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Synthesis of 4- and 4,5-Functionalized Imidazol-2-Ylidenes from a Single 4,5-Unsubstituted Imidazol-2-Ylidene

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Abstract

Using the nucleophilicity of NHCs and aNHCs, as well as the leaving group ability of the former, the carbon-carbon double bond of imidazol-2-ylidenes can be readily mono- and di-functionalized. These results provide also a new light on the formation of abnormal carbene adducts from classical unsaturated NHCs.

Since the discovery by Arduengo *et al.* of the stable 1,3-diadamantyl imidazol-2-ylidene (**1**, R = Ad),[1,2] a myriad of the so-called unsaturated N-heterocyclic carbenes (NHCs) has been prepared, and numerous applications have been found.[3] Because of the commonly practiced synthetic routes, most unsaturated NHCs feature an unsubstituted carbon-carbon double bond or alternatively alkyl or aryl groups are placed at the 4 and 5 positions.[4] The rare exceptions are imidazol-2-ylidenes annulated to a quinone derivative (**A**)[5] or a heterocycle (such as **B** and **C**),[6] the oxazoline-derivatives (**D**, **E**),[7] and NHCs featuring one (**F**, **G**)[8] or two (**H**)[9] heavier main group elements.

Interestingly, it has been shown that the substituents at the carbon-carbon double bond have a dramatic influence on the electronic properties of the carbene center. For example, the dichlorinated derivatives **H** are exceptionally stable, and are certainly the only carbenes that can be handled in air.[9a] Therefore, practical synthetic strategies, allowing the access to symmetrically and unsymmetrically 4- and 4,5-functionalized imidazol-2-ylidenes are highly desirable. Herein we report a convenient route to a variety of these compounds from a single precursor, namely a 4,5-unsubstituted imidazol-2-ylidene of type **1** (Ar = 2,6-diisopropylphenyl, Dipp).[10] In addition, the mechanism of formation of the so-called abnormal carbene-adducts is discussed.

The syntheses of NHCs **A–E** follow classical methods, using precursors already featuring the desired backbone. In contrast, NHCs **F–H** are obtained in a single operation from the corresponding 4,5-unsubstituted NHCs of type **1**. The latter results are reminiscent of the discovery by Crabtree that 2-pyridylmethylimidazolium salts react with $IrH_5(PPh_3)_2$ to give a complex in which the imidazole ring bound the “wrong way” at C5 and not at C2 (Scheme 1, top).[11] The mechanism of formation of C5-bound adducts is still obscure, whether a transition metal is involved or a main group elements as in **F–H**.[12] These adducts correspond to a formal rearrangement of imidazol-2-ylidene **1** into its isomeric C5-deprotonated imidazolium, a so-called abnormal carbene (*a*NHC), followed by addition of the electrophile, and finally deprotonation at C-2. However, the rearrangement of **1** is very unlikely since it is well established that the isomeric *a*NHC is some 70–80 $kJmol^{-1}$ higher

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Supporting Information Available. Full experimental details; X-ray crystallographic data for **4a** and **4f** in CIF format. This material is available free of charge via the internet at htpp://pubs.acs.org.

in energy, corresponding to a pKa value for the C5- proton (~ 33) 9 units higher than that for the C2 proton in the parent imidazolium salt;[13] moreover, a 1,3-hydrogen shift would certainly be energetically costly.[14] Therefore, it is clear that the formation of *a*NHCs can only be favored if the C2-position is protected, and indeed we have recently shown that *a*NHC **2** can be prepared and even isolated (Scheme 1, bottom).[15]

With the aim of tuning the electronic properties of *a*NHCs, we chose to vary the C2-substituent, using NHC **1** (Ar = Dipp) as a starting material. Addition of one equivalent of benzoyl chloride to **1** cleanly afforded the corresponding adduct **3a**. However, deprotonation of **3a** with potassium hexamethyldisilazide at −78 °C did not lead to the expected *a*NHC **2a**, but to its isomeric NHC **4a**, which was isolated in 64% yield (Scheme 2). Its structure was determined unambiguously by single crystal X-ray diffraction (Fig. 2). A plausible mechanism to rationalize these results involves the deprotonation of **3a** with formation of *a*NHC **2a** as a fleeting intermediate. The latter then acts as a nucleophile toward **3a**, generating the bis-adduct **5a** along with **1**. NHC **1** can act as a nucleophile towards the former leading to the observed 4-substituted NHC **4a**, and regenerating the starting material **3a**. To confirm the viability of this hypothesis, stable *a*NHC **2** was added to the 2-benzoyl imidazolium **3a**, and indeed the formation of the penta-substituted imidazolium salt **5b** was observed along with NHC **1**. Then, imidazolium salt **5a**, prepared by addition of benzoyl chloride to **4a**, was reacted with **1**, which led to C5-substituted imidazol-2-ylidene **4a** and C2-substituted imidazol-2-ylidene **3a**.

The scope of this reaction is quite general as shown in Scheme 3. A variety of C4-functionalized NHCs **4a–f** were prepared in moderate to good isolated yields (not optimized). Of special interest, both electron-withdrawing and -donating groups can be used to functionalize the carbon-carbon double bond of NHCs.

These results prompted us to investigate the possibility of using the same synthetic strategy to place two functional groups at the carbon-carbon double bond. As a proof of principle, 4-diphenylphosphino-NHC **4f** was treated with benzoyl chloride, affording the 2-benzoyl-4-diphenylphosphino-imidazolium salt **6** (86% yield). Subsequent treatment with hexamethyldisilazide gave the 4-benzoyl-5-diphenylphosphino imidazol-2-ylidene **7** in 51% isolated yield (Scheme 4).

When combined with the recent discovery of modular syntheses of N,N′-unsymmetrically substituted imidazolium salts,[4] these results pave the way for the preparation of NHCs with virtually any substitution pattern. Particularly appealing is the possibility of placing strong electron-withdrawing groups, such as trifluoromethane sulfonyl, which should decrease the σ-donor and increase the π-acceptor ability of NHCs. Moreover, these results provide a new light on the formation of abnormal carbene adducts from classical unsaturated NHCs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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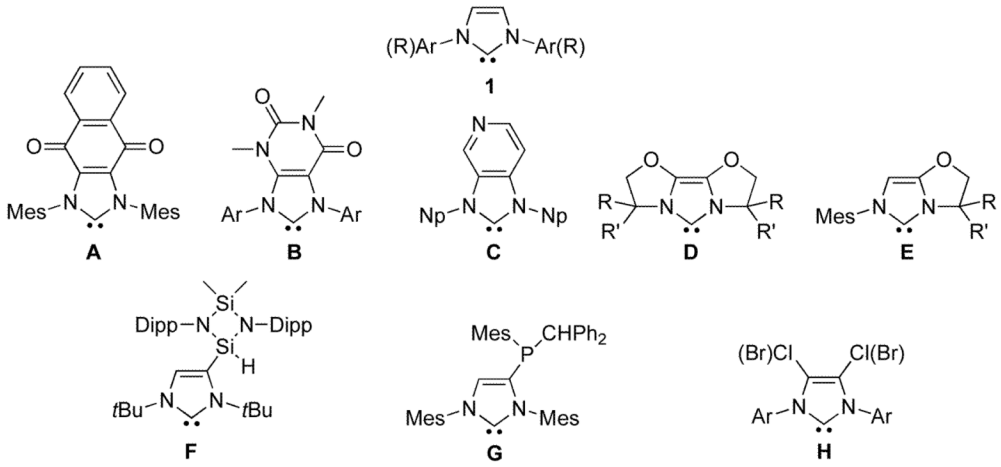


Figure 1.

Imidazol-2-ylidenes **1** and its derivatives **A**–**H** featuring C4 and/or C5 substituents different from H, alkyl, and aryl groups.

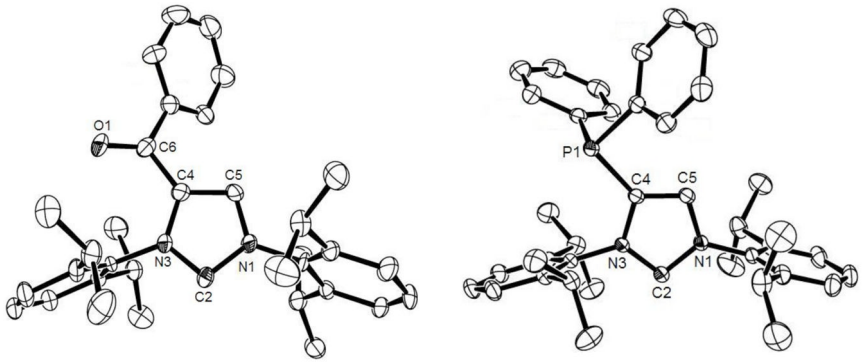
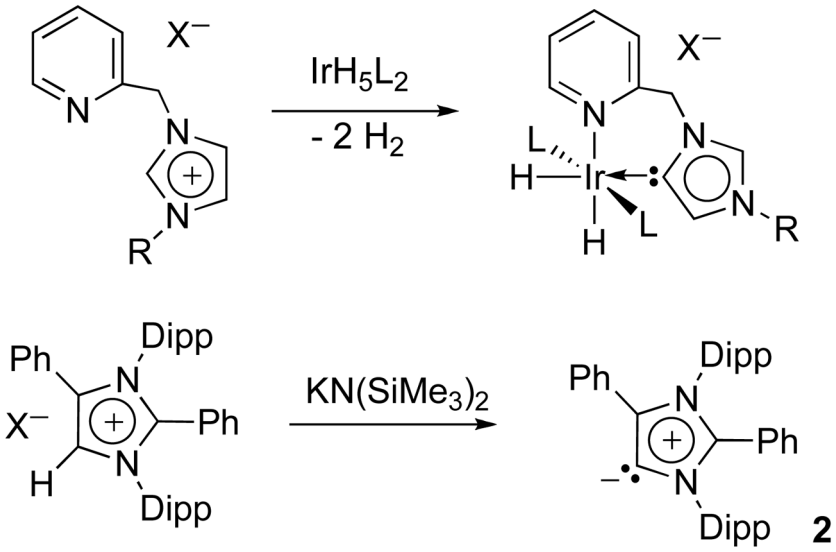
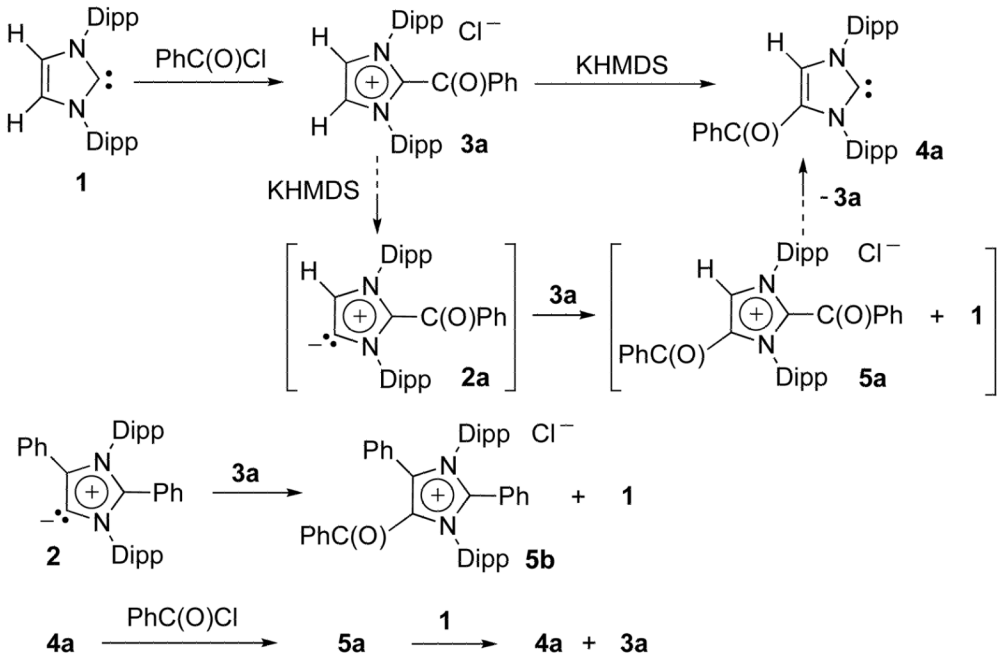


Figure 2.

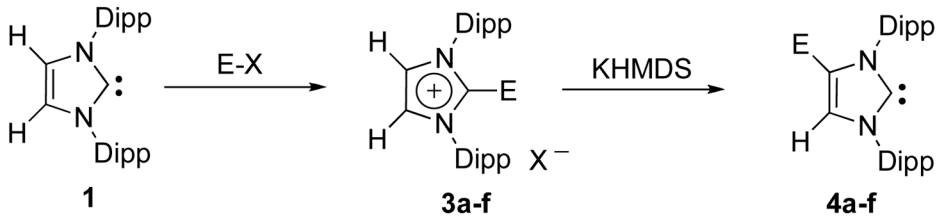
Molecular structures of **4a** (left) and **4f** (right) in the solid state (hydrogen atoms are omitted for clarity; ellipsoids are drawn at 50% probability). Selected bond lengths [Å] and angles [°]; **4a**: N1-C2 1.372(8), N3-C2 1.351(8), N3-C4 1.389(8), N1-C5 1.380(8), C4–C5 1.366(10), C4–C6 1.464(9), C6-O1 1.229(7), N1-C2-N3 101.9(5), **4f**: N3-C2 1.3695(15), N1-C2 1.3714(15), N1-C5 1.3848(15), N3-C4 1.4071(14), C4–C5 1.3510(17), C4-P1 1.8124(12), N3-C2-N1 101.31(9).



Scheme 1.

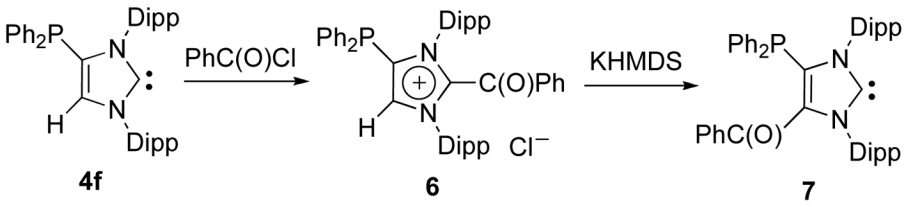


Scheme 2.



		a	b	c	d	e	f
	E	PhC(O)	Cl	Br	CF_3SO_2	Me_3Si	Ph_2P
	X	Cl	Cl	Br	CF_3SO_3	CF_3SO_3	Cl
yield (%)	**3**	79	83	86	72	80	77
	4	64	42	39	72	35	57

Scheme 3.



Scheme 4.