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Catalytic Reductive Dehydration of Tertiary Amides to Enamines under Hydrosilylation Conditions

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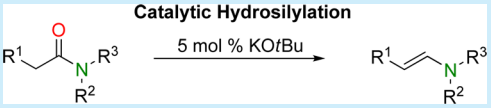
Supporting Information

ABSTRACT: Tertiary amides are efficiently reduced to their corresponding enamines under hydrosilylation conditions, using a transition-metal-free catalytic protocol based on *t*-BuOK (5 mol %) and $(MeO)_3SiH$ or $(EtO)_3SiH$ as the reducing agent. The enamines were formed with high selectivity in good-to-excellent yields.



Enamines are important organic compounds that can participate in a variety of essential transformations such as alkylation, acylation, conjugate addition, formation of heterocycles, and cycloaddition reactions.[1] Enamines can, through asymmetrical hydrogenation, give rise to chiral amines, which are important building blocks for the drug industry and can also serve as organocatalysts or chiral ligands.[2] The main route to enamines involves the direct condensation of an aldehyde or ketone with a secondary amine under Brønsted or Lewis acid catalysis.[1] However, this approach usually requires high reaction temperature, water scavengers, or azeotropic distillation, which prevents the use of heat-sensitive substrates and restricts the use of some functional groups.

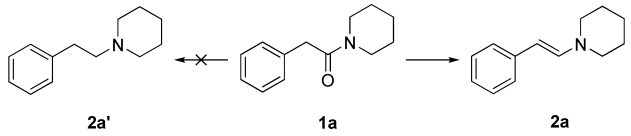
Recently Bélanger and co-workers reported a mild method for obtaining aldehyde-derived enamines.[3] They were able to carry out the reaction at low temperature (0 °C) in the presence of a large amount of molecular sieves (1.16 g/mmol of carbonyl compound). Katritzky et al. developed a mild two-step procedure for the formation of enamines with benzotriazole assistance.[4] Furthermore, a large amount of transition-metal-mediated cross-coupling reactions based on Buchwald–Hartwig-type amination with Pd or Cu catalysts have been reported for enamine formation.[5−8] Beller and co-workers demonstrated the use of $Rh(CO)_2(acac)$ (0.1 mol %) together with naphos (0.2 mol %) in the hydroaminomethylation of a variety of alkenes at relatively high CO/H_2 pressure to obtain enamines in high yields and selectivity.[9]

The catalytic reduction of amides with hydrosilanes is well-known in the literature, and this transformation usually leads to the formation of amines.[10] The direct formation of enamines from amides under hydrosilylation conditions is a reaction much less explored. Buchwald and co-workers developed a hydrosilylation protocol for the reduction of amides to aldehydes, where the initial product was characterized as an enamine.[11] The hydrosilylation was promoted by stoichiometric quantities of $Ti(O^iPr)_4$ in combination with Ph_2SiH_2.

The group of Nagashima has developed several catalytic hydrosilylation protocols for the reduction of amides and, in some cases, noticed that small amounts of enamines were formed as undesired byproducts.[12] Intrigued by this observation, they set out to find a selective catalytic method for the direct transformation of amides to enamines. In their successful study, $IrCl(CO)(PPh_3)_2$ (0.05 mol %) was employed together with 1,1,3,3-tetramethyldisiloxane (TMDS) or polymethylhydrosiloxane (PMHS) as hydride sources to reduce aliphatic and benzylic tertiary amides to enamines at room temperature.[13] To the best of our knowledge this is the only catalytic system that can carry out the direct transformation of tertiary amides to enamines via hydrosilylation in high selectivity and yield.

Recently we developed an efficient NHC/iron-based catalytic system for the reduction of tertiary benzamides to their corresponding amines under hydrosilylation conditions.[14,15] In this protocol, benzylic tertiary amide **1a** proved difficult to reduce. Instead of the expected amine product **2a′** we noticed the formation of enamine **2a** in trace amounts (Scheme 1), the rest being unreacted starting material.

Scheme 1. Direct Catalytic Transformation of Amides to Enamines



In an attempt to facilitate the reduction of substrate **1a**, the reaction temperature was increased from 65 to 120 °C. Still, this did not give any conversion to the amine; instead, an 87% selective conversion to enamine **2a** was observed.[16] Inspired by this interesting result we started to optimize the conditions. By varying the NHC (N-heterocyclic carbene) ligand, a 95% conversion to the enamine was obtained. However, high reaction temperature was still necessary. Investigation of various additives, surprisingly, showed that 20 mol % of lithium chloride could catalyze the reaction without addition of the iron catalyst.[16] More importantly, simple butyllithium could be used as a catalyst for the reduction of tertiary amides to enamines at a reaction temperature of 65 °C (Table 1, entry 1). Evaluation

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Table 1. Reduction of 2-Phenyl-1-(piperidin-1-yl)ethanone (1a) to (*E*)-1-Styrylpiperidine (2a) under Hydrosilylation Conditions[a]

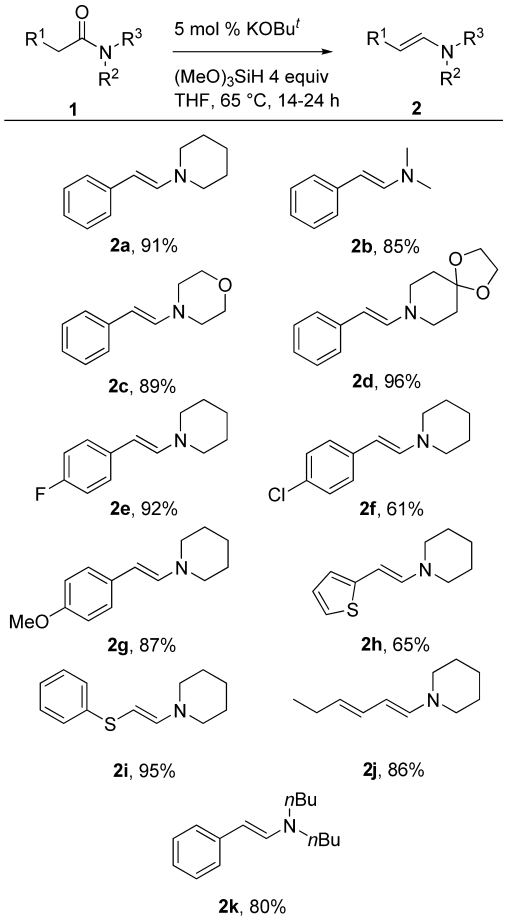
entry	catalyst	silane	solvent	conv (%)[b]
1	*n*BuLi	$(EtO)_3SiH$	THF	37
2	$KOBu^t$	$(EtO)_3SiH$	THF	>95
3	$KOBu^t$	$(EtO)_3SiH$	toluene	80
4	$KOBu^t$	$(EtO)_3SiH$	DCM	0
5	$KOBu^t$	$(EtO)_3SiH$	MeCN	0
6[c]	$KOBu^t$	$(EtO)_3SiH$	THF	43
7[c]	$KOBu^t$	$(MeO)_3SiH$	THF	63
8[c,d]	$KOBu^t$	$(MeO)_3SiH$	THF	74
9[c,d,e]	$KOBu^t$	$(MeO)_3SiH$	THF	90
10[c,d,e,f]	$KOBu^t$	$(MeO)_3SiH$	THF	>95
11[c,e,f]		$(MeO)_3SiH$	THF	0

[a]Reaction conditions: amide (1.0 mmol), dry solvent (3 mL), silane 3 equiv, catalyst (10 mol %), 65 °C, 14 h. [b]Conversion determined by ^1H NMR spectroscopy; [c]5 mol % $KOBu^t$. [d]$KOBu^t$ 99.99% purity was used. [e]2 mL of dry solvent was used. [f]$(MeO)_3SiH$ 4 equiv.

of different bases that could catalyze the reaction showed that potassium *tert*-butoxide was the most active and led to the highest conversion (Table 1, entry 2). Changing the solvent to CH_2Cl_2 or MeCN led to no conversion of the starting amide, while in toluene we observed a slightly lower conversion in comparison to reactions run in THF (Table 1, entries 2−5). Different silanes were compared as reducing agents (PMHS, TMDS, Ph_2SiH_2, $(EtO)_2MeSiH$),[16] and it was established that only triethoxy- and trimethoxysilane were active enough to perform the reaction (Table 1, entries 6 and 7).[17] To confirm that the catalyst (*t*-BuOK) is responsible for carrying out the reaction, we set up a blank experiment that resulted in zero conversion of the starting compound (Table 1, entry 11). To avoid the potential influence of transition metal impurities in the base, extra pure potassium *tert*-butoxide (99.99%) was employed in all further reduction reactions. The use of *t*-BuOK of higher purity also increased the conversion to enamine (Table 1, entries 7 and 8). Further investigation of silane equivalents and concentration dependence revealed the optimal conditions for this reaction (Table 1, entry 10). In order to simplify the process, a stock solution of the catalyst (*t*-BuOK 99.99%) in THF (0.2 M) was used.

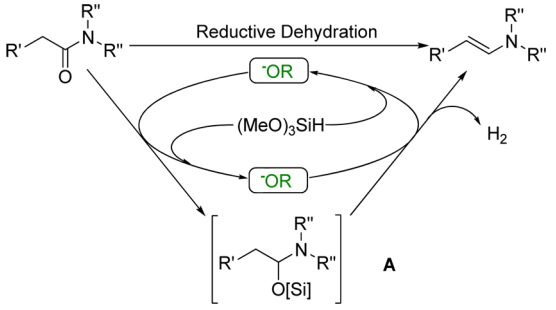
To investigate the scope of the reaction, a variety of different tertiary amides were reduced to enamines using the optimized reaction conditions (Scheme 2). As can be seen in Scheme 2, aromatic, heteroaromatic, and aliphatic enamines were formed from the corresponding tertiary amides in good-to-excellent selectivity and yields. The reaction with substrate **2a** was also carried out in 2-methyltetrahydrofuran as a more environmentally friendly solvent, without any decrease in yield.[18] Synthetically important aromatic halides that are sensitive to reduction remained untouched under the reaction conditions (**2e** and **2f**). Furthermore, enamine **2i**, derived from thiophenol-substituted amide, can be of great value in synthesis since it can lead to a more functionalized compound. Alkoxide-catalyzed hydrosilylation of aldehydes, ketones, and imines toward alcohols and amines has previously been reported,[19,20] and amides containing such functionalities were not compatible with the current protocol. However, we found that olefins could endure under these conditions, and (*E*)-1-(piperidin-1-yl)hex-3-en-1-one was reduced to the corresponding enamine **2j** in 86% yield.

Scheme 2. Scope of the Catalytic Reduction of Amides to Enamines[a]



[a]Isolated yields.

Scheme 3. Plausible Mechanism of Reduction of Amides to Enamines



A plausible reaction path for the conversion of tertiary amides to enamines is shown in Scheme 3. Previously, it has been proposed that the base activates the silane via formation of a pentacoordinated intermediate, which facilitates the transfer of the hydride to the amide carbonyl to generate the tetrahedral intermediate **A** (Scheme 3).[20] Presumably, the intermediate alkoxide is immediately trapped by the silane. In contrast to amide reductions to amines, the α-proton is removed followed by elimination of the silyl ether, which leads to the enamine. There is also a possibility for deprotonation of an initially formed iminium intermediate; however, this is unlikely due to the high reactivity of iminium species toward reducing agents.

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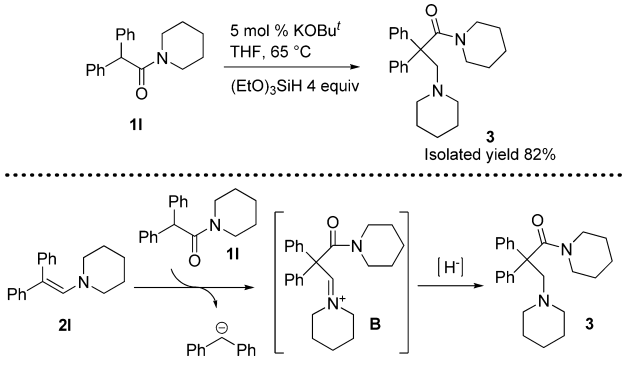
Significant gas evolution was observed during the reaction, which suggests the possibility of hydride acting as a base in the deprotonation step. The latter could also explain the need for more equivalents of the silane reagent.

In the reduction of compound **1l**, a byproduct was formed and characterized as amino amide **3** (Scheme 4). Evidently,

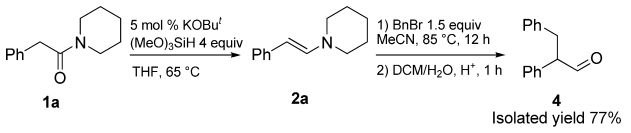
Scheme 4. Unexpected in Situ Trapping of the Formed Enamine



after the initial formation of the enamine, this nucleophilic species attacked remaining starting amide, and after elimination of a stabilized anion, imine intermediate **B** was formed (Scheme 4). The fact that diphenylmethane was isolated in 78% yield further supports the suggested mechanism. Subsequent reduction of the imine generated amino amide **3**. It is possible that the amide functionality in the final product remained untouched due to severe sterical hindrance around that group. Interestingly, if trimethoxysilane was replaced with the slightly more sterically hindered triethoxysilane, compound **3** became the major product with an isolated yield of 82%.

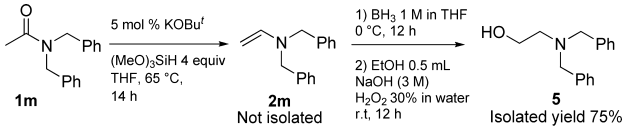
The above-described methodology for the synthesis of different enamines can be successfully extended to generate more complex compounds. Aldehyde **4** was successfully generated from **1a**, via site-selective alkylation of the intermediate enamine **2a** followed by hydrolysis (Scheme 5).[21] The target aldehyde **4** was isolated in 77% yield.

Scheme 5. Enamine Formation Followed by Site-Selective Alkylation



Aliphatic enamines proved difficult to isolate due to their high reactivity (see Supporting Information); however, we were able to utilize enamine **2m** directly, without purification, toward formation of β-amino alcohol **5** by submitting it to hydroboration and subsequent oxidative cleavage (Scheme 6).

Scheme 6. Formation of Aminoalcohol by Hydroboration of Enamine



To conclude, we have developed an efficient transition-metal-free method for the reductive dehydration of benzylic and aliphatic tertiary amides to give enamines with high selectivity and in good-to-excellent yields. In almost all of the cases studied, *trans*-enamines were selectively formed. The enamine formation was performed under hydrosilylation conditions with trimethoxy- or triethoxysilane as hydride source in the presence of catalytic amounts of *t*-BuOK. The possibility of in situ trapping of the generated enamines was demonstrated by the formation of amino amide **3**. Furthermore, addition of benzyl bromide to the enamine formed from tertiary amide **1a** gave aldehyde **4** in good isolated yield after hydrolytic workup. Additionally, highly reactive aliphatic enamines difficult to isolate were efficiently converted to amino alcohols using a hydroboration/oxidation protocol. We were also able to run the reaction in 2-methyltetrahydrofuran, also known as "green THF", without any loss in efficiency in the reduction of model substrate **1a**. The combination of a transition-metal-free catalytic hydrosilylation protocol performed in 2-methylTHF allows for a more environmentally friendly reduction. Alkoxides have previously been known as catalysts for the hydrosilylation of aldehydes, ketones, and imines[19,20] and recently for amides;[22] however, to our knowledge this is the first example of an alkoxide being used as catalyst for the transformation of amides to enamines.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(16) See Supporting Information

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