Zinc-Catalyzed Chemoselective Reduction of Tertiary and Secondary Amides to Amines

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Abstract: General and convenient procedures for the catalytic hydrosilylation of secondary and tertiary amides under mild conditions have been developed. In the presence of inexpensive zinc catalysts, tertiary amides are easily reduced by applying monosilanes. Key to success for the reduction of the secondary amides is the use of zinc triflate and disilanes with dual Si-H moieties.

Keywords: amides • amines • hydrosilanes • reduction • zinc The presented hydrosilylations proceed with excellent chemoselectivity in the presence of sensitive ester, nitro, azo, nitrile, olefins, and other functional groups, thus making the method attractive for organic synthesis.

Introduction

The chemoselective reduction of carboxylic amides to amines under mild conditions is an essential transformation in organic synthesis, which is also of significant interest for the pharmaceutical as well as agrochemical industry.^[1] High selectivity and broad tolerance towards various functional groups are key factors for the acceptance and application of such a methodology. To date, most of the applied reductive transformations of amides to amines still make use of (over)stoichiometric amounts of aluminum and boron hydrides.^[2,3] In spite of their utility, drawbacks of these reagents are their air and moisture sensitivity. In addition, sometimes tedious purification of the products and concomitant formation of salt byproducts are disadvantages of these procedures. Due to these problems, the development of catalytic reductions of amides is highly desired.^[4] Despite progress in recent years, the straightforward hydrogenation of carboxylic acid derivatives is still in its infancy.^[5] On the other hand, hydrosilanes^[6] have become viable reducing agents, which are used in industry on the ton scale for various processes. Notably, they tolerate air and moisture but promote the reduction of aldehydes and ketones along with alkenes and alkynes in the presence of Brønsted^[7] and Lewis acids^[8] and bases,^[9] as well as transition metals.^[10-13]

In the last decade, significant progress has also been achieved for hydrosilylations of carboxamides in the presence of noble-metal-based catalysts.^[4,12] More recently, Nagashima and co-workers as well as our group also developed iron-based catalysts for this transformation.^[13] However, so far most of the known studies have focused on the catalytic

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reduction of tertiary amides. Catalytic reductions of functionalized primary and secondary amides are only scarcely investigated and still constitute a challenge, especially in the presence of other reducible functional groups. For the first time, Ito et al. and Ohta et al.^[14] demonstrated the reduction of secondary amides using a rhodium-triphenylphosphine complex along with Ph₂SiH₂ as reducing agent. Later on, Romão^[15] et al. published an unusual [MoO₂Cl₂]-catalyzed reduction using PhSiH₃. Fuchikami^[16] and co-workers used group 7-10 transition metals along with diethylamine and/or ethyl iodide as co-catalysts in presence of triethylsilane. Very recently, Nagashima^[4,12] and co-workers reported the reduction of secondary amides in the presence of a special ruthenium cluster and commercially available platinum catalysts such as chloroplatinic acid and Karstedt's catalyst. The latter reactions proceed under mild conditions and showed high functional-group tolerance in the case of tertiary amides. However, the selectivity for the reduction of secondary amides in presence of other reducible functional groups was still not fully demonstrated.

Based on our previous investigations on chemoselective reductions with silanes,^[17] herein we report improved zinccatalyzed hydrosilylations of both secondary and tertiary amides. The reaction proceeded under mild conditions and kept other sensitive functional groups such as esters, ethers, double bonds, nitro, nitriles, and azo bonds intact (Scheme 1).

Results and Discussion

Reduction of tertiary amides using methyldiethoxysilane: In 2009, we discovered a general zinc-catalyzed chemoselective reduction of tertiary amides using triethoxysilane.^[17a] Shortly after publication we were informed about potential safety risks of this silane.^[18] Although we have never experienced any safety problems using triethoxysilane during our studies and it is used on an industrial scale in the silane and silicone







Tolerated functional groups - ester, ether, double bond, triple bond, nitro, nitrile, azo bond Scheme 1. Selective reduction of amides in the presence of other reducible functional groups.

industry for the production of organofunctional coupling agents, low-temperature-vulcanizing silicone rubbers and elastomers, as well as specialty monomers, we looked for safer alternatives. Among the various silanes tested for the Zn-catalyzed reduction of N,N-dimethylbenzamide, phenyl silane, diphenyl silane, and methyldiethoxy silane worked excellently at 65 °C. Due to the cheaper price, and with respect to its chemoselectivity, we thought it best to use methyldiethoxysilane as the silane of choice for the reduction of tertiary amides. In fact, by applying a threefold excess amount of methyldiethoxysilane in the presence of catalytic amounts of inexpensive zinc acetate in THF, the reduction of a plethora of tertiary amides took place with excellent chemoselectivity (Table 1). A variety of amides, including aromatic and heteroaromatic amides, were hydrosilylated smoothly with high yields up to 93%. Electron-withdrawing substituents (Table 1, entries 3, 5, and 8) at the para position gave better yields than electron-donating substituents (entry 10). Steric hindrance on the amine part of the amide bond had a significant effect and reduced the rate of reduction. On the other hand, the reaction proceeded well with aliphatic groups and N-piperidinyl as well as N-cyclopentyl moieties. However, no reaction was observed with anilides. Heteroaromatic amides were also reduced in excellent yields (entries 15 and 16). Here furan-based amides were reduced in higher yields than the corresponding thiophene derivatives. This is in contrast to our previous reduction by applying triethoxysilane. Using halide-substituted benzamides the reactions proceeded with excellent chemoselectivity and no other reductive dehalogenation was observed (entries 5–7). Various other functional groups such as double bonds, nitro, azo, nitrile, ester, and ether were satisfactorily accepted under our reaction conditions, too (entries 3, 12, 13, 17, 19, and 20). In none of these cases a reduction of the respective functional group except the ester substituent was observed. Notably, the reaction also tolerated hydroxy groups as well, although it is well known that alcohols might react with the silane (entry 18).^[6b] On the other hand, a methylthio substituent and a keto group were not tolerated under these conditions. In the latter case reduction of the ketone took place. Gratifyingly, scale up of N,N-dimethylbenzamide reaction to 20 mmol-scale resulted in no problem and produced 90% of the corresponding amine.

Reduction of secondary amides using tetramethyldisiloxane (TMDS): It is well known that catalytic hydrogenations of secondary amides are more difficult than the reduction of tertiary amides.^[19]

This reactivity pattern is similar for hydrosilylations. Nevertheless, recently Nagashima and co-workers^[4,12] were able

to achieve this challenging goal by using ruthenium and platinum catalysts in the presence of silanes with dual Si-H moieties. Their elegant work encouraged us to reconsider our zinc-catalyzed procedure by using other silanes. Initially, we investigated N-benzylbenzamide as model substrate for the reduction of secondary amides (Table 2). To our delight, moderate activity (40% yield) was observed by applying the more reactive zinc triflate and 1,1,3,3-tetramethyldisiloxane (3 equiv) at 65 °C. Increasing the temperature gave improved yields. Hence, at 100 °C, 85 % of dibenzyl amine was obtained with full conversion of the starting material. Notably, monosilanes such as phenylsilane and diphenylsilane were significantly less active (10% yield). Methyldiethoxysilane, triethoxysilane, and triethylsilane showed only 2% yield of the desired product, and in all of the cases we recovered only starting material. In contrast to the work of Nagashima's group, 1,1,1,3,3-pentamethyldisiloxane and 1,2bis(dimethylsilyl)benzene also afforded the product in low yield (Table 2, entries 10 and 11). This demonstrates that the sterics and electronics of the disilane are crucial in enforcing the reduction of secondary amides. It is worth noting that the optimized catalytic system for the reduction of tertiary amides was completely unsuccessful for secondary amides even at higher temperature (100°C). By applying commercially available 1,1,3,3-tetramethyldisiloxane, we investigated the effect of various metal triflates and zinc sources for the reduction of N-benzyl benzamide. Clearly, the reaction did not proceed without any catalyst. Other metal triflates such as scandium triflate, iron(II) triflate, iron(III) triflate, ytterbium triflate, and zirconium triflate also did not show any activity, even at 100 °C (Table 3).

However, in the presence of zinc halides (chloride, bromide, and iodide) some activity with up to 20% yield of the product was observed. On the other hand, zinc fluoride, acetate, and nitrate gave no conversion at all. In all these cases, we observed only starting material after the reaction. Attempted lower catalyst loading of zinc triflate (5–10 mol%) led to lower yields of the corresponding amine. Appropriate selection of the solvent is also important in this reductive hydrosilylation. For example, the reaction becomes sluggish in the presence of *n*-butyl ether or 1,4-dioxane, and only 50% of the secondary amine was obtained. To check the influence of metal contaminants^[20] in the precursor, we used zinc triflate from different suppliers (ABCR, Sigma Aldrich, Acros, Alfa Aesar), which all provided similar yields.

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Table 1. Zn-catalyzed chemoselective reduction of tertiary amides.

$\begin{array}{c} R^{1} \stackrel{(1)}{\underset{R^{3}}{\bigvee}} R^{2} & \stackrel{(2n(OAc)_{2} (10 \text{ mol}\%))}{(EtO)_{2} \text{SiMeH/THF/ 65°C}} & \stackrel{(1)}{\underset{R^{3}}{\boxtimes}} R^{1} \stackrel{(N)}{\underset{R^{3}}{\bigvee}} R^{2} \\ R^{3} & 20-30h \end{array}$							
Entry	Amides ^[a]	Amines	Yield ^[b] [%]	Entry	Amides ^[a]	Amines	Yield ^[b] [%]
1	N I	N I	90	11	O N		89
2	O N N	N	70	12			91
3	O O ₂ N I	O ₂ N	75	13	N N	N N	75
4	© N∩	N	80	14	O O N	° N N	<1
5	F N	F	92	15		⟨ ` ∩N`	71 ^[c]
6	Br	Br	93	16	© S N S	⟨∑ _S N)	60 ^[c]
7	N I	I N	76	17	N N O		74
8	F ₃ C	F ₃ C	91	18	O OH OH	N OH	64
9	S S S S S S S S S S S S S S S S S S S	S N	<1	19	MeO ₂ C	MeO ₂ C	50
10	N N		70	20	NC NC	NC	70

[a] Reaction conditions: Zn(OAc)₂ (10 mol%), (EtO)₂MeSiH (3 mmol), THF (3 mL), amide (1.0 mmol.). [b] Yield of isolated product. [c] Product obtained by distillation.

In general, conventional procedures for the reduction of carboxamides by metal hydrides involve safety problems due to their sensitivity to air and moisture. In addition, problems often arise during the purification of the product. Clearly, mildly hydridic silanes are chemically stable and easy to handle. Usually they do not require particular precautions. Indeed, our reaction protocol proceeded smoothly also on a 10 mmol scale without special precautions. Removal of the resulting siloxane concomitantly produced with the amine is easily achieved by treatment of the reaction mixture with sodium hydroxide solution followed by aqueous work up and purification by column chromatography or distillation. Alternatively, the amine can also be purified by the conventional acidification followed by basification and aqueous workup.

With optimized conditions in hand, the scope and limitations of the zinc triflate-catalyzed reductive hydrosilylation of secondary amides were explored. Again, a number of amides including aromatic, heteroaromatic, and aliphatic amides were smoothly reduced with high yield up to 90%. Both electron-donating and electron-withdrawing substituents on the aromatic ring at the *para* or *meta* position had little influence on the yield of the reaction, whereas steric crowding on both sides of the amide bond has a significant 0

Table 2. Reduction of *N*-benzyl benzamide: effect of the silane.

	Zn(OTf) ₂ (20 r H Toluene, 28	nol%)	\bigcirc
Entry	Hydrosilane ([mmol])	Temperature [°C]	Yield ^[a]
1	MeaHSiOSiHMea ^[b] (3)	65	40
2	$Me_2HSiOSiHMe_2^{[b]}$ (3)	80	53
3	$Me_2HSiOSiHMe_2^{[b]}$ (3)	90	65
4	Me ₂ HSiOSiHMe ₂ ^[b] (3)	100	85
5	$PhSiH_3(2)$	100	10
6	Ph_2SiH_2 (3)	100	10
7	(EtO) ₂ MeSiH (3)	100	2
8	(EtO) ₃ SiH (3)	100	2
9	$Et_3SiH(3)$	100	2
10	$Me_3SiOSiHMe_2^{[c]}(3)$	100	3
11	Me ₂ HSi SiHMe ₂	100	5

[a] GC yield with hexadecane as an internal standard. [b] $Me_2HSiOSiHMe_2=TMDS$. [c] $Me_3SiOSiHMe_2=PMDSO$.

Table 3. Reduction of N-benzyl benzamide: effect of different catalysts.

	H TMDS/ Tolu	uene/ 100°C	\bigcirc
Entry	Catalyst	Catalyst loading [mol%]	Yield ^[a] [%]
1	_	_	-
2	$Zn(OTf)_2$	5	8
3	$Zn(OTf)_2$	10	30
4	$Zn(OTf)_2$	15	40
5	Zn(OTf) ₂	20	85
6	$Sc(OTf)_2$	20	-
7	Yb(OTf) ₂	20	_
8	$Fe(OTf)_2$	20	-
9	Fe(OTf) ₃	20	_
10	$Zr(OTf)_4$	20	-
11	ZnF_2	20	-
12	$ZnCl_2$	20	10
13	$ZnBr_2$	20	20
14	ZnI_2	20	13
15	$Zn(OAc)_2$	20	-
16	$Zn(NO_3)_2 \cdot 6H_2O$	20	-

[a] GC yield with hexadecane as an internal standard. [b] Reaction runs for 28 h. [c] After finishing the reaction, the internal standard was added and the mixture was diluted with THF. After one quick filtration, the mixtures were subjected to GC.

effect on the product yield. For example, compared to *N*-benzyl benzamide the reactivity decreased for *N*-aryl benzamides (Table 4, entry 18). In this case, the reaction needed significantly longer time (three days) for completion. In agreement with this, *tert*-butyl-substituted amides showed lower reactivity too (up to 68% yield; Table 4, entries 15 and 19). Amides with alkyl substituents either in the aryl or amine part reacted smoothly (Table 4, entries 2–4, 20, and 21). Furthermore, *para*-fluoro, chloro-, bromo-, and iodo-substituted amides gave the corresponding products in 71–

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83 % yield (Table 4, entries 8–11). In none of the cases did we observe any reductive dehalogenated product. Interestingly, the zinc catalyst worked excellently in the case of heteroaromatic amides such as furan, thiophene, and benzodihydrofuran (Table 4, entries 16 and 17; Table 5, entry 4). In addition, araliphatic *N*-benzyl 3-phenylpropionamide was reduced in good yields (86 %; Table 4, entry 13).

As stated in the Introduction, the chemoselectivity of a given method is a prerequisite for its implication in organic synthesis and natural product synthesis. In this regard, the reduction of amides in the presence of other reducible functional groups is of special importance. Thus, we evaluated the zinc-catalyzed reduction process by grafting different functional groups onto different parts of N-benzyl benzamide. By positioning these functionalities either at the aryl or at the amine part of the amide moiety, we minimized both steric and electronic influence of the functional group on the reaction. To our delight, without further optimization nitrile, azo-, double bond-, nitro-, ether-, and ester-substituted benzamides were well tolerated, thereby providing the corresponding amines in good to excellent yield (Table 5, entries 1-4, 6-8, 10, and 11). It should be noted that in all of the cases no additional reduction of the functional group was observed, thereby demonstrating the excellent chemoselectivity of this reduction process. However, keto and a free amino group were not tolerated under our reaction conditions. In the former case, reduction of the ketone took place again. In general, product separation occurred in an easy manner similar to the tertiary amides. In the case of the ester-substituted benzamides, the resulting amine was first converted to the ammonium salt soluble in water due to the potential hydrolysis problem. This ammonium salt without contamination of siloxane waste was extracted to the aqueous phase, from which the desired amine was easily isolated by treatment with base.

Conclusion

In conclusion, we have established the chemoselective reduction of tertiary and secondary amides to the corresponding amines with commercially available zinc catalysts and silanes. Safe and simple operational procedures, mild conditions, easy purification methods, and excellent functional group tolerance make this new method attractive. Due to the excellent chemoselectivity including functional groups such as ester, nitrile, ether, double-bond, and azo, we believe our protocols will be beneficial for organic synthesis and natural product synthesis without using protecting and deprotecting steps.

Experimental Section

Typical experimental procedures of the reactions are described. Further experimental details and spectroscopic data of the compounds are summarized in the Supporting Information.

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Table 4. Zinc-catalyzed reduction of secondary amides.

		$R^1 \overset{\downarrow}{\underset{H}{}} N^{,R^2}$ $-$	Zn(OTf) ₂ (20 m MDS/ Toluene/ 28–72h	ol%) ───► 100°C	$R^1 \stackrel{N}{H} R^2$		
Entry	Amides ^[a]	Amines	Yield ^[b] [%]	Entry	Amides ^[a]	Amines	Yield ^[b] [%]
1	O T T	N N	80	12	F ₃ C N	F ₃ C	85
2	N H H	M M	65°	13	O N H	N N	86
3	O H H	N H	60 ^[c]	14	N N		85
4	N H		73	15	N H H	N N N N N N N N N N N N N N N N N N N	68
5	N N H		80	16	N N H		76 ^[c]
6	F ₃ C ₀ N	F ₃ C ₀] 50	17	N N H	N H S	75 ^[c]
7	Bn	Bn _O	54	18	N N		70
8	F H	F	83	19	N N N N N N N N N N N N N N N N N N N	N N N N N N N N N N N N N N N N N N N	60
9	CI N H	CI H	72	20	N N N N	N N	72
10	Br H	Br	71	21	N nOct	N ^r nOct	56
11	N H		80				

[a] Reaction conditions: $Zn(OTf)_2$ (20 mol%), TMDS (3 mmol), toluene (3 mL), amide (1 mmol). [b] Yield of isolated product. [c] Product obtained by distillation. Bn = Benzyl.

General procedure for the reduction of tertiary amides: A 10 mL ovendried Schlenk tube that contained a stir bar was charged with zinc acetate (0.1 mmol). Dry THF (2 mL) and methyldiethoxysilane (3 mmol) were added respectively after purging the Schlenk tube with argon. The resulting mixture was stirred for 30 min at 65 °C. After that, the respective amide (1 mmol) in dry THF (1 mL) was transferred to the solution under argon. The mixture was stirred at 65 °C for 20–30 h and monitored by TLC. After complete disappearance of the substrates, the reaction mixture was vigorously stirred with NaOH solution (5 mL, 2 M) in a 25 mL conical flask overnight and then extracted with ethyl acetate (3×5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography by using ethyl acetate/hexane/triethylamine (1%) to afford the pure desired product.

General procedure for the reduction of secondary amides: A 25 mL oven-dried Schlenk tube that contained a stir bar was charged with zinc triflate (0.2 mmol) and the corresponding amide (1 mmol). Dry toluene (3 mL) and tetramethyldisiloxane (TMDS) (3 mmol) were added respectively after purging the Schlenk tube with argon. The resulting mixture was monitored by TLC and stirred at 100 °C until the substrates com-

Table 5. Zinc-catalyzed reduction of secondary amides: functional group tolerance.



[a] Reaction conditions: $Zn(OTf_{12} (20 \text{ mol }\%), TMDS (3 \text{ mmol}), \text{ toluene } (3 \text{ mL}), amide (1.0 \text{ mmol}).$ [b] Yield of isolated product. Bn = Benzyl.

pletely went away. After complete disappearance of the substrates, the reaction mixture was vigorously stirred with NaOH (13 mL, 2 M) or KOH (5 mL, 25%) in MeOH solution in a 50 mL conical flask overnight. It was then extracted with ethyl acetate (3×20 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography using ethyl acetate/hexane/triethylamine (1%) to afford the pure desired product.

Purification method for the amine having ester functional group.^[17] After complete consumption of the starting material, the reaction mixture was filtered through a pad of florisil, and the filtrate was poured into an ethe-

real solution of hydrogen chloride (0.1 M, 10 mL; prepared from commercially available 1 M HCl/ether (1 mL) and ether (9 mL)). The ammonium salt was precipitated as a white powder. The supernatant was separated by decantation or centrifugation. This was followed by washing of the residue with ether to afford silicone residues without contamination. That was then treated with an excess amount of sodium carbonate in wet THF at 0°C for 0.5–1 h. The solid materials were filtered off, and the desired amine was obtained by concentration of the filtrate.

Acknowledgements

This work has been funded by the State of Mecklenburg-Western Pomerania, the BMBF, and the DFG (Leibniz Prize). We thank Ms. Bianca Wendt for excellent technical assistance and Dr. W. Baumann, Dr. C. Fischer, and Mrs. S. Buchholz (all LIKAT) for their analytical support.

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Chem. Eur. J. 2011, 17, 12186-12192

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Received: April 13, 2011 Revised: July 27, 2011 Published online: September 13, 2011

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