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Oxidation

NIS/PhI(OAc)$_2$-Mediated Diamination/Oxidation of *N*-Alkenyl Formamidines: Facile Synthesis of Fused Tricyclic Ureas

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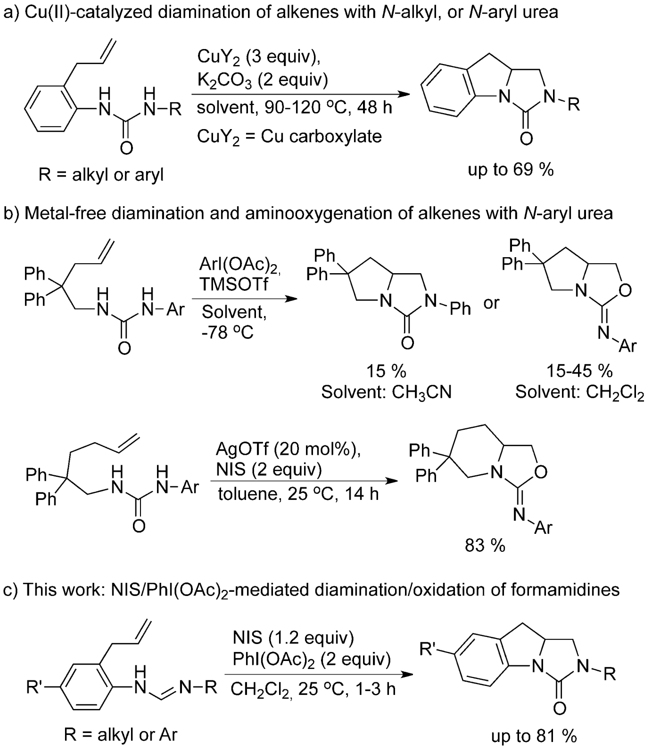
Abstract: Facile synthesis of bicyclic ureas by NIS/PhI(OAc)$_2$-mediated diamination/oxidation of N-alkenyl formamidines is reported. Bulky aromatic groups such as 2,6-diisopropylphenyl and mesityl and alkyl groups were tolerated towards the process. Several control experiments have been performed, and the reaction outcomes indicate that the oxidation process is probably concerted with the diamination cyclization, and succinimide generated from NIS-mediated aminoamidiniumation step promoted the PhI(OAc)$_2$-mediated oxidation step. The new methodology provides an efficient method for the synthesis of fused tricyclic ureas.

Vicinal diamines occur in a variety of bioactive molecules and natural products, and serve as building blocks in organic transformations as well as chiral ligands for stereoselective synthesis.[1] Direct difunctionalization of alkenes is clearly an attractive route to generate vicinal diamines,[2] and, since 2005, increasing attention has been paid to the development of efficient catalytic procedures for Pd^{II}-,[3] Cu^{II}-,[4] Ni^{II}-,[5] and Au^{I}-mediated[6] intramolecular diamination of alkenes. Very recently, metal-free difunctionalization of alkenes has also been established to circumvent the toxicity and cost associated with metal catalysts. Muñiz et al. reported the intramolecular diamination and aminooxygenation of alkenes with *N*-sulfonyl ureas in the presence of the iodonium reagent IPy$_2$BF$_4$ (Py = pyridine).[3d] Widenhoefer et al. further employed *N*-iodosuccinimide (NIS) as an efficient promoter for the intramolecular diamination and alkoxyamination of alkenes with *N*-sulfonyl ureas.[7] Hennecke et al. also reported an intramolecular *anti*-selective diamination reaction of alkenes in the presence of NIS.[8] Recently, Muñiz et al. presented the intramolecular diamination of alkenes with *N*-Boc sulfamides and *N*-sulfonyl ureas employing bromide catalysis with sodium chlorite as an oxidant.[9] Michael et al. reported an intramolecular aminooxygenation of alkenes with ureas using PhI=O and an acid promoter.[10] Wirth et al. also developed the stereoselective aminooxygenation of alkenes with ureas using an ArI(OAc)$_2$/acid system.[11] Chang et al. employed PhI(OAc)$_2$ and a halide additive to improve the intramolecular diamination of alkenes with *N*-sulfonyl ureas.[12]

Most employed alkene substrates in these processes are those having a second *N*-sulfonyl or *N*-carbamate substituent, and very few cases involved those with a second *N*-alkyl or *N*-aryl substituent. *N*-alkyl or *N*-aryl bicyclic ureas could be obtained by Cu^{II}-mediated intramolecular diamination of an alkene,[4] but excess metal oxidant, a high temperature, and an extended reaction time are required to achieve considerable yields (a, Scheme 1). Metal-free methods for intramolecular dia-



Scheme 1. Intramolecular diamination of alkenes with *N*-alkyl or *N*-aryl substrates.

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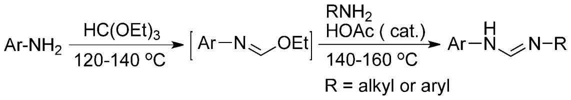
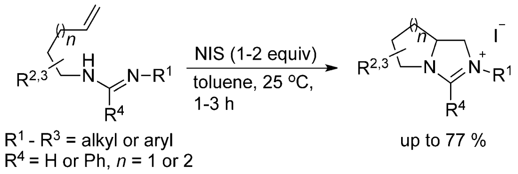
mination of alkenes with *N*-alkyl or *N*-aryl ureas are still rare and often suffer from the formation of aminooxygenation products and poor yield (b, Scheme 1).[7,11]

Recently, we have developed several synthetic strategies for the facile preparation of various N-heterocyclic carbene precursor azolium salts starting from formamidines.[13] Formamidines could be prepared readily from one-pot condensation reactions of two primary amines and orthoformate, and have only two nitrogen reactive sites (Scheme 2). Therefore, we envisiond that formamidines could be used as nitrogen sources for the intramolecular diamination of alkenes. Herein, we report an unprecedented NIS/PhI(OAc)$_2$-mediated diamination/oxidation of *N*-alkenyl formamidines for the synthesis of bicyclic ureas, in which succinimide generated from the NIS-mediated aminoamidiniumation step promoted the PhI(OAc)$_2$-mediated oxidation step (c, Scheme 1).



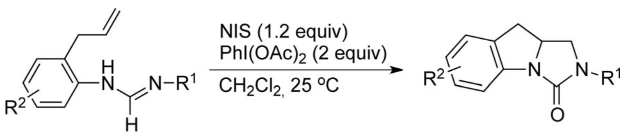
Scheme 2. Synthesis of *N,N'*-disubstituted formamidines.

Very recently, we found an efficient NIS-mediated aminoamidiniumation of amidines for the synthesis of bicyclic imidazolidinium salts (Scheme 3).[14] Besides NIS, PhI(OAc)$_2$ has also been widely employed in both transition metal-catalyzed and Lewis acid-promoted intramolecular difunctionalization of alkenes, due to its high oxidation potential. Therefore, we further examined the reactivity of NIS towards the process in the presence of PhI(OAc)$_2$. Interestingly, combining NIS with PhI(OAc)$_2$ as oxidant led to unexpected formation of bicyclic ureas **2** (Table 1). It was shown that bulky aromatic substituents such as 2,6-diisopropylphenyl and mesityl groups (for **2a** and **2b**, Table 1) and alkyl groups (for **2c**–**2e**, Table 1) were tolerated towards the process. Introducing a methoxy group in the N-aryl substituent resulted in a substrate with lower reactivity (for **2f** and **2g**, Table 1), while, with formamidines **1h** and **1i** bearing a methyl group in the N-aryl substituent, the method proved to be more efficient, and the desired products **1h** and **1i** were formed in good yields (for **2h** and **2i**, Table 1). This result indicates that the presence of a methoxy group in the N-aryl substituent probably led to a lower stability of the intermediate and/or product. Unfortunately, the methodology did not work with N-4-pentenyl formamidine **1j** (Entry 10, Table 1). The structure of **2d** was identified by NMR spectroscopic comparison with an authentic sample.[4b]

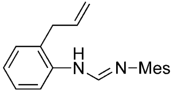
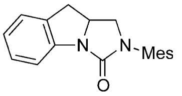
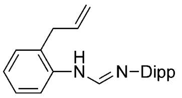
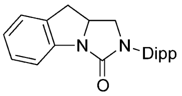
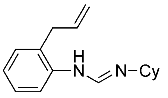
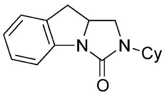
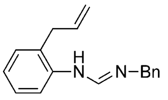
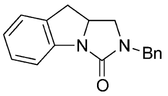
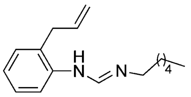
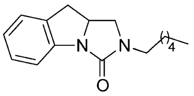
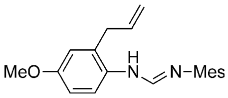
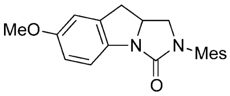
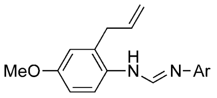
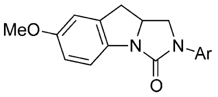
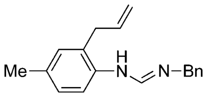
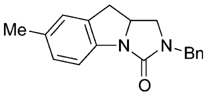
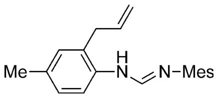
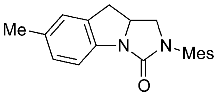
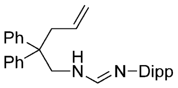
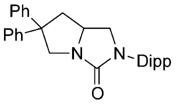


Scheme 3. NIS-mediated aminoamidiniumation of amidines.

Table 1. NIS/PhI(OAc)$_2$-mediated diamination/oxidation of N-alkenyl formamidines: facile syntheses of fused tricyclic ureas.[a]



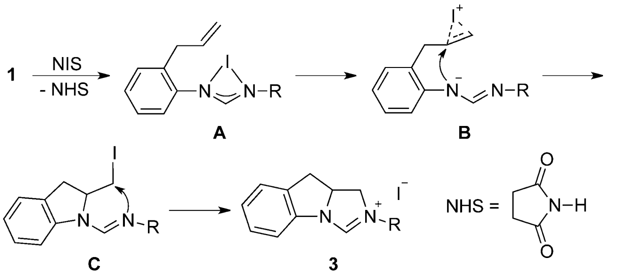
1 **2**

Entry	Starting Material		Product [%][b]	
1		**1a**		**2a** (81)
2		**1b**		**2b** (58)
3		**1c**		**2c** (52)
4		**1d**		**2d** (77)
5		**1e**		**2e** (34)
6		**1f**		**2f** (35)
7	 Ar = 2,6-Et$_2$-Phenyl	**1g**	 Ar = 2,6-Et$_2$-Phenyl	**2g** (30)
8		**1h**		**2h** (81)
9		**1i**		**2i** (77)
10		**1j**		**2j** (0)

[a] Reaction conditions: 1 equiv of NIS, CH$_2$Cl$_2$ (0.1 M), 25 °C, 2–3 h. [b] Isolated yields.

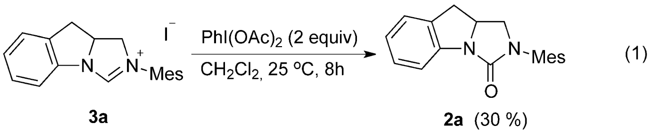
A plausible reaction mechanism for the NIS-mediated aminoamidiniumation is as follows (Scheme 4).[14] Formamidine **1** reacts with NIS to afford an N-iodinated formamidine **A**, the N-I group of which further oxidizes the double bond of the alkene to form a cyclic iodinium ion **B**. Intermediate **B** subsequently undergoes a nucleophilic backside attack of the nitrogen atom to give cyclic formamidine **C**. Intermediate **C** undergoes amidiniumation and closes the second ring to generate aminoamidiniumation product **3**.

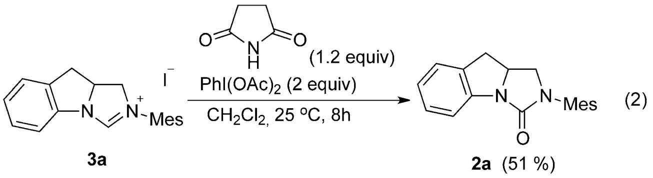
Several control experiments were designed to investigate the mechanism of the unexpected diamination/oxidation process. Firstly, aminoamidiniumation product **3a**, prepared from

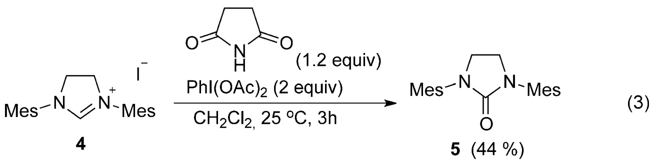


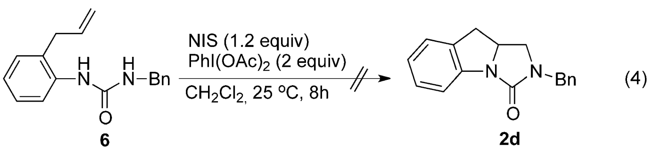
Scheme 4. Proposed reaction mechanism.

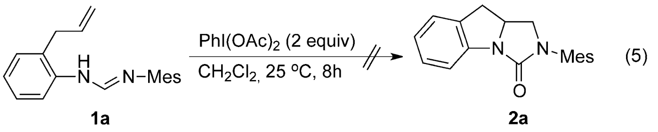
NIS-mediated aminoamidiniumation of **1 a**, was treated with $PhI(OAc)_2$ (2 equiv), and a low yield (30%) was obtained [Eq. (1)]. Considering the transformation of NIS into succinimide during the aminoamidiniumation process and the potential reactivity of succinimide towards $PhI(OAc)_2$,[2r,15] we further reacted **2 a** with $PhI(OAc)_2$ (2 equiv) in the presence of succinimide (1.2 equiv), and an improved yield of 51% was achieved [Eq. (2)]. Although the yield is still lower than that obtained under the reaction conditions of the one-pot diamination/oxidation of **1 a**, it should be noted that succinimide, a byproduct generated from the NIS-mediated aminoamidiniumation step, promoted the $PhI(OAc)_2$-mediated oxidation step. The method also worked for the transformation of monocyclic imidazolidinium salt **4** into the corresponding monocyclic urea **5** [Eq. (3)]. Next, urea **6** was subjected to the standard reaction conditions of the diamination/oxidation process, and the desired product **2 d** was not observed. This excludes the possibility of oxidation of the C1 atom occurring as the initial step [Eq. (4)]. Finally, $PhI(OAc)_2$ (2 equiv) itself could not transform formamidine **1 a** into urea **2 a** [Eq. (5)].





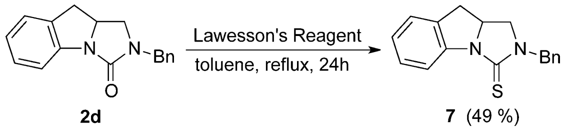






These reaction outcomes indicate that the oxidation process is probably concerted with the diamination cyclization, and succinimide generated from aminoamidiniumation step promoted the oxidation step. The diamination/oxidation process presents a sustainable synthetic strategy to improve the synthetic efficiency and allows the byproduct of one reaction to be used to promote another reaction in a one-pot reaction.

The synthetic utility of fused tricyclic ureas **2** was preliminarily investigated. Imidazolidine-2-thiones have been reported to exhibit a diverse range of biological and pharmaceutical activities,[15] and represent excellent ligands in bioactive coinage metal complexes.[16] Treatment of **2 d** with Lawesson's reagent smoothly afforded the desired thiourea **7** (Scheme 5).



Scheme 5. Transformation of urea **2 d** into thiourea **7**.

In conclusion, we present an unprecedented NIS/$PhI(OAc)_2$-mediated diamination/oxidation of *N*-alkenyl formamidines for the synthesis of fused tricyclic ureas, in which succinimide generated from the NIS-mediated aminoamidiniumation step promotes the $PhI(OAc)_2$-mediated oxidation step. The resulting tricyclic urea could be readily converted into a tricyclic thiourea. The methodology provides efficient ways for the facile synthesis of fused tricyclic ureas and fused tricyclic thioureas.

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Keywords: alkenes · aminoamidiniumation · deamination · *N*-iodosuccinimide · oxidation

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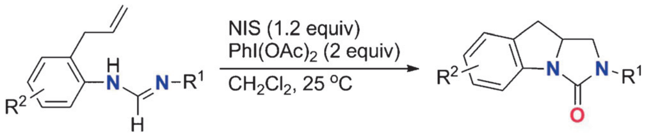

As simple as riding a tricycle: Facile synthesis of fused tricyclic ureas by NIS/PhI(OAc)$_2$-mediated diamination/oxidation of N-alkenyl formamidines is reported. In this approach, succinimide, the byproduct of the diamination step, functions to promote the oxidation step.

Oxidation

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■■–■■

NIS/PhI(OAc)$_2$-Mediated Diamination/Oxidation of *N*-Alkenyl Formamidines: Facile Synthesis of Fused Tricyclic Ureas