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Iodoamination

Facile Syntheses of N-Heterocyclic Carbene Precursors through I_2- or NIS-Promoted Amidiniumation of *N*-Alkenyl Formamidines

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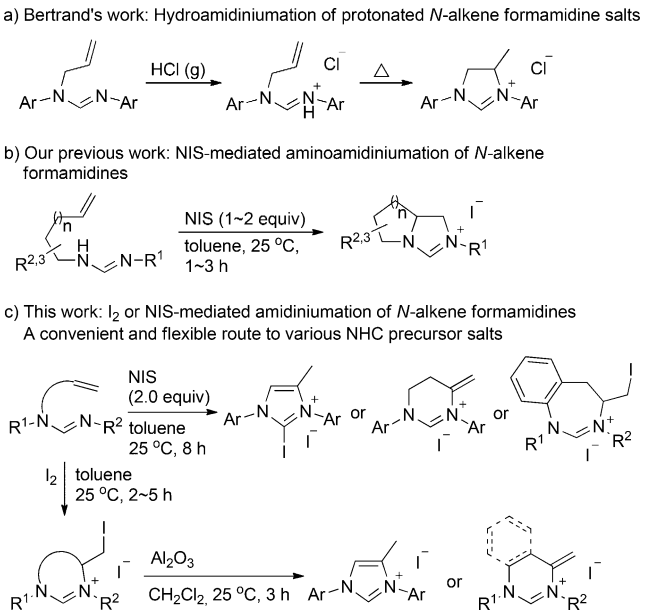
Abstract: We have developed I_2- or *N*-iodosuccinimide (NIS)-mediated amidiniumation of *N*-alkenyl formamidines for the syntheses of cyclic formamidinium salts, some of which could be directly used as N-heterocyclic carbene (NHC) precursors. Treatment of iodine-containing formamidinium salts with Al_2O_3 led to the formation of cyclic formamidinium salts with an unsaturated backbone. A rhodium(I) complex ligated by a representative NHC was prepared by the reaction of $[Rh(cod)Cl]_2$ (cod = 1,5-cyclooctadiene) with the free carbene obtained in situ from deprotonation of the corresponding formamidinium salts. The NHCs prepared in situ can also react with S_8 to afford the corresponding thiones.

Over the last decade, N-heterocyclic carbenes (NHCs) have been paid much attention due to their widespread and spectacular applications as ligands for organometallic catalysis and as organocatalysts.[1] Since the steric and electronic properties of NHCs play a prominent role in catalysis, a variety of fascinating new NHCs with different scaffolds have been developed, in which of special interest are electronic and steric variations resulting from different backbone structures and substituents on the NHCs.[1h,2] The deprotonation of the heterocyclic ring precursor is by far the most commonly used method to obtain a free or ligated NHC, and the most frequently used precursor of NHC is cyclic formamidinium salt.[2b]

We have developed several synthetic strategies for the synthesis of various NHC precursor salts through cyclization of functionalized formamidines, such as *N*-alcohol,[3–5] *N*-carbonyl,[6,7] and *N*-alkynyl formamidines.[8] Bertrand and co-workers reported that protonated *N*-alkenyl formamidines could undergo cyclization under gentle heating, resulting in the cyclic formamidine salts, which are potentially direct precursors of NHCs (Scheme 1 a).[9] Very recently, we found an efficient *N*-iodosuccinimide (NIS) mediated aminoamidiniumation of *N*-alkenyl formamidines for the synthesis of bicyclic imidazolidinium salts (Scheme 1 b).[10] Herein, we report I_2- or NIS-mediated amidiniumation of *N*-alkene formamidines for the syntheses of cyclic formamidinium salts, some of which were previously unknown and which could be used directly as NHC precursors (Scheme 1 c). Treatment of iodine-containing formamidinium salts with Al_2O_3 led to the formation of cyclic formamidinium salts with an unsaturated backbone. The synthetic methodology was applied to synthesize a novel bisimidazolidinium salt. A rhodium(I) complex ligated by a representative NHC can be prepared by the reaction of $[Rh(cod)Cl]_2$ (cod = 1,5-cyclooctadiene) with the free carbene obtained in situ. The transformation of the resulting NHCs into the corresponding thiones is also presented.



Scheme 1. Synthetic strategies for the synthesis of various NHC precursor salts through cyclization of *N*-alkenyl formamidines.

Iodine reagents are often used to activate and oxidize alkenes through the formation of halonium ions and have been successfully applied in the aminohalogenation of alkenes.[11] We started our investigation by allowing I_2 to react with *N*-

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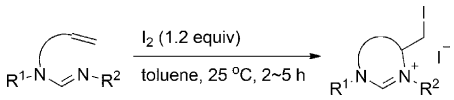
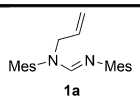
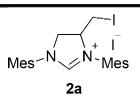
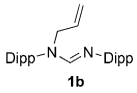
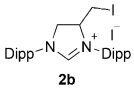
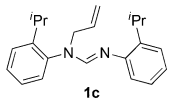
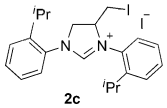
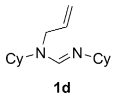
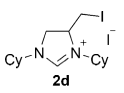
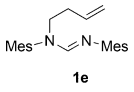
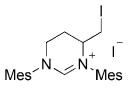
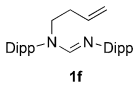
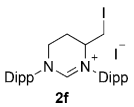
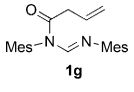
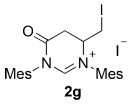
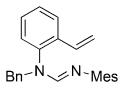
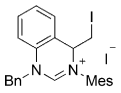
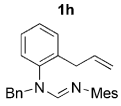
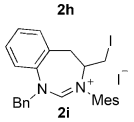
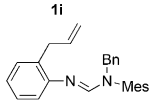
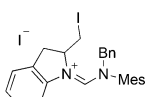
alkene formamidines **1a**–**1j**, which were synthesized through alkylation or acylation of the *N*,*N*′-diarylformamidines (Scheme S1, see the Supporting Information). I_2 (1.2 equiv) efficiently promoted the iodoamination cyclization of *N*-alkenyl formamidines to afford iodine-containing formamidinium salts. Formamidines with sterically demanding aryl N substituents, such as mesityl (Mes) and 2,6-diisopropylphenyl (Dipp) groups, were reactive under the applied conditions (Entries 1 and 2, Table 1). Formamidine **1c** having an *ortho*-monosubstituted aryl group at the nitrogen atom also underwent cyclization to afford the corresponding five-membered imidazolinium salt **2c** in moderate yield (Entry 3, Table 1). Besides aryl groups, an alkyl group at the nitrogen atom was also tolerated (Entry 4, Table 1). Further study revealed the methodology also allowed access to six-membered 3,4,5,6-tetrahydropyrimidinium salts **2e** and **2f** with sterically demanding aryl N substituents (Entries 5 and 6, Table 1). Six-membered formamidinium salts **2g** with a carbonyl-containing backbone and **2h** with a fused benzene ring at the backbone also could be obtained by the method in moderate yield (Entries 7 and 8, Table 1). Iodoamination cyclization of *N*-2-allylphenyl **1i** afforded seven-membered formamidinium salt **2i** (Entry 9, Table 1), while **1j**, the isomer of **1i**, underwent cyclization to give an acyclic formamidinium salt **2j** (Entry 10, Table 1). The X-ray crystal structures of **2h**, **2i**, and **2j** confirmed their constitutions (Figure 1–3).

Table 1. I_2-mediated amidiniumation of *N*-alkene formamidines.[a]



Entry	Starting Material	Product (Yield)[b]	
1	 **1a**	 **2a**	(69%)
2	 **1b**	 **2b**	(67%)
3	 **1c**	 **2c**	(51%)
4	 **1d**	 **2d**	(64%)
5	 **1e**	 **2e**	(85%)
6	 **1f**	 **2f**	(85%)
7	 **1g**	 **2g**	(67%)
8	 **1h**	 **2h**	(73%)
9	 **1i**	 **2i**	(43%)
10	 **1j**	 **2j**	(68%)

[a] Reaction conditions: 1.2 equiv I_2, toluene, 25 °C, 2–5 h. Cy = cyclohexyl, Bn = benzyl. [b] Isolated yields.

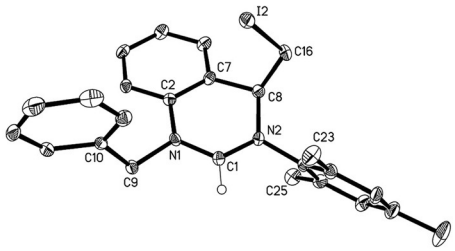


Figure 1. Molecular structure of **2h** with ellipsoids set at 20% probability. The counterion (I^-) and H atoms in aryl rings have been omitted for clarity.

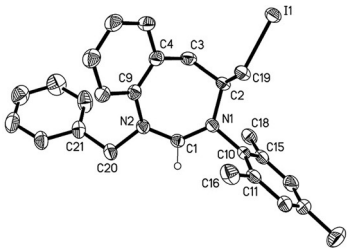


Figure 2. Molecular structure of **2i**·$C_6H_5CH_3$ with ellipsoids set at 20% probability. The counterion (I^-), $C_6H_5CH_3$, and H atoms in aryl rings have been omitted for clarity.

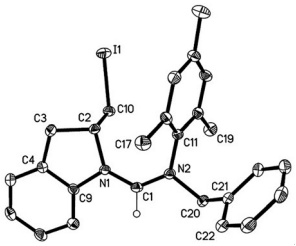
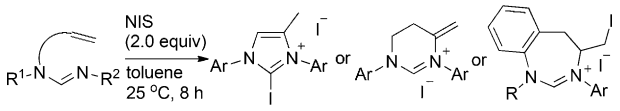
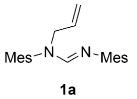
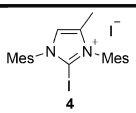
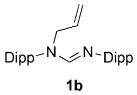
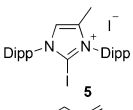
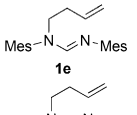
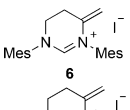
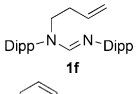
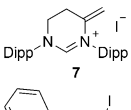
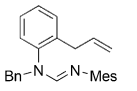
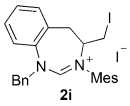
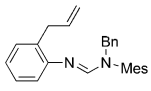
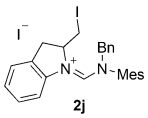


Figure 3. Molecular structure of **2j** with ellipsoids set at 20% probability. The counterion (I^-) and H atoms in aryl rings have been omitted for clarity.

Next, NIS was examined in the iodoamination cyclization of *N*-alkene formamidines (Table 2). In contrast to the I_2-mediated iodoamination cyclization, under activation of NIS, *N*,*N*′-diaryl formamidines **1a** or **1b** underwent cyclization to afford 2-iodo imidazolium salts **4** or **5**, respectively (Entries 1 and 2, Table 2). Treatment of *N*-3-butenyl formamidine **1c** and **1d** with NIS led to the formation of six-membered formamidinium salt **6** and **7**,

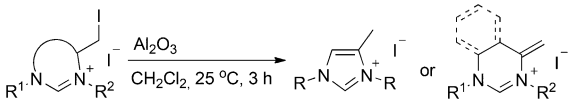
Table 2. NIS-mediated amidiniumation of *N*-alkene formamidines.[a]

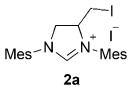
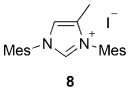
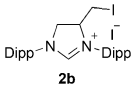
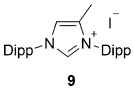
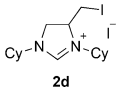
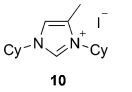
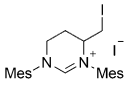
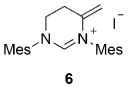
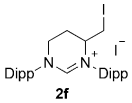
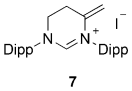
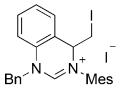
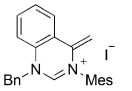


Entry	Starting Material	Product	Yield[b]
1[c]	 **1a**	 **4**	(72%)
2[c]	 **1b**	 **5**	(82%)
3	 **1e**	 **6**	(46%)
4	 **1f**	 **7**	(92%)
5	 **1i**	 **2i**	(47%)
6	 **1j**	 **2j**	(32%)

[a] Reaction conditions: 2.0 equiv of NIS, toluene, 25 °C, 8 h. [b] Isolated yields. [c] 60 °C

Table 3. Synthesis of various unsaturated NHC precursors through HI elimination of iodine-containing NHC precursors.[a]



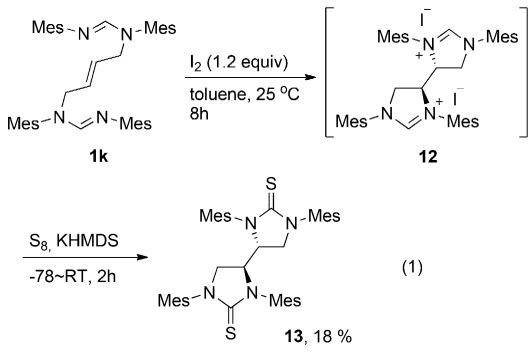
Entry	Starting Material	Product	Yield[b]
1	 **2a**	 **8**	(35%)
2	 **2b**	 **9**	(90%)
3	 **2d**	 **10**	(70%)
4	 **2e**	 **6**	(97%)
5	 **2f**	 **7**	(95%)
6	 **2h**	 **11**	(74%)

[a] Reaction conditions: Al_2O_3, CH_2Cl_2, 25 °C, 3 h. [b] Isolated yields.

respectively, having an exomethylene group (Entries 3 and 4, Table 2). Cyclization products **4**–**7** probably resulted from the HI elimination of the corresponding iodine-containing cyclic formamidinium salts **2a**, **2b**, **2e**, and **2f**. The HI elimination may be promoted by succinimide, a byproduct often released from NIS-mediated reactions. NIS-mediated iodoamination of **1i** and **1j** resulted in the same cyclization products **2i** and **2j** as in I_2-mediated cyclization (Entries 5 and 6, Table 2). The structure of **4** was confirmed by the X-ray crystallography (Figure S1 in the Supporting Information).

With iodine-containing cyclic formamidinium salts in hand, we further evaluated their reactivity. Recently, Diaba and Bonjoch et al. reported an Al_2O_3-promoted transformation of γ-iodoamines, iodoaminocyclization products of β-aminoalkenes, into β-aminoalcohols.[12] Interestingly, under treatment of alumina (Al_2O_3), instead of alcohol-containing product, five-membered imidazolinium salts **2a**, **2b** and **2d** smoothly underwent HI elimination, leading to the formation of the corresponding imidazolium salts **8**–**10** through HI elimination (Entries 1–3, Table 3). Six-membered formamidinium salts **6**, **7**, and **11** having an exomethylene group were obtained through HI elimination of **2e**, **2f**, and **2h**, respectively (Entries 4–6, Table 3).

Using the established iodoamination cyclization method, we could also synthesize a kind of novel bisimidazolinium salt. Treatment of vinylene-bridged *N*-Mes bisformamidine **1k** with I_2 resulted in the formation of a bisimidazolinium salt **12**. The in situ prepared **12** subsequently underwent the deprotonation by $KN(SiMe_3)_2$ (KHMDS) and after reaction with S_8 afforded a dithione compound **13**, the structure of which has been confirmed by NMR and HRMS analyses [Eq. (1)]. ^{1}H NMR analysis of **13** exhibits only one set of proton signals in the aliphatic regions, indicating a symmetric structure of **13**. The ^{13}C NMR signals for C=S appear at $\delta = 181.7$ ppm for **13**. Imidazolidine-2-thiones are important vicinal diamine derivatives, which exhibit a wide range of biological and pharmaceutical activities,[13] represent supported ligands in bioactive coinage metal complexes,[14] and serve as important precursors for the preparation of guanidines.[15]



1k **12** **13**, 18 %

We further attempted to synthesize an *N*-Dipp counterpart of bisimidazolinium salt **12**. Disappointingly, when we treated *N*-Dipp bisformamidine **1l** with I_2, we obtained only a mixture

of several cyclization products which were difficult to separate. All attempts to purify the products failed. NIS was then examined in the transformation. Treatment of **1l** with three equivalents of NIS afforded a new kind of cyclization product **14** [Eq. (2)]. X-ray crystallography reveals there is only one five-membered formamidine salt formed in **14** (Figure 4), probably due to the presence of the two bulkier *N*-Dipp substituents in **1l**, preventing the second cyclization process.

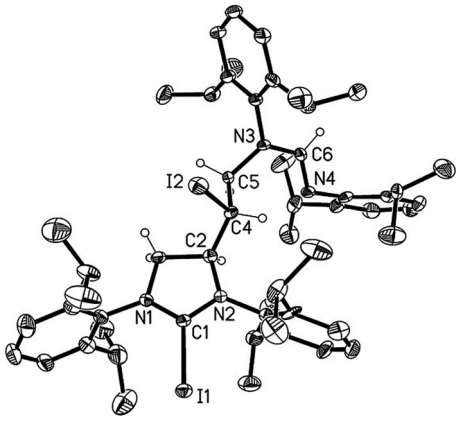
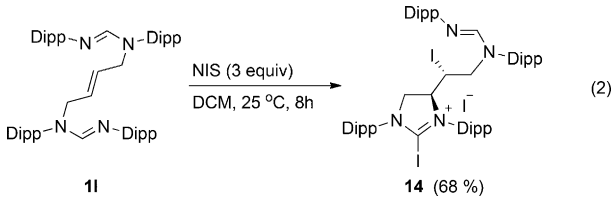


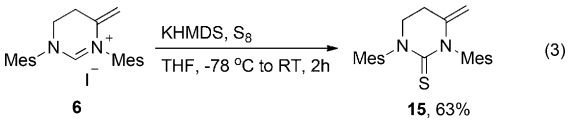
Figure 4. Molecular structure of **14** with ellipsoids set at 20% probability. The counterion (I^-) and H atoms in aryl rings have been omitted for clarity.



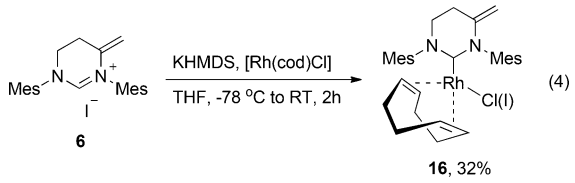
(2)

With the novel formamidinium salts in hand, particularly six-membered **6** having an exomethylene group, we could investigate the reactivity of their corresponding NHCs toward elemental sulfur (S_8). The formamidinium salt **6** was chosen as starting material. The reaction between S_8 and the free carbene prepared in situ from deprotonation of **6** by KHMDS led to the formation of the desired thione **15** [Eq. (3)]. The ^{13}C NMR signal for C=S appears at $\delta = 176.8$ ppm for **15**. The ability of the new six-membered NHC to ligate a transition-metal fragment was also examined. Treatment of the in situ generated free carbene with $[Rh(cod)Cl]_2$ gave the expected NHC complex **16** [Eq. (4)].

In conclusion, we present I_2- or NIS-mediated amidiniumation of *N*-alkenyl formamidines for the synthesis of cyclic formamidinium salts, some of which could be directly used as



(3)



(4)

NHC precursors. Treatment of iodine-containing formamidinium salts with Al_2O_3 led to the formation of cyclic formamidinium salts with unsaturated backbones. Rhodium(I) complex ligated by a representative NHC was prepared by the reaction of $[Rh(cod)Cl]_2$ with the free carbene obtained in situ from the deprotonation of the corresponding formamidinium salts. The NHCs prepared in situ can also react with S_8 to afford the corresponding thiones.

Acknowledgements

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Keywords: alkenes · iodine · iodoamination · N-heterocyclic carbenes · *N*-iodosuccinimide

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