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(Journal of the Korean Chemical Socity)
Vol. 18, No. 5, 1974
Printed in Republic of Korea

수소화붕소나트륨과의 2액상환원에 의한 카르보닐 화합물의 선택환원

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(1974. 7. 13 접수)

Selective Reduction of Carbonyl Compounds Using Two Phase Reduction with Sodium Borohydride

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(Received July 13, 1974)

요 약. 니트릴, 니트로 및 할로겐과 같은 작용기 하나를 가지는 유기화합물과 이들의 작용기 하나와 더불어 카르보닐기를 가지는 10개 유기화합물의 에테르용액을 실온에서 알칼리성 수소화붕소나트륨용액에 작용시키는 2액상환원의 대략적인 반응속도와 화학량적 관계를 알아보았다.

니트릴, 니트로 및 할로겐은 2액상환원 조건하에서는 모두 반응하지 않았다. 따라서 이들 작용기 하나와 카르보닐기를 함께 가지고 있는 화합물들의 선택환원을 알아보았다.

m-니트로벤즈알데히드, *m*-니트로아세트페논, *p*-브로모아세트페논과 *p*-시아노벤즈알데히드는 해당 알코올로 잘 환원되었으며 95~100% 수득률을 얻었다.

Abstract. Approximate rate and stoichiometry of the reaction of ten compounds which contain functional group such as nitrile, nitro, halogen and one of these functional group together with a carbonyl group by the two phase reduction were tested at room temperature.

Nitrile, nitro and halogen were all inert under these condition. Therefore selective reduction of carbonyl group in the presence of these group were examined. Thus *m*-nitrobenzaldehyde, *m*-nitroacetophenone, *p*-bromoacetophenone and *p*-cyanobenzaldehyde were reduced to corresponding alcohols in excellent yields, 95~100 %.

Introduction

Previously it was shown that the aldehydes and ketones can be reduced conveniently by the two phase reduction at room temperature(the reduction of the carbonyl compounds in ether with alkaline sodium borohydride aqueous solution).[1] Since the two phase reduction provides a convenient means of reduction, it is clear that if some functional groups are inert in the condition of the two phase reduction, it could proceed a selective reduction of carbonyl group in the presence of these inert functional group very conveniently. Therefore several functional groups were tested for their inertness and studied the selective reduction.

Experimental

Reagens. Sodium borohydride: The commerical sodium borohydride(Ventron) was used

wihout further purification. Analysis by hydrogen evolution measurement on hydrolysis showed 95% purity.

m-Nitrobenzaldehyde: *m*-Nitrobenzaldehyde was prepared by nitration of benzaldehyde[2], bp. 119~123 °C/4 mm, mp. 58 °C(lit[3]. 57~58 °C).

m-Nitroacetophenone: *m*-Nitroactophenone was prepared by nitration of acetophenone[4], mp. 76 °C(lit[4]. 76~78 °C).

p-Bromoacetophenone: *p*-Bromoacetophenone was prepared by acetylation[5] bp. 130 °C/15 mm, mp. 50 °C(lit[5]. 49~50 °C).

p-Cyanobenzaldehyde: *p*-Cyanobenzaldehyde was prepared from *p*-cyanotoluene *via* *p*-cyanobenzaldiacetate[6], mp. 95 °C(lit[3]. 95~96 °C).

Preparation of Sodium Borohydride Solution. A 0.993 g(26.25 mmole) of sodium borohydride(Ventron, 95% by hydrogen measurement on hydrolysis) was dissolved in 100 m*l* of 0.25 *M* sodium hydroxide solution in order to stabilize the hydride solution. The hydride concentration of this solution was 1.0 *M* in hydride(that is 0.25 *M* in sodium borohydride) as measured by the hydrogen evolution on hydrolysis.

General Procedure for the Two Phase Reduction. The two phase reduction of *m*-nitrobenzaldehyde is described as a representative of the procedure. In a 100 m*l* flask, fitted with an inlet tube, a magnetic stirrer and a reflux condenser through which a gas meter is connected, there was placed a 15 m*l* of 0.25 *M* sodium borohydride solution in 0.25 *M* sodium hydroxide aqueous solution(3.75 mmole in sodium borohydride, that is 15 mmoles in hydride). A 20 m*l* of 0.5 *M* *m*-nitrobenzaldehyde solution in ether was added at a time while the solution was moderately stirred. After 1 hr, the hydrogen evolution was 3.7 m*l* at 20 °C, 765 mmHg, this corresponds to 0.15 mmoles of hydrogen and 0.05 mmoles of hydrogen evolution per mmole of *m*-nitrobenzaldehyde. A 2 m*l* aliquot of the ether solution and 1.5 m*l* of aqueous layer were taken out by the hypodermic syringe and hydrolyzed for the residual hydride successively. There was no hydride in ether layer and 0.398 mmoles of hydride in aqueous solution. This corresponds to 1.102 mmoles of hydride used per mmole of compound since the blank test showed 1.5 mmoles of hydride. Since 0.015 mmole of hydride out of this total 1.102 mmoles of hydride used was consumed for hydrogen evolution, the hydride used for reduction was 1.087 mmoles per mmole compound. After 3 hr, the same measurement was repeated and no further hydride consumption was observed. The reaction was discontinued but in the case when the hydride consumption was continued, the same measurement were also repeated at 6, 12, and 24 hr. The results for the rate and stoichiometry of ten compounds were summerized in *Table* 1.

Two Phase Reduction on a Preparative Scale. *m*-Nitrobenzaldehyde: In 150 m*l* reaction flask, 60 m*l* of 0.5 *M* *m*-nitrobenzaldehyde(4.54 g, 30 mmoles) in ether was treated with 45 m*l* of 0.25 *M* sodium borohydride solution(also in 0.25 *M* sodium hydroxide solution). After two phase reduction for 1 hr, the ether layer was separated and dried over anhydrous magnesium sulfate. On evaporation of ether on water bath, 4.59 g of crude product(100 % yield) was obtained. After recrystallization from hot ethyl alcohol, there was obtained a 4.36 g of pure *m*-nitrobenzyl alcohol(95 % yield) mp. 27 °C(lit[7]. 26~27 °C).

m-Nitroacetophenone: 4.128 g(25 mmoles) of *m*-nitroacetophenone in 100m*l* of ether was treated with 0.3725 g of sodium borohydride(95 %, 9.844 mmole) in 37.5 m*l* of 0.5 *M* sodium hydroxide solution for 3 hr at room temperature. After separation of ether layer and drying over anhydrous magnesium sulfate, there was obta-

Table 1. Two phase reduction of representative organic compouds in ether with alkaline sodium borohydride aqueous solution at room temperature.

Compound[a]	Time (hr)	Hydrogen evolved[b,c]	Hydride used[b]	Hydride used for reduction[b]
Nitrobenzene	3.0	0.000	0.000	0.000
	6.0	0.000	0.000	0.000
	12.0	0.000	0.000	0.000
o-Nitrotoluene	3.0	0.000	0.000	0.000
	6.0	0.000	0.000	0.000
	12.0	0.000	0.000	0.000
o-Nitrochlorobenzene	3.0	0.000	0.000	0.000
	6.0	0.000	0.000	0.000
	12.0	0.000	0.000	0.000
Bromobenzene	3.0	0.000	0.000	0.000
	6.0	0.000	0.000	0.000
	12.0	0.000	0.000	0.000
Acetonitrile	3.0	0.000	0.000	0.000
	6.0	0.000	0.000	0.000
	12.0	0.000	0.000	0.000
Benzonitrile	3.0	0.000	0.000	0.000
	6.0	0.000	0.000	0.000
	12.0	0.000	0.000	0.000
m-Nithrobenzaldehyde	1.0	0.015	1.102	1.087
	3.0	0.015	1.102	1.087
m-Nitroacetophenone[d]	1.0	0.286	0.784	0.498
	3.0	0.469	1.499	1.030
	6.0	0.469	1.499	1.030
p-Bromoacetopheneone	1.0	0.102	0.209	0.107
	3.0	0.121	0.335	0.214
	6.0	0.133	0.578	0.445
	12.0	0.137	0.587	0.450
	24.0	0.143	1.132	0.989
	25.0	0.145	1.155	1.010
	26.0	0.145	1.155	1.010
p-Cyanobenzaldehyde[d]	1.0	0.021	1.027	1.006
	3.0	0.021	1.027	1.006

[a] 10 mmoles of compound (20 m*l* of 0.5 *M* ether solution) was reduced with 3.75 mmoles of sodium borohydride which was dissolved in 15 m*l* of 0.25*M* sodium hydroxide solution.

[b] mmoles per mmoles of compound.

[c] Hydrogen evolved on reaction mixture minus hydrogen evolved from blank.

[d] 10 mmoles of compound (40 m*l* of 0.25 *M* ether solution) was reduced with 3.75 mmoles of sodium borohydride which was dissolved in 15 m*l* of 0.25 *M* sodium hydroxide solution.

ined a 4.09 g of crude product (98 % yield) on evaporation of ether. After recrystallization from hot ethyl alcohol, 3.76 g of pure methyl-(3-nitrophenyl)-carbinol mp. 63 °C (lit[8]. 62.5 °C) was obtained (90 % yield).

p-Bromoacetophenone: 5.97 g (30 mmoles) of *p*-bromoacetophenone in 60 m*l* of ether was treated with 0.447 g of sodium borohydride (95 %, 11.813 mmoles) in 45 m*l* of 0.25 *M* sodium hydroxide solution for 25 hr at room temperature. After separation of ether layer and drying over anhydrous magnesium sulfate, there was obtained a 5.71 g of crude product (95 % yield) on evaporation of ether. On distillation at 134 °C, 15 mmHg, there was obtained a 5.41 g of pure methyl-(4-bromophenyl)-carbinol n_D^{19} 1.5738 (lit[9]. 1.5740) (90 % yield).

p-Cyanobenzaldehyde: 3.276 g (25 mmoles) of *p*-cyanobenzaldehyde (95 %, 9.844 mmoles) in 37.5 m*l* of 0.25 *M* sodium hydroxide solution for 1 hr. After separation of ether layer and drying over anhydrous magnesium sulfate, there was obtained a 3.330 g of crude product (100 % yield) on evaporation of ether. After recrystallization from hot ethyl alcohol, 3.26 g of pure *p*-cyanobenzyl alcohol mp. 41 °C (lit[10]. 41~2°C) was obtained (98 % yield). The results are summerized in *Table* 2.

Results and Discussion

Six compounds; nitrobenzene, *o*-nitrotoluene, *o*-nitrochlorobenzene, bromobenzene, acetonitrile and benzonirile were chosen in order to test the reactivity of nitro, chloro, bromo and cyano functional groups in the two phase reduction with sodium borohydride. As shown in *Table* 1, there were no hydrogen evolution and no reduction at room temperature upto 12 hr, enough time for the reduction of carbonyl compounds. These functional groups are normally accepted as inert to sodium borohydride in hydroxylic solvents, and the inertness was also confirmed in this two phase reduction condition. Therefore there was tried the four following selective reductions. Namely the reductions of *m*-nitrobenzaldehyde to *m*-nitrobenzyl alcohol,

Table 2. Selective reduction in preparative scale

Reagent[a]	Product	Yield(%) Crude	Purified	Identification
m-Nitrobenzaldehyde	*m*-Nitrobenenzyl alcohol	100	95	mp. 27 °C(lit[6]. 26~27°C) IR: OH:3350cm^{-1}(2.98μ), NO_2; 1530cm^{-1}(6.54μ), 1350cm^{-1} (7.40μ)
m-Nitroacetophenone[b]	Methyl-(3-nitrophenyl) carbinol	98	90	mp. 63 °C(lit[7]. 62.5 °C) IR: OH:3367cm^{-1}(2.97μ), NO_2; 1532cm^{-1}(6.53μ), 1340cm^{-1} (7.46μ)
p-Bromoacetophenone	Methyl-(4-bromophenyl) carbiol	95	90	bp. 134 °C/15 mmHg, n_D^{18} 1.5738 (lit[8]. 133~134°C/15 mmHg, n_D^{18} 1.5740) IR: OH;3370 cm^{-1}(2.96μ), Br;*
p-Cyanobenzaldehyde[b]	*p*-Cyanobenzyl alcohol	100	98	mp. 41 °C(lit[9]. 41~42°C) IR: OH;3378cm^{-1}(2.96μ), CN; 2247cm^{-1}(4.45μ)

* out of the tracing region of the Beckman IR spectrophotometer used.

a. 30 mmoles of compound (60m*l* of 0.5 *M* ether solution) was reduced with 11.813 mmoles sodium borohydride which was dissolved in 45 m*l* of 0.25 *M* sodium hydroxide solution.

b. 25 mmoles of compound(100 m*l* of 0.25 *M* ether solution) was reduced with 9.844 mmoles of sodium borohydride which was dissolved in 37.5 m*l* of 0.25 *M* sodium hydroxide solution.

m-nitroacetophenone to methyl-(3-nitrophenyl)-carbinol, *p*-bromoacetophenone to methyl-(4-bromophenyl)-carbinol, and *p*-cyanobenzaldehyde to *p*-cyanobenzyl alcohol. As shown in *Table* 1, the study for rate and stoichiometry show the clean reduction of carbonyl group without attacking the nitro, halo, and cyano functional group present.

m-Nitrobenzaldehyde: *m*-Nitrobenzaldehyde were reduced rapidly within 1 hr at room temperature giving almost quantitative yield of *m*-nitrobenzyl alchol. Previously it was observed that the reaction of benzaldehyde is relatively slow taking 12 hr[1]. Apparently this rate enhancement was due to the —I effect of the nitro group. Chaikin and Brown[10] have reported the same reduction but in methanol in 82 % yield, however, the excellent yield and the convenience of this two phase reduction should prove that this is the method of choice.

m-Nitroacetophenone: *m*-Nitroacetophenone was reduced somewhat slowly as expected, yet a 98 % yield was obtained in 3 hr at room temperature. The rate enhancement was also observed as in *m*-nitrobenzaldehyde(the reduction of acetophenone needed 12 hours at room temperature).

p-Bromoacetophenone: *p*-Bromoacetophenone was reduced slowly, nearly same rate as acetphenone. Almost quantitative yield was obtained in 25 hr at room temperature. Everard[12] have reported the reduction of this compound with lithium aluminum hydride unsuccessfully, probably due to the reduction of bromo group.

p-Cyanobenzaldehyde: *p*-Cyanobenzaldehyde was reduced within 1 hr to *p*-cyanobenzyl alcohol, quantiatively *p*-cyano group also showed the rate enhancement.

Conclusion

It was showm that the nitro, chloro, bromo and cyano functional groups are inert to sodium borohydride in the condition of the two phase reduction, and demonstrated that the four

selective reductions, the reduction of *m*-nitrobenzaldehyde, *m*-nitroacetophenone, *p*-bromoacetophenone and *p*-cyanobenzaldhyde to the corresponding alcohonls, could be carried out conveniently in excellent yields.

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