

NOTIZEN

Deblocking of 2-Bromoethyl Esters via Thiazolium Salts

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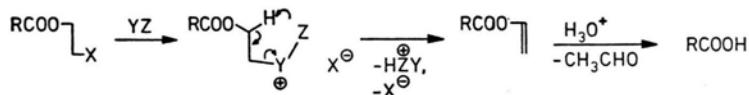
Z. Naturforsch. **33b**, 818-819 (1978); received February 15, 1978

Carboxyl Protection, Cycloelimination, Pyrolysis, Sigmatropic Rearrangement

Carboxylic acids are recovered from 2-bromoethyl esters by successive treatment with 4-methyl-5-thiazoleethanol, sodium bicarbonate followed by pyrolysis and quenching with dilute acid.

Much effort has been spent in finding ways to cleave 2-haloethyl groups with the goal of utilizing these to protect carboxylic acids. Thus, it has been shown that a double displacement which exploits the entropic advantage of intramolecular reaction by first anchoring the nucleophile to the end of the carbethoxy moiety is highly effective to disengage the ester [1]. Substitutive fragmentation [2] involving an oxidoreduction process also represents a viable route for regenerating carboxylic acids. Applications of these esters in peptide synthesis [2b] are now emanating.

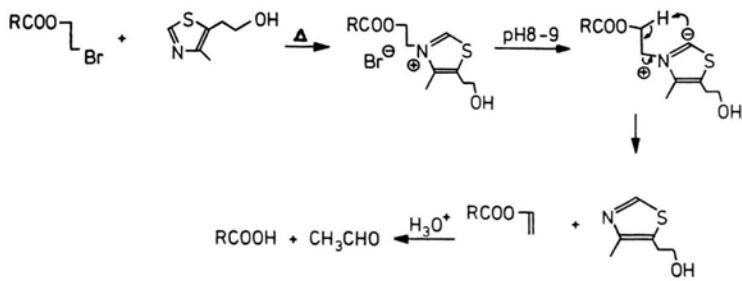
We have entertained the notion that transformation of 2-haloethyl esters into compounds which can undergo a [3.2]sigmatropic rearrangement (see equation) would greatly facilitate the deblocking step, and thereby magnifying the synthetic potential of these esters.



Subsequent search for suitable compounds which incorporate the requisite YZ unit pointed to thiazole and its 2-unsubstituted derivatives as a reasonable choice. Formally the thiazole ring nitrogen is equivalent to Y and C-2 adequately assumes the role of Z. It is now amply documented [3] that quaternization of thiazole with many primary haloalkanes can be induced and thiazolium salts undergo deprotonation at C-2 extremely easily to generate stable ylides. The ylide formation [4] underlies the remarkable catalytic effect of thiamine. Thus, on these premises, the above-specified intermediates should become accessible by reacting 2-haloethyl esters with a thiazole derivatives and deprotonation of the ensuing salts under mild con-

ditions (pH 8-9). It remains establishing experimental procedure for the cycloelimination.

The soundness of the idea has been validated by achieving the reaction with 4-methyl-5-thiazoleethanol as reagent. The choice was dictated by its availability. The entire process was unfortunately somewhat beset by the relatively low nucleophilicity of the thiazole. Generally the quaternization with 2-bromoethyl esters requires heating at 120 °C for more than 48 h, and even under these conditions salt formation appears to be incomplete. The unreacted 2-bromoethyl esters were detectable by spectroscopic examination of the crude reaction mixtures. As expected, 2-chloroethyl esters are even more inert toward thiazoles.



When the crude thiazolium salts were dissolved in anhydrous methanol and treated with sodium bicarbonate, effervescence occurred. Since solvation disfavored polar intramolecular reactions, methanol was driven off before submitting the ylides to thermolysis under an inert atmosphere. Some resinous material was produced (from the resulting vinyl esters?) during heat treatment, but it did not interfere with the isolation of the carboxylic acids.

At this stage of development, the procedure is not particularly attractive in serving a preparative

Table. Regeneration of carboxylic acids from 2-bromoethyl esters via thiazolium salts.

Acid	Yield [%]	m.p. [°C]
Benzoic	61	119–120
p-Chlorobenzoic	61	239–241
p-Anisic	57	182–184
Lauric	52	41–43

role. However, the fair yields attainable suggest that a deblocking sequence based on the cyclo-elimination concept should become viable on further investigation.

Experimental

General procedure for deblocking of 2-bromoethyl esters

A mixture of a 2-bromoethyl ester (5 mmol) and 4-methyl-5-thiazole-ethanol (715 mg, 5 mmol) was heated at 120 °C for 48 h. The crude product was dissolved in dry methanol (5 ml) and treated with NaHCO₃ (462 mg, 5.5 mmol). After effervescence subsided, methanol was removed *in vacuo*, and the solid residue was pyrolyzed at 190–210 °C under nitrogen. The cooled mixture was leached with 2 N HCl (7.5 ml) and extracted with ether. The acidic product was freed from other materials by dissolution into aqueous bicarbonate and reacidification. Identification of the recrystallized acid with an authentic sample was made by spectroscopic measurements.

[1a] T.-L. Ho, *Synthesis* **1974**, 715;
[1b] T.-L. Ho, *Synthesis* **1975**, 510.

[2a] T.-L. Ho, *Syn. Commun.* **8** (1978), in press.
[2b] H. Eckert, *Synthesis* **1977**, 332, and references therein.

[3] R. C. Elderfield (ed.): *Heterocyclic Compounds*, p. 639, Vol. 5, Wiley, New York 1957.

[4] R. Breslow, *J. Am. Chem. Soc.* **80**, 3719 (1958).