DAEHAN HWAHAK HWOEJEE
(*Journal of the Korean Chemical Society*)
Vol. 23, No. 3, 1979
Printed in Republic of Korea

Phthalimido기 존재하에서 Zinc Dust에 의한 2, 2, 2-Trichloroethyl기의 선택적 환원분해[1]

鄭鳳永 · 金永煥

고려대학교 이과대학 화학과

(1979. 4. 2 접수)

Selective Cleavage of 2, 2, 2-Trichloroethyl Group with Zinc Dust in the Presence of Phthalimido Function[1]

Bong Young Chung and **Young-Hwan Kim**

Department of Chemistry, Korea University, Seoul, Korea

(Received April 2, 1979)

요 약. Phthalimido기와 2, 2, 2-trichloroethyl기는 acetic acid와 같은 산성용매에서 zinc dust에 의하여 각각 3-hydroxyphthalimidino기로 환원 되거나 혹은 환원분해된다. 그러나 THF-pH 4.5 buffer 혼합용매를 사용하므로써, free carboxylic acid가 존재하지 않는 경우, phthalimido는 환원시키지 않고 2, 2, 2-trichloroethyl기만을 선택적으로 환원분해시킬 수 있음을 발견하였다. 따라서 2, 2, 2-trichloroethyl 3, 4, 6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-**D**-glucopyranoside (**1**)를 THF-pH 4.5 buffer 혼합용매에서 zinc dust와 반응시키면, 2, 2, 2-trichloroethyl 기만이 선택적으로 환원분해된 3, 4, 6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-**D**-glucopyranose (**5**)를 좋은 수득율로 얻을 수 있었다.

ABSTRACT. In acidic media such as aqueous acetic acid, phthalimide is reduced with zinc dust to give 3-hydroxyphthalimidine while the 2, 2, 2-trichloroethyl esters or glycosides are reductively cleaved. However, it has been discovered that, by employing a mixture of THF and pH4.5 buffer solution as a solvent, 2, 2, 2-trichloroethyl group can be selectively removed with activated zinc dust in the presence of phthalimido function, provided that the reactant or the product does not have any free carboxylic acid function. By applying the above methods, reaction of 2, 2, 2-trichloroethyl 3, 4, 6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-**D**-glucopyranoside (**1**) with activated zinc dust gave a good yield of 3, 4, 6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-**D**-glucopyranose (**5**) in THF-buffer solution, and 3, 4, 6-tri-*O*-acetyl-2-deoxy-2-(3-hydroxyphthalimidino)-β-**D**-glucopyranose (**6**) in aqueous acetic acid.

INTRODUCTION

In organic syntheses, primary amines may be temporarily protected into phthalimido derivatives and carboxylic acids into the corresponding 2, 2, 2-trichloroethyl esters, since the phthalimido group can be easily cleaved with ethanolic hydrazine[2] and the 2, 2, 2-trichloroethyl esters

with zinc dust in aqueous acetic acid[3], formic acid[4], THF[4] or THF-buffer mixture[6].

Phthalimide has also been known to be reduced with zinc dust. As early as 1913, Reissert[7] first reduced phthalimide with zinc dust in aqueous sodium hydroxide to 3-hydroxyphthalimidine. Howard *et al.*[8], however, later obtained phthalide instead of 3-hydroxyphthalimidine under the same reaction condition. In 1974 Matsushiro *et al.*[9] also reported that the reduction of phthalimide with zinc dust in (aqueous) acetic acid at 70 °C produced 3-hydroxyphthalimidine in 90 % yield. This is, to our knowledge, the only published example that employed zinc dust in acidic media for the reduction of phthalimido function.

Recently, Lemieux *et al.*[10] introduced 2, 2, 2-trichloroethyl group as an aglycone in the syntheses of oligosaccharides by taking advantage of its ready cleavage with zinc dust in aqueous acetic acid. However, when the 2, 2, 2-trichloroethyl glycosides in which phthalimido function is also present, such as 2, 2, 2-trichloroethyl 3, 4, 6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (**1**)[11], are treated with zinc dust in aqueous acetic acid, it may be predicted from the above examples that the cleavege of 2, 2, 2-trichloroethyl group will be accompanied with the reduction of phthalimido function. Since the phthalimido function of compound **1** is required to be retained for further reactions, it was necessary to find a reaction condition to selectively remove 2, 2, 2-trichloroethyl group without reducing the phthalimido function.

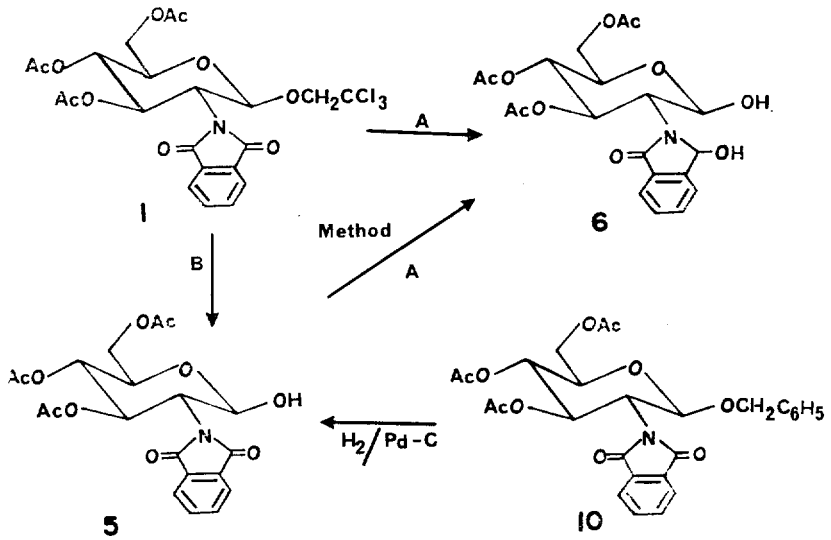
In the present study, we have investigated the reduction of several phthalimido derivatives and of 2, 2, 2-trichloroethyl glycoside (**1**) with the activated zinc dust in aqueous acetic acid and employed THF-pH 4. 5 buffer mixture as a solvent for the selective cleavage of 2, 2, 2-trichloroethyl group.

RESULTS AND DISCUSSION

Reaction of the Phthalimido Derivatives with Zinc Dust in Aqueous Acetic Acid (*Method A*). Reaction of the phthalimido derivatives such as *N*-ethylphthalimide (**2**), benzyl phthalimidoacetate (**3**) and 1, 3, 4, 6-tetra-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranose (**4**) with activated zinc dust in 90 % aqueous acetic acid at room temperature yielded within 30 min the corresponding 3-hydroxyphthalimidino derivatives, **7**, **8** and **9**. The phthalimido absorption bands at 1780 and 1730 cm^{-1} in the ir spectra of the starting compounds could not be observed in those of **7**, **8** and **9**, whereas the newly formed amide band at 1660~1680 cm^{-1} and hydroxyl band at 3300~3500 cm^{-1} appeared. The nmr spectra of the products also showed, in addition to the phenyl multiplets and the other proton peaks of the starting compounds, a broad singlet (for **7** and **8**) or a doublet (for **9**) at δ 5. 80~5. 90 ppm, derived from a methylidyne proton of the resulting benzylic group, and a D_2O exchangeable proton. These spectral data clearly indicated that the phthalimido group was reduced with zinc dust to 3-hydroxyphthalimidine in aqueous acetic acid.

Reactions in THF-pH 4. 5 Buffer Mixture (*Method B*). When the phthalimido derivatives **2**, **3** and **4** were treated with activated zinc dust in THF-pH 4. 5 buffer mixture at room temperature, only the starting compounds were completely recovered even after 24 hr. Since the phthalimido function was not reduced in this reaction system, selective removal of 2, 2, 2-trichloroethyl group of compound **1** was examined.

Reaction of 2, 2, 2-Trichloroethyl 3, 4, 6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (**1**). Treatment of compound **1** with activated zinc dust in THF-pH 4. 5 buffer mixture (*Method B*) gave a 82% yield of 3, 4, 6-tri



-*O*-acetyl-2-deoxy-2-phthalimido-β-**D**-glucopyranose (**5**). The following spectral data indicated that the 2, 2, 2-trichloroethyl group of **1** was selectively cleaved while the phthalimido function preserved. The ir spectrum of **5** still possessed strong phthalimido bands at 1730 and 1780 cm^{-1}, and the nmr spectrum showed the disappearance of methylene protons of 2, 2, 2-trichloroethyl group and exhibited the existence of a new D_2O exchangeable proton. Compound **5** could also be prepared from benzyl 3, 4, 6-tri-*O*-acetyl- 2-deoxy- 2-phthalimido-β- **D**-glucopyranoside (**10**)[12] by catalytic hydrogenolysis[12]. Comparison of the nmr spectra of the products prepared from **1** and **10** confirmed the selective cleavage of 2, 2, 2-trichloroethyl group of **1**.

However, when the compound **1** was treated with zinc dust in 90% aqueous acetic acid (*Method A*), 3, 4, 6-tri-*O*-acetyl-2-deoxy-2-(3-hydroxyphthalimidino)-β-**D**-glucopyranose (**6**) was obtained in 85 % yield. The ir and nmr spectral data of **6** were in accordance with the above discussion; which indicated that the reductive cleavage of 2, 2, 2-trichloroethyl group and the reduction of phthalimido function into 3-hydroxyphthalimidine had taken place at the same time. Zinc reduction of **5**, obtained from either **1** by *Method B* or **10** by catalytic hydrogenolysis[12], in 90 % aqueous acetic acid (*Method A*) also produced **6** in 80 % yield.

CONCLUSION

From the above results, it is evident that the 2, 2, 2-trichloroethyl glycosides can be selectively cleaved with zinc dust in the presence of phthalimido function when THF-pH 4. 5 buffer mixture is employed as a solvent. Investigation of the probable participation of carboxylic acid in the reduction of phthalimido function and modification of the reaction system are in progress in this laboratory.

EXPERIMENTAL

General

All chemicals used were of reagent grade and purified prior to use, if nccessary, by the methods described in the literature. Zinc dust was activated[13] by washing it several times with 3 % HCl, water and methanol, followed by vacuum drying. Buffer solution (pH 4. 5)[14] was prepared

by mixing 100 *ml* of 0.1 *M* potassium hydrogen phthalate and 17.4 m*l* of 0.1 *M* NaOH. Thin-layer chromatography (TLC) was performed on precoated TLC plates (silica gel 60 F 254, EM reagent). Melting points were taken on a Mettler FP-5 m.p apparatus and are uncorrected. IR spectra were recorded on a Hitachi EPI-G grating infrared spectrophotometer. ^{1}H-NMR spectra were obtained on a Varian T-60A spectrometer and chemical shifts are given in ppm downfield (δ) from internal TMS standard.

Syntheses of Starting Materials

Benzyl Phthalimidoacetate (**3**) was prepared from phthaloylglycine and benzyl alcohol by using Sheehan's method[15], m.p 101 °C (*lit.*[15], 101.7 °C).

1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranose (**4**) was prepared from D-glucosamine hydrochloride as described by Lemieux *et al.*[11], m.p 89 °C (*lit.*[11], 90~94 °C).

2,2,2-Trichloroethyl 3,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (**1**) was prepared from **4** as described by Lemieux *et al.*[11], m.p 176° (*lit.*[11], 176~177 °C).

Reaction of the Starting Materials with Zinc Dust

Method A: Each starting material (1.0 g) was dissolved in 90 % aqueous acetic acid (20 m*l*) and activated zinc dust (20 molar equivalents) was added. The mixture was stirred at room temperature and the solid materials removed by filtration. Solvent removal under high vacuum left a solid which was dissolved in chloroform and washed with 3 % HCl, aqueous $NaHCO_3$ and water. Drying over anhydrous Na_2SO_4 and solvent removal yielded the product which was identified.

Reaction of *N*-Ethylphthalimide (**2**). By applying *Method A* with reaction time of 10 min, **2-ethyl-3-hydroxyphthalimidine** (**7**) was obtained in 85 % yield, m.p 105 °C (*lit.*[16], 106 °C); ^{1}H-NMR (DMSO-d_6): δ 7.72~7.45 (*m*, 4, phenyl), 6.50 (broad *s*, 1, OH, D_2O exchangeable), 5.80 (broad *s*, 1, -O-CH-N-), 3.41 (*q*, J=8 Hz, 2, CH_2), 1.20 (*t*, J=8 Hz, 3, CH_3); ir (KBr): 3820 (hydroxyl), 1675 cm^{-1} (amide).

Reaction of Benzyl Phthalimidoacetate (**3**). By applying *Method A* with reaction time of 10 min, **benzyl 3-hydroxyphthalimidino-*N*-acetate** (**8**) was obtained in 90 % yield, m.p 132 °C; ^{1}H-NMR ($CDCl_3$): δ 7.95~7.63 (*m*, 4, phenyl), 7.42 (*s*, 5, benzyl), 5.90 (*d*, J=12 Hz, 1, -O-CH-N-), 5.20 (*s*, 2, CH_2 of benzyl), 4.27 (*s*, 2, -N-CH_2-COO-), 4.00 (broad, 1, OH, D_2O exchangeable); ir (KBr): 3270 (hydroxyl), 1730 (ester), 1660 cm^{-1} (amide).

Anal. Calcd. for $C_{17}H_{15}NO_4$: C 68.6, H 5.10, N 4.71, Found: C 67.9, H 5.12, N 4.92.

Reaction of 1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranose (**4**). With reaction time of 30 min and *Method A*, **1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-(3-hydroxyphthalimidino)-β-D-glucopyranose** (**9**) was obtained in 85 % yield, m.p 101~104 °C; ^{1}H-NMR ($CDCl_3$): δ 7.70~7.44 (*m*, 4, phenyl), 6.34 (*d*, J=10 Hz, 1, H-1), 5.75 (*q*, J=10 and 2 Hz, 1, H-3), 5.84 (broad *s*, 1, -N-CH-O-), 4.70~3.77 (*m*, 5, H-2, H-5, H-6, H-6' and OH, D_2O exchangeable), 2.00, 1.90, 1.85, 1.75 (each *s*, 12, OAc); ir (KBr): 3350~3500 (hydroxyl), 1680 cm^{-1} (amide).

Anal. Calcd. for $C_{23}H_{25}NO_{11}$: C 55.1, H 5.27, N 2.92, Found: C 54.5, H 5.36, N 2.98.

Reaction of 2,2,2-Trichloroethyl 3,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (**1**). By applying *Method A*, but with THF (5 m*l*) as a co-solvent and with reaction time of 30 min, **3,4,6-tri-*O*-acetyl-2-deoxy-2-(3-hydroxyphthalimidino)-β-D-glucopyranose** (**6**) was obtained in 85% yield, m.p

170~172 °C; ^{1}H-NMR ($CDCl_3$): δ 7.76~7.50 (*m*, 4, phenyl), 5.95 (*q*, *J*=10 and 2 Hz, 1, H-3), 5.80 (broad *s*, 1, -N-CH-O-), 5.50 (broad *d*, *J*=8 Hz, 2, H-1 and OH, D_2O exchangeable), 5.15 (*t*, *J*=10 Hz, 1, H-4), 4.70~3.80 (*m*, 4, H-2, H-5, H-6, H-6′), 2.10, 2.05, 1.88 (each *s*, 9, OAc); ir (KBr): 3500~3400 (hydroxyl), 1680 cm^{-1} (amide).

Anal. Calcd. for $C_{20}H_{23}NO_{10}$: C 54.9, H 5.31, N 3.20, Found: C 54.8, H 5.39, N 3.28.

Reaction of 3, 4, 6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranose (5). By applying *Method A* with reaction time of 30 min, compound **6** was obtained in 80 % yield.

Method B: Each starting material (1.0 g) was dissolved in a mixture of THF (5 m*l*) and pH 4.5 buffer solution (5 m*l*), and 20 molar equivalents of activated zinc dust were added. The mixture was stirred at room temperature while the progress of reaction being examined by TLC. In case of no reaction after 1hr, the mixture was kept for 24 hr. The unreacted starting material or the product was purified as described in *Mathod A* and identified.

Reaction of the Compounds 2, 3, and 4. By applying *Method B* with reaction time of 24 hr, only the starting compounds were recovered.

Reaction of 2, 2, 2-Trichloroethyl 3, 4, 6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (1). By applying *Method B* with reaction time of 30 min, **3, 4, 6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranose (5)** was obtained in 82 % yield, m.p 187 °C; ^{1}H-NMR ($CDCl_3$): δ 7.92~7.66 (*m*, 4, phthalimido), 5.82 (*q*, *J*=10 and 2Hz, 1, H-3), 5.70 (broad *s*, 1, OH, D_2O exchangeable), 5.62 (*d*, *J*=9 Hz, 1, H-1), 5.16 (*t*, *J*=10 Hz, 1, H-4), 4.42~3.83 (*m*, 4, H-2, H-5, H-6, H-6′), 2.09, 2.02, 1.85 (each *s*, 9, OAc); ir (KBr): 3500 (hydroxyl), 1780, 1730 (phthalimido), 1730 cm^{-1} (ester).

Anal. Calcd. for $C_{20}H_{21}NO_{10}$: C 55.2, H 4.86, N 3.22, Found: C 55.0, H 4.87, N 3.08.

REFERENCES

1. Presented at the 42nd Annual Meeting of the Korean Chemical Society, Taeku, Korea, October 20, 1978; Supported in part by the grants from Asan Foundation.
2. J. C. Sheehan and K. R. Henery-Logan, *J. Amer. Chem. Soc.*, **79**, 1262 (1957).
3. R. B. Woodward, *Science*, **153**, 487 (1966).
4. E. H. Flynn, "Cephalosporins and Penicillins -Chemistry and Biology", P. 662, E. H. Flynn, Ed., Academic Press, New York, 1972.
5. J. L. Isidor and R. M. Carlson, *J. Org. Chem.*, **38**, 554 (1973).
6. G. Just and K. Grozinger, *Synthesis*, 457 (1976).
7. Reissert, *Ber.*, **46**, 1489 (1913).
8. R. E. Howard and E. B. Miller, *U. S. patent*, 2,919,282 (1959); *Chem. Abstr.*, 54, 11050d (1960).
9. K. Matsushiro and M. Miyashita, *Japan Patent*, 7,461,158 (1974); *Chem. Abstr.*, **81**, 120452t (1974).
10. R. U. Lemieux and H. Driguez, *J. Amer. Chem. Soc.*, **97**, 4069 (1975).
11. R. U. Lemieux, T. Takeda and B. Y. Chung, "ACS Symposium Series, No. 39; Synthetic Methods for Carbohydrates," P. 149, H. S. EL Khadem, Ed., American Chemical Society, Washington, D. C., 1976.
12. R. U. Lemieux and B. Y. Chung, Unpublished Results.
13. S. Yamamura and Y. Hirata, *J. Chem. Soc.*, **C**, 2887 (1968).
14. CRC, Handbook of Chemistry and Physics, 53rd Ed., R. C. Weast, Ed., The Chemical Rubber Co., Cleveland, Ohio, 1972.
15. J. C. Sheehan and D. A. Johanson, *J. Amer. Chem. Soc.*, **76**, 158 (1954).
16. A. Dunet and A. Willemare, *Bull. Soc. Chim. France*, 1945 (1948); *Chem. Abstr.*, **43**, 3806a (1949).