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NHC-catalyzed silylative dehydration of primary amides to nitriles at room temperature†

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Herein we report an abnormal N-heterocyclic carbene catalyzed dehydration of primary amides in the presence of a silane. This process bypasses the energy demanding 1,2-siloxane elimination step usually required for metal/silane catalyzed reactions. A detailed mechanistic cycle of this process has been proposed based on experimental evidence along with computational study.

Nitriles are important functional groups due to their unique reactivity[1–3] and chemical compounds bearing a nitrile functional group are very useful precursors in the manufacture of a large variety of pharmaceuticals, agrochemicals, pigments, dyes, and various fine chemicals.[4–7] Synthesis of nitriles from primary amides or aldoximes is the most commonly used approach in the laboratory as well as in industry.[8–12] Numerous methods have been devoted to this interconversion, which were accomplished using harsh dehydrating reagents such as P_4O_{10},[13] $POCl_3$,[14] $(EtO)_2POCl$,[15] cyanuric chloride,[16,17] $SOCl_2$,[18] and $TiCl_4$[19] in a stoichiometric or excess amount. Recently, several research groups have reported the dehydration of primary amides into nitriles in a catalytic fashion.[20–30] One of the most frequently reported directions focuses on a silane-based dehydration strategy which is catalyzed by metals such as ruthenium, iron, potassium, or f-block elements (Fig. 1, eqn (1)).[20–29] In 2018, Buchwald and co-workers reported an efficient copper catalyzed silylative dehydration of primary amides to nitriles under ambient temperature.[31] However, to date no report is available on metal-free catalytic silylative dehydration of primary amides under ambient conditions.

Metal-free catalysis using N-heterocyclic carbene (NHC) has appeared as one of the attractive fields in organic synthesis in the last two decades.[32–34] As a part of our ongoing investigation to develop an alternative metal-free catalytic approach using abnormal NHC (*a*NHC)[35,36] for primary amide functionalization,[37] herein, we report the first catalytic silylative dehydration of primary amides to nitriles under ambient conditions using an *a*NHC as a metal-free catalyst. Abnormal N-heterocyclic carbene (2 mol%) displayed an excellent catalytic activity for a broad range of amides (30 examples) using silane under additive free conditions at room temperature (Fig. 1, eqn (2)). The idea of using the *a*NHC as a catalyst for dehydration of amides originated from its superior nucleophilic property[38] as well as from the fact that during the dehydration of primary amides using silane, dehydrogenation is known to be the first step.[31] Because of *a*NHC's higher nucleophilicity, it may interact with the electrophilic silicon center to activate the silane which in turn may facilitate a hydride transfer to accomplish the dehydrogenation process.

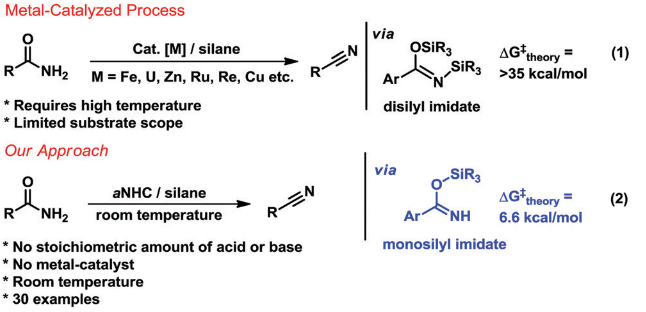

Fig. 1 An overview for the silylative dehydration of primary amides to nitriles (eqn (1)) and our approach (eqn (2)).

In this work, a systematic study was carried out to establish the best condition for the dehydration of amides, employing 2-methylbenzamide (**1a**) as a model substrate (Table 1). To start with, the experiments were conducted either in the absence of a catalyst or a silane revealing no conversion of the starting material (entries 1 and 2, Table 1). Alternatively, the catalytic activity was tested using commercially available catalysts such as pyridine (entry 3, Table 1), triethylamine (entry 4, Table 1) and triphenyl phosphine (entry 5, Table 1) in acetonitrile, which did not result in the formation of any nitrile product. In contrast, an excellent yield (89–94%) was observed when

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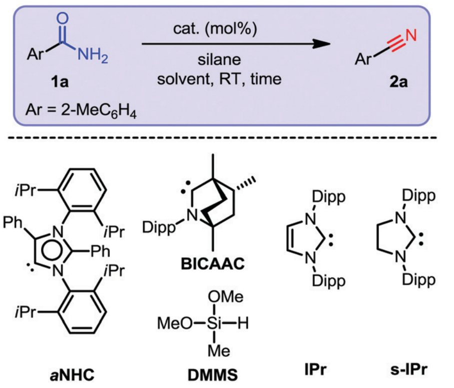
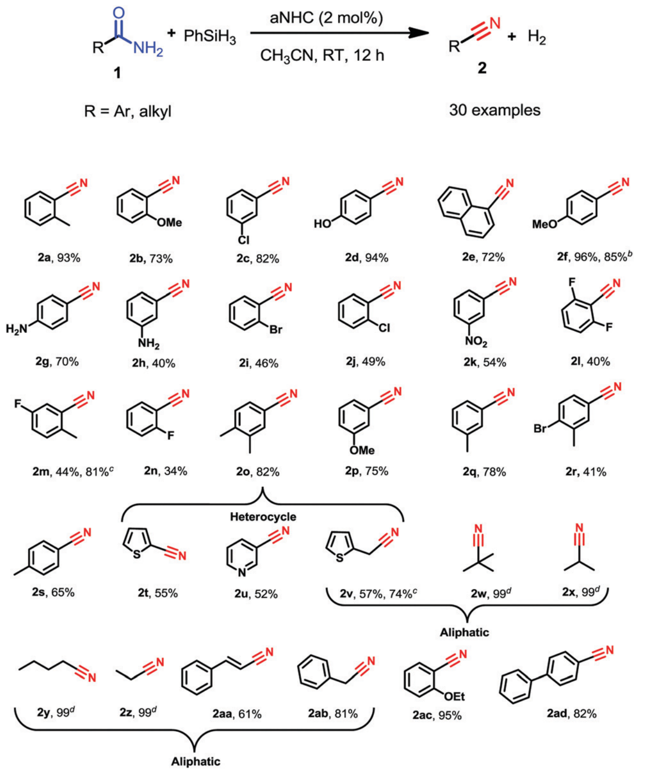
Table 1 Evaluation of conditions of silylative dehydration of primary amides[a]



Entry	Hydrosilane (equiv.)	Catalyst (mol%)	Solvent	Time (h)	Yield (%)
1	$PhSiH_3$ (2)	—	CH_3CN	12	—
2	—	*a*NHC (5)	CH_3CN	12	—
3	$PhSiH_3$ (1)	Pyridine (2)	CH_3CN	24	—
4	$PhSiH_3$ (1)	Et_3N (2)	CH_3CN	24	—
5	$PhSiH_3$(1)	PPh_3 (2)	CH_3CN	24	—
6	$PhSiH_3$ (1)	*a*NHC (2)	CH_3CN	24	94
7	$PhSiH_3$ (1)	*a*NHC (2)	THF	12	89
8	$PhSiH_3$ (1)	*a*NHC (2)	CH_3CN	12	93
9	$PhSiH_3$ (1)	BICAAC(2)	CH_3CN	12	73
10	$PhSiH_3$ (1)	BICAAC(2)	CH_3CN	24	87
11	$PhSiH_3$ (1)	BICAAC(2)	THF	12	35
12	$PhSiH_3$ (1)	s-IPr (5)	CH_3CN	24	48
13	$PhSiH_3$ (1)	IPr (2)	CH_3CN	12	14
14	Butylsilane (1)	BICAAC (2)	CH_3CN	12	11
15	PMHS (2)	BICAAC (5)	CH_3CN	24	—
16	PMHS (2)	*a*NHC (5)	CH_3CN	12	—
17	HMTS (2)	*a*NHC (5)	CH_3CN	24	—
18	DMMS (3)	*a*NHC (2)	CH_3CN	12	91
19	PMHS (5)	*a*NHC (5)	CH_3CN	24	77[b]

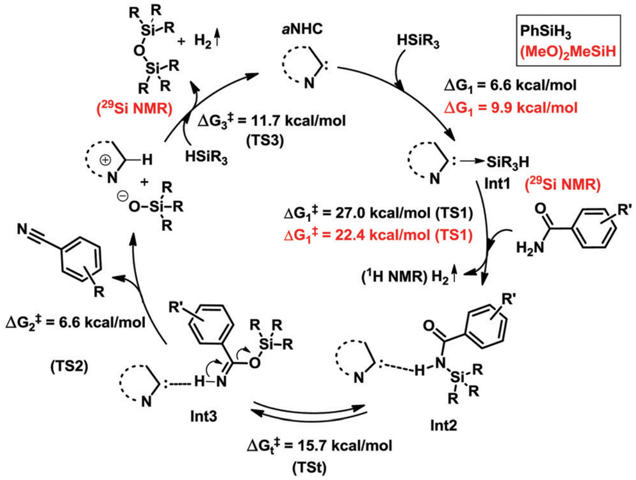
[a] All reactions were conducted with amide (0.5 mmol), phenylsilane (0.5 mmol), and dry solvent (1 mL). Isolated yields based on **1a**. [b] 4-Methoxybenzamide was used as a substrate.



Scheme 1 *a*NHC catalyzed silylative dehydration of primary amides.[a] [a]All reactions were conducted with amide (0.5 mmol), phenylsilane (0.5 mmol), and dry CH_3CN (1 mL). Isolated yields are reported next to the product number. [b]Gram scale reaction. [c]At 80 °C temperature. [d]NMR conversions.

2 mol% *a*NHC was introduced as a metal-free catalyst (entries 6–8, Table 1). The nitrile was obtained in 73% yield by employing bicyclic(alkyl)(amino)carbene (BICAAC) as a catalyst within 12 h (entry 9, Table 1) which was increased to 87% by elongating the reaction time (24 h, entry 10, Table 1). There was a decrease in reactivity when the reaction was attempted in THF (35%, entry 11, Table 1). Using the normal NHCs such as s-IPr and IPr bearing a diisopropylphenyl group on the nitrogen atoms exhibited a significantly lower catalytic activity (48% and 14%, respectively; entries 12 and 13, Table 1) under identical conditions, which clearly supports our assumption of superior nucleophilicity based catalytic activity.[35–37] Next, the performance of other hydrosilanes was also tested using BICAAC and *a*NHC. Butylsilane, PMHS, and heptamethyltrisiloxane (HMTS) did not result in product formation with appreciable yield (entries 14–17, Table 1). Inexpensive silane such as DMMS (dimethoxymethylsilane) or PMHS was employed for this study resulting in 91% or 77% yield (entries 18 and 19, Table 1), however, it required higher equivalents of silane (3 or 5 equiv. unlike $PhSiH_3$). From this study, it was established that *a*NHC is the most effective catalyst, delivering the best yield and we tested further substrate scope using this carbene as the catalyst. To explore the substrate scope, the silylative dehydration of various amides was investigated and the results are summarized in Scheme 1. Here we tested a variety of commercially available amides bearing electron-donating as well as electron-withdrawing substituents including substrates bearing a heterocyclic backbone. The reaction afforded nitriles in good to excellent isolated yields. Dehydration of amides, having an electron donating methyl group at the benzene ring delivered excellent to very good yields of nitrile derivatives **2a** (93%), **2o** (82%), **2q** (78%), and **2s** (65%). The methoxy group on the aromatic ring also delivered the nitrile products in good to excellent yields {**2b** (73%), **2f** (96%), and **2p** (75%)}. Under the reaction conditions, the substrate with an electron withdrawing group such as NO_2 on the aromatic ring afforded **2k** in 54% yield. Aromatic amides having electron-withdrawing chlorine, bromine and fluorine as a halogen group {**2c** (82%), **2j** (49%)}, {**2i** (46%), **2r** (41%)}, {**2l** (40%), **2m** (44%), **2n** (34%)} are also tolerated and showed intermediate reactivity or lower conversions under these optimized conditions. Substrates containing heteroatoms (**2t–2v**) exhibited moderate reactivity and resulted in 52–57% yields. A set of aliphatic amides **2w–2ab** was next assessed and successfully converted into the nitrile derivatives (yield >60%).

It may be noted that using our optimized conditions, 4-hydroxybenzamide delivered excellent yield (94%). Buchwald *et al.* listed the corresponding yields using classical and modern methods for the 4-hydroxybenzamide substrate[31] (2 mol% [Cu],



Scheme 2 Proposed mechanism for the *a*NHC catalyzed silylative dehydration of primary amides.

DMMS, rt, 80%; 5 mol% [Fe], DEMS, 100 °C, 23%; 5 mol% [Fe], DEMS, rt, <5%; $POCl_3$, Et_3N, rt, 27%; T_3P, 100 °C, 48%; 5 mol% TBAF, $PhSiH_3$, 100 °C, 8%; and 5% TBAF, $PhSiH_3$, rt, <5%). Finally, we have synthesized 4-methoxybenzonitrile **2f** in a gram-scale from 4-methoxybenzamide using 1 equivalent of silane at 25 °C. From the results presented in Scheme 1, it appears that the electronic influence of the substituents attached to the substrate plays a key role in the catalytic activity. Therefore, we attempted to correlate the structure–reactivity relationships for the catalytic dehydration of primary amides using Density Functional Theory (DFT) study (B3LYP method). Assuming the catalytic dehydration of amides is initiated by the nucleophilic attack of amide nitrogen to the electrophilic silicon centre, we looked at the atomic charges on the nitrogen atom of the corresponding amide. The electronic properties of the amides were calculated using the Natural Bond Orbital (NBO) model (see the ESI,† Fig. S65). For amides with electron-donating groups (EDGs), the negative charge on the nitrogen atom was expected to be high and the nucleophilic attack will be favourable to afford the higher yield. On the other hand, for amides with electron withdrawing groups (EWGs), a low anionic charge on the nitrogen was calculated (see the ESI,† Fig. S65) leading to low reactivity.[39]

A plausible catalytic cycle is proposed in Scheme 2. Each of the proposed steps is supported by DFT calculations and key steps are also substantiated by experimental evidences (see the ESI†). First, the *a*NHC forms an *a*NHC-silane adduct **Int1**.[40] In the presence of an amide, it undergoes dehydrogenation to form the *N*-silyl imidate with $\Delta G^{\ddagger}$ = 27 kcal mol^{-1} *via* TS1 (see the ESI,† Fig. S62). The *N*-silyl and *O*-silyl imidates readily equilibrate, according to the DFT study ($\Delta G^{\ddagger}_{t}$ = 15.7 kcal mol^{-1}).[30,31] Earlier, theoretical calculations had shown that the proton affinity of *a*NHC (287.0 kcal mol^{-1}) was significantly higher than that of normal NHC (229.9 kcal mol^{-1}).[38] Because of *a*NHC's strong proton affinity, it takes a proton from *O*-silyl imidate and rapidly eliminates the siloxide, which directly forms the desired nitrile product *via* TS2 ($\Delta G^{\ddagger}$ = 6.6 kcal mol^{-1}; C–N, 1.25 Å; C–O, 1.40 Å where in **Int3** C–N, 1.27 Å; C–O, 1.36 Å). Next, another molecule of silane may undergo activation by siloxide followed by a hydride transfer to the imidazolium salt with release of a hydrogen molecule leading to the formation of the siloxane byproduct (see the ESI,† Fig. S6) and regenerates the free *a*NHC catalyst.

In the present study, we have developed the first metal-free catalytic silylative dehydration of primary amides to nitriles at room temperature. We demonstrated that *a*NHC can act as an efficient metal-free catalyst for this dehydration process. This catalytic transformation enables dehydration of 30 different aromatic, heteroaromatic, and aliphatic amides using one equivalent of silane. Characterization of reaction intermediates supported by various experimental evidence and high-level DFT calculations helped us to delineate the mechanistic picture for this conversion.

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Conflicts of interest

There are no conflicts to declare.

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