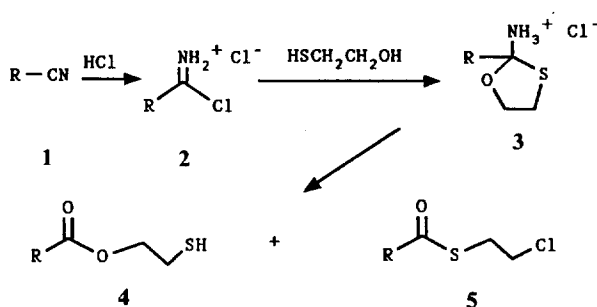


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Scheme 1.

Table 1. Yields of 2-Chloroethyl Thioesters and 2-Mercaptoethyl Esters Formed by Pinner Type Reaction of Diethyl Ether Soluble Nitriles in the Presence of 2-Mercaptoethanol in Anhydrous Diethyl Ether

Nitrile	RCOSCH ₂ CH ₂ Cl	RCOOCH ₂ CH ₂ SH
CH ₃ CH ₂ CH ₂ CN	42.2%	10.2%
Ph-CH ₂ CN	62.0%	5.6%
p-O ₂ N-Ph-CH ₂ CN	23.0%	9.4%
Ph-CN	10.4%	7.3%
Ph-CH(OH)-CN	14.0%	—

Another Evidence for the Formation of 2-Amino-1,3-oxathiolane Tetrahedral Intermediate in the Pinner Type Reaction of Nitriles with 2-Mercaptoethanol; Formation of 2-Chloroethioesters and 2-Mercaptoethyl Esters from Nitriles

Young Bok Lee, Yang Mo Goo*, and Youn Young Lee†

Department of Pharmacy and †Department of Chemistry,
Seoul National University, Seoul 151-742

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We recently proposed a bifunctional group-participated tetrahedral intermediate model for the active sites of the nitrile group hydrolyzing enzymes¹. We examined many bifunctional compounds for the activity of hydrolyzing a nitrile group to the corresponding amide², and found that 2-mercaptoethanol had the highest catalytic activity on the hydrolysis of α -aminophenylacetone nitrile to phenylglycinamide³. Stirring various nitrile compounds with 2-mercaptoethanol in a phosphate buffer (50 mM, pH 7.0) gave amides in good yields⁴. The nitrile group having an α -amino group, or those attached to the electron withdrawing aromatic ring was easily hydrolyzed to the amides⁵. 2-Mercaptoethanol seemed to react with nitrile compounds to produce bifunctional group-participated tetrahedral intermediates, decomposition of which should give the imidate analog, which should hydrolyzed to amides. During investigation of the reaction mechanism, we attempted to synthesize the tetrahedral intermediate, 2-amino-1,3-oxathiolane (3) by Pinner reaction⁶. The Pinner type reaction of nitriles with 2-mercaptoethanol produced amides in good yields. Conversion of nitriles to amides in the presence of 2-mercaptoethanol under anhydrous condition seemed to imply formation of 2-amino-1,3-oxathiolane (3) as an intermediate. Decomposition of this tetrahedral intermediate by at-

tack if the sulfur atom on C-5 carbon atom should yield amides.

α -Amino nitriles-HCl did not dissolved well in diethyl ether and we employed THF for the Pinner type reaction. Recently we tried the same reaction in diethyl ether with diethyl ether soluble nitriles, and we found that nitriles were not converted to amides. Instead, we isolated 2-chloroethyl thioesters and 2-mercaptoethyl esters from the reaction mixture, and these products should be formed also from the tetrahedral intermediate, 2-amino-1,3-oxathiolane (3) and we wish to report our finding in this report.

When the solution of butanenitrile (2.44 mL, 0.028 mol) in freshly distilled (over Na with benzophenone) anhydrous diethyl ether at 0°C was bubbled with dry HCl gas (dried with c-H₂SO₄) in the presence of 2-mercaptoethanol (1.96 mL, 0.028 mol) for 2 hrs, crystals were started to suspend in the reaction mixture. The reaction mixture was stirred for 3 hrs more at the same temperature and then for 10 hrs at 10°C. The crystals suspended in the reaction solution was found to be ammonium chloride. After the crystal was filtered off, the residue obtained after evaporation of the solution was chromatographed over silica gel to give S-(2-chloroethyl) butanethiolate (3.73 g, 44.4% yield)⁷ and 2-mercaptoethyl butanoate (422 mg, 10.2% yield)⁸. Further examination of the reaction with other diethyl ether soluble nitriles gave similar results (Table 1)⁹.

S-(2-Chloroethyl) thiolates should be formed from 2-amino-1,3-oxathiolane (3) in which C-5 carbon atom was attacked by chloride ion with liberation of ammonium chloride. The liberation of ammonium chloride without attack of chloride ion should give the 1,3-oxathiolane carbonium ion, which should be hydrolyzed by water during working up, followed by cleavage of the weak carbon-sulfur bond to produce 2-mercaptoethyl ester (Scheme 1). When THF was employed

for the same reaction with α -amino nitriles-HCl, chloride ion attacked the α -carbon atom of THF instead of the carbon atom in 2-amino-1,3-oxathiolane. The present and the previous results⁵ should firmly support formation of tetrahedral intermediates in the Pinner Type reaction of nitrile compounds with 2-mercaptoethanol.

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7. ¹H-NMR (CDCl₃) δ 0.98 (t, 3H, CH₃) 1.48-1.93 (m, 2H, β -CH₂), 2.56 (t, 2H, α -CH₂), 3.09-3.35 (m, 2H, SCH₂), 3.50-3.71 (m, 2H, CH₂Cl); ¹³C-NMR (CDCl₃) δ 13.10, 18.75, 30.80, 42.40, 45.56, 197.56; IR (neat) 1700 (C=O) cm⁻¹; MS (30 eV), m/z (rel. int.) 166 (M⁺, 1.6), 131 (0.4), 103 (0.8), 71 (100.0), 43 (78.2).
8. ¹H-NMR (CDCl₃) δ 0.96 (t, 3H, CH₃) 1.45 (t, 1H, SH), 1.47-1.81 (m, 2H, β -CH₂), 2.31 (t, 2H, α -CH₂), 2.61-2.88 (m, 2H, SCH₂), 4.19 (t, 2H, OCH₂); IR (neat) 2580 (SH), 1740 (C=O) cm⁻¹; MS (30 eV), m/z (rel. int.) 148 (M⁺, 0.7), 115 (1.2), 101 (1.5), 89 (47.5), 71 (84.5), 60 (100.0), 43 (34.9).
9. Satisfactory Analytical data were obtained.