The titanocene-catalyzed reduction of acetamides to tertiary amines by $PhMeSiH_2$

Kumaravel Selvakumar, Kesamreddy Rangareddy, and John F. Harrod

Abstract: A variety of acetamide derivatives are reduced in excellent yields to tertiary amines by $PhMeSiH_2$ in the presence of Cp_2TiX_2 (X = F or Me) catalysts. The reactions are very clean at 80 °C. At room temperature a secondary reaction, hydrogenolysis of the C(O)—N bond, intervenes and reduces the chemoselectivity. Nevertheless, this chemistry provides a simple methodology for the amide/alkylamine transformation using inexpensive, commercially available reagents.

Key words: amides, reduction, secondary amides, methylphenylsilane, titanocene, catalysis.

Résumé : Divers dérivés de l'acétamide sont réduits avec d'excellents rendements en amines tertiaires par le $PhMeSiH_2$ en présence de catalyseurs du type Cp_2TiX_2 (X = F ou Me). Les réactions sont très propres à 80 °C. À la température ambiante la chimiosélectivité est réduite par l'intervention d'une réaction secondaire, l'hydrogénolyse de la liaison C(O)—N. Néanmoins, cette chimie fournit une méthodologie simple pour la transformation d'amides en alkylamines faisant appel à des réactifs peu coûteux et commercialement disponibles.

Mots clés : amides, réduction, amides secondaires, méthylphénylsilane, titanocène, catalyse.

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Introduction

The use of hydrosilation chemistry to achieve the reduction of carbonyl groups has received a great deal of attention (1–5). Many studies of ketone hydrosilation have been directed towards enantioselective synthesis of carbinols, and excellent results have been achieved with both later and early transition metal homogeneous catalysts (6, 7). Facile hydrosilations of esters and lactones have also been reported (8, 9). Among the early transition metal catalysts, titanocene derivatives are the most effective with respect to both rate and selectivity for all of these reactions.

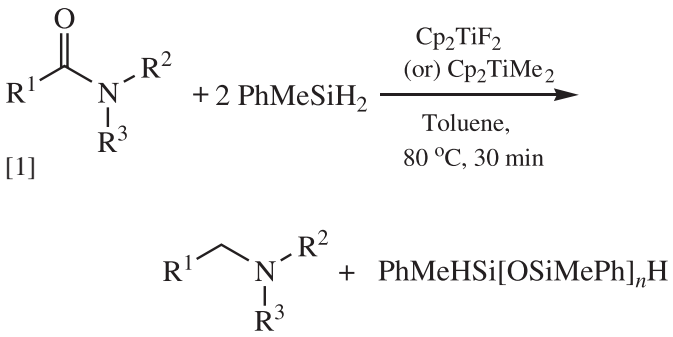
Carboxamides are generally more resistant to reduction than ketones and esters. Nevertheless, the conversion of amides to the corresponding amines is an important transformation in organic synthetic methodology. Catalytic hydrogenation of amides normally requires high pressures and elevated temperatures (10). Consequently, stoichiometric reduction using expensive reactive main group metal hydride complexes is the usual method of choice (11–15).

Literature on the hydrosilation of carboxamides is sparse (16–19). Kuwano et al. (17) and Igarashi and Fuchikami (18) reported efficient reduction of aliphatic amides to amines by catalytic hydrosilation, using late transition metal catalysts. In a preliminary communication (19), we described an unusal titanocene-catalyzed deoxygenation/coupling of aromatic amides to give 1,2-diaminoethanes. Classical hydrosilation products (i.e., those containing either Si—OR or Si—C bonds) have never been observed as products of the reaction of amides under hydrosilation conditions.

In the present paper, we report results for the catalytic reduction of acetamides, under hydrosilation conditions, using titanocene-based catalysts. Although there is still much scope for improving the specificity and yields of catalytic amide reduction reactions, the present work shows that appropriate catalytic hydrosilation conditions can be useful for reduction of tertiary amides to tertiary amines.

Results

The reaction of acetamide derivatives with $PhMeSiH_2$ at moderate temperature in the presence of catalytic amounts of Cp_2TiX_2 (Cp = η-C_5H_5; X = F or Me) takes place as shown in eq. [1].



[1]

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Table 1. Results of Ti-catalyzed reduction of acetamides at 80 °C (reaction [1]).

Entry	R^1	R^2	R^3	Method	Yield (%)
1	Me	Me	Ph	A	93
	Me	Me	Ph	B	89
2	Me	Et	Ph	A	77
	Me	Et	Ph	B	83
3	Me	Bn	Ph	A	89
	Me	Bn	Ph	B	92
4	Me	Bn	Bn	A	91
5	Me	Me	3,4-$(OMe)_2$Ph	A	76[a]
6	Bn	Me	Ph	A	40
7	Me	Ph	4-(OMe)Bn	A	90
8	Me	Ph	Furfuryl	A	92
9	Me	Me	4-(NO_2)Ph	A	—[b]
10	1-Acetylindoline			A	88
11	1-Phenyl-2-pyrrolidinone			A	96
12	*N*,*N*′-Dimethylacrylamide				94 (polymer)

Note: Method A, Cp_2TiF_2 catalyst; method B, Cp_2TiMe_2 catalyst. Yields are given for isolated compounds.

[a]10% secondary amine formed as deacetylated product.

[b]No reaction.

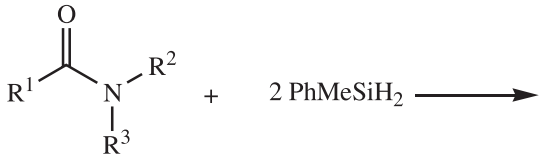
At 80 °C this reaction occurs rapidly and gives excellent yields of the tertiary amine, for a range of substituents R_1, R_2, and R_3. This product results from reduction and deoxygenation of the carbonyl group and contrasts with the coupling, to give vicinal diamines, observed with aromatic amides (19). The present results are very similar to those reported for reactions catalyzed by complexes of Rh (17) and Ru (18). There is, however, a considerable price advantage in using the relatively inexpensive Cp_2TiF_2.

The siloxane product was identified by ^{1}H NMR as a typical mixture of H-terminated oligo(phenylmethylsiloxanes). The resonances occur at 0.2–0.5 ppm (CH_3; broad massif or many singlet and doublet peaks), 4.6–4.8 ppm (Si–H; overlapping quartets), and 6.6–7.5 ppm (Ph; broad massif). The mass spectrum of a crude extract of the siloxane product recorded by chemical ionization mass spectrometry (CI-MS) showed the presence of oligomers of *n* up to a value of ca. 10. The siloxane product was not studied further.

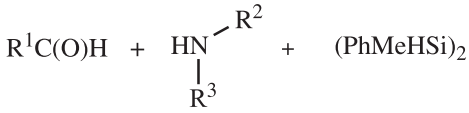
The reaction shows some tolerance for functional groups, as exemplified by entries 5, 7, and 9 in Table 1. Reduction of secondary amides is very slow compared to that of *N*,*N*-disubstituted acetamides. For example, under similar conditions, acetanilide undergoes reduction to give a small amount of *N*-ethylaniline and aniline along with unreacted acetanilide. Incomplete conversion is observed even after 15 h at 80 °C. *N*,*N*-Dimethylacrylamide underwent rapid polymerization under the conditions used in these experiments, probably due to free radical initiation, and there was no evidence for reduction of the amide function.

There is little difference in the performance of Cp_2TiF_2 and Cp_2TiMe_2, but given the long-term stability of the fluoride, its commercial availability (or ease of preparation from the commercially available Cp_2TiCl_2), and its insensitivity to air and humidity, it is the preferred catalyst (20).

At room temperature, reactivity remains high (Table 2), but a side reaction involving hydrogenolysis of the C(O)—N bond (eq. [2]) lowers the efficiency of the reaction in certain



[2]



cases and complicates purification of the tertiary amine product. In some cases, this reaction becomes a major consumer of reactant (Table 2, entries 1, 3, and 7), and in one case (Table 2, entry 10) it is the only reaction observed. In the latter case, if the reaction is carried out in a closed tube, ca. 1 equiv. of acetaldehyde is also detected in solution by ^{1}H NMR. In other cases, where secondary amine is produced in a significant amount, the characteristic quartet of acetaldehyde is also detected in the ^{1}H NMR spectrum.

Catalyst concentration also has a significant influence on the relative contributions of reactions [1] and [2] at room temperature (Table 2, entries 1–6). A similar effect was detected at 80 °C. At a catalyst loading of 10 mol%, the reduction of *N*-benzylacetanilide (Table 1, entry 3) to the tertiary amine occurs with high chemoselectivity. At 5 mol% catalyst concentration, both the rate of reduction and the chemoselectivity are similar to those at 10 mol% catalyst. However, at 2 mol% catalyst concentration, the reaction is slow (1.5 h for complete conversion) and *N*-benzylaniline (24%) is formed along with *N*-ethyl-*N*-benzylaniline (76%).

The reaction mechanism

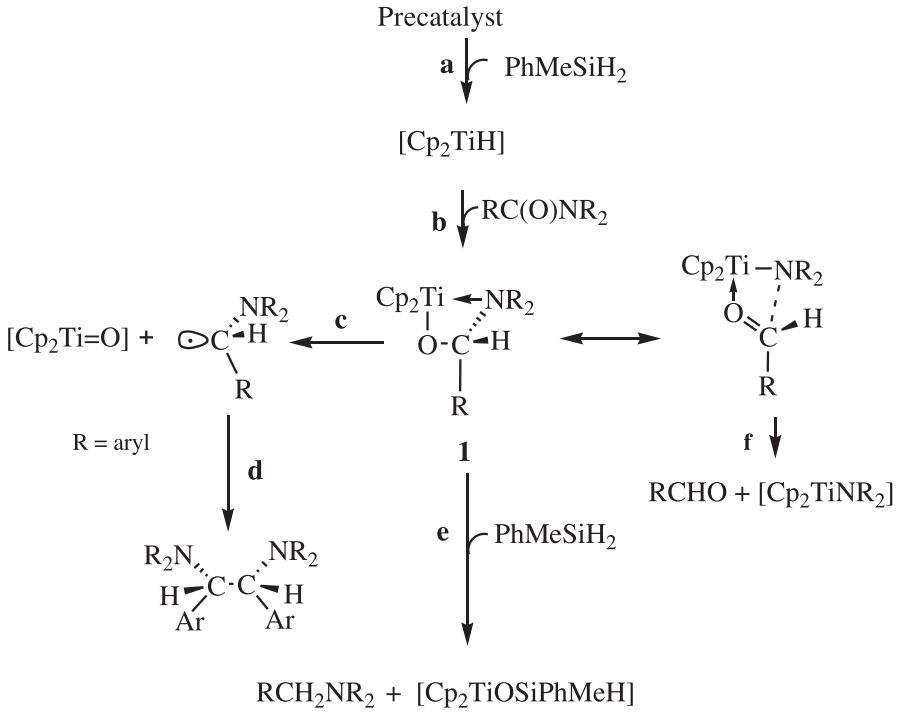
Kuwano et al. (17) suggested a mechanistic cycle for the Rh(I)-catalyzed reaction [1] involving a series of conventional two-electron oxidative addition/elimination steps, in conjunction with a σ-bond metathesis step. In principle, the mechanism of the titanocene-catalyzed reaction could be analogous to that proposed for Rh. This would require a sequence in which the Ti cycles alternately through Ti(II) and Ti(IV). Although such a two-electron cycle is not unreasonable for titanocene, a cycle involving $Ti^{III}H$ and $Ti^{III}Si$ is, in our opinion, more likely. The facile disproportionation of titanocene(III) to titanocene(II) and titanocene(IV) and vice versa makes the distinction between these two possibilities very difficult to draw, but there is ample evidence that all three oxidation states are chemically available in Cp_2TiMe_2/silane reaction mixtures (21). A tentative set of pathways that explain the observed chemistry is shown in Scheme 1. In this scheme, the silane functions as a source of hydride to generate Ti–H (step **a**) and as a receptor for O) but does not give rise to silylated organic products. Addition of Ti–H across the C=O bond (step **b**) generates the highly functionalized alkoxytitanocene intermediate, **1**. This intermediate then undergoes reactions to the various observed products, whose relative importance depends on the substituents on the substrate, on the catalyst concentration, and on the temperature. The various titanocene derivatives produced in the reactions of Scheme 1 will be recycled by appropriate σ-bond metathesis reactions with $PhMeSiH_2$.

Table 2. Results of Ti-catalyzed reduction of acetamides at 25 °C.

Entry	R^1	R^2	R^3	Catalyst concn. (mol%)	Product distribution (%) Tertiary amine	Secondary amine
1	Me	Me	Ph	2	64	36
2	Me	Me	Ph	5	88	12
3	Me	Me	Ph	10	93	7
4	Me	Et	Ph	2	60	40
5	Me	Et	Ph	5	100	—
6	Me	Et	Ph	10	100	—
7	Me	Bn	Ph	10	68	32
8	Me	Bn	Bn	10	94	6
9	Me	Ph	Furfuryl	10	71	29
10	Me	Me	2-Py	10	—	100
11	Me	Ph	4-(OMe)Bn	10	77	23
12	Me	Me	3,4-$(OMe)_2$Ph	10	85	15
13	Me	Me	4-(NO_2)Ph	10	—[a]	—[a]
14	1-Acetylindoline			10	100	—
15	1-Phenyl-2-pyrrolidinone			2	100	—

Note: Ratios of the products were determined by ^{1}H NMR Products were not isolated. Amines were characterized by comparison of the NMR spectra with those of isolated products (Table 1) or commercial samples.
[a]No reaction.

Scheme 1. A $[Cp_2TiH]$-mediated reaction sequence for the reduction, deoxygenation, and coupling of amides in the presence of $PhMeSiH_2$.



A possible mechanism for C—N bond cleavage is shown in Scheme 1. The favoring of the C—N bond cleavage reaction, relative to that of the C—O bond cleavage, at lower catalyst concentrations (Table 2, entries 1–6) could be due to the former involving a rate law that is higher order in catalyst concentration than is the rate law for the latter. Such a situation could arise if the recycling reactions of the titanocene products of reactions **e** and **f** in Scheme 1 are slow enough to contribute to the overall rate. Given the known tendency of titanocene(III) species to form coordination complexes (21–23), intramolecular coordination of the amino group to the Ti is a reasonable possibility. The resulting complex could then decompose in a unimolecular process to give the aldehyde and Cp_2TiNR_2. The latter could then undergo a σ-bond metathesis with Si–H to generate Ti–Si and give the secondary amine product. Finally, Ti–Si can then be converted by a σ-bond metathesis step to Ti–H and the silane dimer.

Buchwald and co-workers (24) have described a synthesis of aldehydes from acetamide derivatives by reaction with $Ti(O\text{-}i\text{-}Pr)_4/Ph_2SiH_2$. In those reactions, the primary product was found to be the enamine, which was then converted to aldehyde by mild acid hydrolysis. With our system, the aldehyde is the direct product in entry 10 of Table 2, and no intermediate vinylamine was detected. In the other reactions where significant amounts of the secondary amine were produced, acetaldehyde was also detected, but not vinylamine. However, the complexity of the reaction products in the latter cases prevented the definitive exclusion of the possible presence of vinylamine.

We attribute the reactivity difference between aromatic amides and acetamide derivatives to the lower stability of the radical intermediate in step **d** when R is an alkyl, rather than an aromatic, substituent. Detailing the mechanisms of these interesting reactions is the subject of continuing studies.

Experimental

Materials

All of the reactant amides were either obtained commercially from Aldrich Chemical Co. or synthesized by standard methods. Cp_2TiF_2 (20) and Cp_2TiMe_2 (25) were prepared according to previously described methods.

A typical procedure for the synthesis of tertiary amines is the following (Table 1, method A). *N*-Methylacetanilide (149 mg, 1 mmol), Cp_2TiF_2 (21 mg, 0.1 mmol), methylphenylsilane (0.28 mL, 2 mmol), and toluene (1 mL) were heated at 80 °C for 30 min in a Schlenk tube. After the reaction mixture had cooled to room temperature, ether (10 mL) was added and the solution was extracted with 1 mol/L HCl solution. Evaporation of the depleted ether solution gave an oily residue, which was shown by ^{1}H NMR to consist of a mixture of oligo(phenyl-methylsiloxanes) and catalyst residues. The acid extract was neutralized with 3 mol/L KOH and extracted with ether. The ether layer was dried with anhydrous $MgSO_4$ and evaporated to give analytically pure *N*-methyl-*N*-ethylaniline. In method B of Table 1, Cp_2TiMe_2 was used instead of Cp_2TiF_2. The identity of all the products listed in Table 1 was determined by comparison of ^{1}H NMR data to literature values and to those of authentic samples.

***N*-Ethyl-*N*-methylaniline** (Table 1, entry 1) ^{1}H NMR (ppm): 1.13 (t, J = 7.2 Hz, 3H), 3.42 (q, J = 7.2 Hz, 2H), 2.91 (s, 3H), 6.70 (m, 2H), and 7.26 (m, 3H).

***N*,*N*-Diethylaniline** (Table 1, entry 2) ^{1}H NMR (ppm): 1.06 (t, J = 7.2 Hz, 6H), 3.26 (q, J = 7.2 Hz, 4H), 6.61 (m, 2H), and 7.14 (q, J = 4.8 Hz, 3H)

***N*-Benzyl-*N*-ethylaniline** (Table 1, entry 3) ^{1}H NMR: 1.30 (t, J = 9.6 Hz, 3H), 3.56 (q, J = 9.6 Hz, 2H), 4.6 (s, 2H), 6.76 (m, 4H), and 7.43 (m, 6H); ^{13}C NMR: 45.43 (CH_3), 54.19 (N–CH_2), 112.4, 116.31, 126.85, 129.5, and 139.58 (aromatic).

***N*,*N*-Dibenzylethylamine** (Table 1, entry 4) ^{1}H NMR: 1.07 (t, J = 9.2 Hz, 3H), 2.50 (q, J = 9.2 Hz, 2H), 3.57 (s, 4H), and 7.22–7.52 (m, 10H).

***N*-Methyl-*N*-ethyl-3,4-dimethoxyaniline** (Table 1, entry 5) ^{1}H NMR: 1.17 (t, J = 7.4 Hz, 3H), 2.79–3.18 (m, 6H), 3.78 (q, J = 7.4 Hz, 2H), 3.85 (t, J = 0.9 Hz, 3H), and 6.57–6.92 (m, 3H).

***N*-Methyl-*N*-(2-phenylethyl)aniline** (Table 1, entry 6) ^{1}H NMR: 2.82 (s, 3H), 2.78 (t, J = 10.04 Hz, 2H), 3.5 (t, J = 10.04 Hz, 2H), 6.64–6.69 (m, 4H), and 7.13–7.24 (m, 6H); ^{13}C NMR: 33.72 (N–CH_3), 38.02 (N–CH_2), 54.99 (CH_2), 112.33, 116.36, 126.43, and 129.04 (aromatic).

***N*-Ethyl-*N*-phenyl-(*p*-methoxy)benzylamine** (Table 1, entry 7) ^{1}H NMR: 1.19 (t, J = 6.8 Hz, 3H), 3.44 (q, J = 6.8 Hz, 2H) 3.79 (s, 3H), 4.56 (s, 2H), and 6.68–7.19 (m, 9H)

***N*-Ethyl-*N*-(2-furoylmethyl)aniline** (Table 1, entry 8) ^{1}H NMR: 1.18 (t, J = 7.1 Hz, 3H), 3.49 (q, J = 7.1 Hz, 2H), 4.58 (s, 2H), 6.69–6.81 (m, 3H), and 7.2–7.4 (m, 5H).

***N*-Ethylindoline** (Table 1, entry 10) ^{1}H NMR: 1.23 (t, J = 10.01 Hz, 3H), 3.02 (t, J = 10.01 Hz, 2H), 3.20 (t, J = 9.2 Hz, 2H), 3.37 (t, J = 9.2 Hz, 2H), 6.55 (d, J = 10.4 Hz, 1H), 6.72 (d, J = 10.4 Hz, 1H), and 7.09 (t, J = 9.2 Hz, 2H); ^{13}C NMR: 28.79 (CH_3), 43.50 (CH_2), 52.57 (N–CH_2), 97.76, 117.89, 124.6, and127.59 (aromatic).

***N*-Phenylpyrrolidine** (Table 1, entry 11): ^{1}H NMR 1.98–2.07 (m, 4H), 3.41 (t, J = 7.2 Hz, 4H), 6.58 (m, 2H), and 7.21 (m, 3H).

***N*,*N*′-Dimethylpolyacrylamide** (Table 1, entry 12): ^{13}C NMR (CP-MAS): 37.5 (CH_3), 69.02, 77.81, 84.27, 128.2, (CH(CO)), and 178.03 (CO).

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