

Synthesis of Polysubstituted Pyridines via a One-Pot Metal-Free Strategy

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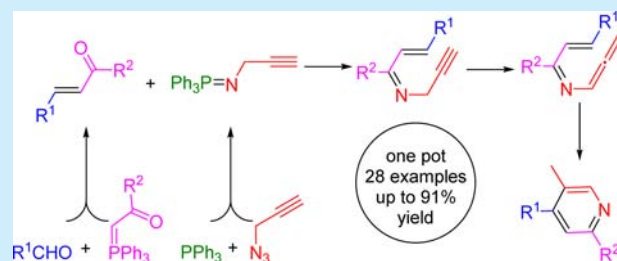
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S Supporting Information

ABSTRACT: An efficient strategy for the one-pot synthesis of polysubstituted pyridines via a cascade reaction from aldehydes, phosphorus ylides, and propargyl azide is reported. The reaction sequence involves a Wittig reaction, a Staudinger reaction, an aza-Wittig reaction, a 6π -3-azatriene electrocyclicization, and a 1,3-H shift. This protocol provides quick access to the polysubstituted pyridines from readily available substrates in good to excellent yields.

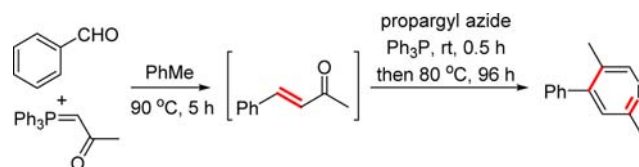


Substituted pyridines are an important class of N-heterocyclic compounds with many roles in natural products, active pharmaceuticals, functional materials, and synthetic intermediates.¹ Development of mild and efficient methods for the synthesis of substituted pyridines remains highly desirable. As a consequence, considerable efforts have been directed to construct these privileged heterocycles.² Currently, many powerful methodologies for the synthesis of pyridine rings rely mainly on one-pot multicomponent reactions,³ condensation of amines and carbonyl compounds, metal-catalyzed cycloaddition reactions,⁴ or 6π -electrocyclization.⁵ However, a literature survey reveals that most of the published approaches involve multistep preparation for the substrates, the usefulness of which is limited by lack of generality. Therefore, an efficient and general procedure for the synthesis of substituted pyridines from readily available substrates under mild reaction conditions is still of considerable interest.

Consistent with what green chemistry advocates, the cascade reactions involving simple operational procedures and equipment are commonly used to save time and energy, to avoid isolating intermediates, and to improve reaction efficiency.⁶ We herein present an efficient one-pot synthesis of substituted pyridines from an aldehyde, a phosphorus ylide, and propargyl azide through a metal-free, multicomponent, one-pot sequence involving Wittig reaction, Staudinger reaction, aza-Wittig reaction, 6π -3-azatriene electrocyclicization reaction, and 1,3-H shift (Scheme 1).

As a pilot experiment, Wittig reaction of benzaldehyde and a phosphorus ylide was conducted at 90 °C in PhMe for 5 h. After benzaldehyde was consumed, the mixture was cooled to

Scheme 1. Synthesis of Pyridines from Benzaldehyde

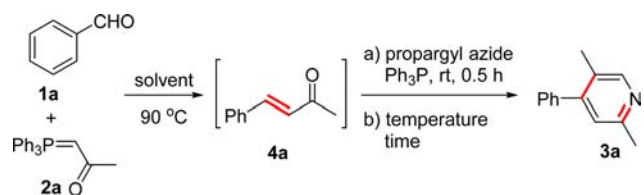


room temperature and propargyl azide along with triphenylphosphine was added. The reaction was maintained at room temperature for 0.5 h, and then at 80 °C for 96 h. To our delight, the expected product, 2,5-dimethyl-4-phenylpyridine, was obtained in 79% yield (Table 1, entry 1). We next investigated the reaction parameters in order to enhance the efficiency of the process. The reaction temperature was first evaluated. The desired product was isolated in 78% yield after 36 h at 100 °C and in 80% yield after 24 h at 120 °C (entries 2 and 3). It is noteworthy that higher temperatures (e.g., 140 °C) failed to further increase the yield (entry 4). The solvent effect was then examined (entry 5–9). When PhH, PhCl, CH₃CN, or THF was used as the solvent, the reaction proceeded smoothly to render the product in moderate to good yields (65–72%). However, DCE was unfit for the process since it almost shut down the reaction completely. Thus, entry 3 in Table 1 reflects the optimized reaction conditions for this protocol.

With the optimized conditions in hand, various aldehydes and phosphorus ylides were screened to investigate the generality of the current synthesis of substituted pyridines.

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Table 1. Optimization of the Reaction Conditions^a

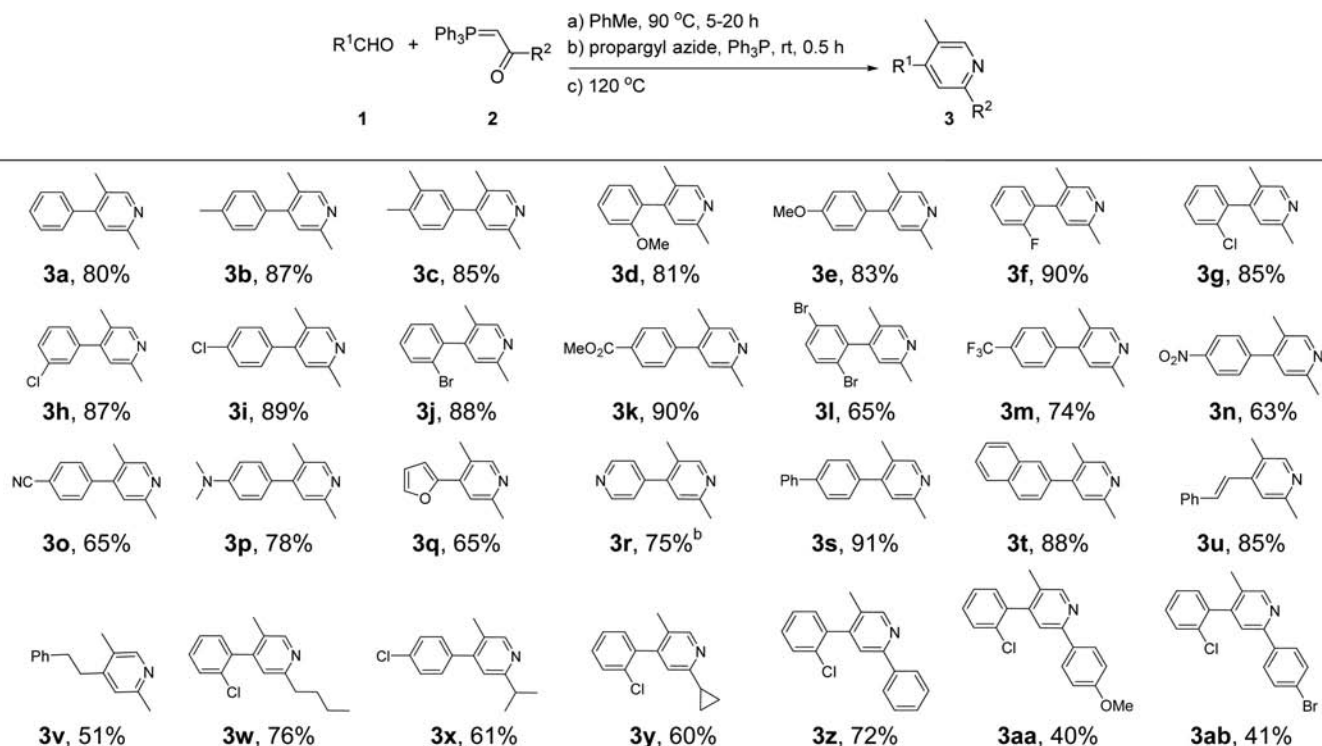
entry	solvent	temperature (°C)	time (h)	yield ^b (%)
1	PhMe	80	96	79
2	PhMe	100	36	78
3	PhMe	120	24	80
4	PhMe	140	15	78
5	PhH	120	24	75
6	PhCl	120	24	70
7	DCE	120	96	trace
8	CH ₃ CN	120	50	62
9	THF	120	35	68

^aReaction conditions: **1a** (0.94 mmol), **2a** (0.99 mmol), azidoprop-1-yne (3.77 mmol), Ph₃P (1.09 mmol), solvent (5 mL) ^bIsolated yield. DCE = 1,2-dichloroethane.

The results are summarized in Scheme 2. The substitution pattern of benzaldehydes was first examined. In general, a wide range of aldehydes bearing various functional groups gave rise to the substituted pyridines in moderate to high yields (**3a–3p**). Aldehydes containing one or two electron-donating groups (Me or MeO, **3b–3e**, **3p**) or a relatively weak electron-withdrawing group (halogen or CO₂Me, **3f–3k**) on the phenyl ring led to pyridines in good yields (78–90%). In contrast, a more electron-deficient phenyl ring within the aldehyde substrate (CF₃, NO₂, CN, or multiple halogen atoms, on the

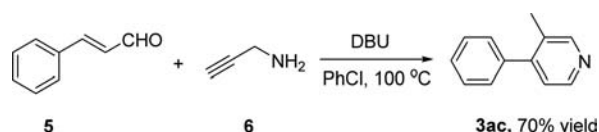
phenyl ring) retarded the reaction to some extent and resulted in relatively low yields for the pyridine products (**3l–3o**, 63–74%). For the latter case, decreased electron density in the π -conjugative system may slow down the rate of 6π -electrocyclization.⁷ However, substrates with a heteroaryl substituent (furanyl or pyridyl) showed good tolerance (**3q**, **3r**). Good yields were also achieved with 4-biphenyl (**3s**, 91%), 2-naphthyl (**3t**, 88%), and 4-styryl (**3u**, 85%), indicating that the steric effect of the R¹ substituent had little influence on the reaction. Moreover, the reaction with an aliphatic aldehyde (phenylpropyl aldehyde) as the substrate proceeded smoothly and provided the desired product (**3v**) in 51% yield. The scope of phosphorus ylides was subsequently evaluated. It was observed that phosphorus ylides with a bulky alkyl group were also accommodated for this process, yet generating the product in slightly low yields (**3w–3y**). Similarly, the substrate bearing a simple phenyl group was suitable for this process (**3z**). However, 4-methoxyphenyl and 4-bromophenyl substituted phosphorus ylides led to much lower efficiency and afforded products in the yields of 40% (**3aa**) and 41% (**3ab**), respectively. Notably, when R² group is H, no expected product (**3ac**) was obtained, probably due to inefficient formation of the imine via a Staudinger reaction. Nevertheless, the disubstituted pyridine **3ac** could be synthesized in reasonable yield via direct condensation of propargylamine and cinnamaldehyde (Scheme 3) and followed by a similar 6π -3-azatriene electrocyclization reaction and a [1,3] hydrogen shift sequence.

A plausible mechanism for the formation of pyridine **3a** is shown in Scheme 4. Initially, α,β -unsaturated ketone **4a** is formed through Wittig reaction of benzaldehyde **1a** and phosphorus ylide **2a**.⁸ Independently, azide **7** reacts with triphenylphosphine to furnish phosphazene **8** via Staudinger

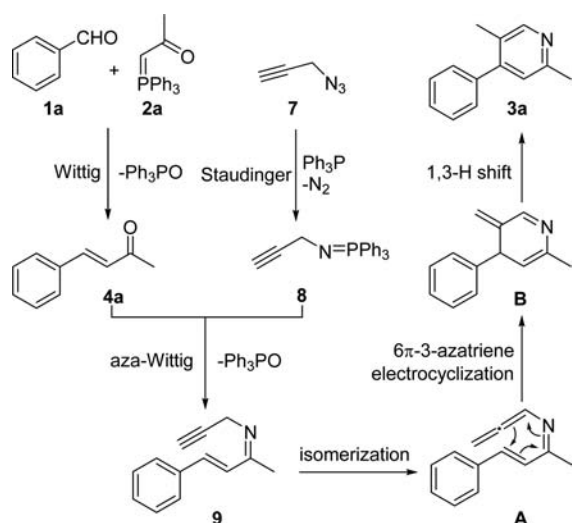
Scheme 2. Synthesis of Pyridines^a

^aIsolated yield. ^bThe yield was determined by ¹H NMR analysis.

Scheme 3. Direct Condensation Approach with Cinnamaldehyde as the Substrate



Scheme 4. Proposed Reaction Mechanism



reaction.⁹ Subsequently, aza-Wittig reaction between phosphazene 8 and ketone 4a gives rise to imine 9,¹⁰ which spontaneously undergoes isomerization to form intermediate A, which features an allene moiety conjugated with α,β -unsaturated imine.¹¹ Then, 6π -3-azatriene electrocyclic cyclization of A was triggered, followed by 1,3-H shift, to render the final trisubstituted pyridine 3a.

In conclusion, we have developed a new, metal-free, and one-pot synthetic route to substituted pyridines, which employs a cascade reaction sequence from an α,β -unsaturated ketone and a phosphazene (both produced in situ), involving an aza-Wittig, a 6π -3-azatriene electrocyclic cyclization reaction, and a [1,3]-hydrogen shift. Based upon advantages such as simple operation, broad functionality tolerance, and significance of the multisubstituted pyridine products, this method should find broad applications in organic synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02903.

Experimental procedures and characterization data for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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