Ammonia N–H activation by a N,N'-diamidocarbene†

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Received 29th March 2010, Accepted 16th April 2010 First published as an Advance Article on the web 18th May 2010 DOI: 10.1039/c0cc00638f

The synthesis and characterization of N,N'-dimesityl-4,6-diketo-5,5-dimethylpyrimidin-2-ylidene is reported; this crystalline N,N'-diamidocarbene was found to split ammonia and engage in other reactions not exhibited by typical N-heterocyclic carbenes.

The activation of industrially-important small molecules, such as ammonia and dihydrogen, has garnered considerable attention over the past two decades.¹ Historically, transition metals have been employed for such purposes,² although main group species capable of facilitating these transformations have been reported more recently.³ Of the two aforementioned small molecules, NH₃ activation remains relatively challenging due to the propensity to form stable Lewis acid–base adducts rather than undergo bond scission.⁴ Recently, Bertrand and co-workers revealed the potential of alkyl amino carbenes to overcome many of these obstacles, resulting in the only hitherto examples of metal-free NH₃ activation.⁵

Herein we demonstrate that readily-accessible N,N'-diamidocarbenes (DACs) split NH₃. These efforts are part of a burgeoning program aimed at expanding the reactivity exhibited by nucleophilic N-heterocyclic carbenes (NHCs)⁶ to include reactions typically displayed by traditional, electrophilic carbenes (e.g., methylidene). For example, we recently reported⁷ that DAC 1 (Fig. 1) exhibited substantial electrophilic character and could effect C–H insertions into unactivated tertiary alkyl groups, reversibly affix carbon monoxide (CO), and quantitatively couple with organic isocyanides to afford diamidoketenimines.

To facilitate our studies into small molecule activation, we sought an isolable DAC. Despite our best efforts, **1** was found to undergo an intramolecular C–H insertion with a methine group of its diisopropylphenyl *N*-substituents⁷ which complicated subsequent reactivity studies. We envisioned that a derivative featuring relatively less activated C–H bonds (*i.e.*, **2**) would



Fig. 1 Examples of N,N'-diamidocarbenes (DACs). Dipp = 2,6-(*i*Pr)₂-C₆H₃, Mes = 2,4,6-(Me)₃-C₆H₂.

inhibit intramolecular C-H insertion and enable access to a stable analogue.

While we were working toward the preparation of 2, Lavigne and co-workers reported⁸ an elegant synthesis of this compound, but encountered difficulties with its isolation. They noted that 2 underwent rapid decomposition upon its generation *via* deprotonation of 2·HCl in THF and must be trapped with S₈ or (Rh(COD)Cl)₂ (COD = 1,5-cyclooctadiene) at -40 °C. Based on our previous studies with 1, which also proved to be problematic when generated in THF,⁷ we reasoned that 2 may be accessed by performing the deprotonation reaction in a non-coordinating solvent.

To test this hypothesis, $2 \cdot \text{HCl}$ was first prepared using a modified procedure reported⁸ by Lavigne *et al.* (Scheme 1). In addition to various spectroscopic techniques,[†] the structure of $2 \cdot \text{HCl}$ was elucidated by X-ray crystallography (see Fig. 2). Close inspection of the solid state data revealed that the C1–Cl1 distance (1.888(2) Å) was relatively elongated compared to the average sp³ C–Cl bond (*ca.* 1.76 Å),⁹ suggesting that the Cl atom was weakly bound to the diamidomethine nucleus (see below for additional discussion).

Treatment of a suspension of 2·HCl in benzene with sodium hexamethyldisilazide (NaHMDS) followed by solvent removal and washing with cold hexanes afforded the desired N,N'-diamidocarbene (2) in 85% isolated yield.[‡] A salient spectroscopic feature of 2 was a low-field ¹³C resonance observed at $\delta = 277.7$ ppm (C₆D₆). This signal was assigned to the carbene nucleus (C1) and determined to be consistent with the



Scheme 1 Conditions: (i) dimethylmalonyl dichloride, Et_3N , CH_2Cl_2 , 0 °C, 1 h; (ii) NaHMDS, C_6H_6 , 25 °C, 30 min. Mes = 2,4,6-(CH_3)₃- C_6H_2 .



Fig. 2 ORTEP diagram of **2**·HCl with thermal ellipsoids drawn at 50% probability. H-atoms except for H1A have been omitted for clarity.

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[†] Electronic supplementary information (ESI) available: Additional synthetic procedures, spectroscopic data and X-ray crystallographic data. CCDC 770147–770151. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0cc00638f



Fig. 3 ORTEP diagram of **2** with thermal ellipsoids drawn at 50% probability. H-atoms have been omitted for clarity.

analogous signal exhibited by 1 (278.4 ppm, C₆D₆).⁷ FT-IR analysis revealed that the ν_{CO} displayed by 2 (1709 cm⁻¹; KBr) was at an energy intermediate of those exhibited by typical amides (*ca.* 1630–1695 cm⁻¹) and ketones (*ca.* 1710–1740 cm⁻¹). To gain additional insight into the structure of 2, X-ray quality crystals were obtained by slow vapor diffusion of hexanes into a toluene solution saturated with this compound. As shown in Fig. 3, the $C_{carbene}$ -N distances (avg. C1-N = 1.37 Å) were found to be significantly shorter than the N-Cacyl distances (avg. $N-C_{acvl} = 1.41$ Å). However, the C–O distances (avg. 1.21 Å) measured in the crystal structure of 2 were only slightly shorter than the analogous C-O distances found in the solid state structure of its amido precursor 2 HCl (avg. 1.22 Å). Collectively, the X-ray crystallography results supported the IR spectroscopic data which characterized the NCO groups in 2 as hybrids of canonical amides and ketones.§

Upon the synthesis and characterization of 2, its reactivity was explored. Similar to that observed with 1, DAC 2 engaged in reactions typically exhibited by electrophilic carbenes (Scheme 2). For example, bubbling CO through a toluene solution of 2 resulted in the immediate formation of a purple color ($\lambda_{max} = 543$ nm) consistent with the formation of N, N'-diamidoketene **3**.⁷ The observation of ¹³C resonances at $\delta = 91.7$ and 246.4 ppm (C₇D₈), corresponding to the carbenoid CCO and ketenoid CCO nuclei, respectively, and a $\nu_{\rm CO}$ = 2091 cm⁻¹ (C₇H₈) confirmed the formation of 3. Notably, this carbonylation reaction was determined to be reversible with a $K_{eq} = 4.78 \text{ M}^{-1}$ in C₇D₈ at 20 °C ($P_{CO} = 15 \text{ psi}$). In contrast, a thermally-robust compound $(mp = 153-154 \degree C)$ was obtained in excellent yield when 2 was treated with 2,6-dimethylphenylisocyanide. This product displayed diagnostic⁷ ¹³C chemical shifts at $\delta = 106.3$ and 202.7 ppm (C_6D_6) that were attributed to the CCN and CCN resonances of diamidoketenimine 4, respectively, as well as a characteristic IR stretching mode at $\nu_{\rm CCN} = 1978 \, {\rm cm}^{-1}$ (KBr).



Scheme 2 Synthesis of diamidoketene 3 and diamidoketenimine 4. *Conditions:* (i) CO, 25 °C, C_7D_8 ; (ii) CN-(2,6-(Me)₂-C₆H₃), 25 °C, C_7H_8 , 1 h. Ar = 2,6-(CH₃)₂-C₆H₃.



Scheme 3 Synthesis of 5. Conditions: (i) NH₃ (liq.), $-78 \text{ °C} \rightarrow 25 \text{ °C}$, 12 h.

Next, our attention shifted toward exploring the ability of **2** to activate NH₃. Condensing NH₃ at -78 °C onto solid **2** followed by slowly warming to ambient temperature over 12 h led to the formation of the desired product (**5**) in nearly quantitative yield (Scheme 3). The ¹H NMR (C₆D₆) spectrum of **5** featured a diagnostic triplet at $\delta = 5.22$ ppm (CH) and a broad doublet centered at 1.15 ppm (NH₂), results similar to those previously observed for the addition of NH₃ across a carbene nucleus.⁵ Additionally, the IR spectrum (KBr) featured two peaks at $\nu = 3415$ and 3339 cm^{-1} , which were consistent with N–H stretching modes of primary amines.¶

Single crystals suitable for X-ray diffraction analysis were obtained by cooling a hexanes : CH_2Cl_2 (2 : 1 v : v) solution saturated with **5** to -30 °C. As shown in Fig. 4, the C1 atom of the respective structure exhibited a high degree of pyramidalization ($\sum_{(N-C-N)} = 339.4^{\circ}$) indicating that the carbene nucleus rehybridized upon reaction with NH₃. Additionally, the C1–N3 distance (1.406(3) Å) was in good agreement with the analogous distance (1.428(7) Å) observed in the solid state structure of an adduct formed between an alkyl amino carbene and NH₃.⁵

To further explore the reactivities of DACs and their precursors, NH₃ was condensed into a toluene solution of 1



Fig. 4 ORTEP diagram of **5** with thermal ellipsoids drawn at 50% probability. H-atoms except for H1A and H3A have been omitted for clarity.



Scheme 4 Synthesis of 5 and 6. Conditions: (i) NH₃ (liq.), $-78 \text{ °C} \rightarrow 25 \text{ °C}$, 12 h.



Scheme 5 Proposed mechanism for the formation of NH₃ adducts 5 and 6 from their respective protonated precursors.

(generated in situ from 1·HCl and NaHMDS) at -78 °C, which resulted in the formation of the expected product (6) in high yield (Scheme 4). Similarly, condensing NH₃ onto solid 2. HCl, $1 \cdot HCl$ or [1H][OTf] (OTf = triflate) followed by warming to ambient temperature also resulted in the formation of 5 and 6, respectively, in excellent yields. The results of the reactions involving the HCl adducts or [1H][OTf] were in accord with previous observations^{7,8} that [1H][OTf] and 2 HCl readily react with alcohols and water to form the corresponding alkoxy or hydroxy adducts, respectively.[†] As such, we suspect that NH₃ added directly to the C1 position of [1H][OTf] (Scheme 5) or displaced the chloride atoms in the aforementioned HCl adducts via a nucleophilic type substitution reaction. || The latter is supported by the relatively long C-Cl bond length observed in the solid state structure of 2.HCl (Fig. 2), an indicator of a weakened chloride bond.

While it is tempting to surmise that the free DACs 1 and 2 reacted with NH₃ in a similar fashion as their protonated adducts (*i.e.*, *via* the formation of a Werner-type complex⁴), this requires the buildup of negative charge on the carbene nucleus. Alternatively, these DACs may be activating the N–H bond of NH₃ in a concerted fashion and in a manner analogous to that proposed for the CAACs.⁵ For example, **5** was observed to form rapidly upon bubbling NH₃ through a dilute solution of **2** in C₆D₆ ([**2**]₀ = 8.9×10^{-2} M, 25 °C).

Unfortunately, no reaction was observed between **2** and H_2 , even under forcing conditions (1000 psi H_2 , 200 °C) in C₆H₆ or 1,4-dioxane.** This lack of reactivity was surprising considering the similar bond-dissociation energies of NH₃ and H₂ (107 and 104 kcal mol⁻¹, respectively)^{10,11} and given that Bertrand's alkyl amino carbenes, a class of substrates that shares many similar reactivities as the DACs, were reported to activate both NH₃ and H₂.⁵ Further investigation is underway.

In conclusion, we report the synthesis and first solid state characterization of a free DAC, and demonstrate the ability of this carbene to split ammonia. These results expand the few known organic⁵ systems capable of activating an industrially important small molecule. An attractive feature of the substrates reported herein is that they can be obtained in high-yield over two steps starting from inexpensive, commercially-available materials and are readily-amenable to further modification. As a result, we believe that DACs offer promise in the development of new synthetic strategies for transforming NH₃ into structurally- and functionally-diverse nitrogen-containing compounds.

We are grateful to the National Science Foundation (CHE-0645563 and 0741973), the Robert A. Welch Foundation (F-1621), the Alfred P. Sloan Foundation, and the Arnold and Mabel Beckman Foundation for their generous financial support.

Notes and references

[‡] Using a similar protocol, **1**·HCl was prepared in 96% yield from N,N'-bis(2,6-di-isopropylphenyl)formamidine. DAC **1** was also generated *via* deprotonation of **1**·HCl with NaHMDS in aromatic hydrocarbons.

§ Under an inert atmosphere, **2** was found to be indefinitely stable in the solid state (mp = 166-168 °C; dec.) and for several days in solution (C₆D₆, C₇D₈ and 1,4-dioxane).

¶ A triazolylidene was reported to insert into the NH bond of morpholine, see: D. Enders, K. Breuer, G. Raabe, J. Runsink, J. H. Teles, J.-P. Melder, K. Ebel and S. Brode, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1021.

|| If the pK_{as} of the conjugate acids of the DACs described herein are significantly lower than those of typical NHCs (16-24),¹² carbene generation *via* NH₃-facilitated deprotonation (followed by NH₃ activation) may be possible. However, Et₃N was found to be insufficiently basic to generate **2** from **2**·HCl or **1** from [1H][OTf].

** At temperatures greater than 200 °C, DAC decomposition was observed and independently confirmed by performing analogous high temperature experiments under an inert atmosphere in sealed vessels.

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