Heteroatom Chemistry
Volume 16, Number 1, 2005

Mildly and Highly Selective Reductive Deoxygenation of *para*-Di- and Monoalkylaminophenyl Ketones by Borane

Tiezheng Wei, Yu Lan, and Jiaxi Xu

Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, Department of Chemical Biology, College of Chemistry and Molecular Engineering, Peking University, Beijing 100871, People's Republic of China

Received 6 October 2003; revised 14 April 2004

ABSTRACT: *Para-di- and monoalkylaminophenyl ketones were reduced selectively to para-alkyl N,N-di- and N-monoalkylanilines in good to excellent yields by borane under mild, convenient, and neutral conditions*. © 2005 Wiley Periodicals, Inc. Heteroatom Chem 16:2–5, 2005; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20062

INTRODUCTION

Reductive deoxygenation of aryl ketones is an important and valuable procedure in organic synthesis [1–4]. There is a great need to develop novel methodologies for defunctionalization, especially for conversion of polyfunctional natural products to useful building blocks and bioactive molecules. Although classical Clemmensen and Wolff-Kishner reduction use rather harsh acidic or basic conditions that are incompatible with the high degree of selectivity required for polyfunctional compounds, a number of milder direct and indirect methods have been proposed. The direct methods include (1) sodium (cyano)borohydride in the presence of some Lewis acids, such as boron trifluoride etherate [5,6], aluminum chloride [7], palladium chloride [8], zinc halide [2], or protic acid such as trifluoroacetic acid [9]; (2) borane in the presence of some Lewis acids [3], such as boron trifluoride etherate, aluminum chloride, zinc halide, titanium chloride, iron chloride, etc. or protic acid trifluoroacetic acid [10]; (3) lithium aluminum hydride in combination with aluminum chloride [11]; (4) trialkyl silane and acids; (5) hydrosiloxane-borane combination [4]. Most of these methods require acidic conditions including protic acids and Lewis acids. Herein, we describe a highly selective deoxygenation of the carbonyl group in *N*-alkyl substituted *para*-aminophenyl ketones with borane only.

RESULTS AND DISCUSSION

All *para*-dialkylaminophenyl ketones **1a–j** and *para*-monoalkylaminophenyl ketones **1k,l** were prepared through alkylation of *para*-aminophenyl ketones, which were synthesized from acylation of acetoaniline with acyl chlorides and followed hydrolysis according to the literature method [12].

Firstly we hoped to reduce *N,N*-dialkylaminophenyl ketones to the corresponding alcohols with borane. When we added borane dimethylsulfide complex into a solution of ketones **1b,c** in THF, we found that the yields of the alcohols **3b,c** were very low and some *para*-alkyl *N,N*-dialkylanilines

Correspondence to: Jiaxi Xu; e-mail: jxxu@chem.pku.edu.cn, jia_xu_99@yahoo.com.
Contract grant sponsor: National Natural Science Foundation of China.
Contract grant number: 20272002.
Contract grant sponsor: Ministry of Education of China.
Contract grant sponsor: Peking University.

2b,c were obtained in moderate to high yields. After optimum reduction conditions, we found that the mode of reduction is addition rate controlled for *N*,*N*-dialkylaminophenyl ketones. The *N*,*N*-dialkyl substituted ketones **1a–j** were reduced to the alcohols using slow addition mode [13]. While for *N*-monoalkylaminophenyl ketones **1k,l**, no corresponding alcohols could be obtained even borane dimethylsulfide complex was carefully added using the slow addition mode (see Scheme 1). All ketones were reduced directly to hydrocarbons with borane under rapid addition conditions. To study the scope of the method, a series of *para*-dialkyl and *para*-monoalkylaminophenyl ketones were reduced to hydrocarbons under rapid addition conditions and the results are summarized in Table 1.

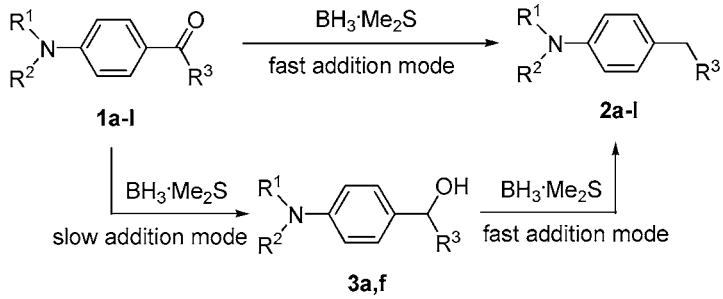
To understand the mechanism of the deoxygenation, two 1-(*para*-dialkylaminophenyl)ethanols **3a,f** prepared from ketones **1a,f** via borane reduction in slow addition mode were also reacted with borane in fast addition mode. They also gave rise to the corresponding hydrocarbons **2a,f** (entries 13 and 14 in Table 1). This indicates that the ketones react with borane to yield a monoalkoxyborane intermediate **4** at first. The monoalkoxyborane **4** undergoes an elimination to produce conjugative imine intermediate **5** under neutral conditions due to the existence of an electron-donating amino group, similar to presumed mechanism in the literature [5]. The imine intermediate **5** was reduced further to the hydrocarbon by borane as shown in Scheme 2.

To establish the generality of the method, *para*-alkyl-, alkoxy-, and alkylthiophenyl ketones (*p*-EtPhCOMe, *p*-MeOPhCOMe, and *p*-MeSPhCOMe) were also reduced under the same conditions. However, all of them were reduced to alcohols, no corresponding hydrocarbon derivatives were found although *para*-alkoxyphenyl ketones could be reduced to hydrocarbons by borane in the presence of boron trifluoride (under Lewis acidic conditions) [5]. It was rationalized that 1-(*para*-alkyl-, alkoxy-, and alkylthiophenyl)alkoxyboranes could not undergo an elimination to form conjugative alkenes under neutral conditions due to the weak electron-donating ability of alkyl, alkoxy, and alkylthio groups. This observation indicates that the neutral reductive deoxygenation is highly selective for the carbonyl group in *N*-alkyl substituted *para*-aminophenyl ketones and for the hydroxy group in *N*-alkyl substituted *para*-aminophenyl alcohols.

In summary, a direct and rapid conversion of carbonyl functionality to methylene group under very mild conditions with high yields was described. The procedure is very simple and convenient. It is highly selective for deoxygenation of the carbonyl group in *N*-alkyl substituted *para*-aminophenyl ketones and of the hydroxy group in *N*-alkyl substituted *para*-aminophenyl alcohols under neutral conditions.

EXPERIMENTAL

Elemental analyses were carried out on an Elementar Vario EL elemental analyzer. The ^{1}H NMR spectra were recorded on a Varian Mercury 200 or 300 spectrometer with TMS as an internal standard in the $CDCl_3$ solution. The IR spectra were taken on a Brucker Vector 22 FT-IR spectrophotometer in film on KBr plate. Mass spectra were obtained on a VG ZAB-HS mass spectrometer. TLC separations were performed on silica gel G plates with petroleum ether (60–90°C)/ethyl acetate (5:1), and the plates were visualized with UV light.



a: $R^1 = R^2 = R^3$ = Me; **b**: $R^1 = R^2$ = Et, R^3 = Me; **c**: $R^1 = R^2$ = *n* -Pr, R^3 = Me;
d: $R^1 = R^2$ = n -Bu, R^3 = Me; **e**: $R^1 = R^2$ = *n* -Am, R^3 = Me; **f**: $R^1 = R^2$ = *n* -Hex, R^3 = Me;
g: $R^1 = R^3$ = Me, R^2 = Et, **h**: $R^1 = R^2$ = Me, R^3 = Et; **i**: $R^1 = R^2$ = *n* -Am, R^3 = Et;
j: $R^1 = R^2$ = Me, R^3 = *n* -Pr; **k**: R^1 = *n* -Am, R^2 = H, R^3 = Me; **l**: R^1 = *n* -Hex, R^2 = H, R^3 = Me

SCHEME 1 Reductive deoxygenation of carbonyl and hydroxy groups to methylene with borane.

TABLE 1 Reductive Deoxygenation of *para*-di- and Monoalkylaminophenyl Ketones and Alcohols by Borane

Entry	*Product*	R^1/R^2	R^3	*Yield (%)*		*Lit*
1	**2a**	Me/Me	Me	25 (85[a])	Oil	104/16 mmHg [14]
2	**2b**	Et/Et	Me	95	Oil	Oil [15]
3	**2c**	*n*-Pr/*n*-Pr	Me	90	Oil	Oil [15]
4	**2d**	*n*-Bu/*n*-Bu	Me	92	Oil	Oil [15]
5	**2e**	*n*-Am/*n*-Am	Me	94	Oil	
6	**2f**	*n*-Hex/*n*-Hex	Me	92	Oil	
7	**2g**	Me/Et	Me	91	Oil	[16]
8	**2h**	Me/ Me	Et	91	Oil	116–118/16 mmHg [14]
9	**2i**	*n*-Am/*n*-Am	Et	97	Oil	
10	**2j**	Me/Me	Pr	95	Oil	137/16 mmHg [14]
11	**2k**	*n*-Am/H	Me	81	Oil	
12	**2l**	*n*-Hex/H	Me	85	Oil	
13	**3a**	Me/Me	Me	83	Oil	Oil [17]
14	**3f**	*n*-Hex/*n*-Hex	Me	99	Oil	

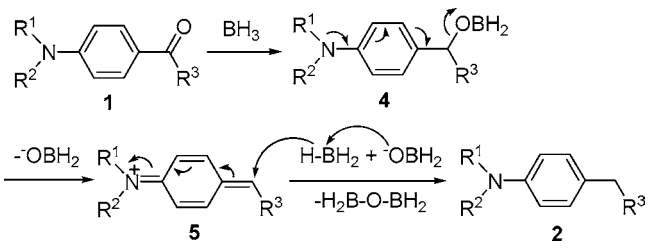
[a]25% in 2 h, 85% more than 10 h.

Reductive Deoxygenation of Carbonyl and Hydroxy Groups to Methylene with Borane

General procedure. To a solution of *N*-alkyl aminophenyl ketone **1** (or *N*-alkyl aminophenyl alcohol **3**) (1 mmol) in anhydrous THF (20 mL) was added rapidly (one-pot) borane dimethylsulfide (0.222 g, 2.2 mmol) in anhydrous THF (10 mL) under stirring at room temperature After having been stirred for 1–2 h at room temperature, the solvent was removed and the resulting residue was separated on a silica gel column with petroleum ether (60–90°C)/ethyl acetate (5:1) as an eluent to give colorless oil *para*-alkyl *N*-alkylaniline **2**.

4-Ethyl-N,N-dipentylaniline **2e**

Colorless oil, yield 94%. R_f 0.40 (petroleum ether: AcOEt = 5:1, silica gel plate). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.03 (d, J = 8.4 Hz, 2H, ArH), 6.58 (d, J = 8.4 Hz, 2H, ArH), 3.21 (t, J = 7.4 Hz, 4H, $2CH_2$), 2.53 (q, J = 7.8 Hz, 2H, CH_2), 1.59 (quintet, J = 8.2 Hz, 4H, $2CH_2$), 1.31 (m, 8H, $4CH_2$), 1.19 (t, J = 7.4 Hz, 3H, CH_3), 0.90 (t, J = 6.8 Hz, 6H, $2CH_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 146.44, 130.92, 128.45, 112.07, 51.21, 29.41, 27.69, 27.02, 22.60, 15.85, 14.06; IR (KBr):υ 2960, 1460, 821 cm^{-1}; EI-MS (m/z): 261 (M^+, 25), 204 (M^+-Bu, 100), 148 (M^+-Bu-$4CH_2$, 53), 119 ($EtPhN^+$, 5.1); Anal. Calcd for $C_{18}H_{31}N$ (261.45): C, 82.69; H, 11.95; N, 5.36. Found: C, 82.42; H, 11.72; N, 5.45.



SCHEME 2 Presumed mechanism of reductive deoxygenation of carbonyl group to methylene with borane.

4-Ethyl-N,N-dihexylaniline **2f**

Colorless oil, yield 92%. R_f 0.40 (petroleum ether: AcOEt = 5:1, silica gel plate). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.03 (d, J = 8.6 Hz, 2H, ArH), 6.58 (d, J = 8.6 Hz, 2H, ArH), 3.21 (t, J = 7.2 Hz, 4H, $2CH_2$), 2.53 (q, J = 7.4 Hz, 2H, CH_2), 1.51 (quintet, J = 7.2 Hz, 4H, $2CH_2$), 1.30 (m, 12H, $6CH_2$), 1.19 (t, J = 7.8 Hz, 3H, CH_3), 0.89 (t, J = 6.4 Hz, 6H, $2CH_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 146.35, 130.82, 128.47, 111.91, 51.23, 31.77, 27.69, 27.25, 26.90, 22.71, 15.91, 14.05; IR (KBr): υ 2959, 1458, 820 cm^{-1}; EI-MS (m/z): 289 (M^+, 18), 218 (M^+-Am, 100), 148 (M^+-Am-$5CH_2$, 47), 134 (M^+-Am-$6CH_2$, 17); Anal. Calcd for $C_{20}H_{35}N$ (289.50): C, 82.98; H, 12.19; N, 4.84. Found: C, 82.99; H, 12.29; N, 4.58.

N,N-Dipentyl-4-propylaniline **2i**

Colorless oil, yield 97%. R_f 0.40 (petroleum ether: AcOEt = 5:1, silica gel plate). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.01 (d, J = 8.6 Hz, 2H, ArH), 6.57 (d, J = 8.6 Hz, 2H, ArH), 3.21 (t, J = 7.2 Hz, 4H, $2CH_2$), 2.47 (t, J = 8.2 Hz, 2H, CH_2), 1.57 (quintet, J = 7.4 Hz, 6H, $3CH_2$), 1.33 (m, 8H, $4CH_2$), 0.93 (t, J = 7.2 Hz, 3H, CH_3), 0.91 (t, J = 7.0 Hz, 6H, $2CH_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 146.42, 130.88, 128.42, 112.10, 51.21, 37.02, 29.41, 27.69, 27.11, 24.83, 15.82, 13.85; IR (KBr): υ 2959, 1460, 822 cm^{-1}; EI-MS (m/z): 275

(M^+, 20), 246 (M^+-Et, 5.0), 218 (M^+-Bu, 100), 162 (M^+-Bu-4CH_2, 40), 148 (M^+-Bu-5CH_2, 13); Anal. Calcd for $C_{19}H_{33}N$ (275.47): C, 82.84; H, 12.07; N, 5.08. Found: C, 83.08; H, 12.30; N, 5.29.

4-Ethyl-N-pentylaniline **2k**

Colorless oil, yield 83%. R_f 0.30 (petroleum ether: AcOEt = 5:1, silica gel plate). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.00 (d, $J = 8.4$ Hz, 2H, ArH), 6.54 (d, $J = 8.4$ Hz, 2H, ArH), 3.40 (s, br, 1H, NH), 3.08 (t, $J = 6.8$ Hz, 2H, CH_2), 2.53 (q, $J = 7.6$ Hz, 2H, CH_2), 1.57 (quintet, $J = 6.8$ Hz, 2H, CH_2), 1.38 (m, 4H, 2CH_2), 1.18 (t, $J = 7.6$ Hz, 3H, CH_3), 0.91 (t, $J = 6.4$ Hz, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 146.55, 132.95, 128.50, 112.86, 44.32, 29.36, 27.90, 22.50, 15.92, 14.00, 13.99; IR (KBr): υ 3450 (NH), 2957, 1459, 819 cm^{-1}; EI-MS (m/z): 191 (M^+, 18), 176 (M^+-Me, 5.4), 134 (M^+-Bu, 100), 119 (M^+-Bu-Me, 5.1); Anal. Calcd for $C_{13}H_{21}N$ (191.31): C, 81.61; H, 11.06; N, 7.32. Found: C, 81.85; H, 11.26; N, 7.19.

4-Ethyl-N-hexylaniline **2l**

Colorless oil, yield 85%. R_f 0.30 (petroleum ether: AcOEt = 5:1, silica gel plate). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.00 (d, $J = 8.2$ Hz, 2H, ArH), 6.54 (d, $J = 8.2$ Hz, 2H, ArH), 3.25 (s, br, 1H, NH), 3.07 (t, $J = 6.8$ Hz, 2H, CH_2), 2.53 (q, $J = 7.6$ Hz, 2H, CH_2), 1.59 (quintet, $J = 7.0$ Hz, 2H, CH_2), 1.33 (m, 6H, 3CH_2), 1.18 (t, $J = 7.4$ Hz, 3H, CH_3), 0.89 (t, $J = 6.0$ Hz, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 146.35, 130.98, 128.41, 112.76, 44.15, 29.20, 27.88, 26.90, 22.60, 15.92, 14.06, 13.99; IR (KBr): υ 3452 (NH), 2960, 1459, 821 cm^{-1}; EI-MS (m/z): 205 (M^+, 17), 190 (M^+-Me, 5.1), 134 (M^+-Am, 100), 119 (M^+-Am-Me, 5.1); Anal. Calcd for $C_{14}H_{23}N$ (205.34): C, 81.89; H, 11.29; N, 6.82. Found: C, 81.69; H, 11.29; N, 6.58.

1-(4-Dihexylaminophenyl)ethanol **3f**

Colorless oil, yield 99%; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.90 (t, $J = 6.4$ Hz, 6H, 2CH_3), 1.25–1.40 (m, 12H, 6CH_2), 1.48 (d, $J = 6.2$ Hz, 3H, 2CH_3), 1.51–1.69 (m, 5H, OH, 2CH_2), 3.24 (t, $J = 7.6$ Hz, 4H, 2CH_2), 4.79 (q, $J = 6.2$ Hz, 1H, CH), 6.60 (d, $J = 8.8$ Hz, 2H, ArH), 7.24 (d, $J = 8.8$ Hz, 2H, ArH). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 14.03, 22.68, 26.84, 27.17, 31.73, 51.09, 70.16, 74.85, 111.43, 126.66, 132.08, 147.70. MS (EI) m/z: 305 (M^+, 11), 287 (32), 234 (47), 216 (100), 164 (9), 146 (28), 132 (20), 43 (33); IR υ(cm^{-1}): 3382 (OH), 2957, 2928, 1614, 1520. Anal. Calcd for $C_{20}H_{35}NO$ (305.50): C, 78.63; H, 11.55; N, 4.58. Found: C, 79.00; H, 11.38; N, 4.54.

REFERENCES

[1] House, H. O. Modern Synthetic Reactions, 2nd ed.; W. A. Benjamin: Menlo Park, CA, 1972; Ch. 4.
[2] Lau, C. K.; Dufresne, C.; Belanger, P. C.; Pietre, S.; Scheigetz, J. J Org Chem 1986, 51, 3038 and references cited therein.
[3] Dehmlow, E. V.; Niemann, T.; Kraft, A. Synth Commun 1996, 26, 1467 and references cited therein.
[4] Chandrasekhar, S.; Reddy, C. R.; Babu, B. N. J Org Chem 2002, 67, 9080 and references cited therein.
[5] Biswas, K. M.; Houghton, L. E.; Jackson, A. H. Tetrahedron 1966, suppl 261.
[6] Breuer, E. Tetrahedron Lett 1967, 1849.
[7] Lau, C. K.; Tardif, S.; Dufresne, C.; Scheigetz, J. J Org Chem 1989, 54, 491.
[8] Satoh, T.; Mitsuo, N.; Nishiki, M.; Nanba, K.; Suzuki, S. Chem Lett 1981, 1029.
[9] Gribble, G. W.; Kelley, W. J.; Emery, S. E. Synthesis 1978, 763.
[10] Kikugawa, Y.; Ogawa, Y. Chem Pharm Bull 1979, 27, 1405.
[11] Nystrom, R. F.; Berger, C. R. A. J Am Chem Soc 1958, 80, 2896.
[12] Jen, Y. F., Kao, I. S. Hua Hsueh Hsueh Pao 1965, 31, 492.
[13] Xu, J. X.; Su, X. B.; Zhang, Q. H. Tetrahedron: Asymmetry 2003, 14, 1781.
[14] Davies, W. C.; Hulbert, F. L. J Soc Chem Ind 1938, 57, 349.
[15] Boeshagen, H.; Geiger, W. Chem Ber 1979, 112, 3286.
[16] Pai, V.; Bloomfield, S. F.; Jones, J.; Corrod, J. W. Biol Oxid Nitrogen, Proc 2nd Int Symp, 1977 (Pub. 1978), 375, Chem Abstr 1978, 89, 100879z.
[17] Pioda, G.; Togni, A. Tetrahedron: Asymmetry 1998, 9, 3903.