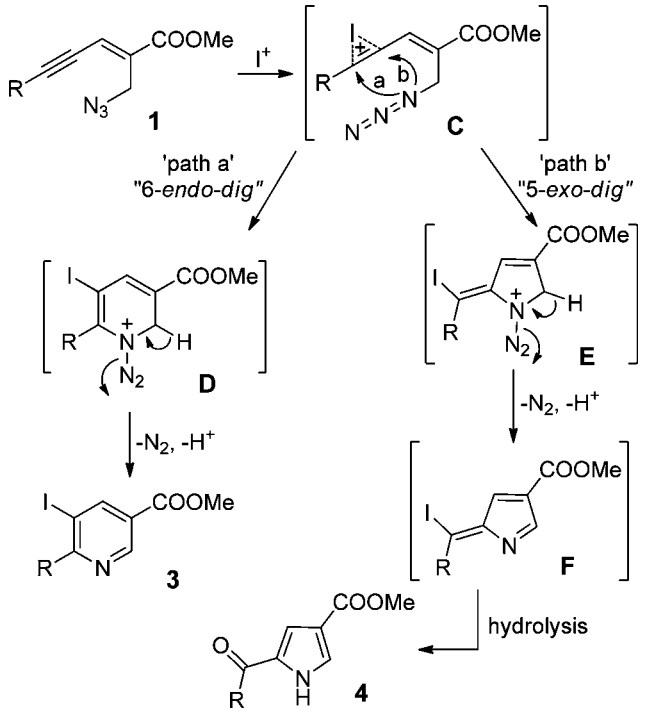
shown in Scheme 3 and are supported by the literature most especially Yamamoto's work.[11c−11d]

Scheme 3. Proposed Mechanism for Ag-Catalyzed Aza-Annulation of (*E*)-2-En-4-ynyl Azide



In the case of I_2-mediated aza-annulations, the reactivity was controlled by the substitution (R) on the alkyne moiety. We presume that the reaction proceeds through the formation of iodonium ion **C**, the opening of which depends on the substitution. If the substituent on the alkyne is electron-rich, 6-*endo*-dig cyclization is favored to give the iodo-pyridine (**3**) via intermediate **D** (Scheme 4, path a), as reported in the

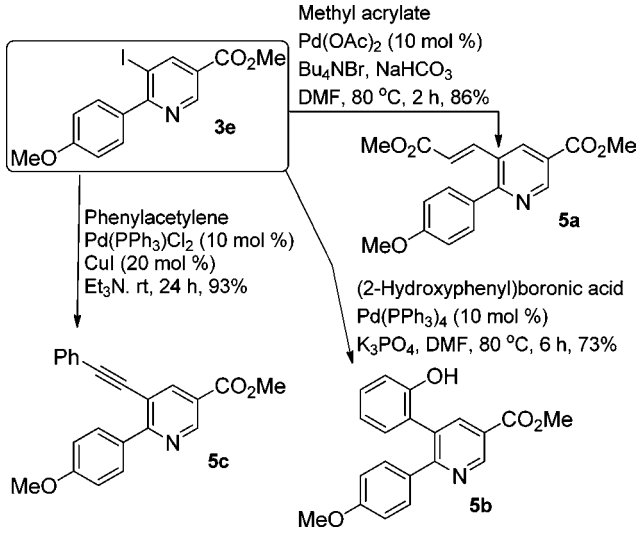
Scheme 4. Proposed Mechanism for I_2-Mediated Aza-Annulation of (*E*)-2-En-4-ynyl Azide



literature.[11a] The substrate having electron-poor substitution on the alkyne favored the 5-*exo*-dig cyclization to give the acyl pyrrole (**4**) via intermediates **E** and **F** (Scheme 4, path b).

Pyridines bearing an iodo group offer an opportunity for further elaboration to access highly functionalized pyridine derivatives. Thus, the Pd-catalyzed coupling reactions of iodo-pyridine **3e** were examined, as shown in Scheme 5. In the first case, compound **3e** was treated with methyl acrylate under

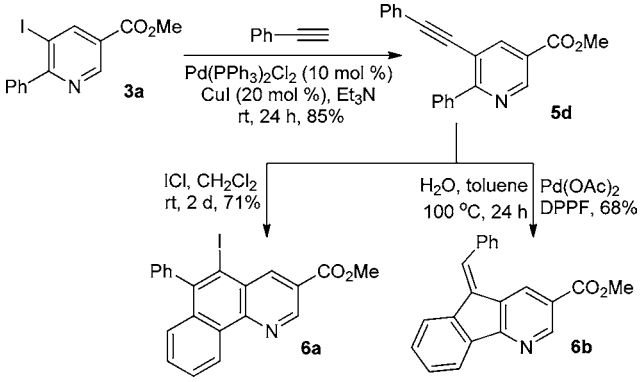
Scheme 5. Functionality Elaboration of 5-Iodopyridine 3e



Heck reaction conditions [$Pd(OAc)_2$, Bu_4NBr, $NaHCO_3$ in DMF], to obtain the coupled product **5a** in 86% yield. Suzuki coupling of **3e** with 2-hydroxyphenyl boronic acid gave the corresponding 5,6-diarylpyridine-3-carboxylate **5b** in 73% yield. Satisfyingly, Sonogashira coupling of **3e** with phenylacetylene was also successful in giving 5-alkynylpyridine **5c** in 93% yield.

Additionally, the obtained 6-aryl-5-iodopyridine-3-carboxylates provide an interesting route for the generation of novel pyridine-fused scaffolds (Scheme 6). Thus, 6-phenyl-5-

Scheme 6. Synthetic Utility of 5-Iodopyridine 3a



iodopyridine-3-carboxylate **3a** was subjected to Sonogashira coupling with phenylacetylene to obtain the corresponding 5-alkynylpyridine **5d** in 85% yield. The latter compound underwent ICl-promoted 6-*endo*-dig cyclization[12a] to produce 5-iodo-6-phenylbenzo[*h*]quinoline **6a** in 71% yield. Alternatively, Pd-catalyzed 5-*exo*-dig-cyclization[12b] of **5d** allowed the synthesis of 4-azafluorene **6b** in 68% yield.

In conclusion, we have successfully established an efficient method for the synthesis of attractively substituted pyridines via the aza-annulation of (*E*)-2-en-4-yn-1-azides. Ag-catalyzed cyclization was found to be regioselective to provide pyridine-3-carboxylates. In the case of I_2-promoted annulation, a substituent controlled reactivity switch was observed to give either iodopyridine or acyl-pyrrole. The present work provides new access to structurally diverse nicotinate (pyridine-3-carboxylate) derivatives which constitute an important group of biologically and pharmaceutically relevant molecules. Addi-

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tionally, the iodopyridine products are useful for elaboration to new molecular entities.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization details, and ^{1}H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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