DAEHAN HWAHAK HWOEJEE
(*Journal of the Korean Chemical Society*)
Vol. 25, No. 6, 1981
Printed in the Republic of Korea

Thiol의 친핵성 첨가물의 합성 (제 2 보). β-nitrostyrene 유도체에 대한 Thioglycolic Acid의 친핵성 첨가반응

金泰麟† · 許泰聖* · 韓仁燮**
고려대학교 이과대학 화학과

(1981. 10. 3접수)

Synthesis of Nucleophilic Adducts of Thiols (II). Addition of Thioglycolic Acid to β-Nitrostyrene Derivatives

Tae-RinKim† Tae-Sung Huh* and **In-Sup Han****
Department of Chemistry, Korea University, Seoul 132, Korea

(Received Oct. 3, 1981)

요 약. β-Nitrostyrene 및 그 유도체에 Thioglycoic acid를 첨가시켜 다음과 같은 8가지 새로운 화합물을 합성하였다.

s-(2-Nitro-1-phenylethyl)-thioglycolic acid; *s*-[2-nitro-1-(*p*-methyl)phenylethyl]-thioglycolic acid; *s*-[2-nitro-1-(*p*-methoxy)phenylethyl]-thioglycolic acid; *s*-[2-nitro-1-(*p*-chloro)phenylethyl]-thioglycolic acid; *s*-[2-nitro-1-(*p*-bromo)phenylethyl]-thioglycolic acid; *s*-[2-nitro-1-(*p*-nitro)phenylethyl]-thioglycolic acid; *s*-[2-nitro-1-(3-methoxy-4-ethoxy)henylethyl]-thioglycolic acid; *s*-[2-nitro-1-(3, 4, 5-trimethoxy)phenylethyl]-thioglycolic acid.

이 물질들의 구조를 원소분석, UV, IR, NMR 스펙트럼등으로 확인하였다.

ABSTRACT. Eight new compounds were prepared by the addition reaction of thioglycolic acid to β-nitrostyrene and its derivatives.

s-(2-Nitro-1-phenylethyl)-thioglycolic acid; *s*-[2-nitro-1-(*p*-methyl)phenlethyl]-thioglycolic acid; *s*-[2-nitro-1-(*p*-methoxy)phenylethyl]-thioglycolic acid; *s*-[2-nitro-1-(*p*-chloro)phenylethyl]-thioglycolic acid; *s*-[2-nitro-1-(*p*-bromo)phenylethyl]-thioglycolic acid; *s*-[2-nitro-1-(*p*-nitro)phenylethyl]-thioglycolic acid; *s*-[2-nitro-1-(3-methoxy-4-ethoxy)phenylethyl]-thioglycolic acid; *s*-[2-nitro-1-(3, 4, 5-trimethoxy)phenylethyl]-thioglycolic acid;

The structure of these compounds were identified by elemental analysis, UV, IR and NMR spectral data.

INTRODUCTION

The addition reactions to the double bonds having electron attracting groups, unlike carbon-carbon double bonds, are nucleophilic.

The addition reactions of sulfhydryl compounds to α, β-unsaturated compounds are interesting because much information has appeared in the literature[1~4] concerning the antiviral and antitumor activities of their adducts.

Jung, *et al.*[5] synthesized N-*t*-butoxycabonyl-s-(2-nitro-1-phenylethyl)-*L*-cysteine by the addition of N-*t*-butoxycarbonyl-*L*-cysteine to β-nitrostyrene. Esterbauer, *et al.*[6~8] prepared adducts from the reactions of many sulfhydryl compounds with α, β-unsaturated carbonyl co-

* Department of Chemistry, Song Sim College for Women, Bucheon, 150-71, Korea
** Department of Chemistry, Gangweon University, Chooncun 200, Korea.

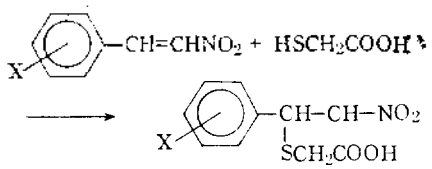
mpounds.

As a part of the series on the synthesis of nucleophilic adducts of thiols, the report on the addition of cysteine to β-nitrostyrene derivatives has been submitted[9] for publication.

The present investigation is a study of the syntheses of thioglycolic acid adducts to various β-nitrostyrene derivatives.

RESULTS AND DICUSSION

When β-nitrostyrene was reacted with thioglycolic acid, the following reaction would occur.



This is one of the typical Michael reaction. β-nitrostyrene and its derivatives were prepared according to Worral method[10] and identified by melting poinis, UV, IR and NMR spectra (*Table* 1).

When X was electron-releasing groups such as *p*-CH_3, *p*-CH_3O and *p*-H, the reaction rates were fast and yields were good. Polar solvents such as methanol increased the rates of these reactions.

When X was electron-attracting groups such as *p*-NO_2 and *p*-Cl, the reactions did proceed well and were favorable by less polar solvent such as acetone.

The structure of the products were confirmed as following:

Since the conjugated system of β-nitrostyrene disappears by forming adduct, the products were easily confirmed by UV, IR and NMR spectra (*Table* 2). The maximum absorption at 311nm of β-nitrostyrene was not observed in the adduct. The absorptions at 1638 cm^{-1} (>C=C<, stretching), 1345cm^{-1}(>C=C<, in plane bending) and 970 cm^{-1}(>C=C<, out of-plane bending) were disappeared and a new peak at 1703 cm^{-1} (>C=O stretching) and a broad band at 2500~3300cm^{-1} (carboxylic OH stretching) appeared. The absorption at 1510 cm^{-1} (-NO_2, stretching) was shifted to shorter wavelength. The two doublets (7.4~8.1 ppm, -CH=CH-) in NMR of β-nitrostyrene were invisible in adduct and new multiplets at 5.00 ppm (-CH-CH_2-), a singlet at 3.25 ppm (S-CH_2-C) and a singlet at 9.20 ppm (-COOH) appeared. The integral ratios of the peaks was 1:5:3:2, which is well in consistent with the structure.

In addition to the spectral data, melting points, elemental analyses, neutralization equivalents and yields were listed in *Table* 2.

Table 1. Melting points and spectral data of β-nitrostyrene derivatives.

derivatives	m. p. (°C) obs.	m. p. (°C) *lit.*	λ_{max}(nm)	ir(cm^{-1})
p-H	56~57	57~58 [10]	311 228	1638 1510
p-CH_3	99~100	99~100 [10]	325 233	1632 1510
p-CH_3O	120~121	123 [11]	351 239	1624 1500
p-Cl	109~110	113~114 [11]	315 228	1638 1500
p-Br	112	115 [12]	310 237	1628 1500
p-NO_2	197~199	201 [13]	303	1646
3-CH_3O 4-C_2H_5O	142	142 [13]	336 259	1636 1502
3,4,5-tri-CH_3O	123~124	120~121 [14]	350 251	1640 1505

EXPERIMENTAL

Benzaldehyde, *p*-nitrobenzaldehyde, triethylamine and nitromethane were obtained from Wako Chemicals. Anisaldehyde, *p*-bromobenzaldehyde and thioglycolic acid were reagent

Table 2. Physical, analytical and spectral data of thioglycolic acid adducts to β-nitrostyrene derivatives.

derivatives	λ_{max} (nm)	ir (cm^{-1})	nmr (ppm)	Surfur (%) analysis		Neutralization equivalent		Yields (%)
				Calc.	Found	Calc.	Found	
p-H	—	1703 2500~3300 1562	3.25 (S, SCH_2) 5.00(M, $CHCH_2$) 7.45 (M, Ph) 9.20(S, COOH)	13.3	13.5	241.26	248.65	64.6
p-CH_3	—	1702 2500~3300 1562	2.21(S, Ph-CH_3) 3.25(S, SCH_2) 5.00(M, $CHCH_2$) 7.40(M, Ph) 10.30(S, COOH)	12.5	12.9	255.29	261.32	72.4
p-CH_3O	253 253	1728 2500~3300 1552	2.60(S, SCH_2) 3.12(S, OCH_3) 4.30(M, $CHCH_2$) 6.40(M, Ph) 9.90(S, COOH)	11.8	12.1	268.37	271.29	55.6
p-Cl	224	1730 2500~3300 1560	3.36(S, SCH_2) 5.10(M, $CHCH_2$) 7.60(S, Ph) 10.0(S, COOH)	11.6	11.7	275.71	268.53	58.5
p-Br	—	1690 2500~3300 1550	3.47(S, SCH_2) 5.25(M, $CHCH_2$) 7.85(M, Ph) 10.2(S, COOH)	10.0	10.1	320.16	315.68	31.3
p-NO_2	265	1718 2500~3300 1555	3.30(S, SCH_2) 5.00(M, $CHCH_2$) 8.25(M, Ph) 9.75(S, COOH)	11.2	11.1	286.27	283.79	36.0
3-CH_3O 4-C_2H_5O	280 237	1700 2500~3300 1558	1.25(T, CH_3CH_2O) 3.30(S, SCH_2) 4.00(M, CH_3CH_2O, CH_3O) 5.00(M, $CHCH_2$) 7.00(M, PH) 9.98(S, COOH)	10.2	10.7	315.36	312.76	50.0
3,4,5-tri-CH_3O	—	1718 2500~3300	3.33(S, SCH_2) 4.00(S, CH_3O) 5.08(M, $CHCH_2$) 7.00(S, Ph) 8.65(S, COOH)	9.7	10.5	331.37	324.76	67.0

grade of Merk Co. *p*-Tolualdehyde and *p*-chlorobenzaldehyde were purchased from Eastman Kodak.

UV spectra were recorded with Hitach Recording Spectrophotometer. IR and NMR spectra were recorded with Hitachi IR Spectrophotometer EP IG_2 and Varian Medel EM 360 (60 MHz) NMR Spectrophotometer, respectively.

β-Nitrostyrene derivatives[10]. Benzaldehyde derivatives (0.5 mole) and nitromethane (30.5g, 0.5 mole) were dissolved in 100 m*l* of methanol. Sodium hydroxide (21.0 g, 0.52 mole) was dissolved in 50 m*l* of water. This cold sodium hydroxide solution was added dropwise to the mixture of benzaldehyde and nitromethane and the mixture was stirred at 10 °C until clear solution was attained. When this reaction mixture was added to hydrochloric acid solution, yellow crystall was precipitated out. The yellow precipitate was collected and recrystallization from ethanol gave β-nitrostyrene derivatives.

***s*-(2-Nitro-1-phenylethyl)-thioglycolic Acid.** Thioglycolic acid (1.8 g, 0.02 mole) and triethylamine (2.0 g, 0.02 mole) were dissolved in 40 m*l* of methanol. β-Nitrostyrene (3.0 g, 0.02 mole) was added to the solution and the reaction mixture was stirred for 4 hours at 10 °C. After evaporating a portion of solvent, 10 m*l* of dichloromethane and cold dilute HCl were added to the solution. After dichloromethane layer was separated it was stored in ice-box overnight. The white precipitate was collected by filtration. Recrystallization from CCl_4 gave 3.1 g (64.6 %) of white crystal of *s*-(2-nitro-1-phenylethyl)-thioglycolic acid melting at 59~60° C.

***s*-[2-Nitro-1-(*p*-methyl)phenylethyl]-thioglycolic Acid.** From the mixture of *p*-methyl-β-nitrostyrene (4.9 g), thioglycolic acid (2.7 g) and triethylamine (3.0 g) in 100m*l* of methanol solution, 5.5g (72.4 %) of *s*-[2-nitro-1-(*p*-methyl) phenylethyl]-thioglycolic

acid melting at 71~73°C was obtained.

s-[2-Nitro-1-(p-methoxy)phenylethyl]thioglycolic Acid. From the mixture of *p*-methoxy-β-nitrostyrene (3.6 g), thioglycolic acid (1.8 g) and triethylamine (2.0g) in 100 m*l* of methanol solution, 3.0 g (55.6 %) of-[2-nitro-1-(*p*-methoxy)phenylethyl]-thioglycolic acid melting at 75~76° C was obtained.

s-[2-Nitro-1-(3-methoxy-4-ethoxy)phenylethyl]-thioglycolic Acid. From the mixture of 3-methoxy-4-ethoxy-β-nitrostyrene (1.1g), thioglycolic acid (0.5 g) and triethylamine (0.6 g) in 100m*l* of methanol solution, 0.8g (50%) of *s*-[2-Nitro-1-(3-methoxy-4-ethoxy) phenylethyl]-thioglycolic acid melting at 93~94° C was obtained.

s-[2-Nitro-1-(3, 4, 5-trimethoxy)phenylethyl]-thioglycolic Acid. From the mixture of 3, 4, 5-trimethoxy-β-nitrostyrene (4.8 g), thioglycolic acid (1.8 g) and triethylamine (2.0 g) in 100m*l* of methanol solution, 4.4 g (67 %) of *s*-[2-nitro-1-(3, 4, 5-trimethoxy)phenylethyl]-thioglycolic acid melting at 110~112°C was obtained.

s-[2-Nitro-1-(p-methyl)phenylethyl]-thioglycolic Acid. *p*-Nitro-β-nitrostyrene (3.9 g, 0.02 mole), thioglycolic acid (1.8 g, 0.02 mole) and triethylamine (2.0 g, 0.02 mole) were dissolved in 40 m*l* of acetone. The reaction mixture was stirred for 30 minutes at 10 °C. After evaporating a portion of solvent, cold dilute HCl was added to the solution and stored in ice-box overnight. The white precipitate was collected by filtration. Recrystallization from CCl_4 gave 2.06 g (36.14 %) of white crystal of *s*-[2-nitro-1-(*p*-nitro)phenylethyl]-thioglycolic acid melting at 109~110 °C.

s-[2-Nitro-1-(p-chloro)phenylethyl]-thioglycolic Acid. From the mixture of *p*-chloro-β-nitrostyrene (5.5 g), thioglycolic acid (2.7 g) and triethylamine (3.0 g) in 40m*l* of acetone, 4.8 g (58.5%) of *s*-[2-nitro-1-(*p*-chloro) phenylethyl]-thioglycolic acid melting at 57~59 °C was obtained.

s-[2-Nitro-1-(p-bromo)phenylethyl]-thioglycolic Acid. From the mixture of *p*-bromo-β-nitrostyne (4.6 g), thioglycolic acid (1.8g) and triethylamine (2.0 g) in 40 m*l* of acetone, 2.0g (31.3 %) of *s*-[2-nitro-1-(*p*-bromo)phenylethyl]-thioglycolic acid melting at 59~60°C was obtained.

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