Selective Hydrolysis of 2-Haloethyl Esters with Sodium Ethanedithiolate

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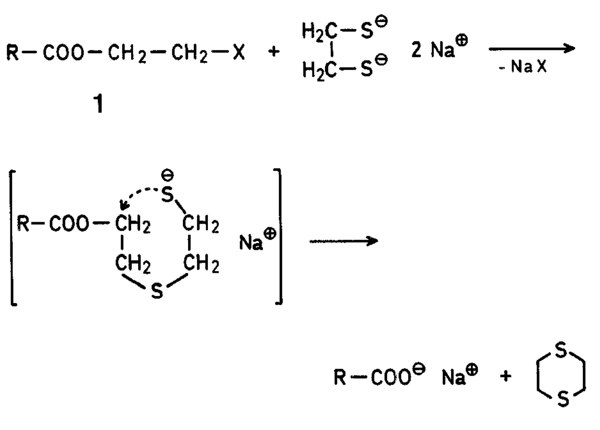
The lack of adequate methods for their specific removal has apparently limited the use of 2-haloethyl groups for protecting the carboxyl function; on the other hand, the 2,2,2-trichloroethyl group[1] continues to enjoy enormous popularity in organic synthesis. Having recently reported on the experience of deblocking 2-haloethyl esters by trithiocarbonate ion[2], we subsequently concluded an investigation of successfully employing ethanedithiolate as an alternative reagent.

The principle of cleavage is the same as that of the trithiocarbonate reaction which involves stepwise expulsion of the halide and the carboxylate; the crucial second step being intramolecular in nature. Subtle variation in reactivities of the nucleophilic thiolate sulfur atoms between the two reagents exists since they are bonded to dissimilarly hybridized carbons (sp^2 *vs* sp^3) and delocalizabilities of their lone-pair electrons are entirely different. However, based on the observation that simple thiolate effectively displaces a carboxylate four or five carbons apart[3], ethanedithiolate was expected to be able to split the 2-haloethyl group from their esters. *p*-Dithiane would be coproduced from this process.



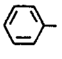
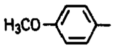
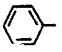
The expectation has been borne out, acids have been regenerated in excellent yields.

To further prove that the reaction proceeds by initial halogen displacement by thiolate ion and that cleavage of the esters is indeed intramolecular, the following experiments were carried out. (i) Heating 2-bromoethyl benzoate with two equivalents of sodium methanethiolate in acetonitrile for 3h, and direct trituration of the crude reaction mixture with benzene allowed *quantitative* isolation of 2-(methylthio)-ethyl benzoate which was identified by comparison with an authentic compound. This observation rules out the possibility of simultaneous attack at carbon attached to the ethereal oxygen of the esters. (ii) Reaction of sodium ethanedithiolate with 2-haloethyl esters in acetonitrile without adding water during reaction gave essentially the same results. Thus the deblocking process is not due to simple saponification.

Cleavage of 2-Haloethyl Esters by Sodium Ethanedithiolate; General Procedure:

To a stirred suspension of sodium ethanedithiolate (2.2 mmol; from sodium hydride + ethanedithiol) in acetonitrile (10 ml) was

Table. Ethanedithiolate Cleavage of 2-Haloethyl Esters

Ester **1**		Acid	
R	X	M.p.	Yield (%)
	Br	120–122°	96
	Br	182–184°	80
n-$C_{11}H_{23}$	Br	42–44°	92
	Cl	120–122°	90

added the 2-haloethyl ester (2 mmol) and heated under reflux for a total of 3h. Water (2 ml) was introduced after 1 h to dilute the thick paste. The final reaction mixture was cooled, poured into water, washed with ether, acidified and extracted with benzene or chloroform. The crude product (T.L.C. pure) was recrystallized from an appropriate solvent, and identified spectrally.

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[1] R. B. Woodward et al., *J. Amer. Chem. Soc.* **88**, 852 (1966).
[2] T.-L. Ho, *Synthesis* **1974**, 715.
[3] T.-L. Ho, C. M. Wong, *Syn. Commun.* **4**, 307 (1974).