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Reduction of Tertiary Amides with Borane in the Presence of Trimethyl Borate

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Various tertiary amides have been subjected to the reduction by borane-THF in the presence of trimethyl borate at 0°C and the product ratio of alcohol and amine have been analyzed in order to find out the possible way to obtain one product exclusively on the basis of the structure of amides. In the case of N,N-dimethyl derivatives of both linear aliphatic and aromatic amides the corresponding alcohols were produced predominantly. However, the bulkier tertiary amides such as N,N-diethyl and hindered acid derivatives afforded amines rather than alcohols. The mechanism of borane reduction of tertiary amides is also discussed.

Introduction

The reduction of tertiary amides with various metal hydrides such as lithium aluminum hydride, aluminum hydride, diborane, etc.¹ generally proceeds with carbon-oxygen fission to give the corresponding tertiary amines. Borane-dimethyl sulfide has also been shown to be an excellent selective reducing agent for the reduction of tertiary amides to the corresponding amines.² On the other hand, the reduction of tertiary amides to the corresponding alcohols is reported only with LiEt₃BH³, 9-BBN⁴ and sodium dimethylaminoborohydride⁵. However, LiEt₃BH is a very powerful reducing agent and many functional groups may not be expected to tolerate this strong hydride. 9-BBN was also reported to give 80% yield of benzyl alcohol from N,N-dimethylbenzamide; however no data is available for the aliphatic tertiary amides. Although sodium dimethylaminoborohydride seems to be a good reagent, it requires a long reaction time at elevated temperature (5-55 h at 66°C) for such reaction. Recently, we have observed an unexpected high ratio of 1-hexanol over N,N-dimethylhexylamine (ca. 9:1) in the competitive reaction of N,N-dimethylhexanamide and butylene oxide with BH₃-NaBH₄ system at 0°C in 1 h.⁶ This suggests the alkoxborane, formed during reaction, might play an important role for the rate enhancement and for the product ratio in the reduction of tertiary amides. Therefore we have decided to explore in detail the reduction of tertiary amides with borane-THF in the presence of trimethyl borate as a catalyst.

Results and Discussion

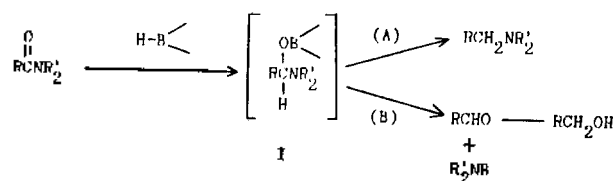
Effect of Temperature. In order to understand the influence of temperature on the reduction of amides, N,N-dimethylhexanamide and N,N-dimethylbenzamide were subjected to the reduction with borane at 65°C, 25°C and 0°C, respectively, and the results are summarized in Table 1. As shown in Table 1, we can see the temperature effect on the formation of products. Generally, the yields of amines increase with increasing reaction temperature and on the contrary the yields of alcohols increase with lowering temperature. Thus, at 65°C both amides were reduced to the corresponding tertiary amines almost exclusively; however, the yield of alcohol was increased with lowering temperature. In the case of reaction at 0°C, N,N-dimethylhexanamide and N,N-dimethylbenzamide gave the corresponding alcohols and aldehydes as major products (66-90%) along with the corresponding amines (34-8%). At 25°C, we found the amount of tertiary amines increased continually with time at the expense of alcohols and aldehydes. Thus, N,N-dimethylhexylamine increased from 35% (1 h) to 78% (6 h) and the amount of alcohol and/or aldehyde decreased from 65% (1 h) to 22% (6 h). The reduction of tertiary amides is generally believed to proceed along two pathways to afford either amines by reductive removal of carbonyl (path A) or alcohols *via* expulsion of amine and reduction of the resulting aldehyde (path B), through the tetrahedral intermediate I.^{1b}

According to this scheme, our results indicate that (1) the

Table 1. Effect of Temperature in the Reduction of N,N-Dimethylhexanamide (1) and N,N-Dimethylbenzamide (2) with Borane in Tetrahydrofuran^a

Amides	H ^c /Cpd	Temp, °C	Time, h	% Yield			
				Alcohol	Aldehyde	Amine	Amide
1	5	65	1.0	7	0	93(95) ^c	0
1	5	25	1.0	47	18	35	0
			3.0	36	5	59	0
			6.0	22	0	78	0
1	5	0	0.5	45	3	7	42
			1.0	49	6	9	32
			3.0	62	5	23	10
			6.0	66	0	34	0
			6.0 ^d	3	64	33	0
2	5	65	1.0	0	0	92(98) ^c	0
2	5	25	0.5	76	14	10	0
			1.0	67	15	18	0
2	5	0	0.5	41	8	3	48
			1.0	53	9	4	34
			3.0	71	19	8	tr.

^aOne mmol of compound in THF was added to 1.7 mmol of BH₃ in THF (0.25 M in compound and 0.42 M in BH₃). ^bYields were determined by GLC. ^cH. C. Brown and P. Heim, *J. Org. Chem.*, **38**, 912 (1973). ^dInstead of water, CH₃CHO was used for quenching the reaction mixture.

**Scheme 1**

tertiary amide reacted fast to give intermediate I completely within 1 h at 25 °C and (2) this intermediate I was reduced to the corresponding amine (path A) rapidly at 65 °C, but rather slowly at 25 °C, and much more slowly at 0 °C. This suggests that the path B, which involves the formation of aldehyde from intermediate I, did not occur during the reaction, and the aldehyde product formed during hydrolysis was reduced further to the corresponding alcohol with borane species, which still possess active hydrides. This was confirmed by the fact that the reaction mixture of N,N-dimethylhexanamide with borane in 6.0 h at 0 °C, upon quenching with acetaldehyde before hydrolysis offered 64% yield of hexanal.

Effect of Trimethyl Borate. The presence of trimethyl borate accelerates the rate of reduction of N,N-dimethylcarboxamides with borane. Thus, in the reaction of N,N-dimethylhexanamide the presence of 20 mol % of trimethyl borate completed the reaction within 0.5 h at 0 °C, while borane alone underwent the reaction only in approximately 50%. The effect in such rate enhancement remains constant whenever the amount of trimethyl borate increase to 60%. The similar results were also observed in the reduction of N,N-dimethylbenzamide (Table 2). At the present time, it is not clear the reason why trimethyl borate enhances the rate of reduction. However, it is interesting to note that the presence of trimethyl borate enhances the reduction of benzoic

Table 2. Effect of the Amount of Trimethyl Borate in the Reduction of N,N-Dimethylhexanamide (1) and N,N-Dimethylbenzamide (2) with Borane in Tetrahydrofuran at 0 °C^a

Amides	H ^c /Cpd	(CH ₃ O) ₃ B ^b	Time, h	% Yield ^c			
				Alcohol	Aldehyde	Amine	Amide
1	5	0	0.5	45	3	10	42
1	6	0	0.5	61	2	11	26
			10	62	12	9	17
1	5	20	0.5	68	14	18	0
			40	73	11	16	0
			60	72	10	18	0
			3.0	71	19	8	tr.
2	6	0	0.5	44	16	3	37
			1.0	57	18	4	20
			3.0	70	21	9	tr.
2	5	20	0.5	82	11	3	4
			1.0	86	13	5	0

^aCompound was added to BH₃(CH₃O)₃B in THF (0.25 M in compound). ^bMol percent of trimethyl borate to borane. ^cYields were determined by GLC.

acid with BMS at room temperature⁷, and the reduction of esters with lithium borohydride in refluxing ether⁸.

Reduction of Tertiary Amides to the Corresponding Alcohols. The reduction of N,N-dimethylhexanamide with BH₃(CH₃O)₃ (1:0.2) system gave 68% of 1-hexanol, 14% of hexanal and 18% of N,N-dimethylhexylamine (Table 2) upon hydrolysis with water. In order to get rid of aldehyde and increase the yield of alcohol, we added a catalytic amount of sodium borohydride to the reaction mixture at the beginning. We obtained 93% yield of 1-hexanol. Apparently borohydride catalyzed the reduction of aldehyde with borane species. We applied this method to 14 representative tertiary amides and the results are summarized in Table 3. As shown in Table 3, the reduction rates and products are appeared to be dependent critically on the substituents. Thus, N,N-dimethylamides (entries 1, 2, 9, 11, 12, 13, and 14) consistently afforded high yields of the corresponding alcohols (81-93%). However, as the size of alkyl groups on nitrogen increase, the amount of alcohol produced falls sharply with a concomitant rise in the yield of amine. Thus, for N,N-dimethyl, pyrrolidine, and N,N-diethyl derivatives of hexanamide (entries 1, 3, and 4), the yields of 1-hexanol were 93%, 52%, and 11%, respectively, while the amount of corresponding tertiary hexylamines produced rose from 7% for N,N-dimethyl amide to 87% for N,N-diethyl amide, and as shown in entry 5 the two bulky isopropyl groups on nitrogen not only gave the amine exclusively but also retarded the reaction rate tremendously. Presumably the intermediate (Scheme 1) is less stable when the alkyl group on nitrogen becomes larger than the methyl, which is relieved by the carbon-oxygen fission due to the steric congestion. The similar tendency was also observed in the reduction of N,N-dimethylcyclohexanecarboxamide and N,N-dimethylpivalamide which gave corresponding tertiary amines in the yield of 57% and 48%, respectively, while N,N-dimethylhexanamide afforded

Table 3. Reaction of Various Tertiary Amides with the $\text{BH}_3\text{-(CH}_3\text{O)}_3\text{B}$ (1:0.2) System in Tetrahydrofuran at 0°C^a

Entry	Amides	Time h	% Yield ^b		
			Alcohol	Amine	Amide
1	N,N-Dimethylhexanamide	0.5	93(87) ^c	7	0
2	N,N-Dimethyloctanamide	0.5	88	12	0
3	1-Hexanoyl pyrrolidine	1.0	52	48	0
4	N,N-Diethylhexanamide	3.0	11	87	2
5	N,N-Diisopropylhexanamide	3.0	4	22	74
6	N,N-Dimethylcyclohexanecarboxamide	3.0	43	57	0
7	N,N-Dimethylpivalamide	6.0	37	63	3
8	N,N-Diethylpivalamide	6.0	14	72	14
9	N,N-Dimethylbenzamide	1.0	91(84) ^c	5	0
10	N,N-Diethylbenzamide	1.0	4	89	0
11	N,N-Dimethyl- <i>o</i> -toluamide	3.0	81	16	0
12	N,N-Dimethyl- <i>p</i> -toluamide	3.0	84	7	0
13	N,N-Dimethyl- <i>p</i> -anisamide	1.0	86	13	0
14	N,N-Dimethyl-4-nitrobenzamide	1.0	85 ^c	—	—

predominantly 1-hexanol (a 93% yield).

Conclusion

The presence of 20 mol % of trimethyl borate accelerates the rate of reduction of N,N-disubstituted amides with borane-THF solution. In addition, $\text{BH}_3\text{-(CH}_3\text{O)}_3\text{B}$ in THF produces the different ratio of amines and alcohols, depending upon the steric bulkiness of amides. Although the real mechanism is not clear, we are now in a position to produce one of two possible products, alcohols or amines from less hindered N,N-dimethylamides.

Experimental Section

Materials. Tetrahydrofuran(THF) was distilled from sodium-benzophenone ketyl and stored under dry nitrogen atmosphere. Borane solution in THF (2 M) was prepared from sodium borohydride and boron trifluoride etherate.⁹ The borane-THF solution was standardized by hydrolyzing a known aliquot of the solution with a 2 N H_2SO_4 -THF mixture and measuring the hydrogen evolved. Most of the organic compounds utilized in this study were the commercial pro-

ducts of the highest purity. They were further purified immediately prior to use when necessary according to the standard procedures.¹⁰ Tertiary amides were prepared by the method of Brown and Tsukamoto.¹¹ All reductions were carried out under a dry nitrogen atmosphere. Hypodermic syringes were used to transfer the solution.

Reduction of Tertiary Amides with Borane. The reduction of N,N dimethylhexanamide with borane at 25°C is typical of the procedure followed. A 50-ml oven-dried flask equipped with a side arm, fitted with a rubber septum, a magnetic stirring bar, and a reflux condenser which connected to a mercury bubbler, was cooled down to 25°C in a water bath under a stream of dry nitrogen. To the flask was added 2.5 ml (5.0 mmol) of 2.0 M borane solution in THF and 6.5 ml of THF. Then 3 mmol each of N,N-dimethylhexanamide and dodecane (internal standard) in 3 ml of THF was introduced. Now the mixture is 0.25 M in compound and 1.25 M in hydride (0.417 M in BH_3). The reaction mixture was maintained at 25°C with water bath. After 1 h of reaction time, 1 ml of the reaction mixture was withdrawn by a hypodermic syringe and quenched with 1 ml of water. The separated organic layer was dried with anhydrous K_2CO_3 and analyzed by GLC, revealing that it contains 47% of 1-hexanol, 18% of hexanal and 35% of N,N-dimethylhexylamine. At different intervals of time, the reaction mixture was quenched and analyzed as described above. These results were summarized in Table 1.

Reduction of Tertiary Amides with $\text{BH}_3\text{-(CH}_3\text{O)}_3\text{B}$ (1:0.2) System in the Presence of NaBH_4 . The reduction of N,N-dimethylbenzamide with $\text{BH}_3\text{-(CH}_3\text{O)}_3\text{B}$ (1:0.2) system in the presence of NaBH_4 is representative. Into a 50-ml flask, typically equipped above, about 0.01 g of NaBH_4 (ca. 0.3 mmol) was placed and 5.9 ml of THF was introduced. The flask was immersed in an ice-water bath and 3.0 ml (6 mmol) of a 2.0 M borane solution in THF was introduced, followed by 0.12 ml (3 mmol) of methanol with vigorous stirring.¹² Hydrogen gas (75 ml, 3.0 mmol) was evolved. After 10 min, 3 mmol each of N,N-dimethylbenzamide and dodecane (internal standard) in 3 ml of THF solution was added. After 1 h, the reaction mixture was hydrolyzed with 5 ml of water and stirred for an additional 30 min. The reaction mixture was made alkaline with 4 N NaOH solution and extracted three times with 10-ml portions of ether. The combined organic layer was then dried over anhydrous K_2CO_3 , concentrated, and analyzed by GLC. Analysis revealed the presence of 91% of benzyl alcohol and 5% of N,N-dimethylbenzylamine.

Preparative Procedure for Reduction of Tertiary Amides to Alcohols. The following preparative procedure for the reduction of N,N-dimethyl-*p*-nitrobenzamide to *p*-nitrobenzyl alcohol is representative. Into a dry, 300-ml flask was placed about 1 g of NaBH_4 in 100 ml of THF. The flask was immersed in an ice bath, and 42 ml (84 mmol) of a 2.0 M borane solution of THF was introduced, followed by 1.7 ml (42 mmol) of methanol with vigorous stirring. Vigorous hydrogen evolution occurred during the methanol addition. After 10 min, 8.20 g (42 mmol) of N,N-dimethyl-*p*-nitrobenzamide in 30 ml THF solutions was introduced. After 1 h, the reaction mixture was hydrolyzed with 30 ml of water and stirred for additional 1 h. Then 40 ml of 3 N hydrochloric acid was added. The reaction mixture was extracted with ether (3 × 100 ml), and dried over anhydrous potassium car-

bonate, filtered, and concentrated to dryness on a rotary evaporator. Further drying in vacuum oven gave 6.12 g (90%) of a light-yellow crystalline solid. The solid was washed with hot hexane, and dried in a vacuum oven, giving 5.46 g (85%) of *p*-nitrobenzyl alcohol, mp 92-93.5 °C (lit.¹³ mp 93 °C), with IR and NMR spectrum identical with the authentic material.¹⁴

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Tandem Mass Spectrometry of some s-Triazine Herbicides

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Mass spectral fragmentations of some s-triazine herbicides have been investigated using tandem mass spectrometry. Major pathways driven by the side chains have been confirmed. However, most of the previously proposed pathways which were thought to be characteristic of the ring have been found unlikely. A class of ring cleavage reactions characteristic of s-triazine rings with alkylamino side chains has been found and the mechanism has been proposed. In addition, tandem mass spectrometry has been utilized to differentiate tautomeric structures and to analyze the fragmentation reactions occurring from the mixture of isobaric ions.

Introduction

Mass spectrometry is a powerful method for the structural determination and quantitation of organic, inorganic, and biological molecules.^{1,2} Various ionization methods such as electron ionization (EI), chemical ionization (CI), fast atom bombardment (FAB), etc. are used to produce molecular ions or quasi-molecular ions from samples. These ions undergo further fragmentation in the ion source depending on their internal energies, producing fragment ions. The resulting ions are analyzed according to their mass-to-charge (*m/z*) ratios.

For the interpretation³ of mass spectra and hence for the structural determination various empirical correlations such as the mechanistic pathways are employed to explain the various ions appearing in the spectra. Also, determination of the accurate masses through high resolution mass spec-

trometry aids the spectral interpretation by providing unequivocal elemental compositions of ions. However, lack of detailed knowledge about the fragmentation pathways for a compound class has been a major weakness in the interpretation procedure.⁴

In tandem mass spectrometry or mass spectrometry/mass spectrometry (MS/MS),^{4,6} ions with given *m/z* are selected and their fragmentation reactions are observed directly. Namely, while the fragmentation mechanisms are deduced indirectly from the mass spectral pattern in the ordinary mass spectrometry, similar information is obtained through direct observation in MS/MS, hence removing any ambiguity on the reaction pathways.

s-Triazines are widely used as pre-emergence selective herbicides, simazine (I, 2-chloro-4,6-bis(ethylamino)-s-triazine), atrazine (II, 2-chloro-4-ethylamino-6-isopropylamino-s-triazine), propazine (III, 2-chloro-4,6-bis(isopropylamino)-s-