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Vinylation of α-Aminoazoles with Triethylamine: A General Strategy to Construct Azolo[1,5-*a*]pyrimidines with a Nonsubstituted Ethylidene Fragment

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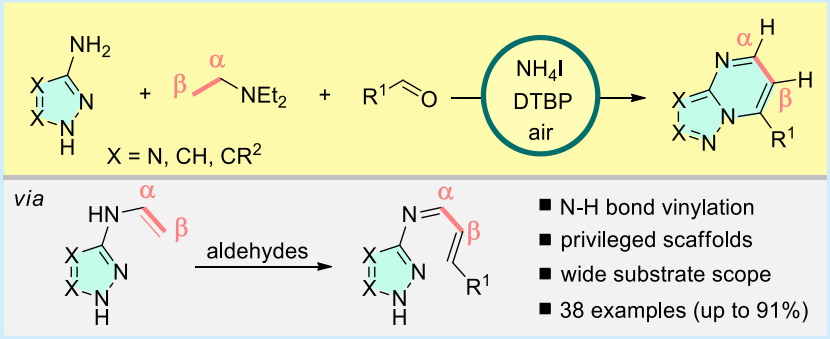

ABSTRACT: A new general synthesis of pharmaceutically important azolo[1,5-*a*]pyrimidines starting from widely available 3(5)-aminoazoles, aldehydes, and triethylamine is developed. The key is to enable the vinylation reaction that allows the in situ generation of elusive acyclic enamines and the subsequent annulation reaction to occur. This direct and practical strategy is capable of constructing a range of 5,6-unsubstituted pyrazolo[1,5-*a*]pyrimidines and [1,2,4]triazolo[1,5-*a*]pyrimidines. More importantly, this protocol provides a concise synthetic route to prepare the clinically used zaleplon.

The development of highly efficient and new routes to fused-ring skeletons has been among the most active areas of research in synthetic chemistry.[1] Especially attractive in this area are annulation reactions that employ readily available feedstock materials as C2 building blocks for the assembly of polycyclic (hetero)aromatic scaffolds.[2] Despite their significance, most of these reactions cannot install a nonsubstituted vinylene fragment, which significantly restricts the practical value of these methods in medicinal and pharmaceutical chemistry.[3] Although acetylene represents the simplest and inexpensive C2 unit, the methods of acetylene annulation are still quite limited.[4] This might stem from safety concerns about operating with the gas-phase reactant. Therefore, new acetylene surrogates have been explored for the construction of nonsubstituted vinylene-fused compounds. Early in 2014, Raw and coworkers described the rhodium-catalyzed annulation for the synthesis of 3,4-unsubstituted isoquinolones using vinyl acetate as a safe alternative to acetylene.[5] Similarly, the Cheng team successfully synthesized 3,4-unsubstituted isoquinolines from vinyl acetate and ketoximes in the rhodium-catalyzed reaction systems.[6] In 2019, *N*-vinyl formamide as an acetylene surrogate was applied to form 3,4-unsubstituted isoquinolones by the Chen group.[7] Furthermore, You realized a rhodium-catalyzed three-component approach to ring-fused pyridiniums, wherein 1,2-dichloroethane served as a vinyl equivalent to generate *N*-vinylpyridiniums.[8] Most recently, Miura et al. used vinylene carbonate as a vinylene transfer agent to achieve the assembly of a nonsubstituted vinylene-fused scaffold.[9] Obviously, there is a continuous need for new reagents that could be used as a C2 building block in the vinylene annulation protocol. Herein we report a novel vinylation reaction of α-aminoazoles with triethylamine, enabling the regioselective synthesis of 5,6-unsubstituted azolo[1,5-*a*]pyrimidines with wide substrate scopes.

Heterocycle-fused pyrimidine represents one of the most privileged motifs across pharmaceuticals.[10] Among them all, pyrazolo[1,5-*a*]pyridine derivatives that possess a broad spectrum of potential biological activities may become a vital building block in drug discovery.[11] Several approved drugs,

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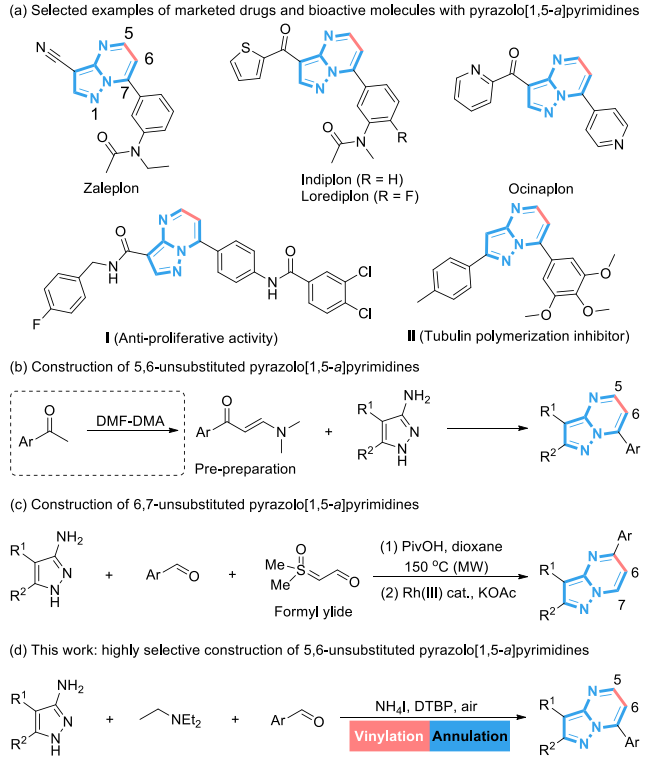
namely, zaleplon, indiplon, loredipIon, and ocinaplon, which belong to nonbenzodiazepine sedative and hypnotic agents, are used in clinical practice. These marketed drugs and other bioactive molecules with pyrazolo[1,5-*a*]pyrimidines share common structural features, including 5,6-unsubstitution and diverse (hetero)aryl groups at the C-7 position (Scheme 1a).[12]

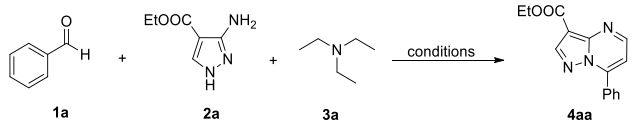
Scheme 1. Selected Examples of Bioactive Pyrazolo[1,5-*a*]pyridines and Methods for the Synthesis of Pyrazolo[1,5-*a*]pyridines



However, to date, access to 5,6-unsubstituted pyrazolo[1,5-*a*]pyrimidines generally relies on the cyclocondensation reaction of 3(5)-aminoazoles with *β*-enaminones, but this method has poor regioselectivity and requires the preliminary preparation of *β*-enaminones (Scheme 1b). In 2018, Ellman disclosed formyl sulfoxonium ylide as a potential C2 building block to obtain pyrazolo[1,5-*a*]pyrimidines possessing no substitution at the C-6 and C-7 positions with opposite regioselectivities (Scheme 1c).[13] Driven by these studies, we present the first direct vinylation of 3(5)-aminoazoles with triethylamine to provide a new general route to 5,6-unsubstituted 7-arylpyrazolo[1,5-*a*]pyrimidines (Scheme 1d). Moreover, the vinyl reaction is superior to the rapid background reaction from the condensation between 3(5)-aminoazoles and aldehydes to form terminal enamines. This transformation enriches the synthesis of the important drug-like scaffolds in a simple, efficient, and practical process.

Initially, commercially accessible benzaldehyde (**1a**), ethyl 3-amino-1*H*-pyrazole-4-carboxylate (**2a**), and triethylamine (**3a**) were selected as the model substrates to commence our investigation (Table 1). The reaction was performed using NH_4I and DTBP in PhCl at 130 °C when the desired product ethyl 7-phenylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (**4aa**) was obtained in 83% yield (Table 1, entry 1). It is noteworthy that only isomer **4aa** was gained under this condition. In

Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3a 4aa

entry	[I]	oxidant	solvent	temp. (°C)	yield (%)[b]
1	NH_4I	DTBP	PhCl	130	83
2	NIS	DTBP	PhCl	130	69
3	I_2	DTBP	PhCl	130	70
4	KI	DTBP	PhCl	130	trace
5	TBAI	DTBP	PhCl	130	74
6	NH_4I	TBHP	PhCl	130	trace
7	NH_4I	DCP	PhCl	130	81
8	NH_4I	BPO	PhCl	130	trace
9	NH_4I	TBPB	PhCl	130	trace
10	NH_4I	CHP	PhCl	130	trace
11	NH_4I	H_2O_2	PhCl	130	0
12	NH_4I	air	PhCl	130	trace
13	NH_4I	DTBP	dioxane	130	62
14	NH_4I	DTBP	CH_3CN	130	63
15	NH_4I	DTBP	DCE	130	24
16	NH_4I	DTBP	DMF	130	34
17	NH_4I	DTBP	DMSO	130	30
18	NH_4I	DTBP	THF	130	57
19	NH_4I	DTBP	toluene	130	87
20	NH_4I	DTBP	toluene	140	87
21	NH_4I	DTBP	toluene	120	76
22	NH_4I	DTBP	toluene	110	62
23[c]	NH_4I	DTBP	toluene	130	68
24[d]	**NH_4I**	**DTBP**	**toluene**	**130**	**87**
25[e]	NH_4I	DTBP	toluene	130	67
26[f]	NH_4I	DTBP	toluene	130	65

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), **3a** (1.5 mmol), [I] (0.5 mmol), oxidant (1.5 mmol), solvent (2 mL) for 10 h. [b]Isolated yields. [c]NH_4I (0.1 mmol, 20 mol %). [d]NH_4I (0.5 mmol) and **3a** (1.0 mmol). [e]NH_4I (0.5 mmol) and **3a** (0.5 mmol). [f]**1a** (10 mmol), **2a** (10 mmol), and **3a** (20 mmol).

contrast, the present reaction did not work when KI was used instead of NH_4I (Table 1, entry 4). Then, we found that the selection of peroxide was important for this annulation reaction. DTBP was the best oxidant, followed by DCP, and other peroxide oxidants, such as TBHP, BPO, TBPB, CHP, and H_2O_2, were all ineffective (Table 1, entries 6−11). Notably, a trace amount of **4aa** was produced in the absence of an additional oxidant (Table 1, entry 12). To obtain higher yields, we next conducted a survey of several solvents. Unfortunately, most of the tested solvents including dioxane, acetonitrile, 1,2-dichloroethane, DMF, DMSO, and THF could not increase the yield of this transformation (Table 1, entries 13−18). Delightedly, the yield of **4aa** could be slightly increased to 87% in toluene (Table 1, entry 19). In addition, reducing the reaction temperature and the amount of NH_4I had an adverse influence on the reaction (Table 1, entries 21−23). Finally, the reaction using 2.0 equiv of **3a** provided a uniform result. Significantly, the efficiency and selectivity were not affected when the transformation was carried out on a gram scale (Table 1, entry 26).

With the optimized reaction conditions in hand, we further examined several cyclic and acyclic ethyl amines (**3b**−**3k**) as the C2 building block to react with benzaldehyde and ethyl 3-amino-1*H*-pyrazole-4-carboxylate for the preparation of 5,6-

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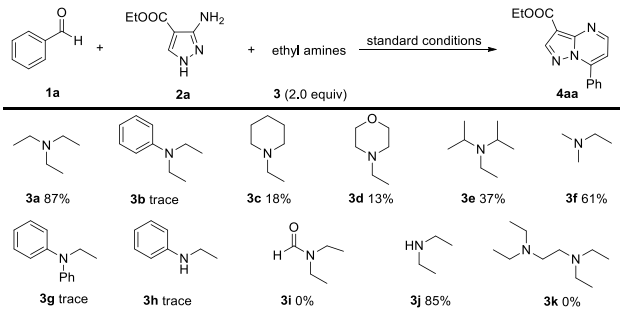
unsubstituted pyrazolo[1,5-*a*]pyrimidines (Scheme 2). Although *N*,*N*-diisopropylethylamine (**3e**), *N*,*N*-dimethyle-

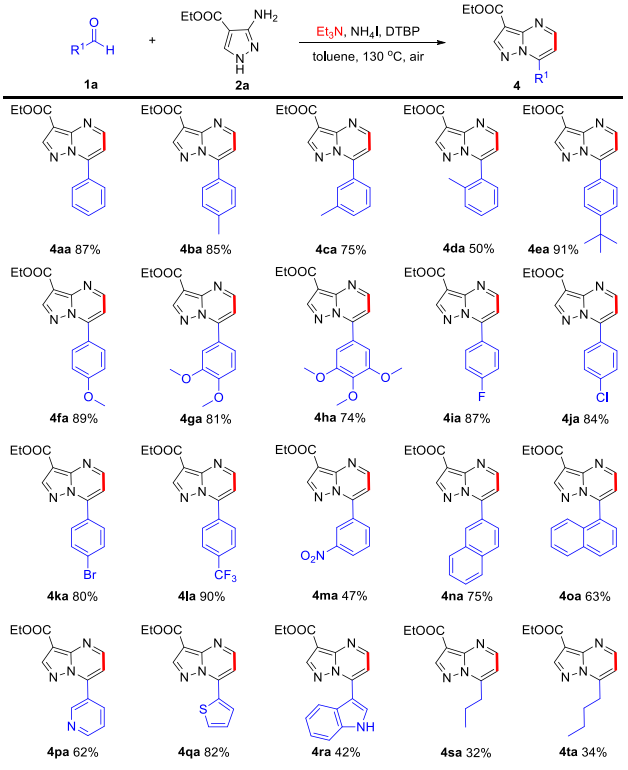
Scheme 2. Representative Ethyl Amines



thanamine (**3f**), and diethylamine (**3j**) gave **4aa** in yields of 37, 61, and 85%, respectively, the ethyl groups installed on other amines were not amenable to this transformation.

Next, we investigate the compatibility of this novel annulation process with a wide range of aldehydes (Scheme 3). Benzaldehydes with a methyl at the para and meta positions

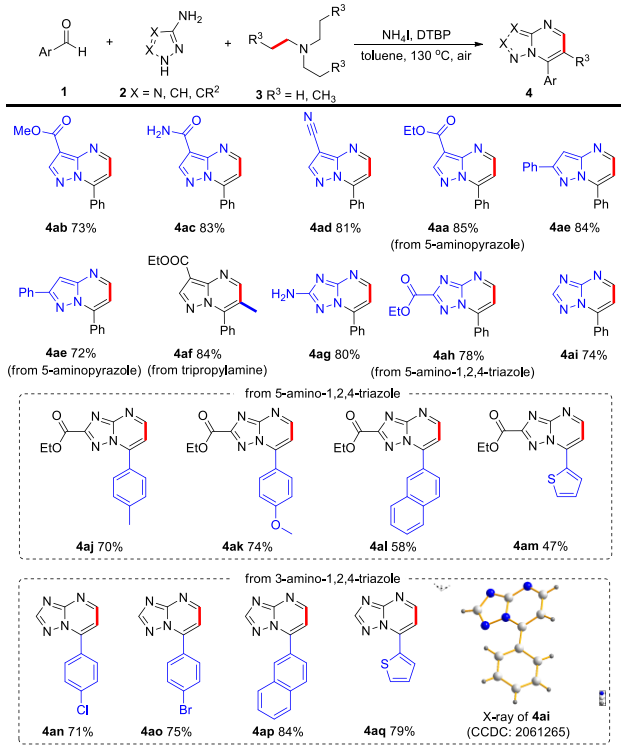
Scheme 3. Substrate Scope of Aldehydes



furnished the desired bicyclic-fused pyrimidines in good yields (75−85%, **4ba** and **4ca**), whereas only a 50% yield of **4da** was obtained from *ortho*-methylbenzaldehyde. These results demonstrated that the position of the substituent could affect the reaction yield. Other substituents such as *tert*-butyl (91%, **4ea**), methoxy (89%, **4fa**), fluoro (87%, **4ia**), chloro (84%, **4ja**), bromo (80%, **4ka**), and trifluoromethyl (90%, **4la**) at the para position were all compatible, and multisubstituted aldehydes also efficiently reacted to afford the final products **4ga** and **4ha** in 74−81% yields. Remarkably, a substrate bearing the strongly electron-withdrawing nitro group was still compatible with this annulation reaction and provided the desired product **4ma** in 47% yield. Further investigation manifested that other aromatic aldehydes such as 2-naphthaldehyde, 1-naphthaldehyde, pyridine-3-carbaldehyde, formylthiophene, and indole-3-carboxaldehyde were at least moderately favorable to this transformation and gave rise to the target products **4na**−**4ra** in 42−82% yields. It is notable that no formation of a 5-arylpyrazolo[1,5-*a*]pyrimidine side product was observed in any example. Astonishingly, aliphatic aldehydes that are liable to intervene in iminium from **3a** could also deliver the corresponding alkylated pyrazolo[1,5-*a*]-pyrimidines (**4sa** and **4ta**), albeit in lower yields (32−34%).

We next evaluated the scope of α-aminoazoles (Scheme 4). In the case of 3-aminopyrazoles, a number of electron-deficient

Scheme 4. Substrate Scope of α-Aminoazoles, Tertiary Alkylamines, and Aldehydes



functionalities such as ester (73%, **4ab**), amide (83%, **4ac**), nitrile (81%, **4ad**), and phenyl (84%, **4ae**) were tolerated in this present NH_4I-based reaction system. In contrast, 5-methyl-1*H*-pyrazol-3-amine was not an effective substrate, as an inseparable mixture was formed. Meanwhile, 5-aminopyrazoles as substrates also tolerated this transformation well and displayed similar reactivities as 3-aminopyrazoles. Tripropylamine could also be subjected to the annulation reaction to produce a 6-methylpyrazolo[1,5-*a*]pyrimidine derivative in satisfactory yield (84%, **4af**). Intriguingly, the versatility of this protocol was further mirrored by the successfully used 3(5)-amino-1,2,4-triazole, which provided a robust access to a series of [1,2,4]triazolo[1,5-*a*]pyrimidines (74−80%, **4ag**−**4ai**). In fact, it is well known that [1,2,4]triazolo[1,5-*a*]pyrimidine widely occurs in bioactive compounds.[14] Recent drug discovery efforts with [1,2,4]triazolo[1,5-*a*]pyrimidine derivatives have focused on anti-influenza,[15] anti-Alzheimer's disease,[16] and anticancer therapeutics.[17] Hence, several (het)arylaldehydes and 3(5)-amino-1,2,4-triazole smoothly

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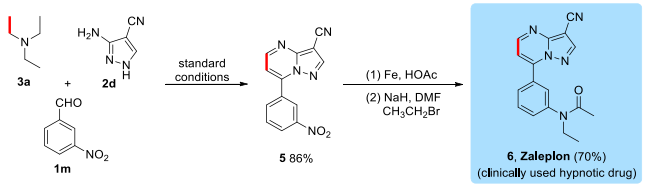
underwent this procedure with complete regioselectivity, leading to the corresponding products (**4aj**–**4aq**) in 47–84% yields.

To further explore the practical utility of this annulation strategy in medicinal chemistry settings, this approach was applied for the concise synthesis of the clinically used hypnotic drug zaleplon (Scheme 5). Starting from commercially

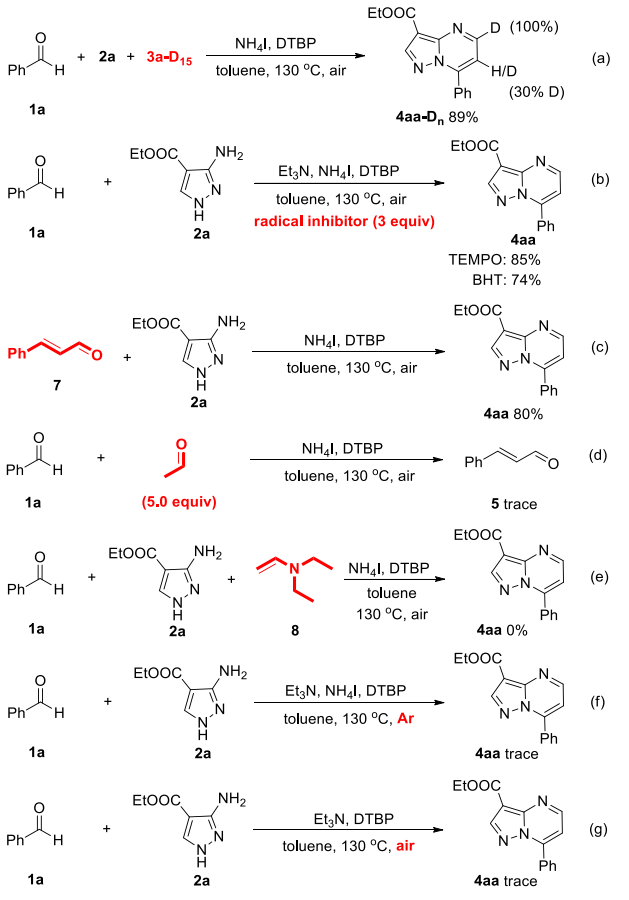
Scheme 5. Concise Strategy for the Synthesis of Zaleplon



available 3-nitrobenzaldehyde (**1m**), 3-amino-4-cyanopyrrole (**2d**), and triethylamine (**3a**), the three-component annulation protocol proceeded smoothly and gave the precursor **5** in 86% yield. The desired zaleplon **6** was subsequently obtained in 70% yield (overall yield for two steps) from **5** via hydrogenation–acetylation followed by ethylation. Thus the synthesis of zaleplon can now be accomplished in only three steps and in good overall yield.

To gain better insight into this transformation mechanism, the present annulation with **3a-D$_{15}$** was investigated, and the target deuterated product **4aa-D$_n$** was obtained in 89% yield (Scheme 6a). This result reveals that the two carbons of the

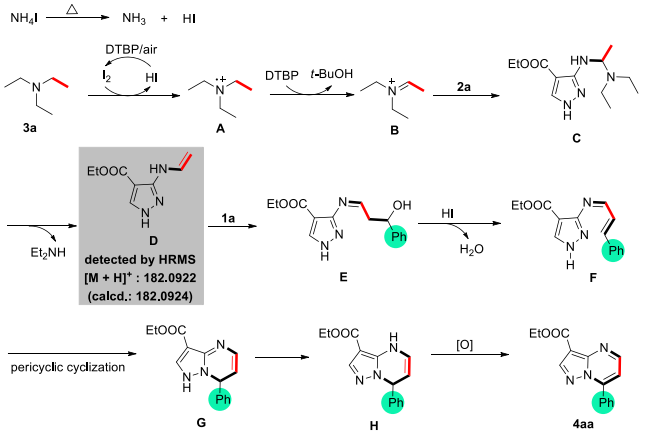
Scheme 6. Control Experiments



pyrimidine rings are derived from triethylamine. We then attempted to add radical scavengers TEMPO and BHT to stop the reaction; however, the reaction could still proceed normally (Scheme 6b). These findings support the notion that the present process may not involve a radical intermediate. Although the treatment of cinnamaldehyde (**7**) with 3-aminopyrazole (**2a**) generated the desired pyrazolo[1,5-*a*]pyrimidine in 80% yield (Scheme 6c), it was not considered to be the intermediate because cinnamaldehyde was barely detected when benzaldehyde (**1a**) reacted with acetaldehyde under the standard conditions in the absence of **2a** (Scheme 6d). It is known that triethylamine could also generate *N*,*N*-diethylethenamine;[18] however, this was not the case for this reaction because the reaction performed with enamine (**8**) did not occur (Scheme 6e). Furthermore, we analyzed the mixture after 30 min of reaction, in which the vinylation product of 3-aminopyrazole was clearly detected by HRMS. (See the Supporting Information.) This observation indicates that 3-aminopyrazole prefers to capture imine intermediates produced by Et$_3$N. In addition, aerial oxygen and NH$_4$I were identified as indispensable for the preparation of **4aa** (Scheme 6f,g).

On the basis of the above results and previous reports,[19] a plausible mechanism has been proposed (Scheme 7). The heat

Scheme 7. Plausible Mechanism



splits NH$_4$I, which is believed to be the initial step. This produces HI followed by further rapid oxidation to generate I$_2$. Then, the oxidation of Et$_3$N with elemental iodine and DTBP results in the formation of the iminium intermediate **B**, which proceeds through the nucleophilic addition of 3-aminopyrazole (**2a**) to afford the intermediate **C**. Next, the key vinylation product **D** is formed from **C** through the elimination of Et$_2$NH. Significantly, the aldehyde can react with intermediate **D** to render intermediate **F**. Then, intermediate **F** undergoes direct pericyclic sigmatropic cyclization followed by hydrogen and double-bond shifts leading to dihydropyrazolo[1,5-*a*]-pyrimidine **H**. Finally, **H** translates into product **4aa** through oxidative aromatization.

In summary, we have developed a new general strategy for the regioselective synthesis of a wide range of 5,6-unsubstituted pyrazolo[1,5-*a*]pyrimidine and [1,2,4]triazolo-[1,5-*a*]pyrimidine derivatives from commercially available building blocks by using an appropriate combination of NH$_4$I and DTBP with aerial oxygen. The unique nature of this reaction was that the undesired condensation, a prevalent

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reaction from 3(5)-aminoazoles and aldehydes, was prevented by the direct vinylation reaction. Notably, the reaction is enabled by an NH_4I-based reaction system that allows the in situ generation of acyclic enamines that act as nucleophiles in this annulation process. The synthetic utility of this reaction is further demonstrated by the concise synthesis of the clinically used hypnotic drug zaleplon.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00571.

General experimental procedures and spectroscopic data for the corresponding products (PDF)

Accession Codes

CCDC 2061265 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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