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Simple Conversion of Enamines to 2*H*-Azirines and Their Rearrangements under Thermal Conditions

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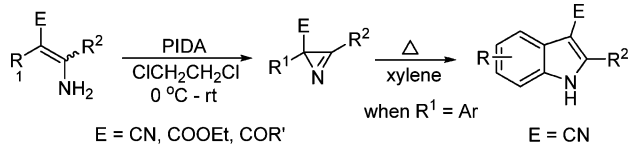
ABSTRACT



A variety of substituted enamine derivatives were first found to be conveniently converted to the corresponding 2*H*-azirines mediated by phenyliodine (III) diacetate (PIDA). The formed 2-aryl-2*H*-azirines could be applied in the synthesis of indole-3-carbonitriles or isoxazoles via thermal rearrangements.

2*H*-Azirines, a class of highly strained and reactive molecules with a C═N bond incorporated into a three-membered ring, have been extensively studied for their presence in natural products[1] and high synthetic potential in the synthesis of functionalized aminoderivatives and *N*-containing heterocycles.[2] In particular, 2*H*-azirines bearing an α-aryl group, are impressive intermediates for the preparation of various substituted indoles: this unique approach starts from an alkyl-substituted arene and joins the *N*-moiety on the side-chain to the benzene ring via aryl C−H amination at the last synthetic stage.[3]

Existing strategies for the synthesis of 2*H*-azirines can be generalized[2,4] into the following types: (1) The classic Neber process, which is most extensively used (route **a** in Figure 1). (2) Pyrolysis or photolysis of vinyl azide (route **b** in Figure 1). (3) Elimination reaction or Swern oxidation of aziridine derivatives (route **c** in Figure 1). (4) Ring contraction of isoxazoles, oxazaphospholes or azete derivatives (route **d** and **e** in Figure 1). (5) Intermolecular reactions between nitriles and carbenes or nitrenes and acetylenes (route **f** and **g** in Figure 1). To the best of our knowledge, there has been no report on the synthesis of 2*H*-azirines

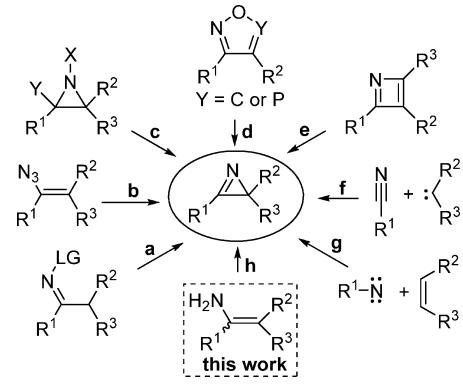


Figure 1. General strategies for the construction of 2*H*-azirine skeleton.

(1) (a) Miller, T. W.; Tristram, E. W.; Wolf, F. J. *J. Antibiot.* **1971**, *24*, 48–50. (b) Stapley, E. O.; Hendlin, D.; Jackson, M.; Miller, A. K.; Hernandez, S.; Mata, J. M. *J. Antibiot.* **1971**, *24*, 42–47. (c) Molinski, T. F.; Ireland, C. M. *J. Org. Chem.* **1988**, *53*, 2103–2105. (d) Salomón, C. E.; Williams, D. H.; Faulkner, D. J. *J. Nat. Prod.* **1995**, *58*, 1463–1466. (e) Skepper, C. K.; Molinski, T. F. *J. Org. Chem.* **2008**, *73*, 2592–2597.

(2) For reviews, see: (a) Palacios, F.; Ochoa de Retana, A. M.; Martinez de Marigorta, E.; Manuel de los Santos, J. *Org. Prep. Proc. Int.* **2002**, *34*, 219–269. (b) Palacios, F.; Ochoa de Retana, A. M.; Martinez de Marigorta, E.; Manuel de los Santos, J. *Eur. J. Org. Chem.* **2001**, *13*, 2401–2414. (c) Pinho e Melo, T. M. V. D.; Rocha Gonsalves, A. M. d'A. *Curr. Org. Chem.* **2004**, *1*, 275–292.

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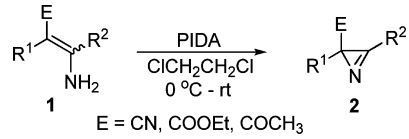
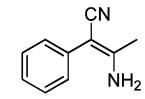
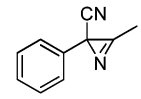
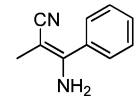
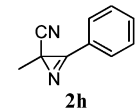
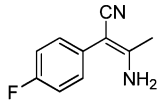
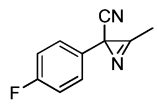
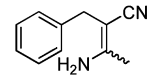
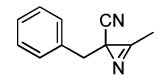
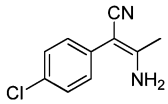
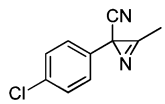
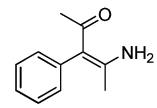
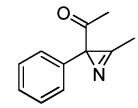
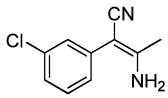
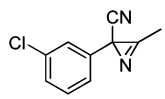
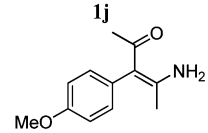
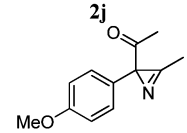
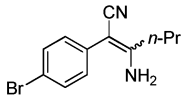
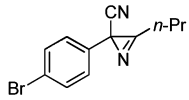
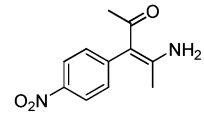
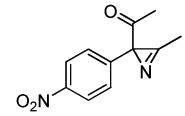
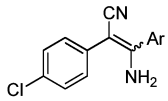
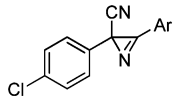
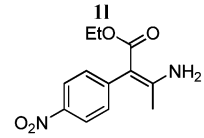
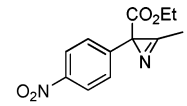
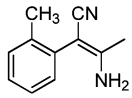
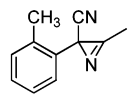
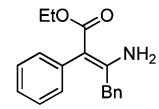
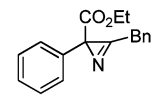
Table 1. Intramolecular Azirination of Enamines Mediated by PIDA[d]



entry	enamine **1**	2*H*-azirine **2**	time (h)	yield(%)[a]	entry	enamine **1**	2*H*-azirine **2**	time (h)	yield(%)[a]
1	 **1a**	 **2a**	10	72	8[c]	 **1h**	 **2h**	7	85
2	 **1b**	 **2b**	6	76	9	 **1i**	 **2i**	10	65
3	 **1c**	 **2c**	7	70	10	 **1j**	 **2j**	8	80
4	 **1d**	 **2d**	7	83	11	 **1k**	 **2k**	5	68
5[c]	 **1e**	 **2e**	8	76	12	 **1l**	 **2l**	5	88
6[b,c]	 **1f**	 **2f**	7	80	13[c]	 **1m**	 **2m**	8	70
7[c]	 **1g**	 **2g**	11	65	14	 **1n**	 **2n**	8	50

[a] Isolated yields after silica gel chromatography. [b] Ar herein represents 4-chlorophenyl group. [c] Reactions occurred at rt. [d] Conditions: all reactions were carried out with 1 equiv of **1**, 1.2 equiv of PIDA in $ClCH_2CH_2Cl$ at 0 °C unless otherwise stated.

utilizing enamine derivatives as starting materials (route **h** in Figure 1). In this communication, we report that various substituted enamine compounds could be oxidized by phenyliodine(III) diacetate (PIDA), a readily available hypervalent iodine reagent, into an assortment of 2-functionalized 2*H*-azirine derivatives. Literature survey indicated that this could represent the first example of the formation of such smallest unsaturated nitrogen heterocycles via intramolecuar azirination of enamine derivatives.

In our previous work,[5] the formation of a variety of *N*-arylated or *N*-alkylated indole derivatives were realized via intramolecular cyclization of 2-aryl-3-arylamino (or alkylamino)-2-alkenenitriles mediated by phenyliodine bis(trifluoroacetate) (PIFA). However, this approch was not desirable for the synthesis of the *N*-unsubstituted indoles since the reaction of the corresponding *N*-unsubstituted 2-arylethenamines with PIFA under the same conditions would afford an inseparable, complex mixture of unidentifiable compounds. Further study on the reaction conditions led us to discover that mediated by phenyliodine (III) diacetate (PIDA), a less potent oxidant than PIFA, a variety of 2-arylethenamines could be conveniently converted to the corresponding 2*H*-azirine derivatives.

The required enamine substrates could be easily obtained via condensation by the known procedures[6] (see Supporting Information for details). Thus intramolecular azirination of various substituted enamine compounds[7] was carried out under optimized conditions[8] to study the scope and generality of the process, and the results are summarized in Table 1. A variety of β-enaminonitriles with different substitution patterns could be used to the methodology (entries 1−7, Table 1), and the corresponding 2-aryl-2*H*-azirine-2-carbonitriles

were achieved in appreciable yields (65−83%). We next prepared substrate **1h**, structurely differing from **1a** by exchanging the position of the phenyl and methyl group, and found that it could also conveniently give 3-aryl-2*H*-azirine-2-carbonitrile **2h** (85%) by the described method. This result indicated that the α-aryl group in ketonitriles **1a**-**g** was not indispensable for the azirination to occur. The conversion of **1j** to azirinated product **2j** could further support the above conclusion and clearly implied that both R^1 and R^2 substituents in substrate **1** could be alkyl groups.

The *cyano* group in substrates **1a**−**i** was crucial for maintaining the enamine, rather than the imine tautomer. In light of this, we were intrested in replacing the *cyano* group with other electron-withdrawing groups, for example, a substituent with a carbonyl moiety. To our delight, the enamines (**1j**−**l**) of 3-arylacetylacetones also rendered the correponding 2*H*-azirines (**2j**−**l**) in desirable yields (68−88%) under the same reaction conditions, and both electron-withdrawing and electron-donating aromatic substituents were well tolerated. However, when the electron-withdrawing group was an ethoxycarbonyl group, we got only the two desired azirine products **2m** and **2n** prepared from the enamine substrates **1m** and **1n**, repectively. Similar substrates **1o** and **1p** (Figure 2), differing from **1m** by replacing the

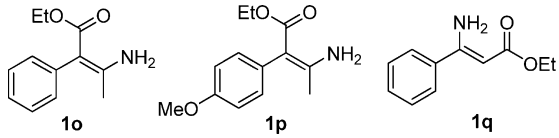


Figure 2. Other models that failed to afford 2*H*-azirine products.

nitro group with H or methoxy substituents, yielded no desired corresponding azirine product in each case. Another closely related substrate **1q**[9] (Figure 2) also failed the azirination under the same reaction conditions.

In addition to the spectroscopic data, X-ray crystallography of the colorless crystals of both **2c** (shown in Figure 3) and **2l** (see Supporting Information for details) were achieved, which unambiguously confirmed the structures of the obtained 2*H*-azirine compounds.

A plausible mechanism for the above azirination process is shown in Scheme 1. Initially, enamine compound **1** would

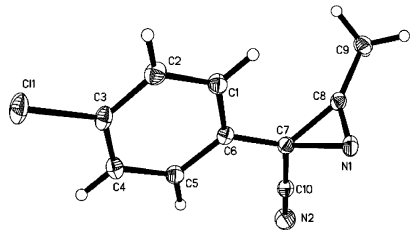
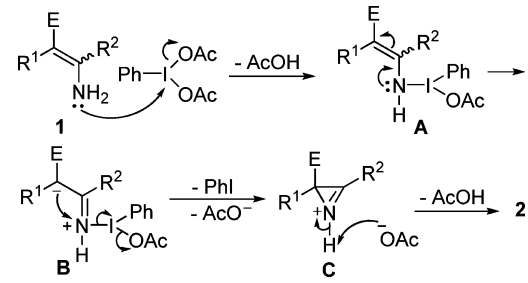


Figure 3. X-ray crystallography of 2*H*-azirine **2c**.

Scheme 1. Proposed Pathway for the Azirination of Enamine Derivatives **1**



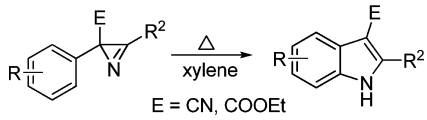
react with PIDA to form intermediate **A** by losing one equivalent of AcOH. Then tautomerization of **A** would generate an imine ylide **B**, in which the carbanion could be greatly stabilized by the electron-withdrawing substituents (E groups). Next, the carbanion would nucleophilicly attact the nitrogen center, with the concomitant release of phenyl iodide and acetate anion, to produce intermediate **C**. Finally, the positively charged nitrogen atom in **C** was deprotonated by the acetate anion and thereby gave the title 2*H*-azirine compounds **2**. Based on the fact that an ethoxycarbonyl group is less electron-withdrawing than a *cyano* or an acetyl group, we tentatively propose that the unsuccessful or low-yield azirination of **1o**−**p** or **1n** might be explained by the fact that the cabanions in corresponding **B** (if formed) would act more strongly as bases to seize a proton, rather than as nucleophiles to attack the nitrogen center.

It is worth noting that the substituted 2*H*-azirine-2-carbonitriles (**2a**−**i**) achieved by our approch should be superior to the classic Neber reaction in that the requisite α-*cyano* ketone oximes for the Neber process were unstable and always afforded the intramolecularly cyclized 5-aminoisoxazole derivatives in the reaction system.[3b,10]

One important application of the obtained 2-aryl-2*H*-azirine derivatives **2** we can envisage is to transform them into various indole compounds via a thermal rearrangement[3a−h] or metal-catalyzed isomerization process.[3i−k] Thus pyrolysis of various prepared 2-aryl-substitued 2*H*-azirine derivatives was tested in xylene under N_2 protection. The results listed in Table 2 demonstrated that by heating in xylene at 140 °C, all 2-aryl-2*H*-azirine-2-carbonitriles (**2a-g**, Table 2) could be efficiently rearranged to the correponding indole-3-carbonitriles in good yields. For the *meta*-substituted 2*H*-azirine **2d**, a mixture of 7-substituted and 5-substituted regioisomeric indole products were both achieved, in a yield of 70 and 20%, respectively.

For substrate **2n**, in which E represents an ethoxycarbonyl group, the indole product **3n** was obtained in relatively low yield (42%), with concominant formation of other unidentified byproducts. Unfortunatly, no desired indole product was detected when the thermolysis of **2m** was conducted in the same way. The deactivation of the aromatic ring by the *nitro* group might be the reason for the failure of the expected rearrangement process under thermolysis

Table 2. Preparation of 3-Functionalized Indoles **3** via Thermolysis of 2-Aryl-2*H*-azirines (E = CN or COOEt)[a]



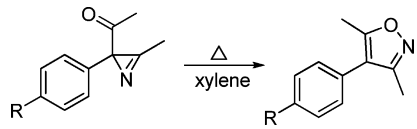
		indole **3**					
entry	**2**	R	R^2	E		time (h)	yield (%)[b]
1	**2a**	H	Me	CN	**3a**	10	85
2	**2b**	6-F	Me	CN	**3b**	4	90
3	**2c**	6-Cl	Me	CN	**3c**	5	94
4	**2d**	5-Cl/7-Cl	Me	CN	**3d/3d′**	5	72/20
5	**2e**	6-Br	*n*-Pr	CN	**3e**	6	88
6	**2f**	6-Cl	4-Cl-Ph	CN	**3f**	12	85
7	**2g**	4-Me	Me	CN	**3g**	6	92
8	**2n**	H	Bn	COOEt	**3n**	6	42

[a] Conditions: all reactions were carried out in xylene at 140 °C under N_2. [b] Isolated yields after silica gel chromatography.

conditions, and future studies should be directed to the use of metal catalysis[3i−k] for this conversion.

To our surprise, an exceptional result was obtained for the thermolysis of the 2*H*-azirine compounds, where E was an acetyl group. Under identical conditions, substrate **2j-l** underwent an intramolecular O−N bond formation, which resulted in the formation of isoxazole derivatives[11] (**3j-l**, Table 3) in pleasant yields (80−92%),without any detection of the desired indole compounds. Literature survey implied that these results were consistent with previous reports on the thermolysis of such similar azirine compounds.[12]

Table 3. Formation of Isoxazoles via Thermolysis of 2-aryl-2*H*-azirines (E = acetyl group)



entry	**2**	isoxazole **3**	time (h)	yield(%)[b]
1	**2j**	**3j** (R = H)	6	86
2	**2k**	**3k** (R = OMe)	6	80
3	**2l**	**3l** (R = NO_2)	4	92

[a] Conditions: all reactions were carried out in xylene at 140 °C under N_2. [b] Isolated yields after silica gel chromatography.

To summarize, we demonstrated herein the first example of intramolecular azirination of enamine derivatives by using PIDA as the oxidant. The obtained 2-aryl-2*H*-azirine-2-carbonitriles could readily undergo the known thermal rearrangement process[3a−h] to afford a variety of indole-3-carbonitriles, which might be useful building blocks in the synthesis of complex indole compounds.

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Supporting Information Available: Detailed experimental procedures and spectral data for all new compounds and X-ray structural data of **2c** and **2l**. This material is available free of charge via the Internet at http://pubs.acs.org.

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