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Reactivity of a *N*-heterocyclic carbene, 1,3-di-(1-adamantyl) imidazol-2-ylidene, with a pseudo-acid: structural characterization of Claisen condensation adduct†

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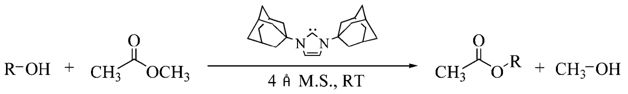
The reactivity of a *N*-heterocyclic carbene (NHC) with a pseudo-acid (ester in this case) is described. The product results from an unusual C–H bond activation. The structure of the product has been established by a single crystal diffraction study.

Significant advances have been achieved in the area of *N*-heterocyclic carbenes (NHC) since the initial work of Wanzlick[1] and the first successful isolation of a NHC by Arduengo.[2] Numerous studies on neutral singlet carbenes[3] have suggested that the major contributor to their stabilization is the π–π electron donation from the nitrogen electron-pairs into the formally vacant π orbital of the carbenic carbon, making it nucleophilic.[4] Apart from extensive use in organometallic chemistry,[5] the NHCs have also been known to act as organic catalysts.[6,7] We and Hedrick have described the use of NHCs as efficient catalysts for transesterification reactions.[8] The activity of different NHCs and of their precursors in catalyzing transesterification reactions involving alcohols and esters has been reported.[9] Amongst NHCs, we have highlighted IAd (IAd = 1,3-di-(1-adamantyl)-imidazol-2-ylidene) as an effective catalyst leading to quantitative conversions at room temperature (Scheme 1).

On the basis of the behavior of NHCs in catalysis revolving around the transesterification reaction, we were interested to determine the reactivity of these compounds with methyl esters. Herein, we wish to report a preliminary synthetic and structural study dealing with NHCs and esters. We have observed that the alkyl-substituted NHC, IAd, reacts with excess methyl acetate at room temperature to give a white solid, insoluble in low polarity organic solvents. The ^{1}H-NMR of the resulting compound in THF-d$_8$ shows a downfield proton resonance at 11.1 ppm characteristic of imidazolium salts (the resonance corresponding to the tetrafluoroborate salt is 8.6 ppm). At this point we speculated that IAd might possibly be involved in abstraction of a proton α to the carbonyl of methyl acetate, to form an enolate species.

To unequivocally establish the structure of the product (**I**), single crystal X-ray diffraction studies were performed on crystals grown from toluene (Fig. 1).[10] The existence of the proton on the carbenic carbon (C2), present at low field in the ^{1}H-NMR was confirmed by the X-ray structure. The C(2)–N(1) and C(2)–N(3) bond distances are 1.333(2) and 1.338(19) Å respectively as compared to the known value of 1.32 Å for the imidazolium salt. The N–C–N bond angle (109.26° (13)) is also in agreement with the known value (109.7°) for the corresponding imidazolium salt.[2]



Scheme 1 IAd catalyzed transesterification.

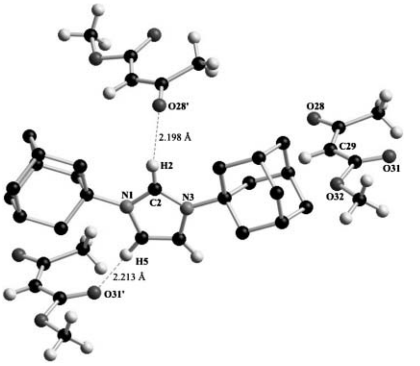


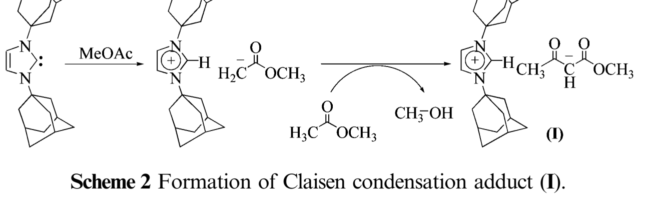
Fig. 1 Solid state structure of the Claisen condensation adduct (**I**).[11]

An unusual hydrogen bond at the C5 position of the imidazole backbone was also observed. The carbonyl oxygen (O31′) from the Claisen carbanion from a neighbouring adduct interacts with the hydrogen on C5 (H5), (Fig. 1). The H(5)–O(31′) bond distance is 2.213(15) Å. Such reactivity at C5 in NHCs is reminiscent of unusual C5 bound metal–NHC complexes. Lebel *et al.* have synthesized "abnormal" C5 bound palladium–NHC complexes and reported them to be active mediators of Suzuki and Heck cross-coupling reactions.[12] Crabtree and Faller have prepared similar C5 bound Ir(I) and Ir(III)–NHC complexes.[13]

Apart from the H(5)–O(31′) hydrogen bond, the formation of a second hydrogen bond from the proton on the carbenic carbon (C2) is also observed. The alkoxy oxygen (O28′) from the counterion of the symmetry generated adduct forms a hydrogen bond with H2, further stabilizing the structure. The H(2)–O(28′) bond distance is 2.198(16) Å. Presumably, the negative charge on the carbanion is dispersed *via* the H bond network imparting stability to the product, allowing for the isolation and characterization of the adduct.

Evidently, in the presence of excess methyl acetate, this unstable enolate anion can attack another molecule of methyl acetate resulting in the formation of a Claisen condensation carbanion (in the solid state) (Scheme 2). In solution, the carbanion can exist as the more stable enolate with the negative charge dispersed on the central carbon and the two electronegative oxygen atoms (hydrogens of CO$_2$CH$_3$ and OCH$_3$ show resonances at 3.3 and 2.2 ppm respectively).

It should be mentioned that this type of reactivity of a NHC with a pseudo-acid leading to formation of a Claisen condensation adduct with stabilization *via* H bond formation has not been



Scheme 2 Formation of Claisen condensation adduct (**I**).

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† Electronic supplementary information (ESI) available: experimental details and X-ray data for **I**. See http://www.rsc.org/suppdata/cc/b4/b410986d/

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reported previously. Fürstner *et al.* have shown that the NHCs can co-exist with acidic C–H bond containing compounds.[14] In their efforts directed towards synthesis of *N*-ester and *N*-nitrile substituted carbenes they have indicated a lack of reactivity between NHC and esters. However, Clyburne and Davidson have isolated adducts from reaction of an aryl (mesityl) substituted NHC, IMes (1,3-di-(2,4,6-trimethylphenyl)imidazol-2-ylidene) with diphenylamine and 2,6-di-*tert*-butyl-4-methylphenol.[15] While amine was shown to make a neutral carbene–amine adduct, the phenol proceeded to protonate the NHC and form imidazolium aryloxide. In related work, the corresponding saturated NHC, SIMes (1,3-di-(2,4,6-trimethylphenyl)imidazolin-2-ylidene) was shown to undergo C–H insertion with acidic C–H bonds.[16]

This type of acid–base reactivity would be expected since alkyl-substituted NHCs are strong bases. Alder *et al.* have shown that 1,3-diisopropyl-4,5-dimethylimidazol-2-ylidene is a much stronger base than nitrogen bases such as DBN and DBU in DMSO-d$_6$ (pK_a = 24),[17] while Streitwieser and Kim determined a similar value for 1,3-di-*tert*-butylimidazol-2-ylidene (pK_a = 22.7).[18] Yates and Cavell have reiterated the claims of high basicity of NHCs in a recent report describing theoretically calculated pK_a values of various carbenes.[19] Amongst imidazol-2-ylidenes, the *N*-aryl substituted were found to be less basic (pK_a values 16.0–16.6 in DMSO) than their *N*-alkyl substituted counterparts. Although the pK_a value for IAd was not calculated, we believe that it has a pK_a similar to the reported upper end values for alkyl substituted NHCs (21–27 in DMSO) since it is able to deprotonate methyl acetate which has an approximate pK_a value of 24.[20] However, the behavior of NHCs with respect to pseudo-acids is less predictable for want of more fundamental studies on NHC basicity.

In conclusion, the *N*-heterocyclic carbene (IAd) behaves as a strong base abstracting a weakly acidic proton from methyl acetate giving the enolate species which, in excess methyl acetate, forms the Claisen condensation carbanion stabilized by hydrogen bond formation. Ongoing work includes labelling studies and reactivity studies of different NHCs with other organic pseudo-acids in particular aldehydes. Further elucidation of NHC reactivity behaviour with pseudo-acids would especially benefit understanding of systems such as the recently reported NHC catalyzed conversion of α-haloaldehydes to acylating agents by Rovis *et al.*, in which the formation of acyl-azolium intermediates *via* nucleophilic attack of the NHC on the carbonyl carbon of the α-haloaldehydes is described.[21] Such fundamental studies would possibly allow for the elaboration of this chemistry to other applications in organic synthesis.[22]

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10 X-Ray structure of **I**: colourless crystals, $[C_{23}H_{33}N_2]^+[C_5H_7O_3]^-$, FW = 452.62, monoclinic, space group $P2(1)/n$, a = 13.5366(13), b = 11.6995(12), c = 15.7153 Å, α = 90.00, β = 93.217(2), γ = 90.00, V = 2484.9(4) Å^3, Z = 4, λ(MoKα) = 0.71073 Å, μ = 0.078, ρ_{calcd} = 1.097 g cm^{-3}, T = 150(2) K, F(000) = 896. A single crystal was placed in a capillary tube and mounted on a Bruker SMART CCD X-ray diffractometer. Data was collected using Mo Kα radiation at 150 K. The structure was solved using direct methods (SHELXS-97)[23] (a total number of 32438 reflections of which 7384 independent reflections were collected (θ_{max} = 31.07°)) and refined by full-matrix least-squares techniques (SHELXL-97), 458 number of parameters, R_1 = 0.0266, wR_2 = 0.0740 (all data). All H atoms were refined isotropically. CCDC 244497. See http://www.rsc.org/suppdata/cc/b4/b410986d/ for crystallographic data in .cif or other electronic format.

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