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Short Communication

A One-Pot Reductive Amination of Ketones to Primary Amines Using Borane–Dimethyl Sulfide Complex

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Direct transformation of aldehydes and ketones into secondary and tertiary amines via reductive amination is a versatile tool in synthetic chemistry.[1] There are, however, few reports on direct conversion of carbonyl compounds into primary amines[2] and no asymmetric preparation of amines directly from a carbonyl compound has yet been reported.[3] Furthermore, the use of boranes is not common practice in reductive aminations, although a few papers have appeared.[4] Using boranes is especially attractive, since a large diversity of asymmetric borane reagents are readily available.[5] Here, we report a reductive amination procedure for primary amines from ketones using borane–dimethyl sulfide complex for the reduction of an *in-situ* formed iminium salt. In several cases, the method can be used for the preparation of secondary amines, although the yields of tertiary amines from pyrrolidine are generally lower. Borane–THF complex gives lower yields. Other borane complexes were not examined.

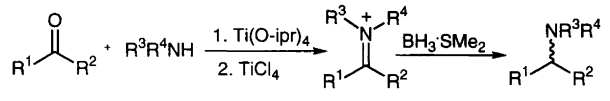
In a recently published reductive amination protocol, molecular sieves are used together with pyridine–borane.[6] The molecular sieves are of vital importance for the removal of the equivalent of water formed from condensing a carbonyl compound and an amine to an imine, thus forcing the equilibrium towards the imine. More commonly used additives for promoting the amination are Lewis acids such as $TiCl_4$[7] and Ti(O-*i*Pr)$_4$.[8] The exact role of Lewis acids such as these is ambiguous and it is likely that their impact on the reaction is a result of several actions.

In our procedure, a combination of $TiCl_4$ and Ti(O-*i*Pr)$_4$ is used for the condensation and borane–dimethyl sulfide complex as the reducing agent (Scheme 1). The intermediate iminium salt precipitates and the ensuing reduction proceeds cleanly. Purification of the products after work-up was generally not necessary, as the crude products were at least 95% pure on GC. The isolated yields are shown in Table 1. In the general procedure, a mixture of ammonia or amine and ketone in diethyl ether is stirred with an excess of Ti(O-*i*Pr)$_4$ at 0 °C for 1 h, after which $TiCl_4$, in an equimolar amount to Ti(O-*i*Pr)$_4$, is added whereupon an iminium salt is formed. With ammonia, the solvent is evaporated off and ether is added to the residue. The heterogeneous solution is treated with borane–dimethyl sulfide complex (Method A, Table 1). When a primary or secondary amine is used, the evaporation is omitted (Method B, Table 1).

The reaction was performed with four different classes of ketones (Table 1) to probe some of its limitations. The yields of primary amines were acceptable for all ketones examined, although the yield from acetophenone was never higher than 60%, despite considerable effort. When using an amine instead of ammonia, the yields tended to go down as the steric crowding increased for the products formed.

The ammonia procedure was initially a source of some frustration, since two by-products, resembling one another, were formed along with the desired primary amines. They accounted in some cases for as much as 25% of the total yield. The by-products were identified as diastereomeric diamines, most probably formed by reductive coupling of imines in the presence of Ti^{IV} and a reducing agent, in analogy with the McMurry reaction (Scheme 2).[9]

With an excess of ammonia, there is an equilibrium between the iminium salt and the corresponding imine.



Scheme 1.

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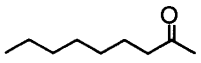
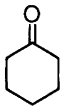
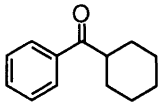
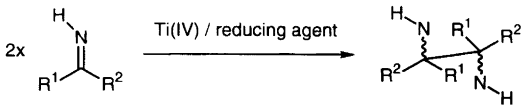
Table 1. Reductive aminations of ketones as shown in Scheme 1.

Entry	Ketone	Amine	Yield (%)[a,b]	Method[d]
1		Ammonia	60	A
2		Isopropylamine	79	B
3		Pyrrolidine	60	B
4		Ammonia	83	A
5		Isopropylamine	54	B
6		Pyrrolidine	43	B
7		Ammonia	75	A
8		Isopropylamine	80	B
9		Pyrrolidine	49	B
10		Ammonia	80	A
11		Isopropylamine	17	B
12		*n*-butylamine	26	B

[a] Yields refer to isolated material, except for 7. [b] All products were more than 95% pure by GC and needed no further purification. [c] The yield was determined by deducting the amount of isopropyl alcohol from the ^{1}H NMR spectrum of the product. [d] For experimental details of methods A and B, see the Experimental.



Scheme 2.

Evaporation of the reaction mixture *in vacuo* after addition of Ti(*O-iPr*)$_4$ and $TiCl_4$ to dispose of excess ammonia effectively removed any traces of McMurry-type coupling products.

A few additional comments on the above described procedures should be made. Other Lewis acids such as $SnCl_4$ and $BF_3 \cdot Et_2O$ gave only trace amounts of amines, the main product being alcohol from ketone reduction. With $TiCl_4$ or Ti(O-*i*Pr)$_4$ alone the yields were low and the reaction sluggish. We also tried preformed mixtures of $TiCl_{4-n}(O\text{-}iPr)_n$. Of these, only $TiCl_2(O\text{-}iPr)_2$ was an equal candidate to sequentially added Ti(O-*i*Pr)$_4$ and $TiCl_4$, but was far more difficult to handle. Diethyl ether appears to be the best solvent. Neither more polar solvents, such as THF or nitromethane, nor less polar solvents, such as CH_2Cl_2, have a positive effect on the yield and the chemoselectivity.

The formation of an intermediate iminium salt should also be noted. Treatment of a ketone–amine mixture in diethyl ether at 0 °C with $TiCl_4$ produced a red to yellow precipitate. NMR analysis showed the presence of an iminium salt. Thus, Ti(O-*i*Pr)$_4$ is not necessary for iminium salt formation. To simplify the NMR spectra, a simple ketone–amine mixture was selected and, hence, 1 equiv. of acetone was mixed with 3 equivs. of *n*-propylamine in dry ether under argon at 0 °C. The solution was treated with 1.6 equivs. of $TiCl_4$ as a 2 M solution in hexane. The resulting slurry was stirred for 30 min and the solvent was evaporated off. The residue was dissolved in methanol-d_4 and ^{1}H and ^{13}C NMR spectra of the solution were recorded. The spectra are consistent with an iminium salt.[10] In the ^{13}C NMR spectrum, a single peak at 194 ppm indicated the presence of a quaternary iminium carbon. No traces of enamine could be detected and neither could any amino acetal[11] nor remaining acetone be observed. It is possible to dissolve the precipitate in 99.5% ethanol and reduce the salt with $NaBH_4$. The yields for this procedure are in some cases high for the preparation of secondary amines, but the reaction fails completely with ammonia, giving rise solely to the alcohol from ketone reduction.[12]

In conclusion, primary amines can be prepared from gaseous ammonia and a ketone in a one-pot procedure, in which Ti(*O-iPr*)$_4$ and $TiCl_4$ are used for the condensation and borane–dimethyl sulfide complex for the reduction. Secondary amines and some tertiary amines can in several cases also be prepared by the same method. An attractive feature of the method lies in the potential to utilize a wide variety of asymmetric borane reagents to prepare optically active primary amines directly from ketones. Work in this field is presently underway in our laboratory.

Experimental

Procedure A. The reaction between acetophenone and ammonia is typical. Acetophenone (0.5 ml, 4.3 mmol) was dissolved in dry diethyl ether under argon. Gaseous ammonia was bubbled through the solution for a few min. The solution was cooled to 0 °C and 2 M Ti(O-*i*Pr)$_4$ in pentane (3.4 ml, 1.6 equiv.) was added. The clear solution was stirred at 0 °C for 1 h, after which 2 M $TiCl_4$ in pentane (3.4 ml, 1.6 equiv.) was added and a pale yellow precipitate was formed. After being stirred for 30 min, the ether–ammonia mixture was evaporated *in vacuo* at room temperature for 60–90 min. The residue

was again dissolved in dry diethyl ether, cooled to 0 °C and borane–dimethyl sulfide complex (0.41 ml, 1 equiv.) was added. The reaction mixture was stirred for 14 h, during which time the solution slowly attained room temperature. The mixture was transferred to an Erlenmayer flask and a solution of 2 M NaOH (about 50 ml) was cautiously added. Stirring was continued until the slurry had changed colour from dark blue to white (approximately 1 h). The solution was then filtered through Celite and the two phases were separated. The ether phase was extracted with 2 M HCl (3 × 40 ml). The acidic solution was made alkaline with 2 M NaOH and extracted with ether (3 × 30 ml). The combined ether layers were dried with Na_2SO_4 or $MgSO_4$ and the solvent was evaporated off to give a pale yellow oil (0.312 g, 60%).

Procedure B. Instead of evaporating the reaction slurry after addition of $TiCl_4$, stirring was continued for 30 min, after which borane–dimethyl sulfide complex was added. From here on, the procedure is identical with procedure A.

Characterization of the compounds. Spectral data for the new compounds are presented below. NMR and mass spectra for the other amines are in accordance with previously reported data.

2-Isopropylaminononane. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (3 H, t, *J* 6.8 Hz), 1.01 (3 H, d, *J* 6.8 Hz), 1.03 (3 H, d, *J* 6.0 Hz), 1.05 (3 H, d, *J* 6.0 Hz), 1.27 (11 H, m), 1.42 (1 H, m), 2.69 (1 H, m), 2.90 (1 H, m, *J* 6.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.40, 21.08, 22.90, 23.35, 24.06, 26.32, 29.56, 30.07, 32.09, 37.81, 45.45, 50.00. MS: *m/z* (rel. intensity) 185 (3), 184 (2), 171 (4), 170 (29), 142 (2), 128 (3), 87 (8), 86 (100), 70 (4), 44 (33).

1-(2-Nonyl)pyrrolidine. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (3 H, t, *J* 6.8 Hz), 1.07 (3 H, d, *J* 6.4 Hz), 1.27 (11 H, m), 1.59 (1 H, m), 1.77 (4 H, m), 2.20 (1 H, m), 2.55 (4 H, m).^{13}C NMR (100 MHz, $CDCl_3$): δ 14.29, 18.24, 22.85, 23.59, 26.09, 29.50, 30.22, 32.05, 35.67, 51.63, 59.59. MS: *m/z* (rel. intensity) 197 (8), 196 (3), 183 (4), 182 (32), 110 (3), 99 (17), 98 (100), 70 (6), 57 (5), 56 (5), 43 (4), 41 (7).

α-Cyclohexylbenzylamine. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.60–1.70 (11 H, m), 1.76 (1 H, m), 1.95 (1 H, m), 3.60(1 H, d, *J* 7.0 Hz), 7.18–7.35 (5 H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.11 (2 C), 26.63, 29.70, 30.29, 45.39, 61.89, 126.92, 127.28, 128.32, 145.72. MS: *m/z* (rel. intensity) 189 (1), 177 (3), 149 (9), 118 (25), 107 (75), 106 (100), 104 (34), 91 (33), 79 (100), 77 (54), 69 (11), 55 (28), 41 (31).

N-Isopropyl-α-cyclohexylbenzylamine. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.55–1.65 (10 H, m), 0.95 (3 H, d, *J* 8.71 Hz), 0.98 (3 H, d, *J* 9.11 Hz), 1.72 (1 H, m), 1.95 (1 H, m), 2.50 (1 H, m), 3.42 (1 H, d, *J* 7.52 Hz), 7.18–7.32 (5 H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.10, 24.63, 26.49, 26.75, 30.07, 30.68, 44.58, 45.73, 65.94, 126.64, 128.05, 128.07, 143.89. MS: *m/z* (rel. intensity) 231 (0.7), 230 (4), 188 (4), 173 (12), 149 (100), 148 (100), 146 (19), 132 (30), 117 (16), 115 (18), 107 (35), 106 (100), 91 (100), 79 (71), 77 (37), 55 (34), 41 (55).

N-Butyl-α-cyclohexylbenzylamine. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.78–1.66 (14 H, m), 0.85 (3 H, t, *J* 6.78 Hz), 1.73 (1 H, m), 1.93(1 H, m), 2.34 (2 H, t, *J* 6.86 Hz), 3.30 (1 H, d, *J* 8.57 Hz), 7.20–7.33 (5 H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.17, 20.62, 26.46, 26.52, 26.71, 30.00, 30.51, 32.54, 44.40, 47.82, 69.20, 126.70, 128.03, 128.15, 143.55. MS: *m/z* (rel. intensity) 245 (2), 244 (8), 173 (19), 164 (15), 163 (100), 162 (100), 161 (20), 132 (15), 129 (14), 119 (19), 118 (62), 117 (23), 115 (21), 106 (100), 105 (29), 104 (38), 91 (100), 79 (73), 77 (29), 69 (26), 67 (20), 55 (43), 63 (49), 41 (97).

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10. Iminium salt formed from *n*-propylamine and acetone: ^{1}H NMR (400 MHz, MeOD-d_3) δ 1.24 (3 H, t, *J* 5.7 Hz), 1.92 (2 H, m), 2.64 (3 H, s), 2.72 (3 H, s), 3.79 (2 H, br *t*, *J* 7.6 Hz).
11. For one example of the ^{13}C NMR shift of an amino acetal, see Alcaide, B., Plumet, J., Rodriguez-Campus, I., García-Blanco, S. and Martínez-Carrera, S. *J. Org. Chem. 57* (1992) 2446.
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