Organic LETTERS

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Transition-Metal-Free Synthesis of Substituted Pyridines via Ring Expansion of 2-Allyl-2*H*-azirines

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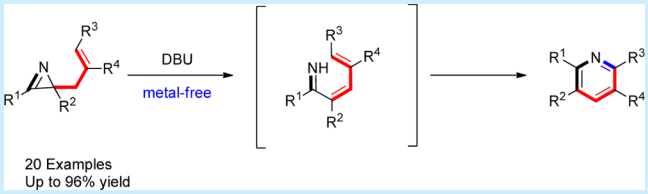
Supporting Information

ABSTRACT: A new strategy to open the 2-allyl-2*H*-azirines by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) promotion in metal-free conditions affording 1-azatrienes that *in situ* electrocyclize to the pyridines in good to excellent yields is reported. The reaction displays a broad substrate scope and good tolerance to a variety of substituents including aryl, alkyl, and heterocyclic groups. In addition, one-pot synthesis of pyridines from oximes via *in situ* formation of 2*H*-azirines was achieved.



Pyridine moieties represent one of the most important classes of heterocycles found in many natural products, pharmaceuticals, functional materials, and valuable ligands in organic synthesis.[1] A variety of methods have been developed for the preparation of pyridines in the past few decades.[2] While traditional methods employ condensation of carbonyl compounds with ammonia,[3] modern strategies largely rely on transition-metal catalysis, C−H functionalization, and cycloaddition reactions.[4] Despite this progress, it is still highly desirable to develop a more flexible, operationally simple method with broad functional group tolerability.

2*H*-Azirines, the smallest nitrogen-containing unsaturated heterocycles, have been extensively explored in synthetic and biological applications.[5] Due to their high ring strain, 2*H*-azirines serve as a versatile source of nitrenes, electrophiles, dienophiles, and dipolarophiles[6] and are extensively used in the construction of various N-heterocycles such as indoles, pyrroles, isoxazoles, and pyrazolo[1,5-*a*]pyridines.[7] Typically, 2-aryl-2*H*-azirines and 2-vinyl-2*H*-azirines are believed to give indoles and pyrroles via nitrene intermediates upon thermolysis and transition metal catalysis (Figure 1, eq 1, n = 0).[8] However, unlike aryl and vinyl-substituted azirines, few successful examples of N-heterocycle synthesis involving 2-allyl-2*H*-azirines, which contain remote double bonds, have been reported; Padwa and co-workers reported in a limited number of examples that thermal generation of nitrenes from 2-allyl-2*H*-azirines leads to the formation of mixtures of pyridines, pyrroles, and indoles (Figure 1, eq 1, n = 1).[9] Ohe et al. reported palladium-mediated decarboxylative aziridination of 4*H*-isoxazol-5-ones in which selective formation of pyrroles have been achieved via 1-azabicyclo[3.1.0]hex-2-ene intermediates formed by the addition of putative nitrene−metal complexes to pendant allyl groups.[10] Recently, Gagosz et al. reported the gold-activated triple bonds of 2-propargyl-2*H*-azirines for synthesis of

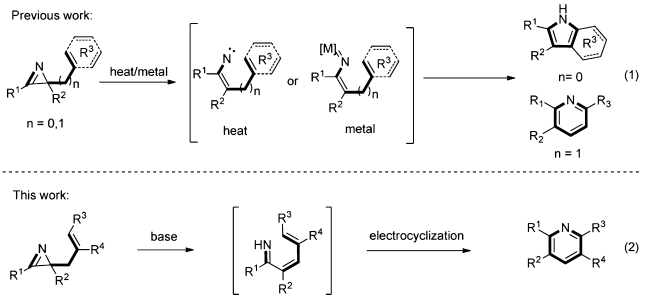


Figure 1. Ring expansion of 2*H*-azirines to C−N bond construction.

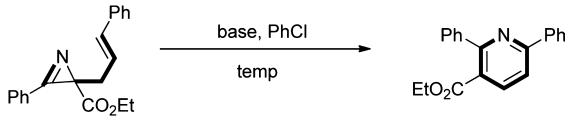
substituted pyridines.[11] In our continued efforts for the development of N-hetercycle synthesis by an organic base,[12] we report herein the efficient synthesis of pyridines from 2-allyl-2*H*-azirines by DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) promoted electrocyclization[13] (Figure 1, eq 2).

The substrate 2-allyl-2*H*-azirine **1a** was easily prepared by using the Neber reaction[14] (see Supporting Information) and was examined for pyridine formation under various conditions. When treated with TMEDA in chlorobenzene at 130 °C, **1a** provided ethyl 2,6-diphenylnicotinate **2a** in poor yield (Table 1, entry 1). Attempts to improve the yield by employing other bases turned out to be unsuccessful; the use of DMAP failed to give any product (entry 2), while quinine, DABCO, and TEA gave similar results as TMEDA (entries 3−5). Gratifyingly, the yield could be improved to 95% when DBU was employed as the base (entry 6). In contrast, no conversion was observed in the absence of DBU ruling out the possibility of simple thermal rearrangement (entry 7). Reduction of the amount of base or

Received: April 7, 2014

   dx.doi.org/10.1021/ol501010k | *Org. Lett.* XXXX, XXX, XXX−XXX

Table 1. Base Promoted Synthesis of Pyridines



1a 2a

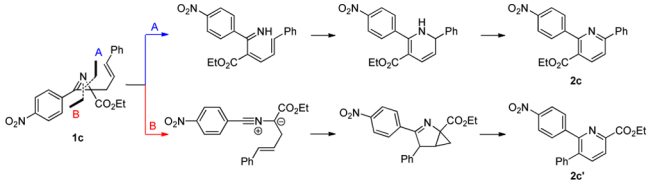
entry[a]	base	sovlent	yield[b,c] (%)
1	TMEDA	PhCl	17
2	DMAP	PhCl	0
3	DABCO	PhCl	17
4	quinine	PhCl	16
5	TEA	PhCl	13
6	**DBU**	**PhCl**	**95**
7	–	PhCl	0
8	DBU	$PhCH_3$	77
9	DBU	DCE	26
10[d]	DBU	PhCl	75
11[e]	$FeBr_2$	PhCl	23
12[f]	$Rh_2(OAc)_4$	PhCl	25

[a]Unless otherwise noted, reactions were performed using **1a** (0.1 mmol), base (0.3 mmol) in solvent (0.1 M, 1 mL) at 130 °C for 48 h under a nitrogen atmosphere. [b]Yields determined by NMR vs standard. [c]The remaining materials were **1a**. [d]2.2 equiv of DBU. [e]20 mol % $FeBr_2$. [f]2 mol % $Rh_2(OAc)_4$. TMEDA = Tetramethylethylenediamine, DMAP = 4-Dimethylaminopyridine, DABCO = 1,4-diazabicyclo-[2.2.2]octane, DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene.

reaction temperature resulted in decreased yields (entries 8–10). Interestingly, metal complexes commonly employed for the generation of nitrenes gave **2a** in poor yields (entries 11–12).[15]

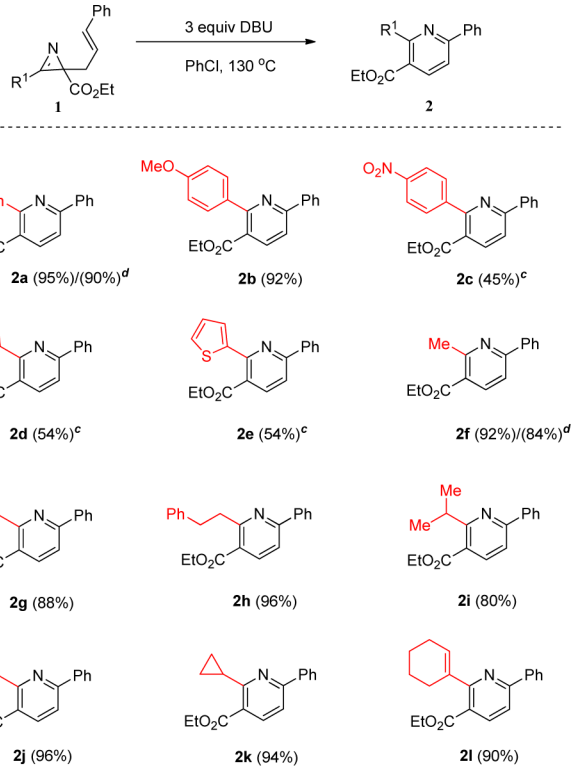
Encouraged by the results, we investigated the substrate scope of the reaction (Scheme 2). In general, the reaction tolerated a broad range of substitution to give trisubstituted pyridines in good to excellent yields. To examine the electronic effect on the R^1 substituent, substrates with aryl groups bearing electron-donating and -withdrawing groups were subjected to the reaction conditions. Whereas those with phenyl and electron-rich aryl groups provided excellent yields of pyridines (**2a** and **2b**, respectively), a competing reaction providing a mixture of regioisomers **2c** and **2c′** was observed with a substrate bearing an electron-deficient aryl group. We reasoned that the formation of the minor product **2c′** proceeds through 1,3-dipolar cycloaddition of the nitrile ylide intermediate arising from C–C bond cleavage of the azirine ring (Scheme 1).[9]

Scheme 1. Proposed Pathway for Pyridines



Likewise, a similar competing reaction was observed with heteroaryl-substituted substrates **1d** and **1e**. In contrast, the competing nitrile ylide pathway was completely suppressed with alkyl-substituted substrates providing single regioisomers in excellent yields (**2f–k**, Scheme 2). Substituents such as cyclopropyl and vinyl groups remained intact during the reaction (**2k** and **2l**); However, styryl substitution led to an unexpected product **2h** in which the alkenyl moiety was saturated,

Scheme 2. Substrate Scope[a,b]



[a]Unless otherwise noted, reactions were carried out using **1** (0.2 mmol), DBU (0.6 mmol) in chlorobenzene (0.1 M, 2 mL) at 130 °C for 48 h under nitrogen atmosphere. [b]Isolated yields. [c]**2c′** = ethyl 6-(4-nitrophenyl)-5-phenylpicolinate (38%); **2d′** = ethyl 6-(furan-2-yl)-5-phenylpicolinate (32%); **2e′** = ethyl 5-phenyl-6-(thiophen-2-yl)-picolinate (23%). [d]Reactions were carried out using **1** (1.0 mmol), DBU (3.0 mmol) in chlorobenzene (0.1 M, 10 mL) at 130 °C for 48 h under nitrogen atmosphere.

presumably due to the isomerization of the alkene into the dihydropyridine.[16]

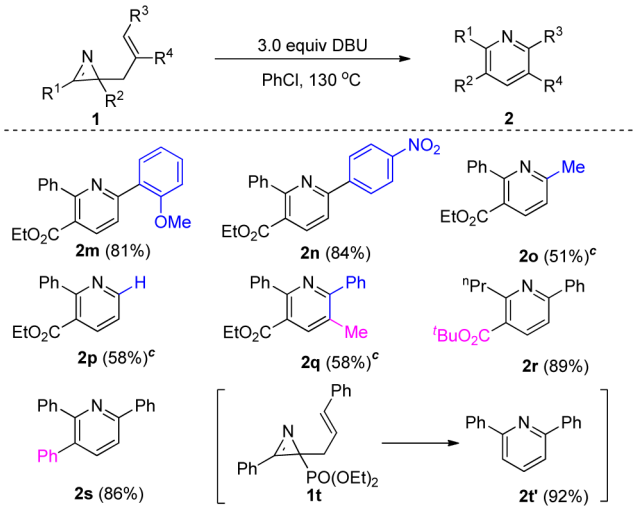
Next, we turned our attention to examine the influence of the substituents at the 2-position of 2*H*-azirines (Scheme 3). Unlike the substitution at R^1, substrates with both electron-rich and -deficient aryl groups at the terminal position of the allyl groups (R^4) proceeded smoothly to give single regioisomers (**2m** and **2n**). However, replacement of the aryl groups at R^4 with a methyl group resulted in a mixture of **2o** and **2o′** resulting from the competing nitrile ylide pathway. Likewise, **1p** bearing an unsubstituted allyl group gave a regioisomeric mixture. Interestingly, introduction of a methyl group at R^3 (**1q**) also promoted the nitrile ylide pathway, even in the presence of an aryl substituent at R^4. In addition to the ester group, we also examined different functional groups for R^2. Thus, **1s** bearing a phenyl group reacted well to provide **2s** in excellent yield. Elimination is favored over oxidation to give 3-unsubstituted pyridine **2t′** in 92% yield when the phosphonate group was employed for R^2.

Since the preparation of substrates in the Neber reaction employs DBU, we reasoned that one-pot synthesis of pyridines from oximes via in situ formation of 2*H*-azirines could be achieved. To our delight, **2a** was formed in 85% yield from oxime **3** by using 3 equiv of DBU (Scheme 4).

In summary, we have developed a novel method for the synthesis of highly substituted pyridines through DBU-mediated

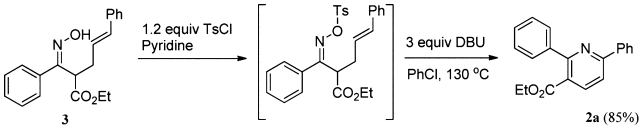
dx.doi.org/10.1021/ol501010k | *Org. Lett.* XXXX, XXX, XXX–XXX

Scheme 3. Substrate Scope[a,b]



[a]Unless otherwise noted, reactions were carried out using **1** (0.2 mmol), DBU (0.6 mmol) in chlorobenzene (0.1 M, 2 mL) at 130 °C for 48 h under nitrogen atmosphere (1 atm). [b]Isolated yields. '**2o**′ = ethyl 5-methyl-6-phenylpicolinate (37%); **2p**′ = ethyl 6-phenylpicolinate (27%); **2q**′ = ethyl 3-methyl-5,6-diphenylpicolinate (24%).

Scheme 4. One-Pot Synthesis of Pyridine



ring opening of 2-allyl-2*H*-azirines. 6π-Electrocyclization of the resulting 1-azatrienes provides pyridines in good yields.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and characterization data. 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.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the Nanyang Technological University and the Singapore Ministry of Education Academic Research Fund Tier 2: MOE2011-T2-1-013 for TPL and MOE2012-T2-1-014 for SC, and the National Environment Agency (NEA-ETRP Project Ref. No. 1002 111), and University of Science and Technology of China.

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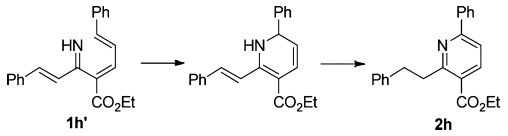

dx.doi.org/10.1021/ol501010k | *Org. Lett.* XXXX, XXX, XXX−XXX