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Phthalimido기 존재하에서 아연분말에 의한 2, 2, 2-Trichloroethyl 에스테르의 선택적 환원분해

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Selective Cleavage of 2, 2, 2-Trichloroethyl Esters with Activated Zinc Dust in the Presence of Phthalimido Group

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요 약. Phthalimido기와 2, 2, 2-trichloroethyl기를 공유한 화합물들, 즉 2, 2, 2-trichloroethyl phthalimidoacetate (**1a**), 2, 2, 2-trichloroethyl 6-phthalimidohexanoate (**2a**), 2, 2, 2-trichloroethyl 2-phthalimidopropanoate (**3a**) 및 2, 2, 2-trichloroethyl N-phthaloylcarbamate (**4a**)를 합성하여 초산수용액 (방법 A), THF 수용액(방법 B) 및 triethylamine을 포함한 THF 수용액(방법 C)에서 아연분말과 각각 반응시킨 결과, 방법A 및 B의 경우에는 2, 2, 2-trichloroethyl기가 환원분해 됨과 동시에 phthalimido기도 3-hydroxyphthalimidino 기로 환원됨을 알았으며, 방법C의 경우에는 phthalimido기는 환원되지 않고 2, 2, 2-trichloroethyl 기 만이 선택적으로 환원 분해됨을 발견하였다.

ABSTRACT. Four 2, 2, 2-trichloroethyl esters possessing a phthalimido group, 2, 2, 2-trichloroethyl phthalimidoacetate (**1a**), 2, 2, 2-trichloroethyl 6-phthalimidohexanoate (**2a**), 2, 2, 2-trichloroethyl 2-phthalimidopropanoate (**3a**) and 2, 2, 2-trichloroethyl N-phthaloylcarbamate (**4a**) were prepared and treated with zinc dust in aqueous acetic acid (*Method A*), in aqueous THF (*Method B*), and in aqueous THF containing triethylamine (*Method C*). By *Methods A* and *B*, 2, 2, 2-trichloroethyl ester linkage of the compounds **1a**, **2a** and **3a** was reductively cleaved with concurrent reduction of phthalimido group to a 3-hydroxyphthalimidino group. By employing *Method C*, however, 2, 2, 2-trichloroethyl ester linkage of all the four compounds was selectively cleaved while the phthalimido group was preserved.

INTRODUCTION

It is common especially in β-lactam chemistry that free carboxylic acid is temporarily protected into 2, 2, 2-trichloroethyl ester because of its ready cleavage with zinc dust in aqueous acetic acid or formic acid[1]. Phthalimido group, a potential precursor of a primary amine, is also reduced with zinc dust in refluxing acetic acid[2] to the 3-hydroxyphthalimidino group, from which a primary amine could not be obtained with hydrazine treatment. Since both 2, 2, 2-trichloroethyl and phthalimido groups react with zinc dust in acidic media, it would be worthwhile to find out, by employing simple compounds possessing both of the functional groups, a proper condition for the selective cleavage of 2, 2, 2-trichloroethyl linkage without

concurrent reduction of the phthalimido group.

In the previous papers[3,4], we have reported that a selective cleavage of 2, 2, 2-trichloroethyl group of some glycosides possessing phthalimido function, *eg.*, 2, 2, 2-trichloroethyl 3, 4, 6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-*p*-glucopyranoside, can be accomplished with zinc dust in aqueous THF or THF-buffer. We have also briefly mentioned[4] the selective cleavage of 2, 2, 2-trichloroethyl esters with zinc dust in the presence of phthalimido group.

In the present study, we have extended our investigation on the selective cleavage of 2, 2, 2-trichloroethyl esters in the presence of phthalimido group, and phthalimido carboxylic acids and their 2, 2, 2-trichloroethyl esters were subjected to the activated zinc dust in aqueous THF containing triethylamine.

RESULTS AND DISCUSSION

Four 2, 2, 2-trichloroethyl esters possessing a phthalimido group, 2, 2, 2-trichloroethyl phthalimidoacetate (**1a**), 2, 2, 2-trichloroethyl 6-phthalimidohexanoate (**2a**), 2, 2, 2-trichloroethyl 2-phthalimidopropanoate (**3a**) and 2, 2, 2-trichloroethyl N-phthaloylcarbmate (**4a**) were prepared from phthalimidoacetic acid (**1c**), 6-phthalimidohexanoic acid (**2c**), N-phthaloylalanine (**3c**) and phthalimide (**4c**), respectively, and all the eight compounds were treated with excess amounts of activated zinc dust in 90% aqueous acetic acid (*Method A*), in 90% aqueous THF (*Method B*), and in 90% aqueous THF containing 1~2 equivalents of triethylamine (*Method C*).

Reaction of Esters 1a, 2a and 3a

Method A. Treatment of the esters **1a**, **2a** and **3a** with activated zinc dust in 90% aqueous acetic acid at room temperature produced within 30 min the corresponding 3-hydroxyphthalimidino carboxylic acids **1b**, **2b** and **3b** in nearly 60% yield. The carbonyl absorption bands of phthalimido and ester groups appeared at 1730~1780cm^{-1} in the IR spectra of the starting compounds could not be observed in those of **1b**, **2b** and **3b**, whereas new carbonyl absorption bands at 1710~1720cm^{-1}, simple amide bands at 1660~1670cm^{-1} and broad hydroxyl bands at 2500~3400cm^{-1} appeared in the IR spectra of the products. The ^{1}H-NMR spectra of the products also showed the disappearance of the methylene protons of 2, 2, 2-trichloroethyl group (around δ 4.80 ppm) and exhibited the presence of two new D_2O exchangeable protons and of a methylidyne proton of the 3-hydroxyphthalimidino group (around δ 5.80 ppm).

These spectral data clearly indicated that the phthalimido group was reduced to a 3-hydroxyphthalimidino group and that at the same time, the 2, 2, 2-trichloroethyl esters were also reductively cleaved to the free carboxylic acids.

Method B. Reaction of **1a**, **2a** and **3a** with activated zinc dust in 90% aqueous THF also yielded **1b**, **2b** and **3b**, although it took longer than 4 hrs for the completion of reaction. TLC examination of the reaction showed that the phthalimido carboxylic acids **1c**, **2c** and **3c** were produced at the beginning, but the new spots corresponding to the 3-hydroxyphthalimidino carboxylic acids **1b**, **2b** and **3b** started to appear before the complete disappearance of the starting esters.

Method C. When the esters **1a**, **2a** and **3a** were treated with activated zinc dust in 90% aqueous THF containing 1~2 equivalents of triethylamine, only the 2, 2, 2-trichloroethyl group was selectively cleaved even after 24 hrs and phthalimido carboxylic acids **1c**, **2c** and **3c** were obtained in more than 85% yield. The IR spectra of these products showed that the strong phthalimido absorption bands at 1730 and 1780

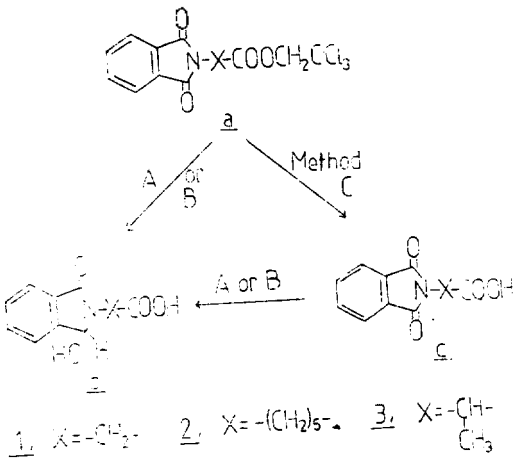

Fig. 1.

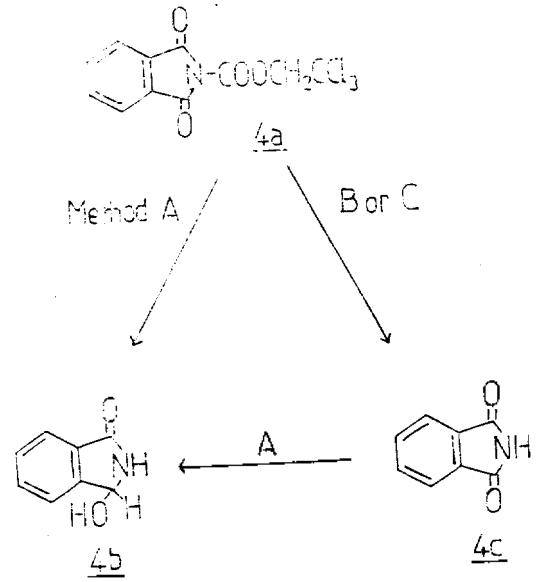

Fig. 2.

cm^{-1} were still present and that the characteristic absorption bands of a carboxylic acid, *i.e.*, broad hydroxyl absorptions at 3400~2500cm^{-1} and carbonyl absorptions at around 1720 cm^{-1} newly appeared. The ^{1}H-NMR spectrd also showed the disappearance of methylene protons of the 2, 2, 2-trichloroethyl group and exhibited the existence of a new D_2O exchangeable proton. These spectral data confirmed the selective cleavage of 2, 2, 2-trichloroethyl esters with the phthalimido group preserved (*Fig.* 1).

Reaction of Carboxylic Acids 1c, 2c and 3c

When the phthalimido carboxylic acids **1c**, **2c** and **3c** were treated with *Method C*, only the starting compounds were completely recovered even after 24 hrs However, with *Method A* (30 min) or *Method B* (4 hrs), the reduced products, 3-hydroxyphthalimidino carboxylic acids **1b**, **2b** and **3b**, were obtained.

Reaction of 4a and 4c

When 2, 2, 2-trichloroethyl N-phthaloylcarbamate (**4a**) was treated with *Method A*, 3-hydroxyphthalimidine (**4b**) was obtained in 95% yield. With *Method B* or *C*, however, phthalimide (**4c**) was obtained in more than 90% yield. In these reactions, the unstable carbamic acid derivatives could be formed as intermediates, which were decarboxylated spontaneously to give **4b** or **4c**. Treatment of phthalimide (**4c**) with zinc dust in aqueous acetic acid also produced **4b**, but with *Method B* or *C*, only starting phthalimide (**4c**) was completely recovered even after 24 hrs (*Fig.* 2).

CONCULSION

It is evident from the above results that 2, 2, 2-trichloroethyl ester is selectively cleaved with activated zinc dust in the presence of phthalimido group when the aqueous THF containing 1~2 equivalents of triethylamine is employed as a solvent. It is also evident that the rate of the reductive cleavage of 2, 2, 2-trichloroethyl ester is faster than that of the reduction of phthalimido group under the experimental condition of *Method C* It is clear that the free carboxylic acids actively participate in the reduction of phthalimido group as a proton donor. According to the present results the distance between carboxylic acid unit and phthalimido group, or the steric crowdness around the

carboxylic acid of the reacting compounds does not seem to exert any significant influence on the reduction of phthalimido group.

EXPERIMENTAL

General

Melting points were taken on an Electrothermal mp apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a Varian EM 360A spectrometer (60 MHz) and the chemical shifts are given in ppm downfield (δ) from the internal TMS standard. IR spectra were obtained on a Hitachi EPI-G grating IR or a JASCO DS 710G diffraction grating IR spectrophotometer. TLC was performed on a precoated silica gel plate (E. Merck, $60F_{254}$). All chemicals used were of reagent grade and purified prior to use, if necessary, by the methods deseribed in the literature. Zinc dust was activated by washing it several times with 3% apueous HCl, water and methanol, followed by vacuum drying.

Synthesis of Starting Materials

2, 2, 2-Trichloethyl Phthalimidoacetate (**1a**). To a solution of N-phthaloylglycine **1c** (4.10g, 20mmole) and 2, 2, 2-trichloroethanol (3.29g, 21mmole) in toluene (150m*l*), were added catalytic amounts of *p*-TsOH and the mixture was refluxed for 5 hrs with continuous removal of water. Toluene was removed under reduced pressure and the resulting solid was dissolved in chloroform. The chloroform solution was washed with aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4 and evaporated. The crude solid was recrystallized from ethanol (3.77g, 56% yield), mp 108°C.

^{1}H-NMR ($CDCl_3$): 8.05~7.70 (*m*, 4H, phthalimido), 4.80 (*s*, 2H, $-CH_2-$), 4.55 (s, 2H, $-NCH_2-$). IR (KBr): 1780, 1730 (phthalimido), 1730cm^{-1} (ester).

6-Phthalimidohexanoic Acid (*2c*). Pyrolysis of phthalic anhydride (19.2g, 0.13mole) and 6-aminohexanoic acid (13.1g, 0.1mole) at 180~185°C for 20min, and recrystallization of the cooled product from ethanol yielded colorless solid (14.1g, 54% yield), mp 111°C.

^{1}H-NMR ($CDCl_3$): 10.7 (*br*, 1H, COOH, D_2O exchangeable), 7.94~7.46 (*m*, 4H. phthalimido), 3.60 (*t*, J=7.0 Hz, 2H, $-NCH_2-$), 2.28 (*t*, *J*=7.0 Hz, 2H-CH_2 COO-), 1.82~1.10 (*m*, 6H). IR (KBr): 3400~2500, 1720(-COOH), 1780, 1730 cm^{-1} (phthalimido).

2, 2, 2-Trichloroethyl 6-Phthalimidohexanoate (**2a**)[6]. To a cooled solution of 2, 2, 2-trichloroethanol (4.48g, 30mmole) and thionyl chloride (24.0g, 0.2mole), was added 6-phthalimidohexanoic acid **2c** (2.62g, 10mmole), and the solution was stirred for 24 hrs at room temperature. After evaporation of excess thionyl chloride, the oily residue was dissolved in chloroform, washed with aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4 and evaporated. Recrystallization of the sticky solid from ethanol yielded colorless solid (2.04g, 52% yield), mp; 49~50°C.

^{1}H-NMR ($CDCl_3$): 7.98~7.53 (*m*, 4H, phthalimido), 4.82 (*s*, 2H, $-CH_2CCl_3$), 3.68 (*t*, *J*=7.0Hz, 2H, $-NCH_2-$), 2.48 (*t*, *J*=7.0 Hz, 2H, $-CH_2COO-$), 2.0~1.30 (*m*, 6H). IR (KBr): 1780, 1730(phthalimido), 1735cm^{-1}(ester).

N-Phthaloylalanine (**3c**). Pyrolysis of phthalic anhydride(1.3mole) and *L*-alanine (1.0 mole), and recrystallization yielded the colorless solid (95% yield), mp: 156~158°C.

^{1}H-NMR ($CDCl_3$): 11.2 (*s*, 1H, COOH, D_2O exchangeable), 7.75 (*s*, 4H, phthalimido), 5.00 (*q*, *J*=8.0Hz, 1H, -NCH), 1.70 (*d*, *J*=8.0Hz, 3H, $-CH_3$). IR (KBr): 3400~2500, 1710 (-COOH), 1780, 1730cm^{-1} (phthalimido).

2, 2, 2-Trichloroethyl 2-Phthalimidopropanoate (**3a**) was prepared in 60% yield from N-phthaloylalanine **3c** by following the procedure

for the preparation of ester **1a**, mp, 78°C.

^{1}H-NMR (acetone-d_6): 7.90 (*s*, 4H, phthalimido), 5.18 (*q*, *J*=8.0 Hz, 1H, -NCH-), 4.84 (*s*, 2H, $-CH_2CCl_3$), 1.78 (*d*, *J*=8.0 Hz, 3H, $-CH_3$). IR (KBr): 1780, 1730 (phthalimido), 1735cm^{-1}(ester).

2,2,2-Trichloroethyl N-Phthaloylcarbamate (**4a**). To 2,2,2-Trichloroethyl chloroformate (2.12 g, 10mmole) was added to a THF solution of phthalimide **4c** (1.47g 10mmole) and triethylamine (1.01g, 10mmole). The mixture was stirred for 12 hrs at room temperature and filtered. The filtrate was evaporated under reduced pressure and the resulting solid was recrystallized from ethanol (2.96g, 92% yield), mp 147°C.

^{1}H-NMR (acetone-d_6): 8.02 (*s*, 4H, phthalimido), 4.94 (*s*, 2H, $-CH_2-CCl_3$). IR (KBr): 1780, 1730 (phthalimido), 1735cm^{-1} (ester).

Reaction of the Starting Materials with Zinc Dust

Method A. *Each starting material (1.0g) was dissolved in 90% aqueous acetic acid (20ml) and 20 molar equivalents of activated zinc dust were added. The mixture was stirred at room temperature and solid materials removed by filtration. Solvent removal under reduced pressure left a solid which was dissolved in ethyl acetate, washed with 3% aqueous HCl and water. The ethyl acetate solution was extracted with aqueous NaOH and the aqueous layer was acidified again with 3% aqueous HCl in the presence of ethyl actate. The organic layer was washed with water, dried over anhydrous Na_2SO_4, filtered and evaporated to a solid, which was identified.*

Mefhod B. *Method B was similar to Method A except the solvent system employed was 90% aqueous THF.*

Methd C. *Method C was similar to Method A except 90% aqueous THF containing 1~2 equivalents of triethylamine was used as a solvent.*

Reaction of 2,2,2-Trichloroethyl phthalimidoacetate (1a) After 30 min of reaction with *Method A*, **3-hydroxyphthalimidinoacetic acid (1b)** was obtained in 70% yield, mp 105°C. ^{1}H-NMR (DMSO-d_6): 7.63~7.28 (*m*, 4H, phenyl), 5.84(br, 1H, -O-CH-N-), 4.00 (*q*, *J*=17.0 Hz, 2H, $-CH_2-$), 4.60~3.75 (*br*, 2H, -OH and -COOH, D_2O exchangeable). IR (KBr): 3350 (hydroxyl), 3500~2500, 1710 (-COOH), 1670 cm^{-1}(amide). *Method B* also gave the compound **1b** in 75% yield after 6hrs of reaction, but with *Method C*, **N-phthaloylalocine (1c)** was obtained in 85% yield even after 24 hrs of reaction, mp 191°C (*lits.*, 191~192°C).

Reaction of 2,2,2-Trichloroethyl 6-Phthalimidohexanoate (2a). After 30 min of reaction with *Method A*. **6-(3-hydroxyphthalimidino)-hexanoic acid (2b)** was obtained in 60% yield, mp 48~52°C. ^{1}H-NMR (DMSO-d_6): 7.85~7.45 (*m*, 4H, phenyl), 5.80 (*br*, 1H, -OCHN-), 4.25~3.85 (*br*, 2H, -OH and -COOH, D_2O exchangeable), 3.68 (*t*, *J*=7.0 Hz, 2H, $-NCH_2-$), 2.48 (*t*, J=7.0 Hz, 2 H, $-CH_2COO-$), 2.0~1.30 (*m*, 6 H). IR (KBr): 3400~2400, 1715(-COOH and hydroxyl), 1665 cm^{-1} (amide). *Method B* also gave the compound **2b** in 65% yield after 6 hrs of reaction, but with *Method C*, **6-phthalimidohexanoic acid (2c)** was obtained in 80% yield even after 24 hrs of reaction, mp 111°C.

Reaction of 2,2,2-Trichloroethyl 2-Phthalimidopropanoate (3a). After 30min of reaction with *Method A*, **2-(3-hydroxyphthalimidino)-propanoic acid (3b)** was obtained in 63% yield, mp: 89~91°C. ^{1}H-NMR (DMSO-d_6): 7.62~7.45 (*m*, 4H, phenyl), 5.85 (*br*, 1H, -OCH N-), 5.00 (*q*, J=8.0Hz, 1H, -NCHCOO-), 4.45-3.80 (*br*, 2H, -OH and -COOH, D_2O exchangeable), 1.70 (d, J=8.0Hz, 3H, $-CH_3$).

IR (KBr): 3400~3500, 1710cm^{-1}(—COOH and hydroxyl), 1660cm^{-1} (amide). *Method B* also produced the compound **3b** in 60% yield after 6 hrs of reaction, but with *Method C*, **N-phthaloylalanine (3c)** was obtained in 85% yield even after 24 hrs of reaction.

Reaction of 2, 2, 2-Trichloroethyl N-Phthaloylcarbamate (4a). with *Method A*. **3-hydroxyphthalimidine (4b)** was obtained in 95% yield after 10 min of reaction, mp 178°C (*lit.*, 178°C). *Method B*, however, did not produce the compound **4b** and **phthalimide (4c)** was obtained in 90% yield. *Method C* also gave the compound **4c** in quantitive yield.

Reaction of Carboxylic Acids 1c, 2c and 3c. with *Method A* or *B*, 3-hydroxyphthalimidino carboxylic acids **1b, 2b** and **3b** were obtained. with *Method C*, however, only the starting compounds were fully recovered even after 24 hrs.

Reaction of Phthalimide (4c). with *Method A*, **3-hydroxyphthalimidine (4b)** was obtained within 10 min, but with *Method B* or *C*, only the starting compounds were completely recovered even after 24 hrs.

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