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Lithium Aluminum Hydride Reduction Studies of Rigid α-Oximino Ketones

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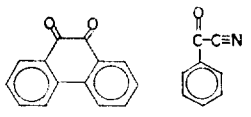
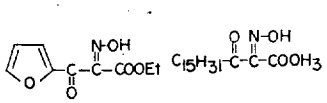
Rigid α-oximino ketones containing two functional groups such as 2-oximino-1-acenaphthenone and 2-oximino-1-indanone were synthesized and the simultaneous reduction of the two functional groups of α-oximino ketones by $LiAlH_4$ gave the corresponding amino alcohols, 2-amino-1-acenaphthenol and 2-amino-1-indanol. The yields of the reduction products of the α-oxinino ketones remarkably increased, as the increase of molar ratio of hydride used to the reactant. The use of 24 moles of $LiAlH_4$ was found to afford the best result in the reduction of the rigid α-oximino ketones to the corresponding amino alcohols. The yields was not affected by the variation of solvents such as ether, THF and diglyme.

Introduction

Lithium aluminum hydride is one of the most powerful hydride transfer reagents, which reduces a wide variety of functional groups such as ketones, esters and acids. Numerous reviews on reductions done with $LiA1H_4$ have been reported.[1] However, Reductionxs of the compounds with the two adjacent reducible functional groups with $LiAlH_4$ have not been studied systematically, Simultaneous reductions of 9,10 -diketo-phenanthrene (**1**) and α-cyano phenylketone (**2**) with $LiAlH_4$ were reported to give high yields of the corresponding alcohols,[2-4] but ethyl 2-oximinofuroyl acetate (**3**)[5] and methyl 2-oximino-3-keto-octadecanoate (**4**)[6] reductions gave no reduction products.

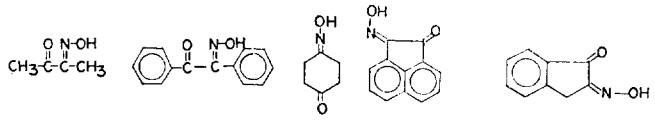




1 **2** **3** **4**

The objective of this investigation is to deal with the $LiAlH_4$ reductions of the oximino ketones such as biacetyl monooxime (**5**), benzil monooxime (**6**) 1,4-cyclohexanedione monooxime (**7**), 2-oximino-1-acenaphthenone (**8**) and 2-oximino-1-indanone (**9**). The cyclic α-oximino ketones, **8** and **9** are structurally different from **5**, **6** and **7**.

The yields of reduction products of **5**, **6** and **7** by 6–10 molar excess of $LiAlH_4$ were moderate (20–40 %), but the cyclic α-oximino ketones, **8** and **9** gave extremely low yield (0–10 %) under the same conditions. When 24 moles excess of $LiAlH_4$ to reactant were employed to reduce **8** and **9**, the yields were increased significantly (≈57 %). The theoretical amount of $LiAlH_4$ required to reduce 1 mole of α-oximino ketones needs only 1.25 moles. Therefore, 24 moles used were exceedingly in excess of $LiAlH_4$, where in ordinary cases, the reduction yields have been known to be decreased due to the high reactivity of $LiAlH_4$.



5 **6** **7** **8** **9**

The observed $LiAlH_4$ reductions of the cyclic α-oximino ketones such as 2-oximino-1-acenaphthenone (**8**) and 2-oximino-1-indanone (**9**) represent to the best of our knowledge the first demonstration of this action, although a number of other functional groups caused by $LiAlH_4$ have been noted.[1]

Results and Discussion

The oximino ketones, **5**, **6**, **7**, **8** and **9** were made by the selective monooximation followed by the fractional crystallization of the mono and dioximes, and 2-oximino-1-indanone was prepared by the nitrosation of 1-indanone with

TABLE 1: The Yields of the Reduction Products of α-Oximino Ketones by $LiA1H_4$. Various Solvents.[b]

Mole Ratio[b]	4		6		8		10		12		18		24		30	
Compound	Reaction time (h)	yield (%)	Reaction time (h)	yield (%)	Reaction time (h)	yield (%)	Reaction time (h)	yield (%)	Reaction time (h)	yield (%)	Reaction time (h)	yield (%)	Reaction time (h)	yield (%)	Reaction time (h)	yield (%)
5	2	6	2	27	2	30	2	27	6	10	4	8				
	3	15	3	40	3	37	3	20	8	11	6	5				
	4	19	4	38	4	29	4	30	10	11	8	10				
6	6	10	6	26	6	26	6	24	6	12	4	10				
	8	15	8	34	8	29	8	30	8	17	6	10				
	10	12	10	32	10	25	10	28	10	14	8	9				
7	3	7	3	14	3	10	3	8	6	8	4	2				
	4	8	4	18	4	14	4	11	8	10	6	7				
	5	5	5	17	5	10	5	9	10	10	8	3				
8			6	6					6	8	4	35	4	48	4	30
			8	15					8	22	6	44	6	57	6	35
			10	13					10	16	8	41	8	51	8	32
9			6	24					6	34	4	33	4	47	4	26
			8	35					8	38	6	45	6	53	6	37
			10	36					10	33	8	41	8	42	8	32

[a] Variations of solyents such as Ether, THE and diglyme did not affect the yields very much. Only One to 2% yields variations was observed. *b*. Mole ratio of $LiAlH^4$ to reactant. *c*. Yield based on the integration of the nmr amido methyl proton peaks of the products and acetamide. in Pyridise-ds.

n-butyl nitrite.

Reaction Conditions and Yields. The yields of the reduction products by the molar ratio of $LiAlH_4$ to the α-oximino ketones (**5,6,7,8** and **9**) are recorded in Table 1. From the several experimental examinations with different molar ratios of $LiAlH_4$ in anhydrous sovents such as ether, THF and diglyme, the yields of reduction products of **5,6** and **7** by 6–10 mol exess of $LiAlH_4$ were relatively moderate (20–40 %). However, the use of 24 moles of $LiAlH_4$ was found to afford the best result in the reductions of the rigid cyclic α-oximino ketones **8** and **9** to the corresponding amino alcohols. Variations of the solvents used did not affect the yields as shown in Table 1.

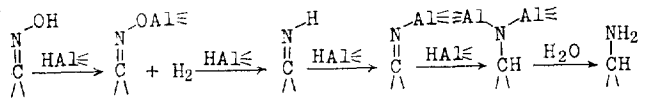
Quentitization of the reduction Products. the clorresponding 3-amino-2-butanol (**10**), 2-amino-1,2-diphenylethanol (**11**), 4-amino-cyclohexanol (**12**), 2-amino-1-acenaphthenol (**13**) and 2-amino-1-indanol (**14**) obtained from the $LiA1H_4$ reductions of the respective **5,6,7,8** and **9** were difficult to isolate as pure forms because of small a mounts of oily characteristics (The corresponding amino alcohol reduction products **10, 11, 12, 13** and **14** were identified ; the ir spectra showed disapperances of the respective $\sqrt{c}=0$ at 1680–1735 cm^{-1}, and $\sqrt{c}=N$ at 1630–1655 cm^{-1} and appeared a new broad peak at 3250–3400 cm^{-1} (NH_2 and OH groups) and directly acetylated to obtain the respective 3-acetamide-2-butanol (**15**), 2-acetamido-1,2-diphenylethanol (**16**), 4-acetamide-cyclohexanol (**17**) 2-acetamido-1-acenaphthenol (**18**) and 2-acetamido-1-indanol (**19**). The ir spectra indicate that the acetylation underwent selectively to the amino group, intact to the alcoholic function. The amido group appeared at 1640 cm^{-1} in the ir spectra. The yields of the reducation products were antitatively analyzed by the nmr spectroscopic method; to the crude acetamides, **12, 13, 14, 15, 16** and **17** were added an exact weighed amount of 0.05g of a standard acetamide dissolved in pyridine-d_5, and measured the amide methyl proton peaks by integration, For example, if the intensity of the two amido peaks is the same after using 0.1 g of **8**, the yield should be calculated in the following:

$$\frac{0.05}{0.1}\times\frac{\text{M.W. (Amide 12)}}{\text{M.W. (Acetamide)}}\times\frac{\text{M.W. (8)}}{\text{M.W. (Amide 12)}}\times 100$$

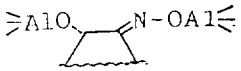
Observations on the Yields. The yields of reduction products of **5,6** and **7** by **6–10** moles excess of $LiA1H_4$ were relatively moderate. However, the yields of the reduction products of the cyclic α-oximino-1-acenaphthenone (**8**) and α-oximino-i-indanone (**9**) remarkably increased as the increase of mol ratio of hydride to the reactants as shown in the Table 1. The use of 24 moles of $LiAlH_4$ was found to afford the best result in the reductions of the rigid cyclic α-oximino ketones, **8** and **9** to the corresponding amino alcohol products.

In order to reduce 1 mole of carbonyl function, 1 mole of hydride (0.25 mole of $LiAlH_4$) is needed to be consumed, which is equivalent to 0.25 mole of $LiAlH_4$ and in case of 1 mole of oxmino group, 2 moles of hydride is needed (even to generate H_2 gas) which is equivalent to 1 mole of $LiAlH_4$, In other words, 1.25 molar ratio of $LiAlH_4$ are required to reduce theoretically 1 mole of oximino ketones containing the two functional groups such as **5, 6, 7, 8** or **9**. Smith, *et al*[8] reported that the best yields were obtained when the molar of $LiAH_4$ to oxime was 1.5, and the carbonyl function is best reduced when 0.5 mole excess of $LiAlH_4$ was used. Therefore in any cases, 6 to 30 mole ratios of $LiAlH_4$ to α-oximino ketones (**5,6,7,8** or **9** used) are extremely large, even though we consider $LiAlH_4$ loss and consumptions due to the trace of H_2O, and CO_2 in air during the long periods of reaction time. It is quite surprising fact that the yields of the reduction products of rigid cyclic α-oximino ketones (**8** and **9**) in-

creased as the increase of molar ratio of hydride to the reactant to ca, 24 mole excess. The use of 30 moles excess of $LiAlH_4$ did not increase the yield, but rather decreased the yields. The yields were also not affected significantly by the variations of the solvents such as ether, THF and diglyme; One to 2 % yields variation in various solvents were not Significant in terms of experimental errors and other effects, if any. Carbonyl reduction mechanism by $LiAlH_4$ is well established,[9] the oxime reduction mechanism has not been well understood. Yoon and Brown[10] proposed the following mechanism. Since the carbonyl group is reduced relatively



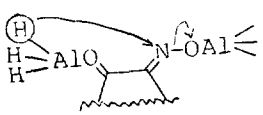
faster than the oxime,[11] and the hydrogen gas generation step in the oxime reduction is also fast enough, the alkoxyaluminum hydride complex such as **20** should be initially formed from the α-oximino ketones, **8** and **9** as soon as the reaction begins to initiate. There will be formed also disproportionated products of di-or tri-or tetra-alkoxy aluminum hydrides during reduction of **20**[12] since the alkoxy aluminum hydride complex such **20** obtained from the secondary alcohol is easily to disproportionated.[13]



20

One may assume that the sterically less hindered complex **20** undergoes easy reduction by AlH_4^-, in comparison with the disproportionate complexes which are highly hindered for the hydride attack. The openchained α-oximino ketones such **6** and **5** are freely rotated to be less crowded *anti*-conformation, so as to obtain moderate reduction yields on ower concentration of $LiAlH_4$, while the cyclic α-oximino ketones, **8** and **9** are so rigidly fixed that the disproportionated complexes are totally hindered for the AlH_4^- attack. Accordingly the disporportionated complexes are required higher concentration of $LiAlH_4$ and longer reaction periods to obtain moderate yields of reduction products.

The possibility of intramolecular hydride transfer from the initially formed alkoxy aluminium hydride has not been eliminated. However, in the case of α-oximino ketones, the hydride transfer seemed to work for the negative direction for the lower yields.



Experimental

General

All the chemicals used were of reagent grade and purified prior to use, if neccessary by the known methods. Anhydrous ether, THF and diglyme were purified with $LiAlH_4$. The ^{1}HNMR spectra were recorded on Varian HA-100 or Varian EM-360L. Unless otherwise stated, deuterated dimethyl sulfoxide was used as a solvent,and TMS as an internal standard. All the chemical shift values are described in τ, and the following descriptive abbreviations are used; s=singlet, d=doublet, m=multiplet. Infrared spectra were measred on a Hitachi EMT-G2 or Perkin-Elmer 267 Grating or 7355-B on KBr pellet, and the absorption frequency was reported in cm^{-1}.

Syntesis

2-Oximino-1-acenaphthenone **(68)**. The mixture of 5.46g (0.03mole) of acenaphthequinone, (2.29g) (0.033 mole) of $NH_2OH \cdot HCl$ and (4.5g) (0.033 mole of $CH_3COONa \cdot 3H_2O$ in 100 m*l* of MeOH and 30 m*l* of H_2O, was refluxed for 30 min. With stirring. The cooled reaction mixture was poured into 200 m*l* of ice-H_2O, and filtered, and (the solid) was dried. Crystallization from MeOH (active charcoal) gave 4.31 g (73 %) of yellow cyrstals. mp 208-212°(dec) Ir(KBr): 3250 (ν_{O-H}), 1735 ($\nu_{C=O}$), 1655 ($\nu_{C=H}$). nmr: τ-2.8(*s*, 1H), 1.2-2.2 (*m*, 6H).

Anal. Obs (Calc, %), C, 79.50 (79.54); H. 3.89(3.89) N, 7.69 (7.73).

2-Oximino-1-indanone (**9**). To a solution of 5 g (0.038 mole) of 1-indanone[7] in 30 m*l* of methyl cellosolve and 10 m*l* of conc. HCl were added slowly 3 m*l* of *n*-butyl nitrite with stirring. After the solids appeared, additional 2m*l* of *n*-butyl nitrite was added, and stood at room temperature for 30 min. After pouring into 200 m*l* of ice-cold water, the separated solids were crystallized from MeOH to give 3.9g(64%) of white needles. mp 207-216 °C(dec) (*lit.*[4] mp 210-220 °C) Ir(KBr): 3200(ν_{O-H}) 1730($\nu_{C=O}$), 1660 ($\nu_{C=N}$), Nmr: -2.7 (*s*, 1H), 2.1-2.7 (*m*, 4H), 6.2 (*s*, 2H).

2-Acetamido-1-acenaphthnol (18). The mixture of 0.114g (0.003mole) of $LiAlH_4$ and 0.1g (0.0005mole) of 2-oximino-1-acenaphthenone in 50 m*l* of anhydrous ether (THF or diglyme) was refluxed for 6 hours and cooled. The excess $LiAlH_4$ was decomposed by addition of 0.1 m*l* of H_2O, 0.1 m*l* of 15% NaOH and 0.3 m*l* H_2O in order, and filtered. The solids were washed with ether several times. The combined filtrates and ether washings were dried (K_2CO_3), and concentrated to dryness. The dried residues were dissolved in 25 m*l* of anhydrous ether and passed through HCl gas to obtain 2-amino-1-acenaphthenol hydrochloride; Ir(KBr): 3325 (ν_{O-H}), 3030 and 2920 (broad $\nu_{NH^+_3}$). The dried residues were directly acetylated with acetic anhydride. mp 217-219 °C Ir(KBr): 3210(ν_{N-H}, ν_{O-H}), 1650 ($\nu_{C=O}$). Nmr: 2.10-2.80 (*m*, 6H), 2.98 (*m*, broad, 1H), 5.30 (*m*, 2H), 5.60 (*m*, 1H) 7.72 (*s*, 3H).

Anal Obs. (Calc. %) C, 73.87 (73.99) H, 5.70 (5.76), N, 6.12 (6.16).

2-Acetamido-1-indanol (19). The mixture of 0.228 g (0.006 mole) of $LiAlH_4$ and 0.161 g (0.0005 mole) of 2-oximino-1-indanone in 30 m*l* of anhydrous ether (THF, diglyme) was refluxed for 6 hours. The rest of the procedures is the same as the **18**. mp 132-133 °C. Ir(KBr): 3270 (ν_{N-H}), 3150 (ν_{O-H}), 1650 ($\nu_{C=O}$). nmr: 2.22-2.86 (*m*, 4H), 6.58-7.02 (*m*, 4H), 7.73 (*s*, 3H), 2.87 (*m*, 1-H).

Anal. Obs. (Calc. %) C, 68.97 (69,09), H, 6.78 (6.85), N,

7.32 (7.33).

4-Acetamido-cyclohexanol (**15**). The mixture of 0.78 g (0.024 mole) of $LiAlH_4$ and 0.404g (0.004mole) of 3-oximino-2-butanone in 50 m*l* of anhydrous ether (THF or diglyme) was refluxed for 3 hours. The rest of the procedures is the same as **18**. mp 106-106.5 °C. Ir: 3400 (ν_{O-H}), 2310-1850 ($\nu_{NH_3^+}$), 1647 ($\nu_{C=O}$). nmr; 5.89 (*d*, 1H), 6.95 (*m*, 1H), 7.70 (*s*, 3H), 7.92-8.53 (*m*, 1 OH).

Anal. Obs. (Calc. %) C, 59.60 (59.72),: H, 9.38(9.30); N, 8.49 (8.58).

2-Acetamido-1,2-diphenylethanol (**16**). The procedures is the same as **15**. mp 191-191.5 °C. Ir(KBr); 3300 (ν_{O-H}), 1650 ($\nu_{C=O}$), 1550 (ν_{N-H}). nmr: 2.29 (*m*, 1H), 2.70-2082 (*m*, 10H), 5.78-7.27 (*m*, 2H), 7.70 (*s*, 3H).

Anal. Obs (Calc. %) C, 74.10 (73.97); H, 6.61 (6.47); N, 5.40 (5.28).

3-Acetamide-2-Butanol (**17**). The procedure is the same as **15**. mp 77-78 °C. In(KBr); 3040 (ν_{O-H}), 2020-1960 ($\nu_{NH_3^+}$) 1650 ($\nu_{C=O}$) nmr; 2.67 (*m*, 1H), 6.10-6.40 (*m*, 1H), 7.03-7.47 (*m*, 8H), 7.75 (*s*, 3H).

Anal. Obs (Calc. %) C, 53.31 (53.21); H, 9.69 (9.74); N, 10.36 (10.09)

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Enzyme Kinetics of Multiple Inhibition in the Presence of Two Reversible Inhibitors

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In order to extend our understanding on the multiple inhibition enzyme kinetics, a general equation of an enzyme reaction in the presence of two different reversible inhibitors was derived by what we call "match-box mechanism" under the combined assumption of steady -state and quasi-equilibrium for inhibitor binding. Graphical methods were proposed to analyze the multiple inhibition of an enzyme by any given sets of different inhibitors, *i.e.*, competitive, noncompetitive, and uncompetitive inhibitors. This method not only gives an interaction factor (α) between two inhibitors, but also discerns α_1 and α_2 with and without substrate binding, respectively. The factors involved in the dissociation constants of inhibitors can also be evaluated by the present plot. It is also shown that the present kinetic approach can be extended to other forms of activators or hydrogen ions with some modification.

Introduction

Studies of the combined effect of two different inhibitors on enzyme systems are useful for understanding mechanisms of inhibition as well as active sites of an enzyme. This also provides useful information on the relationship of two inhibitors that interact with an enzyme. Triple relationship among inhibitor, hydrogen ion, and substrate interactions with an enzyme can also be analyzed by studying the kinetics of multiple inhibition.

Kinetic studies dealing with the combined effect of two inhibitors have been developed in various ways to analyze